National Institute for Health and Care Excellence

Version 1.0 Pre-consultation

Cystic Fibrosis: diagnosis and management

Appendix G

Appendix

Evidence Tables

04 May 2017

Draft for Consultation

Developed by the National Guidelines Alliance, hosted by the Royal College of Obsetricians and Gynaecologists

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

ISBN:

Contents

Appendix G: Evidence tables

G.1 Diagnosis of cystic fibrosis

Review question: In infants, children, young people and adults (including those that have undergone newborn screening) when should cystic fibrosis be suspected?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Grimaldi, C., Bremont, F., Berlioz-Baudoin, M., Brouard, J., Corvol, H., Couderc, L., Lezmi, G., Pin, I., Petit, I., Reix, P., Remus, N., Schweitzer, C., Thumerelle, C., Dubus, J. C., Sweat test practice in pediatric pulmonology after introduction of cystic fibrosis newborn screening, European Journal of Pediatrics, 174, 1613-20, 2015 Ref Id 449541	Sample size N=502 children presenting respiratory symptoms Asthma: n=358 Chronic cough: n=263 Lower airway infections: n=212 Bronchiectasis: n=35 Characteristics Mean age±SD (range): 36±28 months (1 month to 10 years) Gender: 282 boys (56.2%) No differences in the distribution of age and gender across hospitals Inclusion Criteria Children born in France after 1 January 2003 with a prior negative newborn screening test,	Tests Clinical symptoms: asthma chronic cough lower airway infections bronchiectasis No definitions given. Reference standard: sweat chloride test Thresholds for patients >6 months: Positive ST: ≥60 mmol/l. Intermediate ST: 40 to 59 mmol/l. Negative ST: ≤39 mmol/l. Thresholds for infants up to 6 months: Positive ST: ≥60 mmol/l. Intermediate ST: 29 to 59 mmol/l. Negative ST: ≤29 mmol/l.	Methods Sample selection: Retrospective, descriptive and multicentre study. Children identified from sweat test laboratories of each hospital. Procedure: Most children (94%) had 1 sweat test, 5.4% had 2 tests, and 3 children had ≥3 tests 538 sweat test performed in 502 children (this represents 15 to 25% of all sweat tests performed in each hospital) Number of sweat test per hospital ranged from 5 to 121 4 methods of sweat collection and sweat chloride dosage were used:	Results Clinical diagnosis of CF based on sweat test: In children with asthma: n=1; 0.3% In children with chronic cough: n=4; 1.5% In children with lower airway infections: n=4; 1.8% In children with bronchiectasis: n=2; 5.7% Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	Limitations The quality of this study was assessed using the tool proposed by Hayden et al. (2006), as suggested by NICE methods manual (2014) (Full citation: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37) 1. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results. Yes (All children had a negative CF newborn screening)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Country/ies where the study was carried out France Study type Descriptive Aim of the study To describe the current indications of sweat test prescription and to evaluate their interest in children with negative cystic fibrosis (CF) newborn screening referred to paediatricians specialized in respiratory diseases. Study dates January to December 2012 Source of funding Not reported.	for whom a paediatric pulmonologist prescribed a sweat test for respiratory symptoms between 1 January and 31 December 2012 Inpatient or outpatient Exclusion Criteria Patients born outside France Patients born before 1 January 2003 Patients without a newborn screening test If test was made to confirm a positive CF screening, or because of meconium illeus or a diagnosis of CF in siblings If the test was not prescribed by a hospital paediatric pulmonologist If the test result was unknown		Filter paper + Schales and Schales (3 hospitals) Exsupatch® + Exudose® (6 hospitals) Exsupatch® + Exudose® or Macroduct + Sweat Check® (2 hospitals) Macroduct coil + coulometric titration (3 hospitals) Definitions for symptoms not provided Data collection: Laboratory records Data analysis: Descriptive analysis. Critical confounders not taken into consideration.		2. Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). Unclear (the study does not indicate if data is available for all people) 3. The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (prognostic factor measurement). No (Definition for symptoms not provided) 4. The outcomes of interest are adequately measured in study participants to sufficiently limit potential bias (outcome measurement). Yes (The study gives details about how the sweat test was conducted, and the thresholds for diagnosis)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). No (the study does not indicate whether participants presented with other signs suggestive of CF. This is a very serious limitation of the study) 6. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). Yes (data analysis is not reported, but authors only conducted descriptive analysis) Overall quality: very low Other information Conflict of interest: the authors declare that they have no conflict of interest.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					All children had a negative CF newborn screening.
Full citation Hubert, D., Fajac, I., Bienvenu, T., Desmazes-Dufeu, N., Ellaffi, M., Dall'ava-Santucci, J., Dusser, D., Diagnosis of cystic fibrosis in adults with diffuse bronchiectasis, Journal of Cystic Fibrosis, 3, 15-22, 2004 Ref Id 332804 Country/ies where the study was carried out France Study type Descriptive Aim of the study To assess retrospectively the contribution of the sweat test and	Sample size N=601 adults with diffuse bronchiectasis Characteristics N=601 patients referred for diffuse brochiectasis n=46 diagnosed with CF (7.6%) Gender: 24 males and 22 females Mean age (range): 31 years (18 to 56) Inclusion Criteria All adult patients who were referred to the Pulmonary Department with diffuse bronchiectasis and who were diagnosed with CF between 1992 and 2001. Exclusion Criteria Not reported	Tests Clinical symptom: diffuse bronchiectasis Diffuse bronchiectasis was defined as chronic mucopurolent sputum production and recurrent lower respiratory tract infection, were confirmed by high-resolution CT. Reference standard: sweat chloride test The pilocarpine iontophoresis test was performed on both arms with measurements of sweat weight. Concentrations were measured using Gibson and Cooke method. Thresholds: Diagnosis of CF: >60 mmol/l. Suggestive, but not diagnostic of CF: 40 to 60 mmol/l.	Methods Sample selection: As described in inclusion criteria Procedure: All suspected cases of bronchiectasis were sent for CF testing. Two sweat test were performed for each patient. Data collection: Data was collected retrospectively from medical records. Statistical analysis: Descriptive analysis. Critical confounders not taken into consideration.	Results Clinical diagnosis of CF based on sweat test: Confirmed CF diagnosis: n=37; 6.16% Borderline CF diagnosis: n=9; 1.50% Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	Limitations The quality of this study was assessed using the tool proposed by Hayden et al. (2006), as suggested by NICE methods manual (2014) (Full citation: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37) 1. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results. No (It is unknown whether these patients underwent newborn screening, but seems unlikely as newborn screening was implemented in France in 2002)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
genotyping in the diagnosis of cystic fibrosis (CF) in adults with diffuse bronchiectasis. Study dates 1992 to 2001 Source of funding Not reported					2. Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). Unclear (the study does not indicate if data is available for all people) 3. The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (prognostic factor measurement). Yes(Definition for bronchiectasis provided) 4. The outcomes of interest are adequately measured in study participants to sufficiently limit potential bias (outcome measurement). Yes (The study gives details about how the sweat test was conducted,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					and the thresholds for diagnosis) 5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). No (the study does not indicate whether participants presented with other signs suggestive of CF. This is a very serious limitation of the study) 6. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). Yes (data analysis is not reported, but authors only conducted descriptive analysis) Overall quality: very low Other information Conflict of interest: not reported It is unknown whether these patients

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					underwent newborn screening, but seems unlikely as newborn screening was implemented in France in 2002 (Grimaldi 2015)
Full citation Lucidi, V., Alghisi, F., Dall'Oglio, L., D'Apice, M. R., Monti, L., De Angelis, P., Gambardella, S., Angioni, A., Novelli, G., The etiology of acute recurrent pancreatitis in children: a challenge for pediatricians, Pancreas, 40, 517-21, 2011 Ref Id 369280 Country/ies where the study was carried out Italy Study type Descriptive Aim of the study	Sample size N=78 infants, children and young people with acute recurrent pancreatitis Characteristics Mean age ± SD (range): 8.8±5.1 years (4 months to 18 years) 60% of patients complained of abdominal pain suggestive of biliopancreatic origin All patients had pancreatic sufficiency 42.3% (n=33) patients had a positive family history of chronic pancreatitis/ cystic fibrosis and/ or positive genetic testing and/ or altered sweat test Inclusion Criteria Paediatric patients affected by acute recurrent pancreatitis	Tests Clinical symptom: recurrent pancreatitis Defined as 2 or more separate documented episodes of acute pancreatitis with serum amylase and/ or lypase levels at least 3 times the upper reference limit Reference standards: Sweat test Thresholds for diagnosis of CF not reported. CFTR mutation	Methods Sample selection Retrospective descriptive study All consecutive patients affected by acute recurrent pancreatitis referred to the centre during the period 2003 to 2008 Procedure All patients were submitted to endoscopic retrograde cholangiopancreatography to exclude biliopancreatic malformation All patients were tested for CF by a sweat chloride test according to Gibson and Cooke method Most patients were also searched for the following gene mutations: CFTR, PRSSI and SPINKI Data collection	Results Clinical diagnosis of CF based on sweat test: Diagnosis of CF with ST: n=1; 1.3% Borderline diagnosis of CF with ST: n=7; 9% Genetic test: CFTR mutation: 39.6% (data available for n=53) SPINKI mutation: 7.1% (data available for n=42) PRSSI mutation: 4.5% (data available for n=44) Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	Limitations The quality of this study was assessed using the tool proposed by Hayden et al. (2006), as suggested by NICE methods manual (2014) (Full citation: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37) 1. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results. Unclear (The authors indicate 42.3% of patients had a positive family history of chronic pancreatitis/ cystic fibrosis and/ or positive genetic testing and/ or altered sweat test. However it is

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
To assess specific etiologies of acute recurrent pancreatitis at a single cystic fibrosis (CF) paediatric centre. Study dates 2003 to 2008 Source of funding Not reported.	Exclusion Criteria Not reported		Medical data was collected by reviewing clinical charts Data analysis Descriptive analysis. Critical confounders not taken into consideration.		unknown whether all these patients underwent newborn screening) 2. Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). Unclear (the study does not indicate if data is available for all people) 3. The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (prognostic factor measurement). Yes (Definition for pancreatitis provided) 4. The outcomes of interest are adequately measured in study participants to sufficiently limit potential bias (outcome measurement). Unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					(The study gives details about how the sweat test was conducted, but it does not report the thresholds for diagnosis) 5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). No (the study does not indicate whether participants presented with other signs suggestive of CF. This is a very serious limitation of the study) 6. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). Yes (data analysis is not reported, but authors only conducted descriptive analysis) Overall quality: very low

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Other information Conflict of interest: not reported 42.3% (n=33) patients had a positive family history of chronic pancreatitis/ cystic fibrosis and/ or positive genetic testing and/ or altered sweat test. However it is unknown whether all these patients underwent newborn screening.
Full citation Ooi, C. Y., Dupuis, A., Ellis, L., Jarvi, K., Martin, S., Gonska, T., Dorfman, R., Kortan, P., Solomon, M., Tullis, E., Durie, P. R., Comparing the American and European diagnostic guidelines for cystic fibrosis: same disease, different language?, Thorax, 67, 618-24, 2012 Ref Id	Sample size N=208 people with single organ manifestations of CF People with idiopathic chronic sinopulmonary disease: n=72 People with idiopathic recurrent, acute or chronic pancreatitis: n=44 Men with infertility due to obstructive azoospermia: n=92 Characteristics People with idiopathic chronic sinopulmonary disease:	Tests Clinical symptoms: Idiopathic chronic sinopulmonary disease Idiopathic sinopulmonary disease was defined as recurrent or chronic sinusitis (including sinusoidal pain, nasal discharge, and postnasal drip), nasal polyps, recurrent or chronic bronchitis, recurrent pneumonia and/or bronchiectasis for at least 6 months. All enrolled subjects with sinopulmonary disease had three or more of these symptoms. If not	Methods Sample selection Participants were prospectively and consecutively enrolled into the study. Data collection Sweat testing was conducted following Gibson and Cooke or Macroduct methods. American and European diagnostic guidelines were used. Extensive genotyping was performed in all subjects. The 23 CFTR mutations recommended by ACMG	Results People with idiopathic chronic sinopulmonary disease Clinical diagnosis of CF: Classic CF: n=14; 19.4% CFTR dysfunction: n=3; 4.2% Inconclusive: n=1; 1.4% Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	Limitations The quality of this study was assessed using the tool proposed by Hayden et al. (2006), as suggested by NICE methods manual (2014) (Full citation: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37) 1. The study sample represents the population of interest on key characteristics,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
449720 Country/ies where the study was carried out Canada Study type Descriptive Aim of the study To evaluate the diagnostic outcomes of prospectively recruited undiagnosed individuals referred to CF clinics with single organ manifestations of CF. Study dates 1994 to 2008 Source of funding Research grants from the Canadian CF Foundation and Genome Canada	Mean age ± SD (range): 38.5±15.9 (9.9 to 66.7) years Gender: 70.8% (n=51) women People with idiopathic recurrent, acute or chronic pancreatitis: Mean age ± SD (range): 24.3±13.2 (7.9 to 59.9) years Gender: 59.1% (n=26) women Men with infertility due to obstructive azoospermia: Mean age ± SD (range): 34.8±5.3 (25.4 to 56.6) years Inclusion Criteria Undiagnosed individuals with single organ manifestations of CF. These included: idiopathic chronic sinopulmonary disease, idiopathic recurrent, acute or chronic pancreatitis or men with infertility due to obstructive azoospermia	done prior to referral, RESP subjects were tested for immunodeficiency, a-1-antitrypsin deficiency, allergic bronchopulmonary aspergillosis, non-tuberculous mycobacteria, and primary ciliary dyskinesia. Patients were also screened for conditions known to be associated with bronchiectasis (eg, rheumatoid arthritis, other collagen vascular diseases and inflammatory bowel disease). Patients diagnosed as having any of these disorders were excluded from the study. Idiopathic recurrent, acute or chronic pancreatitis A diagnosis of idiopathic recurrent acute pancreatitis was accepted following at least two episodes of abdominal pain associated with raised serum amylase and/or lipase (more than two times the upper limit of the reference range), and/or imaging evidence of acute pancreatitis such	were used as initial screening. Data analysis Descriptive analysis. Critical confounders not taken into consideration.	People with idiopathic recurrent, acute or chronic pancreatitis Clinical diagnosis of CF: Classic CF: n=2; 4.5% CFTR dysfunction: n=6; 13.6% Inconclusive: n=1; 2.3% Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable. Men with infertility due to obstructive azoospermia Clinical diagnosis of CF: Classic CF: n=19; 20.7% CFTR dysfunction: n=21; 22.8% Inconclusive: n=9; 9.8% Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable	sufficient to limit potential bias to the results. Unclear (It is unknown whether all these patients underwent newborn screening) 2. Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). Unclear (the study does not indicate if data is available for all people) 3. The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (prognostic factor measurement). Yes (Definition of symptom provided) 4. The outcomes of interest are adequately measured in study participants to

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	No patients were excluded on the basis of sex or race (defined by patient self report self report). Exclusion Criteria Not reported	as pancreatic oedema, haemorrhage or necrosis. Patients with chronic pancreatitis had chronic pain in association with pancreatic calcifications and/or characteristic ductal changes. Infertility due to obstructive azoospermia A diagnosis of obstructive azoospermia (congenital unilateral or bilateral absence of vas deferens) was confirmed by physical examination, transrectal ultrasound and evidence of azoospermia on two separate occasions. Reference standard: sweat test Thresholds for the diagnosis of CF according to European consensus recommendations.			sufficiently limit potential bias (outcome measurement). Yes (The study gives details about how the sweat test was conducted, and the thresholds for diagnosis) 5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). No (the study does not indicate whether participants presented with other signs suggestive of CF. This is a very serious limitation of the study) 6. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). Yes (data analysis is not reported, but authors only conducted descriptive analysis) Overall quality: very low

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Other information Conflict of interest: none It is unknown whether these patients underwent newborn screening.
Full citation Seear,M., Wensley,D., Chronic cough and wheeze in children: do they all have asthma?, European Respiratory Journal, 10, 342-345, 1997 Ref Id 208109 Country/ies where the study was carried out Canada Study type Descriptive Aim of the study The study aimed to answer two questions: do such diagnostic orphans exist? And if so, can	Sample size N=81 children with a history of >3 months of productive cough Characteristics Not reported Inclusion Criteria Children with productive or rattly cough, with or without wheezing, on most days for three consecutive months or more. Exclusion Criteria Children with known causes of productive cough (cystic fibrosis, immunodeficiencies, bronchiectasis and bronchopulmonary dysplasia).	Tests Clinical symptom: productive cough No definition given. But just children with a history of >3 months of productive cough, of unknown cause, were included Reference standard: sweat test Thresholds for diagnosis of CF not reported.	Methods Sample selection Children referred to the respiratory clinic of British Columbia's hospital who fulfilled the inclusion criteria were prospectively recruited. Procedure and data collection All children completed the following test; chest radiograph, pulmonary function tests (if old enough), Mantoux test, sweat chloride test, full blood count, and immunoglobulin levels. If clinically indicated, subsequent tests included chest computed tomography (CT)-scan, flexible or rigid bronchoscopy, expanded immune investigations and lung biopsy.	Results Clinical diagnosis of CF: Diagnosis of CF: n=1; 1.23% Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	Limitations The quality of this study was assessed using the tool proposed by Hayden et al. (2006), as suggested by NICE methods manual (2014) (Full citation: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37) 1. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results. Unclear (the study does not say if the participants had undergone newborn screening)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
they be classified in a clinically useful manner? Study dates December 1993 to December 1995 Source of funding Not reported			Data analysis Descriptive analysis. Critical confounders not taken into consideration.		2. Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). Unclear (the study does not indicate if data is available for all people) 3. The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (prognostic factor measurement). Yes (history of > 3 months of productive cough) 4. The outcomes of interest are adequately measured in study participants to sufficiently limit potential bias (outcome measurement). Unclear (the study does not give details on how sweat test was conducted)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). No (the study does not indicate whether participants presented with other signs suggestive of CF. This is a very serious limitation of the study) 6. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). Yes (data analysis is not reported, but authors only conducted descriptive analysis) Overall quality: very low Other information Conflict of interest: not reported It is unknown whether these patients underwent newborn screening.

G.2 Information and support

Review question: What information and support should be given to children, young people and adults with cystic fibrosis?

Study details	Participants	Methods	Findings	Comments
Full citation Angst, D. B., Deatrick, J. A., Involvement in health care decisions: parents and children with chronic illness, Journal of Family Nursing, 2, 174-194, 1996 Ref Id 473335 Study type Qualitative study with interviews. Aim of the study To describe how children with chronic illness and their parents are involved in health care decisions through a	Sample size N=20 children with CF and both parents of each child (20 families). Characteristics Age of children: range 7 to 11 years (median 9 years). Severity of illness: mild to severe, with majority in the mild and moderate categories. All families were intact, two-parent families. Inclusion criteria Children with CF and their parents. Exclusion criteria Not reported.	Setting Not reported. Sample selection Not reported. Data collection Data was collected through interviews regarding family demographics, and health/illness status of the child. All interviews were transcribed verbatim and processed. Data analysis Data was coded into categories, and analysed by each investigator. Themes derived were further explored and used for secondary analysis.	Themes/categories CF data set Decision making: Information from the health care provider Parents did not see themselves as having much room to make decisions. Decisions were based on recommendations made by health care professionals. None of the families recalled talking to the health care professional regarding decision making, or how or when to include their children in health care decisions (author's comment). "We pretty much get the plan from [the doctor] and then we just implement it...I just do what he tells me, basically. I think if I had something that was a nagging concern, I certainly know he would listen and respond to those concerns, but to date I've just not had any...I figure when he wants to change the programme, he'll tell me and we'll just do it" (mother of child with CF). Parents viewed the outcome of decisions about their child's health as potentially very serious. They identified the outcome of making the wrong decision as illness progression and even death, which is why they considered the health care professional's recommendations seriously. (author's comment) Most families were not given information about alternative care (for example, home vs hospital antibiotic therapy, and different means to enhance their child's nutritional status). (author's comment)	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was not reported. The relationship between the researcher and the participants was not reported. Data collection: Data collection relied on the semi-structured interviews. Description of data collection method was vaguely described. Data analysis: The analytical process was reported vaguely. Description of emerging and overarching themes was reported, but saturation of data was not reported. Findings/results: Results were presented clearly (e.g., citation/data and the researchers' own input distinguished) Overall quality: Low Other information Population included two data sets, one set with children who had CF, and the second set included children with scoliosis

Study details	Participants	Methods	Findings	Comments
secondary analysis of two data sets. Country/ies where the study was carried out USA Study dates Not reported Source of funding Not reported			Parents as decision makers: Most parents viewed themselves as involved in the decision making process (discussion with the health care provider, decisions at home regarding enzymes and respiratory therapies). (author's comment) Fathers acknowledged that they were less involved in looking after their children due to unavailability to attend clinics. Most parents did not view their children to be involved in decisions or planning related to ongoing care, and considered themselves to make ultimate decisions about whether and what their children received: "I don't think he really should have much choice. I think we should just tell him. He certainly has as much right to ask questions and get answers as I do, but I want him to know that it's very important to do what we're told in this case. Not to be a creative thinker." (mother's comment) Parents decisions not to involve children regarding gastronomy tor central lines for supplemental nutritional therapies: Children considered for gastronomy tubes or central lines for supplemental nutritional therapies were not involved in the decisions. Children were not consulted on their feelings or opinions related to these interventions: "It was presented as a need for him to get back to approximately where he was on the growth curve. And if he does, then he avoids the tube. If he doesn't, then he gets the tube...We don't have that much that's negotiable...I don't see that there's two equivalent paths of therapy that are offered. Generally there's only	secondary to another chronic illness, Duchenne's muscular dystrophy, cerebral palsy, systemic juvenile rheumatoid arthritis, and Werdnig-Hoffman's disease.

Study details	Participants	Methods	Findings	Comments
			one. Therefore, there's no need for discussion." (father's comments) Health care professional not acknowledging children in planning or decision making: Children did not see themselves as involved in planning or decision making: "When I go to clinic, he doesn't usually talk to me...when I loose weight, he yells at my mom for it". (Girl's comment) When children should be involved in decision making: Parents did not previously think about involving their children in decision making as they waited for a cue from the health care providers as to when it was appropriate to involve their children: "I guess I never thought to ask [child]...I guess as he's gotten older, there's no reason not to ask his opinion". (mother's comments) "As a parent, I guess I need to push or just be told it's OK to do this now. You know that this is the stage that the child can handle it. You know, because when [the health care professional] tells you it's OK, it's a lot easier than you making that decision". (father's comments) Children's satisfaction of involvement: Most children liked being uninvolved; however, many children wanted greater involvement: "Sometimes they want me to take more medicine, and I don't even know what the medicine is, and if I stop taking other medicines. And so I have to ask my parents and they have to ask. If they at least told me, I think I would feel a little better about why I'm taking this medicine..I think I'd feel more comfortable if I got to talk to them". (girl's comment)	

Study details	Participants	Methods	Findings	Comments
Full citation Bagnasco, A., Petralia, P., Furnari, S., Ghio, S., Calza, S., Sasso, L., Paediatric nurses' perception of the child-family dyad's autonomy in managing a chronic disease situation: the experience of an Italian paediatric department, Journal of Preventive Medicine & Hygiene, 54, 124-9, 2013 Ref Id 363810 Study type Qualitative study Aim of the study	Sample size Number of pediatric nurses for CF=7. Characteristics Nurses working in the CF unit Inclusion criteria Not reported Exclusion criteria Not reported	Setting Children's hospital Sample selection Nurses working in the CF Unit. Participants were personally contacted to participate. A priori written consent was obtained from the participants. Data collection Data collected through individual semi structured interviews inside the hospital unit. Question was both general as well as technical aimed at identifying the major factors influencing the field. Data analysis All the interviews were transcribed, analysed and coded according to the 'thematic analysis'. The three researchers analysed them independently, and then compared the codes they had identified to reach an	Themes/categories Attitude of nurses towards education: All nurses stated that they play a crucial role in helping parents and their children to increase the level autonomy and safety. "Our job is to educate parents to help them increase both their self-esteem and their confidence in our competences and in nursing techniques". Adolesence and transition All nurses reported that, at least in the hospital, they tend to give greater independence and priority to young adults, and reduce the role of the parents. "You have to communicate with him/her as if he/she wasn't ill, for example, you have to ask simple questions related to his/her hobbies, favourite movies / books. This relationship based on mutual trust helps us to make fun of the disease" Parents' attitude in facing the chronic disease All nurses reported that children are less rebellious than young adults and influenced by their parent's perspective and knowledge. "The acceptance or denial of the disease of the child are related to the parents' perspective and ideas" Availability of information Nurses reported that the information were easily available in the internet which is helpful but may also create confusion and mistrust.	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Mixed sample with Neuro muscular and CF unit. No clear differentiation with overlap between samples. The relationship between the researchers and the respondents not clearly reported. Data collection: Data collection relied on the semi structured interviews for CF. No information on structure of interview or whether topic guide reported. Description of how "themes" were arrived at was discussed but information was not sufficient to conclude if data collection process was robust. No information on data saturation and full exploration of theme. Data analysis: The analytical process was described with description of themes and categories. No critical review of the researchers' role in the process. Findings/results: Results were presented clearly with themes supported by quotes. Researchers' role and

Study details	Participants	Methods	Findings	Comments
To explore how nurses perceived autonomy in parents, adolescents, and children related to the management of chronic disease. Country/ies where the study was carried out Italy Study dates 2011-2011 Source of funding Not reported		agreement on the emerging categories.	"The Internet is the most consulted tool for the resolution of their cares, although in some cases, it is a source of misunderstanding"	potential influences in the analytical process not critically reviewed. Overall quality: Poor Other information Ethical approval process not described. Consistency between the researchers not reported.
Full citation Barker, D., Driscoll, K., Modi, A., Light, M., Quittner, A., Supporting cystic fibrosis disease management during adolescence:	Sample size 24 Young adults Characteristics Young adults with cystic fibrosis Inclusion criteria Not reported Exclusion criteria Not reported	Setting Not reported Sample selection Recruited from two specialty care clinics in South Florida and Cincinnati. Participants were identified by the medical teams, sent a letter informing them about the study and	Themes/categories Adolescents' perceptions of non-supportive treatment-related behaviours: Young adults clearly identified some treatment-related behaviours, such as nagging, annoying or feeling unwanted from families. They were reluctant to rate family members or friends as being 'unsupportive' even when annoyed by them. They recognized the need for persistent reminders and their benefits even when they are annoyed by them.	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported. The relationship

Study details	Participants	Methods	Findings	Comments
The role of family and friends, Child: care, health and development, 38, 497-504, 2012 Ref Id 473360 Study type Qualitative semi structured interview study Aim of the study To explore the role of family and friends in supporting		approached following a regularly scheduled clinic visit. Parent consent were obtained prior to participation. Data collection The semi-structured interviews address both supportive and non-supportive behaviours from family and friends. Interviews were audiotaped and then transcribed for coding Data analysis The transcripts were coded using template analysis in which specific supportive and non-supportive behaviours were first identified and then assigned to hierarchical categories based on a template developed from prior literature. This template was then modified through an iterative process to better represent the data from the transcripts.	One participant reported, "[Mom] keeps telling me to do it whether I want to or not, she knows that it's going to help me so it's pretty supportive." While another stated, "[Mom] usually tells me to do [airway clearance] daily 'cause sometimes I don't like doing it so she usually has to tell me or else I won't do it." One adolescent stated, "Their intentions are good but the way they pursue it isn't that wonderful. I'd rather them tell me to do it instead of them yelling at me to do it. I mean I'm a person, too, I forget things." Similarly, one adolescent talked about reminders from her friend, She pretty much says, "Hey ok, if we're going to go out, you know, just like, let's get your meds done.' She wouldn't say, 'Ok you have to do your meds now' she'd say, 'So let's get your meds done just before we go or whatever so we don't have to do it later.' She'll present it in the way that it's not like something I have to do." She rated her friends' reminders as very supportive because they were as encouraging and not as demanding the treatment be completed. Young adults reported becoming annoyed when reminders were given after the treatment was completed or when the adolescent has a plan to complete the treatment. For example, one youth stated, "I get annoyed 'cause sometimes [mom] reminds me and I already did them. When talking about support from a close friend,"	between the researcher and the respondents not clearly reported. Data collection: Data collection relied on the semi-structured interviews. Process for semi structured interview was clearly reported but topic guide was not reported. Data analysis: The analytical process was described, with the use of predefined template analysis from the literature. No description of how "themes" were arrived at; researchers did not critically review their own roles in the process. Findings/results: Results were presented clearly with the generous use of quotes where appropriate (e.g., citation/data and the researchers' own input distinguished; the researchers' roles and potential influences in the analytical process not critically reviewed Overall quality: Moderate Other information Study approved by review boards. Multiple researchers but

Study details	Participants	Methods	Findings	Comments
cystic fibrosis disease management during adolescence Country/ies where the study was carried out USA Study dates Not reported Source of funding National Institutes of Health Postdoctoral Training Grant (T32 DK063929). Cystic Fibrosis Foundation Therapeutics, Inc. Student Traineeship (BARKER09A O);			another participant said, "It starts to get a little nagging at times, he's like 'You gotta do it, you gotta do it.' And I'm like, 'I know, I have a set time for this. I'll do 'em, don't worry!" They also found reminders annoying when the reminder interrupted other activities. For example, one participant stated, "Well, like they'll tell me to do stuff. And if I'm talking on the phone or hanging out with my friends, then I don't want to do it and it gets on my nerves." Another participant said, "Well sometimes like when I want to watch a show or something, she tells me to do my treatment, so I have to stop the activity and I go do it – that gets annoying." One adolescent said, "cause sometimes she'll say it and it'll really get to me and I'll be like, 'Don't tell me what to do' or 'I'll do whatever I want', you know, 'I can take care of myself '. So it's not that she's saying anything differently, it's just the way I'm perceiving it that day." Another adolescent stated, "If I'm in one of those aggressive type of 'Don't tell me what to do' kind of moods, if somebody reminds me to do something, it makes me very angry, and I'll not do it just to spite them."	consistency between them not reported
Full citation Beresford, B. A., Sloper, P., Chronically ill adolescents' experiences of communicating with doctors: a	Sample size N= 63 children and young people Characteristics Respondents had chronic conditions which were CF, juvenile chronic arthritis,	Setting Individual interviews took place in respondents' homes. The group meetings were held in venues that were geographically close to	Themes/categories Features of the encounter: "It would be better just to have one doctor so we could move on to different parts of epilepsy instead of getting the same questions again and again." "You don't tell the doctor anything because you don't want them [student doctors] to hear."	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question

Study details	Participants	Methods	Findings	Comments
qualitative study, Journal of Adolescent Health, 33, 172-9, 2003 Ref Id 366784 Study type Qualitative study with semi structured interviews Aim of the study To explore the experiences of chronically ill adolescents in communicating with health professionals, including the identification of factors which hinder or facilitate their use of health professionals as an information source. Country/ies where the study was carried out United Kingdom	diabetes, epilepsy, Duchenne muscular dystrophy (N=11 with CF). There were 27 boys and 36 girls. They fell into one of two age bands: 10–12 years (n=29) and 14–16 years (n=34) Inclusion criteria A diagnosis of chronic condition had been made at least 12 months prior to participation Exclusion criteria Not reported	participants and, where appropriate, were accessible to people with physical impairments. Sample selection Recruitment letters and project information leaflets (different versions for parents, younger and older adolescents) were sent out by the hospital consultants. Families interested in taking part contacted the research team. The average response rate was 46%. Written informed consent was obtained from the adolescent and a parent during a home visit. Data collection Individual interviews (n=63) and group discussion meetings (total number of meetings=20) Data analysis Data were analyzed by a process of data reduction, data display and drawing/verifying conclusions	Parental presence: “I go to see him, but not sure why ‘cos mum talks about things.” Issue of status: “He doesn’t talk at my level. He ignores me and talks to my mum.” Doctor-centred factors: The communication skills of the doctor affected information exchange. “‘How are you?’ is not a good question!” Adolescent-centred factors: Lacking communication skills. “I’m normally quiet. I never know what to say.” The type of information needed: Specific nature of an information need could act as a barrier to communication. “Sometimes I think the question would be hard for the doctors, and the answer might not be a nice answer. I might not want to know it... One day I might get so weak I can’t move. I might like to know but it might make me sad, so I don’t want to know. I’ll just wait until it happens and I’ll manage it.”	Sample selection: Sample selection was clearly reported. The relationship between the researcher and the respondents not clearly reported. Data collection: Data collection relied on the semi-structured interviews and group meetings. Unclear about topic guides and limited information about group meetings. Data analysis: The analytical process was not described in detail, no description of how "themes" were arrived at; researchers did not critically review their own roles in the process. Findings/results: Results were presented clearly (e.g., citation/data and the researchers' own input distinguished; the researchers' roles and potential influences in the analytical process not critically reviewed Overall quality: Low Other information The study was not clear about ethical issues or the number of

Study details	Participants	Methods	Findings	Comments
Study dates 1997-1999 Source of funding NHS (Executive), UK; Research & Development Programme (Mother and Child Health): Project Number MCH: 16-12.				researchers involved in data collection/interviews.
Full citation Braithwaite, M., Philip, J., Tranberg, H., Finlayson, F., Gold, M., Kotsimbos, T., Wilson, J., End of life care in CF: patients, families and staff experiences and unmet needs, Journal of Cystic Fibrosis, 10, 253-7, 2011 Ref Id 406070 Study type	Sample size N= 42 (12 patients, 10 family members of people with CF who had died and 20 staff) Characteristics All participants were over 18 years and were able to speak and understand English, without obvious cognitive impairment as judged by the CF coordinator. Inclusion criteria Not reported Exclusion criteria Not reported	Setting All interviews and focus groups were conducted at the Alfred Hospital. Sample selection A randomised block design was employed. Using a measure of lung function, Forced Expiratory Volume in the first second (FEV1), as a measure of illness severity, patients were allocated to one of three groups (FEV1 severe >40%, moderate 41–70% and mild >70%) until 4 participants were recruited into each	Themes/categories Knowledge of Palliative care: Patient: “Oh, there really is no hope for me.” Family: “I had only seen my mother die and she had cancer so I guessed it may be similar but it wasn't and it would have been helpful to have known more.” Psychological frame: Patient: “I would need some psychological support … I worry about my family and how they will cope… knowing there is counselling is a comfort to me.” Family: “we had spoken about death and his wishes ....I could just focus on (patient), say the things I needed to say… have no regrets… prepare myself for the worst…which I think helped me to accept” Treating team: Patient: “The team has rescued me a number of times now and I hope they can just keep doing that until transplant” Family: “Even though there is no new information we still want to hear from	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported. The relationship between the researcher and the respondents clearly reported Data collection: Data collection relied on the semi-structured interviews and group meetings. Structure of interview and topic guide decided by the experts within the hospital Data analysis: The analytical process was described in detail. Description of

Study details	Participants	Methods	Findings	Comments
Qualitative study Aim of the study To explore the unmet needs and key issues for people with CF, their families and the staff providing their care while awaiting organ transplantation Country/ies where the study was carried out Australia Study dates Not rerported Source of funding Research grant from the Australian Cystic Fibrosis Research Trust.		group. The next of kin (determined from the medical record) of the CF patients who had died in the past 4 years were recruited. Alfred Cystic Fibrosis staff, currently providing clinical care to CF patients (excluding those involved in the projects research group) Data collection Semi-structured interview format (developed by the research team consisting of medical consultants, palliative care consultants, psychologist, nurse, and medical social worker) conducted by the same investigator who had both psychology and research experience (neither known to the patients, families or staff). Data analysis Interviews and focus groups were audio-taped, transcribed and analysed using thematic analysis. All investigators read and	the team …otherwise you know you're not being abandoned but you feel abandoned". Communication: Patient: "Probably the CF team [should initiate end of life discussions] because I'll be forever in hope that I won't need it. Patient: Sometimes you want to know; sometimes you don't. When you're feeling good you want to know and when you're not feeling good you don't want to know." Family: "You get a bit overwhelmed by the information … when you think about it later you think, Oh, what did they say?" Engagement with palliative care service Patient: "I would not want my care managed by another team but happy for others input" Family: "I would have accepted the advice of palliative care expertise" Unmet needs: Patient: "I need to ask more questions but sometimes I don't even know what to ask" Family: "I would have liked more information when (patient)'s health was better so I wasn't in shock."	how "themes" were arrived at; saturation of data and exploring all the themes in detail was reported Findings/results: Results were presented clearly (e.g., citation/data and the researchers' own input distinguished Overall quality: High Other information The study unclear about ethical process but ethical approval obtained. Study conducted by lone researcher and may lack some of the formal research vigour

Study details	Participants	Methods	Findings	Comments
		independently coded the transcripts. The research team generated coding categories from the data until no further new categories were forthcoming (saturation) and then applied the entire set of coding categories to all transcripts to identify emergent themes.		
Full citation Coates, Nicola, Gregory, Maggie, Skirton, Heather, Gaff, Clara, Patch, Christine, Clarke, Angus, Parsons, Evelyn, Family communication about cystic fibrosis from the mother's perspective: An exploratory study, Journal of Research in Nursing, 12, 619-634, 2007 Ref Id 473478	Sample size Mother of CF children (N=8) Characteristics Mother of living CF children Inclusion criteria Mothers of living children who were born between 1996 and 2000 and who had been diagnosed with CF shortly after birth Exclusion criteria Not reported	Setting Participants' homes. Sample selection All participants were recruited through a specialist paediatric respiratory unit. Specialist nurses working within the unit identified mothers who were eligible for study. Mothers were invited to be involved in the study via a study information pack sent to them by post. Response rate was 62% out of 13 mothers contacted. Data collection Participants were	Themes/categories Reason for disclosure to family members Two primary reason for disclosure elicited. Firstly disclosure for support from close relatives. "I think it was just that we were saying because it was all too much for us … so … it was really nice because they were there just … to support us at the time …" "I think I'd rather just get on with it myself, I think … moan to my mother." And secondly, to make them aware of the risk of CF. "When Thomas was born and I found out he had cystic fibrosis, it was the fact … that I had 3 younger sisters to me … and I knew one day they were going to have children … like every time they phone up pregnant I'm like,"go and get tested". Barriers to disclosure	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported although the number of sample was lower (n=8). The relationship between the researchers and the respondents not clearly reported. Data collection: Data collection relied on the semi structured interviews. Structure of interview and topic guide reported. Description of how "themes" were arrived at was discussed. Data saturation and

Study details	Participants	Methods	Findings	Comments
Study type Qualitative study Aim of the study The aim of this study was to supplement existing research to gain insight into mothers' experiences of informing relatives about CF and to look at patterns of communication within these families. Country/ies where the study was carried out UK Study dates Not reported Source of funding Not reported		interviewed in their homes after obtaining consent. Semi-structured interview based on previous literature was conducted. As this was an exploratory study, new emerging themes were taken into account and the schedule was modified accordingly. All interviews were audio-recorded and later transcribed. Data analysis The anonymised transcripts were analysed using existing method described. No computer-based analysis done because of small sample. Coding took place both within and across transcripts (axial coding).The themes discussed in the results were organised according to the topic areas.	The main barrier was the lack of closeness or contact with other family members. "… He's never been tested anyway 'cause they [referring to her father and his brother] are not in close contact." Information and support from health professionals Mothers reported that they were not given specific advice/ support about whom they should disclose information in the family. "I think … when it … comes to actually going down that road of like we were talking about earlier,with kids and things like that,then obviously … I think I'd rather have someone come in … and see him, you know tell him myself but also have that person … as back up … to answer questions." However in other instances, doctors had been very helpful. "He [the doctor] did say … whatever relatives you want to be told … like immediate ones and that, you know, they can all come and he sat down and he explained … cystic fibrosis to them.…" Leaflets were particularly useful in informing relatives as suggested by most of the mothers. "....There was one leaflet, I remember, with a diagram of … the like 1 in, say 25, and then the 4 and one red for the CF and one blue for the, and the two green for the in-betweens … that was good. Like once you told people and they'd have a look at that.…"	full exploration of theme not clear. Data analysis: The analytical process was described with description of themes and categories. No user of any specific software for analysis as the data generated was too low. Whether sufficient data were gathered to fully explore the themes is not clear. No critical review of the researchers' role in the process. Findings/results: Results were presented clearly with themes and quotes and with citation/data. Researchers' role and potential influences in the analytical process not critically reviewed. Overall quality: Moderate Other information Ethical approval process described. Discrepancies between the researchers were addressed by the senior researcher with oversight.
Full citation	Sample size	Setting Not reported	Themes/categories Losing Ground:	Limitations Aim(s):

Study details	Participants	Methods	Findings	Comments
D'Auria, J. P., Christian, B. J., Henderson, Z. G., Haynes, B., The company they keep: the influence of peer relationships on adjustment to cystic fibrosis during adolescence, Journal of Pediatric Nursing, 15, 175-182, 2000 Ref Id 473508 Study type Qualitative study Aim of the study To explore the influence of peer relationships on adjustment to CF Country/ies where the study was carried out USA Study dates Not reported	N=15 young people and adults. Characteristics Repondents' with CF age between 17 -22 years with mean age of 19 years. Inclusion criteria Not reported Exclusion criteria Not reported	Sample selection Recruited from a regional CF center in the Southeast. Other information not available. Data collection A retrospective interview approach was used to explore the meaning and nature of chronic illness for these youths with CF. All interviews were collected by experienced advanced practice pediatric nurses who were not members of the CF team. Open-ended questions were used to explore past and present details of their chronic-illness experiences. Data analysis Transcribed interview data were analysed systematically by using the constant comparative method. The investigators checked each transcription against the original audiotape to ensure accuracy of data. Each interview was read several	“I think it’s hard for people that have CF because they’re different because a lot of them look perfectly normal . . . like there’s nothing wrong with them. But, it’s inside and sometimes when you can’t see what’s wrong with you, you don’t think there’s something wrong with you.” Being out of a loop: “CF makes it harder in terms of I’m not at school as much as some of the others, so you’re kind of out of the loop when you come back after 3 weeks. Who’s seeing who, you know. That can change radically in 3 weeks.” Finding a new company of friends: “There were 16 cystic fibrosis patients on the floor that holds maybe 30. We all went out to dinner. That’s the kind of thing that balances out even though you miss school and the occasional homecoming dance. You have at least something to balance out and just say, Yeah, I missed that, but I’ve made a lot of good friends here, too.’’ Fighting a never ending battle: “It [CF] just keeps coming back. I’ll get better, and then I’ll get sick again. . . . I just don’t understand why I can’t take something like people with cancer. They take their chemotherapy, and they’ll get rid of it. . . . I’m just fighting to get rid of something for a certain amount of time. . . . It’s a never-ending battle.”	Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was not clearly reported. The relationship between the researcher and the respondents not clearly reported Data collection: Data collection relied on the open ended interviews. Structure of interview and topic guide not reported. Description of how "themes" were arrived at was discussed. No any discussion on whether saturation has been reached for any of the themes reported. Data analysis: The analytical process was described with description of themes and categories. No critical review of the researchers’ role in the process Findings/results: Results were presented clearly (e.g., citation/data and the researchers' own input distinguished. Researchers’ role and potential influence s in the analytical process not critically reviewed Overall quality: low Other information

Study details	Participants	Methods	Findings	Comments
Source of funding University Research Council Grant from the University of North Carolina at Chapel Hill		times, and a summary of themes for each participant was prepared. Text base Alpha was used for data management and comparative analysis of qualitative data.		The study did not report ethical approval or described the ethical process such as confidentiality of research. Study conducted by multiple researchers but the level of consistency between them not reported
Full citation Dellon, E. P., Sawicki, G. S., Shores, M. D., Wolfe, J., Hanson, L. C., Physician practices for communicating with patients with cystic fibrosis about the use of noninvasive and invasive mechanical ventilation, Chest, 141, 1010-7, 2012 Ref Id 366826 Study type Web based survey followed by qualitative study using	Sample size Cystic fibrosis physicians completing the survey=34 Cystic fibrosis physicians interviewed=26 Characteristics Cystic fibrosis physicians at the University of North Carolina and Children's Hospital Boston CF care centers Inclusion criteria Pulmonologists (physicians) currently providing care to patients with cystic fibrosis Exclusion criteria Not reported.	Setting Survey was web based. Setting for interview not reported. Sample selection No reported. Data collection Survey questions were based on existing surveys. In the follow up interview, seven semi structured interview questions with scripted probes was developed based on survey responses. Interviews were conducted in person or by telephone and were recorded and transcribed verbatim. Data analysis Summary statistics used for survey questionnaire. For interview, two independent coders	Themes/categories Timing and content of communication Incorporating into routine CF care “normalizes” a difficult topic “We have standards for everything else about the care of these patients. This seems like in many ways the most important thing you could possibly discuss and yet we have no standards.” Proactive rather than a reactive approach “Maybe if we can find a way of bringing this up at earlier points in the disease it wouldn’t become such a heavy weight on the patient. It would be helpful to be able to say, ‘This is not something we are doing uniquely for you, this is just part of what we do.’” Ensures access to same information for all patients and families “It would be helpful to formalize the structure. We do a lot of this stuff in a pretty informal ad-hoc fashion.” Educational and decision support tools for patients and families Balanced, unbiased information is essential to the process of informed decision making	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method (semi structured interview) was appropriate for answering the research question Sample selection: Sample selection was process was not clearly reported. The relationship between the researcher and the participants was not reported. Data collection: Data collection relied on the survey followed by semi-structured interviews. Development of interview questionnaire which was based on responses to web based survey was not clearly described. Description of data collection method was vaguely described and the setting of the interview was unclear. Data analysis:

Study details	Participants	Methods	Findings	Comments
semistructured interview Aim of the study To give an account of physician perspective on communication with patients about the use of non invasive and invasive mechanical ventilation for respiratory failure Country/ies where the study was carried out USA Study dates Not reported Source of funding Supported by a Junior Faculty career Development Award from the National Palliative Care research Center		reviewed interview transcripts. Deductive coding was used to categorise the findings and qualitative content analysis was used to delineate themes.	"Some sort of handbook would be helpful because a lot of times when you talk about things like this, they remember very little of it or they kind of get things kind of messed up. So if they had something they could refer to later, this would reinforce some of the discussions." Educational and decision support tools may prompt in-depth discussions about treatment options and preferences "Having tools to facilitate the discussion would help. We may misread the kind of information people want. And if you are trying to explain treatments, I have no materials to give people about things like bilevel pressure ventilation." Multidisciplinary care Use the multidisciplinary CF care team to facilitate communication The multidisciplinary care team is the current standard for CF care in the United States "The best person to start these discussions is the person who knows the patient well. It may be the physician, a social worker, a nurse coordinator. It has to be someone who has a good feel for the patient and is in a position of trust" Providers from different disciplines may help to keep each other on task Support from the team makes discussing diffi cult issues easier for everyone involved "It is all about communication. It is a question of including everybody as much as possible."	The analytical process was reported vaguely. No information on validity and reliability of interview questionnaire which was developed in response to web based survey. Description of emerging themes and data saturation was not reported. Findings/results: Results were presented clearly (e.g., citation/data and the researchers' own input distinguished) Overall quality: Low Other information

Study details	Participants	Methods	Findings	Comments
Full citation Fair, A., Griffiths, K., Osman, L. M., Attitudes to fertility issues among adults with cystic fibrosis in Scotland. The Collaborative Group of Scottish Adult CF Centres, Thorax, 55, 672-7, 2000 Ref Id 366844 Study type Postal open ended questionnaire survey Aim of the study The aim of the study was 1) to determine attitudes about fertility and pregnancy among subjects with cystic fibrosis aged 16 years and over	Sample size N= 195 N (responded)= 136. Male =82, female=54 Characteristics Participants were aged 16 years and over and recruited from Scottish Cystic Fibrosis clinics Age: Male 24.5 (20-31), Female 24.0 (19-31) Age at diagnosis: Male 1.3(<1-2.3), Female 2 (<1-10) FEV1 (%predicted): Male 52.6 (32.3-72.6), Female 59.9 (44.5-75.5) BMI(KG/m2): Male 20.1 (18.5-22.6), Female 21.0 (19.1-23.1) Inclusion criteria Not reported Exclusion criteria Not reported	Setting Postal questionnaire at participant's home Sample selection All the population were from four Scottish Cystic Fibrosis clinics Data collection Collected through open ended postal questionnaire. A questionnaire was developed by nurses from the cystic fibrosis clinics, consultants, and representatives of National services division, NHS. This was pilot tested and amended before finalising the questionnaire. Data analysis Statistical software used for summarising quantitative data. The NUD*ist package used to classify open ended qualitative responses.	Themes/categories General questions about fertility Participants commented on how they would feel talking to a HCP about having a child. Talking to health professionals “I have never had the courage to bring up the subject” (M, 26 years, FEV1 65% predicted). “I would welcome an honest opinion because I wouldn’t want to make the wrong decision” (F, 19 years, FEV1 53% predicted). “When I was pregnant with my second the doctor at the maternity said to me ‘Who gave you permission to have another child?’” (F, 41 years, FEV1 47% predicted). (The doctor said to me) “I hope you’re not going to get pregnant because if you do it will kill you” (F, 20 years, FEV1 20% predicted). How would you feel if a health professional questions if you should have a child? “I would be very angry because you are a normal woman and if in a relationship both you and your partner feel the same as any young couple and having a family may feel like the next step” (F, 32 years FEV1 58% predicted). “I think this would be beneficial, but sad if he/she tells you it’s best not to have a child. It is best if they tell you the exact truth” (F, 17 years, FEV1 66% predicted). “It’s up to the individual, nothing to do with anyone else” (25 years, FEV1 43% predicted). Women	Limitations Aim(s): Clearly reported Aim of the study clearly reported. Research method was adequate for answering the research question. However, qualitative study design would have been better for answering the research question. Sample selection: Sample selection was not clearly reported with no information on inclusion or exclusion criteria. The relationship between the researcher and the participants was not reported. Data collection: Data collection relied on the open ended postal questionnaire. Limited information on the development of questionnaire. The response rate of 70% was adequate. Study design limits the exploration of themes or development and eliciting further information. Data analysis: The analytical process of interpreting open ended question was not reported although use of specific qualitative software (NUD*ist) reported. No information on data saturation or identification of specific themes Findings/results:

Study details	Participants	Methods	Findings	Comments
attending the clinics and 2) to determine satisfaction with communication on this issue from health professionals. Country/ies where the study was carried out UK Study dates Not reported Source of funding National Services Division, NHS, Scotland			Women commented on the information they thought should be given. Three themes emerged from female responses: (1) wanting more information about health consequences of pregnancy "(explain that) you will feel ill during and maybe for years after giving birth and when you have your baby, there's almost no time to be unwell yourself which can cause problems" (F, 23 years, FEV1 44% predicted). "Information about general health during pregnancy and risks about the actual birth" (F, 16 years, FEV1 50% predicted). (2) suggesting information to give to other women, particularly about the long term health effects from pregnancy "To let them know that 14 days of IVS will be administered at home after the birth of the baby" (F, 29 years, FEV1 60% predicted). (3) describing satisfactory and unsatisfactory discussion with cystic fibrosis doctors and nurses. "I felt no one would help me at least try and come to a decision. I had so little information. I was constantly told the risks were too high and now it's too late and I feel there's a huge gap in my life" (F, 33 years, FEV1 62% predicted). Men Men suggested what information they wanted and seemed to divide into those who wanted "the facts:	Results were presented clearly (e.g., citation/data and the researchers' own input distinguished). Overall quality: Low Other information Ethical approval process not described. Consistency between the researchers either in developing the questionnaire or in analysis not reported.

Study details	Participants	Methods	Findings	Comments
			"Simple cans and can'ts, facts ... to the point, no 'maybe you can but ... etc'." (M, 20 years) "I feel that there should be discussions and literature handed out in CF Clinic at an earlier stage e.g. not later than 16" (M, 20 years, FEV1 65% predicted). "Facts as they stand with hope via assisted fertility information" (M, 28 years, FEV1 22% predicted). and those who wanted the emotional impact of infertility to be recognised by their health professionals: "I do feel this can be a very emotional issue" (M, 23 years, FEV1 45% predicted). "Make sure he knows about it early so he can learn to accept it easier" (M, 27 years, FEV1 40% predicted). Lack of knowledge about assited fertility Most men did not seem to be aware of the relatively low success rate of assisted fertility treatment. Of 30 comments from men, nine were on the positive chance that they would be able to have children through assisted fertility and no man commented on the low success rate of fertility programmes (authors comment). The authors noted that younger men aged < 20 years were much less likely than women or older men to make any comment on what information they wanted. Older men with good lung function seemed most likely to be distressed by their infertility: "I would like more information on how other people are handling the fact that they cannot have children" (M, 35 years, FEV1 84% predicted).	

Study details	Participants	Methods	Findings	Comments
			"Give some hope of being able to father and try and make them not feel a failure if they can't father children" (M, 31 years, FEV1 96% predicted). "It is terrifying for men not to be able to father a child" (M, 34 years, FEV1 84% predicted).	
Full citation Filigno, S. S., Brannon, E. E., Chamberlin, L. A., Sullivan, S. M., Barnett, K. A., Powers, S. W., Qualitative analysis of parent experiences with achieving cystic fibrosis nutrition recommendations, Journal of Cystic Fibrosis, 11, 125-30, 2012 Ref Id 367036 Study type Qualitative study with semi-structured interview. Aim of the study To better understand	Sample size N=8 parents of children with cystic fibrosis Characteristics Mean age of children at the time of interview=8.2 years (SD 0.8). 5/8 children were male. BMI of children ranged from 30.7% to 97.5%. Forced expiratory volume in 1 second ranged from 71% to 120%. Inclusion criteria Parents of children with CF. Exclusion criteria Not reported	Setting Interviews were conducted via telephone or while the child was admitted to the CF inpatient unit. Sample selection Parents were recruited from a clinical trial that had been completed 5 years previous to this study. Data collection The interviews were conduced over the telephone or face to face while the child was admitted to the CF inpatient unit. The average length of the interviews was 24 minutes (SD=8.8). Interviews were audio-taped. Information was systematically collected from parents by asking uniform stem questions while offering parents flexibility to provide	Themes/categories Behaviour and nutrition: Parents recalled that learning how to deliver both positive consequences (praises and rewards) and negative consequences (removal of privileges) to manage mealtime behaviour was helpful. Parents also reported intense desperation to get their child to eat, inkling preparing meals for the child so that the child would eat. Parents found that an ongoing challenge was general behavioural non-compliance including refusal to eat, take enzymes, and complete a fecal fat test. Parents found challenges with transfer of treatment responsibility from them to their child for certain aspects of CF management. Transition to school: Parents/families reported that managing transition to school was difficult as parents were not able to monitor their child's nutrition during the school day, and found that they were compensating their child's food intake at home (dinner). Parents also reported that there was a negative impact of missing school due to hospitalisation and illness. Parents struggled with partnering with schools to ensure that their children received appropriate accommodations.	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question. Sample selection: Sample selection was clearly reported. The relationship between the researcher and the respondents clearly reported Data collection: Data collection relied on the semi-structured interviews. Description of data collection method was described Data analysis: The analytical process was reported. Description of emerging and overarching themes, and saturation was reported. Use of specific software for data collection and analysis reported. Coding done based on the approach widely recommended in the literature. Findings/results: Results were presented, however, quotations/citations

Study details	Participants	Methods	Findings	Comments
how families used the strategies taught in a behaviour-nutrition intervention and to identify the challenges with CF management families experienced during this developmental transition, particularly nutrition. Country/ies where the study was carried out USA Study dates Not reported. Source of funding National Institutes of Health.		additional relevant information Data analysis Interviews were audio-taped using USBBLASTTM recordi ng device and were anonymise with unique identification number. Thematic analysis was informed by grounded theory. Interview content/transcripts were coded using the recommended approach described in previous literature. Themes were identified, reviewed, defined, and refined. Each transcript was reviewed independently, and themes were excluded when saturation was achieved.		from respondents/author were not reported clearly Overall quality: Moderate Other information
Full citation Grob, R., Is my sick child healthy? Is my healthy child sick?: changing	Sample size N=35 parents of children diagnosed with CF (33 mothers and 2 fathers) Characteristics	Setting Not reported. Sample selection Not reported. Data collection	Themes/categories Diagnosis of CF Delayed diagnosis: Parents were concerned about their observations and suggestions being	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question

Study details	Participants	Methods	Findings	Comments
parental experiences of cystic fibrosis in the age of expanded newborn screening, Social Science & Medicine, 67, 1056-64, 2008 Ref Id 332737 Study type Qualitative study with semi-structured interviews Aim of the study To explore how rapid growth in the USA of mandatory new born screening leading to a diagnosis of CF is changing, for affected families, their experience of illness versus disease Country/ies where the study was carried out	Parents: 34/35 were Caucasian, 1/35 was Hispanic. Parents ages ranged from 23 to 53 years (mean 34 years). Approximately 2/3 of parents interviewed were of middle class, 1/3 of parents was of working class. Inclusion criteria Children were diagnosed with CF via new-born screen, prenatally or after development of symptoms. Exclusion criteria Not reported.	Semi-structured interview format. No other information about data collection was reported. Data analysis Interviews were recorded and fully transcribed, and analysed using a grounded theory methodology. Overarching themes and specific categories were derived from the data, which were reviewed twice to verify congruence of the data.	dismissed by the health care professional regarding their child's health: "At the doctor's office, I would cry every time because he wasn't gaining [weight]. I think they kind of looked at me like this hysterical first-time mother, and the doctor whom I kept going to see kept saying 'Oh he'll kick in, some babies take a while to kick in.' That was really hard, being so powerless..." (mother of child who had delayed diagnosis) However, parents were relieved when they received a diagnosis of CF: "..when we got it I was totally relieved. Even though he cystic fibrosis and I knew what it was and I knew the outcome of it, it was a relief, because I knew I was gonna be treated correctly. I knew..that I wasn't crazy, that I wasn't looking for something to be wrong with him, you know?" (mother of a child aged 7 years with delayed diagnosis of CF) Information about new born screening: One mother reported that she received little information from the paediatrician about new born screening, and none about CF when discussing screening results of her child: "I didn't know anything about it and I got sent home with a little bit of information but it was like a week later before I had my first clinic. I was there all by myself and calling like half of [city name] it felt like trying to find somebody that...was home and that could talk...They told me it was genetics but I didn't understand what genetics truly meant either so I was like well what did I do and you know what I can have done different.." (Mother of a one month old infant diagnosed with CF).	Sample selection: Sample selection was not reported. The relationship between the researcher and the respondents not reported. Data collection: Data collection relied on the semi-structured interviews. Description of data collection method was not described clearly. Data analysis: The analytical process was reported, but vague in description. Description of emerging and overarching themes was reported, but saturation of data was not reported. Findings/results: Results were presented clearly with adequate discussion of findings (e.g., citation/data and the researchers' own input distinguished). Overall quality: Low Other information New born screening for diagnosis of CF

Study details	Participants	Methods	Findings	Comments
USA Study dates Not reported Source of funding The Investigator Awards in Health Policy Research from Robert Wood Johnson Foundation Programme			Another mother reported that she did not know of CF until she received a positive new-born screen result for CF: "[Margo was] chunky,'' she recalls. ''She was over nine pounds at birth, so I mean there was no indicators, you know, I mean visually, you knowlooking at her there wasn't anything to think therewas anything wrong with her..'' (Mother of child of 2.5 years diagnosed at birth). Support at diagnosis (at birth): Mothers reported that they seek support from professionals upon receiving a positive screening test for CF: "Well, I would say in the very beginning [when we got the NBS diagnosis]. me and my husband, we were both kind of like what do you [doctors] want to do,what do you think we should do, what do you think we should do, what do you think is best? You guys are the doctors, you know" (mother of a new born infant). Seeking reassurance: Mothers reported that they contacted the health care professional for advice, expertise, reassurance and instructions about caring for their infant: "Once I found out that she possibly could have the CF, I called so many times in the middle of the night. I'm like 'Oh my god, she's breathing really heavy, I don't know if this is right..' There was just a lot of follow-up that came from the hospital that helped.' (mother of one month old infant) One mother found it difficult to approach the health care professional as they regarded her as being overly needy: "What was hard I think in the beginning [was] being new as a parent for one and not knowing	

Study details	Participants	Methods	Findings	Comments
			what was normal for children. and then dealing with the disease, the health care.. The people in health care were somewhat hard to deal with... because I would call a lot because I didn't know, because Iwas so scared, because there was such a fear..I would call the nurse a lot and say 'I don't know if this normal or not, this doesn't seem right.' (Mother of new born infant diagnosed with CF). Confidence in seeking support over time: Parents developed expertise about their child's condition over time, with many becoming assertive and confident advocates: "In the beginning, everything that any doctor ever had to say was gospel. You took that to be the truth, you took that to be the absolute answer. You did not question, that's just the way it was. It took a long time. to get an education within myself. that I needed to question some of the stuff that was going on.. Now I'm not above calling and telling anyone what I think about them or their assessment of my child.. I'm not afraid to ask for what I think Rose needs, and I think that I have certainly evolved in that respect" (parent of child with health problems) Coping with infant with CF (after discharge from hospital): Parents felt overwhelmed when their infant was discharged from hospital: "..It just seemed like everything changed.. It was like there is so much more now to taking care of her, and are we really fit to do that?.. [I]t was just so overwhelming. I mean the first time we went to the clinic they were like well, you have to do this and this. And we met with nutritionists, respiratory therapists and pulmonologists and social workers and you know it was just all so overwhelming, all this stuff we were going to	

Study details	Participants	Methods	Findings	Comments
			have to do. I remember leaving there thinking "how am I going to do all this stuff in one day?' ". (parent of infant diagnosed with CF, after discharge from hospital) Parents seeking information about CF: Some parents felt it was necessary to learn everything about CF immediately after discovering their child had CF: "I'm the kind of person, I'm really proactive, so if I find out about a problem or an issue I want to dive into it and figure out what's the best way to do this, or what should we do? So I want all the information I can get.. I don't just want to be clueless and think, 'Oh she'll be fine, she'll beat the odds.' I want to know the dirty truth. I want to know what these people [with CF] go through so that I know how I can prepare myself and how I can prepare Alexandra". (parent of child with CF diagnosis) Parents did not want professionals to withhold information: ''One problem I have with some doctors is that they talk down to you and don't explain things thoroughly". (Parent of a child with CF diagnosis) Mothers wanted information about CF at a pace that was comfortable for them: ''They had some hand-outs and things...as far as treatment and dietary concerns, you know,'' "But ''there was just too much at that time to absorb, so we [would] look at it a little bit [at a time]..'' (mother of a child with CF diagnosis) Mothers did not want to receive statistical or complicated information about their child's future from the health care professional:	

Study details	Participants	Methods	Findings	Comments
			We had one doctor. and we walked into the room and she sat down and we sat down and she said, 'Having cystic fibrosis is not a good prognosis.' And I sort of thought 'I don't really need to hear this. I'm well aware of what it does.' I didn't really think that was very thoughtful to say to someone while holding their new baby.. This one doctor. could be quite callous. And not really think about how you might be feeling as a parent..[What I needed was] the basics for the moment. You can find out everything else as you go along. It's not necessary to know everything right from the start". (mother of a child with CF diagnosis)	
Full citation Grossoehme, D. H., Filigno, S. S., Bishop, M., Parent routines for managing cystic fibrosis in children, Journal of clinical psychology in medical settings, 21, 125-135, 2014 Ref Id 473660 Study type Qualitative study Aim of the study	Sample size N=25 parents of children with CF Characteristics Parents of children with CF Inclusion criteria Parent with a child at least three months post-CF diagnosis and the child aged between 3 months to 13 years, which has been defined as the period of time when parents may be assumed to bear up to 80% of treatment responsibility Exclusion criteria Inability to speak English	Setting Parents home with telephone interview Sample selection 83 parents were enrolled in the primary study of treatment adherence and completed questionnaires in the CF center. A convenience sub sample of 25 sequentially approached parents were recruited to participate in a telephone interview Data collection Parents participated in a semi-structured telephone interview that included	Themes/categories Support outside of the family system: The presence of an in-home respiratory therapist was identified as a facilitator to creating a daily routine and teaching children about airway clearance techniques. Parent stated "So, a respiratory therapist was able to come out and help with the treatment and that really, really helped a lot and helped to get established and…."	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported. The relationship between the researchers and the respondents not reported. Data collection: Data collection relied on the semi structured interviews based on previous research. Structure of interview reported. Description of how "themes" were arrived at was discussed in depth. Data saturation and full exploration of theme reported. Ethical approval process reported. Data analysis:

Study details	Participants	Methods	Findings	Comments
To describe parent experiences developing and utilizing CF care routines. Country/ies where the study was carried out USA Study dates Not reported Source of funding Not reported		questions about daily CF treatments. The interview guide created to collect data on general parental coping and spiritual coping. Data analysis Interview transcripts processed using NVivo 10.0. Narrative data were coded and Phenomenological methodolgy was used to guide data analysis.		The analytical process was described with description of themes and categories and use of specific software for processing. No critical review of the researchers' role in the process. Findings/results: Results were presented clearly with output classified into sub themes and categories. (e.g., citation/data and the researchers' own input distinguished). Researchers' role and potential influences in the analytical process not critically reviewed. Overall Quality: Moderate Other information The study did not described the ethical process of research. Study conducted by multiple researchers but the level of consistency between the researchers not reported.
Full citation Hilliard, M. E., Hahn, A., Ridge, A. K., Eakin, M. N., Riekert, K. A., User Preferences and Design	Sample size N=16 adults with CF who consented to participate in the study Characteristics (n=15 (one participant did not complete an online survey)	Setting Interviews were conducted by telephone and by completing an online survey. Sample selection	Themes/categories General information not useful "Sometimes I'll [wonder when] something happens health-related to me, 'Is that normal for everyone or…is that happening to me because I have CF?' And it's hard to find particular sources where I can find that out." (Age 35, Female)	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported. The relationship

Study details	Participants	Methods	Findings	Comments
Recommendations for an mHealth App to Promote Cystic Fibrosis Self-Management, JMIR MHealth and UHealth, 2, e44, 2014 Ref Id 405826 Study type Mixed methods study with qualitative content using semi-structured interview. Aim of the study The aim of this mixed-methods study was to involve individuals with CF in guiding the development of engaging, effective, user-friendly adherence promotion apps that meet their preferences and self-management needs.	Age in years, mean (SD) (range): 30.2 (5.9) (21-43) Race, n % : Caucasian 15 (100%) Gender, n, %: female 7 (47%) Marital status, n, %: married/partnered 11 (73%) Education, n, %: college degree or beyond 11 (77%) Work, n, %: full or part time 11 (73%) Inclusion criteria Age 18 years or above, diagnosis of CF, currently treated at the hospital's adult clinic, prescribed at least one pulmonary medication (eg, inhaled mucolytic, inhaled or oral antibiotic therapy, hypertonic saline), and own or use a mobile device (eg, smartphone, tablet) Exclusion criteria Not diagnosed with CF, not prescribed any CF medications, and not a smartphone owner.	Participants were identified from the patient roster of the adult CF clinic at a large, urban hospital in the mid-Atlantic United States. Data collection Participants completed a 30-45 minute semi-structured telephone interview with study staff. A naturalistic inquiry approach was used with open-ended probes. The interviews were digitally recorded and transcribed to facilitate coding and interpretation. Participants were also emailed a secure link to a password-protected Web-based survey to be completed within 2 weeks. Data analysis To identify themes and develop an initial coding guide, five interview transcripts were collaboratively reviewed.	Accessible information: Participants expressed the need for an accessible resource for general information about CF: "Sometimes I'll [wonder when] something happens health-related to me, 'Is that normal for everyone or…is that happening to me because I have CF?' And it's hard to find particular sources where I can find that out." (Age 35, Female) Preference of storage of personal information: Participants preferred central accessible storage for personal CF data/information: "I think that CF can be kind of overwhelming and it's really nice to have one central location to keep important information and data." (Age 34, Female) "Whenever you go to [a] doctor [they ask], 'What's your current list of medications?'…It'd be nice to have the whole history…and then have a place for notes for how well it worked." (Age 48, Female) Communication (with medical team): Participants reported that CF providers may not be responsive if contacted via telephone or email between visits, and would prefer to see the provider in person: "I'm not always in a place where I can call them, so if I can just shoot a text…that would be convenient…If they want me to do something out of the ordinary...I want to [ask], 'How exactly did you want me to do this?' " (Age 23, Male) "In the everyday world [electronic communication] just seems to be replacing talk and conversation and you know, communicating that way, I don't want that to happen [with my doctors]." (Age 35, Female	between the researcher and the respondents clearly reported Data collection: Data collection relied on the semi-structured telephone interviews. Researchers did not justify the use of telephone instead of face to face interviews Data analysis: The analytical process was described in detail. Description of how "themes" were arrived at; saturation of data and exploring all the themes in detail was reported Findings/results: Results were presented clearlyand findings were discussed in detail (e.g., citation/data and the researchers' own input distinguished Overall quality: High Other information The study involves identifying user preferences and design recommendations for an mHealth application to promote CF self-management Mixed methods study (qualitative and quantitative content) Adults with CF

Study details	Participants	Methods	Findings	Comments
Country/ies where the study was carried out USA Study dates Not reported. Source of funding Cystic Fibrosis Foundation Therapeutics.		Two study team members coded the remaining transcripts using the initial coding guide. Discrepancies and coding scheme modifications were resolved through group discussion in an iterative fashion, repeated every five interviews until thematic saturation was reached. A total of 16 interviews were conducted before thematic saturation was reached.	Communication (with family): Participants reported that they would not need another channel of communication with family regarding monitoring adherence: "I would use other more direct messages." (Age 28, Male) "I would probably continue to communicate with them the way I already do." (Age 33, Female) Social (support from people with similar experiences): Some people show this as a novel opportunity to network, given prohibitions on face-toface contact "Because people with CF can't be in the same room as each other,…being able to see someone else with CF is much more profound than just exchanging emails with some anonymous person." [Age 28, Male] Other could feel discouraged or guilty seeing others doing better or worse than you "I don't like hearing about CF people that aren't doing well. I have a hard time distancing myself from it. It's hard having to filter through all this sadness to get kind of connected with someone." [Age 26, Female] "I didn't really like it only because some people had it worse than me and if it kind of brought me down because I felt like this is where I'm heading and I just didn't like that…So I don't know if I'd really want to talk to any other people with CF, I don't want to like be depressed." [Age 32, Male] Social (support for families, partners, caregivers of people with CF):	

Study details	Participants	Methods	Findings	Comments
			Participants considered social networking to be appealing for family members or partners of people with CF: “I think that support for the family and friends is important…for people who have CF…talking to significant others of people who have CF.” (Age 28, Male)	
Full citation Hummelinck, A., Pollock, K., Parents' information needs about the treatment of their chronically ill child: A qualitative study, Patient education and counseling, 62, 228-234, 2006 Ref Id 473703 Study type Qualitative study with semi structured interviews	Sample size N=20 (sets of) parents of 21 chronically ill children and young people Characteristics Children had chronic conditions which were asthma, CF, diabetes, epilepsy, epilepsy+special needs, leukaemia, other cancers, severe eczema (N=4 with CF). There were 12 boys and 9 girls. They fell into the following age categories: 0-5 years (n=3), 6-10 years (n=12), and 11-15 years (n=6) Inclusion criteria	Setting Details of study methods and recruitment were reported in Hummelinck 2004 study Sample selection Eligible parents were approached consecutively following hospital admission or outpatient clinic attendance at the paediatric department of a district general hospital in the West Midlands. The researcher sent or handed parents a letter with an information sheet and	Themes/categories Parents' need for information (as a means of reassurance) Parents experienced difficulties immediately after diagnosis as they felt confused and frightened when presented with information because they could not find answers to specific questions or resolve anxieties that confronted them: "I felt I was standing outside, watching it all going on, I did not even know...the IV's he was having straight away and I did not even know what that was all about. And they were just pumping all these drugs into him. It was just one injection after the other in, pretty scary actually. You are left on your own in a room, you know. Sitting there, waiting for the next lot of IV's which of course I did not know when that would be. I did not know how many he had to have. It was difficult. " (Mother of a child with CF age 7 years)	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported. The relationship between the researcher and the respondents clearly reported Data collection: Data collection relied on the semi-structured interviews. Data collection method was not described in detail and cross referenced to other study for detail information Data analysis: The analytical process was clearly reported. Unclear if saturation of data was achieved. Development of theme was described. No report on

Study details	Participants	Methods	Findings	Comments
Aim of the study To explore the complexity of parents' information needs and how current information provision is evaluated Country/ies where the study was carried out United Kingdom Study dates Not reported Source of funding Not reported	Child's age within range 0-16 years Child suffering from a chronic illness Child's treatment plan includes ≥1 drug to be administered daily for a minimum of 1 week Child living with respondent Each individual parent (as a representative of the child) may only enter the study once Exclusion criteria Respondent(s) lacking English skills Personal reasons (e.g., terminal illness)	reply slip, inviting them to take part in a semi-structured interview. The total positive response rate before and after sending out a reminder letter to non-responders was 31% and 51% respectively (of whom 20 were interviewed) Data collection Semi structured interviews ranged from 45 minutes to 3 hours (average 1-1.5 hours). Detailed information reported in Hummelinck 2004 study Data analysis Data was organised by establishing concepts from the text and subsequently coded, which was refined as the analysis progressed. Emerging themes and hypotheses were continually checked against the data. Interview codes were summarised under relevant categories, which were used to map the range	Parents' reasons for wanting information (as a means of establishing control) Parents wished for more information to feel involved in management of their child's illness and to be able to understand decisions being made. Understanding what was happening helped some parents to cope with the illness and re-establish a sense of control: "I want everything [all there is to know about cystic fibrosis] now. Because then when something arises, you can go [snaps his fingers] 'Right, I recognise that, we have got to do this' or 'I know what that is, we do not need to panic'. We know, we are in control. I think we are in control anyway, but when he's not well...It might not be nice, knowing what might be, but it's better to know. At least you are in control that way". (Father of a child with CF age years) Parents' view on adequacy of information provided Parents of children with CF (that strictly required multidisciplinary care input and secondary care management) reported receiving an 'information overload', particularly at the time of diagnosis (author reported)	transcribing interview, validation or use of qualitative software for processing of information Findings/results: Results were presented clearly and the findings discussed in detail (e.g., citation/data and the researchers' own input distinguished) Overall quality: Poor Other information Study included parents of children with conditions other than CF. Study dates were not reported.

Study details	Participants	Methods	Findings	Comments
		of findings, and associations of themes and explanations for the findings were developed		
Full citation Jessup, M., Douglas, T., Priddis, L., Branch-Smith, C., Shields, L., Arest, C. F., Parental Experience of Information and Education Processes Following Diagnosis of Their Infant With Cystic Fibrosis Via Newborn Screening, Journal of Pediatric Nursing, 31, e233-41, 2016 Ref Id 473728 Study type Qualitative study Aim of the study	Sample size N=10 parents from 7 families of infants with CF (n=7 mothers, n=3 fathers) Characteristics Parents with child having unequivocal diagnosis of CF Inclusion criteria Not reported Exclusion criteria Not reported	Setting Tertiary pediatric hospital in Australia Sample selection Participants were recruited through the CF clinic of a large metropolitan pediatric hospital in Australia. Potential participants were identified from the clinic database and sent an information letter. They were invited to telephone a nominated researcher to register their interest, at which point a convenient interview time was organized. Data collection Data were collected during a single, semi-structured interview lasting about one hour. Guided by a phenomenological intent, these were conversational in style. An interview guide	Themes/categories Personal searching: “I got the initial diagnosis over the phone…. they don’t tell you much. It’s like: “We think she’s got cystic fibrosis and we want you to come in and talk about, and I can see you in two or three days’ time’. And then it’s like: ‘Oh my God,’ and ‘Help, Google!’… People: A team of People: “all very friendly, very positive… really quite a dedicated team.” Likewise: “The people there seemed to want to build a relationship with us straight away.” Such connections were missing in the online world. Too many People: One person's team was another's crowd: “We would just see all these people coming towards us every day and we’d just switch off. We’d go blank … There were just too many people.” “All I can remember is five people in a room watching me cry, feeling like a real goose.” Pumped of People: “They are quite a pumped up team.” “I understand that these guys are so passionate about their job, and I suppose in their eyes it is a little bit more.” Which People: Despite parents often being surrounded by many people, there was a sense of isolation within a crowd, and several felt over whelmed and uncertain regarding who to connect with and of whom to enquire: “I felt quite teary. It was really, really draining …I remember people asking me questions…and I didn’t know who to ask, and I just felt like I was	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported. The relationship between the researchers and the respondents not clearly reported. Data collection: Data collection relied on the open ended interviews. Structure of interview and topic guide reported. Description of how "themes" were arrived at was discussed. Data saturation determining further sample recruitment was reported. Ethical approval reported. Data analysis: The analytical process was described with description of themes and categories. No critical review of the researchers’ role in the process. Findings/results:

Study details	Participants	Methods	Findings	Comments
To explore the education needs of ten parents following their infant's diagnosis with CF via newborn screening Country/ies where the study was carried out Australia Study dates Not reported Source of funding National Health and Medical Research Council of Australia CRE grant 515370		was developed, informed by the current literature, team members' experience, and the study objective. This guide was deliberately broad and open-ended in order to encourage participants to recount their experiences from the initial diagnosis phase and the subsequent three-day education period. Data analysis Thematic analysis was used to analyse the data. Transcripts of the interviews were read and analysed individually by all members of the research team, each member highlighting and grouping similar phrases and experiences to synthesize common topics into the identification of themes. Interpretation of the data was then discussed and moderated at regular meetings attended by all.	surviving." One mother recalled: "We came in on the three days. It was sort-of like people came and saw you and then you waited for the next lot of people to come through, and then you waited some more…It was such a nightmare… It was the actual doing, it was terrible." Process: Amount and timing: This presents a challenge when parents have differing requirements. For one: "We were just trying to get everything we could"; whereas for another: "I think at that point for us it was probably all we needed"; and another: "I think the only thing is to ease parents into it." In reality, there is no easy way: "You're given probably more than you want but it's what you need. I don't think there's anything that you could stop or take away from that process. I don't think there is any right way to do it… It's just a process that you have to go through." It is all about confidence and comfort: "You're not ready to hear what'll happen in three years or things like that. You're more ready to hear that stuff once you've found your platform of confidence and comfort." Pragmatics: Numbers and visuals: "We received a sheet … with genetics with some basic pointers about CF… but the very first line on it was the life expectancy for CF… and the number … it's really confronting to have that as one of the first pieces of information." Another vividly remembered: "The first thing you see when you open their website is that 30% of teenagers died from CF … To see that figure is like 'Oh my God.'" and one father explained: 'This is what we got at the time … All we could see, there's a little kid in jail: 'Just one cell mutation can trap you for life'…. It's just awful." Staggered and	Results were presented clearly (e.g., citation/data and the researchers' own input distinguished. Researchers' role and potential influence s in the analytical process not critically reviewed Overall quality: Moderate Other information The study did not described the ethical process of research. Study conducted by multiple researchers but the level of consistency not reported.

Study details	Participants	Methods	Findings	Comments
			practical: "… Just the practical day to day stuff would be great … maybe when the baby is about 6 months, it would be great to have some day to day tips about CF: things to avoid, things to do." Parents could relate to: "Definitely the food …. and then the physio because they are our things to do … the immediate things we needed to do." Several referred to the practical instructions given by the physiotherapist, which represented something they could do. "You know what was terrific was the little physio card that she made up for us…So when we're home going 'What do we do next?' we could go back to the card and check." Format: Format was commented on by all participants, with recommendations from simple fact sheets, to brochures, booklets, DVDs and a map. They needed developmentally relevant information delivered at intervals during their child's first year. "So I think It'd be better to have a booklet day one up to may be six months pre food and then another booklet that's relevant for that time ….Some more of these fact sheets….and use those as a thing to go through with parents over time, rather than overload with information all at once." Relevance: Participants had to be selective of information materials: "We just got a booklet that was produced in America and it wasn't relevant here, and there was so much ambiguity." Reassurance and empowerment: "It would have been a bit more empowering if I'd more information … Because you kind of want parents to become experts." The unknown exacerbated fear: "I think the biggest thing was not knowing what might happen, which gives you a bit of a panic." Knowing included more than hearing about prognosis and care. Parents	

Study details	Participants	Methods	Findings	Comments
			quickly identified that there would be costs to be extracted by time, emotion and dollars: “what they might need in the future so you can save for things.” Hope: “So that’s the most important thing, that optimism is really important for parents.” This was particularly so because it: “…moves you out of a ‘victim’ state to a ‘move on with it’ state.” As one mother declared: “I just wanted to get on with bringing up my baby”. Parents sought information that enabled them to assign their child's position on the ‘severity spectrum’ of CF disease, explained by this father: “I want to kind of put the severity of CF on a spectrum, and then ask: ‘Where does my child fit? Is she worse or better off compared to someone else?’” However, in spite of the best intentions and sources of current information, prognosis evolves and eludes: “I know obviously they can’t tell you for various reasons because they don’t know themselves, but that’s one question that I was asking myself a lot … because we still don’t know.”	
Full citation Jessup, M., Parkinson, C., "All at sea": the experience of living with cystic fibrosis, Qualitative Health Research, 20, 352-64, 2010 Ref Id	Sample size N=8 families with a son/daughter with CF (n=7 people with CF, n=17 parents either as couples or individually) Characteristics Age of people with CF: range: 2-21, average: 10.5	Setting Participants were recruited from a regional CF clinic in Tasmania, Australia. Interviews took place in their homes. Sample selection Purposive sampling. Participants were approached in the first instance by the	Themes/categories Fight for information: "We wanted to know all the details, and there would be things where we would ask the question and they would hedge as if to say, “We really don’t like to tell everybody all those details to start with.” Because we were both biology trained, we just wanted the absolute details . . . it seemed like getting blood out of a stone." (couple of parents) “not just the stuff they want the parents to hear” (one parent who read whatever she could	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported and was appropriate for the research question. Data collection:

Study details	Participants	Methods	Findings	Comments
406255 Study type Qualitative phenomenological study Aim of the study To explore the experiences of living with CF Country/ies where the study was carried out Australia Study dates Not reported Source of funding The study was funded by an Australian Postgraduate Award.	Sex of people with CF: 4 males, 3 females At the time of the interview all people with CF were medically stable, not in the hospital nor receiving intravenous antibiotics. Inclusion criteria Person with CF or his/her parents Exclusion criteria Siblings of people with CF	directing nurse. She invited potential participants as they arrived for their appointments. After assent, participants were given information sheets and consent forms and were told that they would be contacted by phone to arrange an interview time. Data collection Data were collected during single, unstructured, conversational-style interviews, which commenced with the participant being invited to tell his or her story. Conversation with younger children was initiated by an invitation to draw. This took place in the presence of their parents, who remained in close proximity. Interviews were conducted in the participants' homes, and were tape recorded and transcribed verbatim. Some parents and the older children with CF	and said that she could recognize the erroneous facts she received from health care professionals) Some parents were "snowed under" by initial information: “blah, blah, blah” (one parent) Fight in the legal arena "Now I don’t know a lot about the legal system, but if I knew what I know now, he wouldn’t be going anywhere, because my lawyer would just make mincemeat out of him. I’ll never forgive him. He didn’t know what he was talking about. He should never have discussed CF because he was just a fool." (parent recalling their initial consultation with a pediatrician)	The authors clearly explained and justified clearly how the data were collected. They also explained that interviews were conducted in the participants' own homes in order to dispel notions of clinical context or interrogation. However, the authors did not discuss data saturation. The relationship between the researcher and the participants was not adequately considered. Data analysis: There was an in-depth description of the analysis process. It is clear how the themes were derived from the data. Sufficient quotations were presented to support the findings. Contradictory data were taken into account. However, there was no critical review of the researcher's role in the process. Findings/results: Findings are explicit and adequately discussed. A colleague with expertise in phenomenology challenged perceived anomalies in the analysis. However, the total number of analysts involved was unclear. There was no respondent validation due to concerns about the research burden on the CF population. Overall quality: Moderate

Study details	Participants	Methods	Findings	Comments
		chose to be interviewed alone, while half of the parents chose to be interviewed as a team. Data analysis The process of explicating the phenomenon began during the initial recounting by participants. Distinct themes were then identified through a process of subsequent reading and rereading of transcripts, listening again to the tapes to verify and to recall subtle nuances. This was informed by a continual turning from the word spoken to the context with a hermeneutic attitude (Walsh, 1996). Interview transcripts were analyzed for recurring themes in light of van Manen's (1990) approach to hermeneutic phenomenology. Therefore, the four lifeworld existentials of space, time, body, and		Other information Ethical approval was obtained from the applicable combined hospital and university research ethics committee. Written informed consent was obtained for all participants, including parental consent for those less than 18 years old. In addition, verbal and observational acquiescence by this group was assured because children were observed for any reluctance or coercion on the part of their parents. Noninvolvement was met with assurance that there was neither obligation nor impact on future care. Other information

Study details	Participants	Methods	Findings	Comments
		relationship were utilized. By analysing the data through the filters of time, body, space, and relationship, distinct themes were identified. This process was underpinned by the awareness of the subtle difference between those themes that van Manen calls incidental and those that are essential and exclusive to the phenomenon under investigation. The authors received feedback from appropriate clinicians on both the participants' contributions and the analysis of them and gave several presentations of the study during its execution in order to verify creditability of the study. Moreover, a colleague with expertise in phenomenology challenged perceived anomalies in the analysis. Transcripts were not returned to		

Study details	Participants	Methods	Findings	Comments
		the participants for comment because of concerns about the research burden experienced by the people with CF. A research journal was undertaken to formalize the reflective process. This consisted of field notes written as immediately after the interview as possible, usually within 30 minutes, plus reflections that were written subsequently and convey a deeper synthesis of impressions.		
Full citation Johannesson, M., Carlson, M., Brucefors, A. B., Hjelte, L., Cystic fibrosis through a female perspective: psychosocial issues and information concerning puberty and motherhood, Patient Education &	Sample size N=17 women selected N=14 women interviewed Characteristics Mean age diagnosis: 1.6 years (range 0.5–5) Mean age menarche: 15.3 years (range 13–18) Mean weight menarche: 20.5 S.D. (range22.5 to 11.5) Mean height menarche: 10.5 S.D. (range 22 to 12)	Setting Women were interviewed at the hospital by the first two authors. Sample selection Women who attended a CF centre in Stockholm were selected for the study. Data collection Data was collected through individual in-depth interviews that lasted 2 hours, and performed by the first	Themes/categories Information provision Pubertal development and fertility: Women recalled that doctors provided information that delay in sexual maturation was related to their CF (authors comment) Women recalled that doctors provided information about problems with fertility: "it was terrible to hear that I might never become a mother" (one participant) "I took it for granted that I couldn't have kids since I knew I would die young" (one participant) Women recalled that they did not talk about it even though they were worried (authors comment)	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported. The relationship between the researcher and the respondents was clearly reported Data collection: Data collection relied on in depth interviews. Description of data collection method was vaguely described and no information on use of topic guide

Study details	Participants	Methods	Findings	Comments
Counseling, 34, 115-23, 1998 Ref Id 366885 Study type Qualitative study with in-depth interviews Aim of the study To investigate psychological issues concerning puberty and motherhood among CF adult females, to see how they had obtained and conceived information on these matters and how they would like information to be given. Country/ies where the study was carried out Sweden Study dates 1994-1996	Mean age at investigation: 28 years (range 22–34) Organ transplants at investigation: 2 (at 24 and 25 years resp.) Married at investigation: 8 Mothers: 2 Inclusion criteria Diagnosis of CF in childhood (positive sweat test according to Gibson and Cook (>80 mmol cl / l [26] together with symptoms compatible with CF) Monthly visits for clinical evaluation at Stockholm CF centre More than 20 years of age Exclusion criteria Not reported.	two authors, audio-taped and typewritten. Data analysis Data analysis was carried out independently by each interviewer and evaluated by both to obtain a combined interpretation, which was further discussed between authors for final conclusion to obtain reliability and validity of data.	New information about fertility and thoughts about motherhood: Women received information about different methods to overcome their problems to become pregnant by their gynaecologist/CF-doctor (authors comment) Women learned about new methods through general information through the patient association (authors comment) Women experienced mixed feelings about the new information: Some women were positive over new possibility of becoming a mother: "you become more motivated to keep in good shape" (one participant) However, some women were in despair when hearing that they could not become pregnant: "I felt cheated. The gynaecologist said there was no problem because they could help me with insemination, but when I finally met my CF-doctor she said no. She though that my lung function wasn't good enough for a pregnancy. It was a knockout" (one participant) "it was very disturbing that the CF-team should decide whether or not I was allowed to become pregnant" (one participant) Receiving information about puberty and fertility (when, how and who with) When information should be provided: Women reported that they would like information concerning puberty and fertility at 13-14 years age by the CF doctors in a sensitive manner depending on each patient's requirement (authors comment) Older women reported it was important to receive information about possibilities of motherhood to encourage young girls to adhere	Data analysis: The analytical process was not clearly reported. Description of how emerging and overarching themes were reached was not reported, saturation of data was not reported. Insufficient information on the processing of the data or the use of specific qualtiative software. Findings/results: Results were presented clearly supported with quotes and findings discussed in depth (e.g., citation/data and the researchers' own input distinguished) Overall quality: Poor Other information

Study details	Participants	Methods	Findings	Comments
Source of funding Swedish Cystic Fibrosis Association. 'Fo¨renade Liv' Mutual Group Life Insurance Company, Stockholm, Sweden.			to medical treatment and avoid destructive behaviour (e.g., smoking): "It is so hard for man during adolescence. You have to tell positive things so they understand..." (one participant) How information is provided: Women reported that information could be given in smaller discussion groups with CF-girls at the same age, facilitated by two older CF-women (one who had been pregnant, and one who had difficulties to become pregnant) (authors comment) Who should provide information: Women wanted a first visit to a specialist gynaecologist working closely with a CF-team at 16-17 years age (authors comment)	
Full citation Kazmerski, T. M., Borrero, S., Tuchman, L. K., Weiner, D. J., Pilewski, J. M., Orenstein, D. M., Miller, E., Provider and Patient Attitudes Regarding Sexual Health in Young Women With Cystic Fibrosis, Pediatrics, 137, 2016	Sample size N=22 women with CF aged 18-30 years N=16 CF program directors Characteristics Women with CF. CF program directors because of their expertise in CF care and ability to reflect on overall center practices in addition to personal practice. Inclusion criteria Not reported Exclusion criteria	Setting US CF care center Sample selection Sample of women recruited with CF at an accredited adult US CF care center during inpatient or outpatient visits. Thirty potential participants (program directors) were selected based on geographic diversity. Sixteen directors agreed to be interviewed (a 53% participation rate).	Themes/categories Sexual and reproductive health (SRH) is important to discuss in the CF care setting: Patients: "It's always just like you don't talk about it [SRH], it's one of those things that's left to the side, it's […] like they [CF providers] feel it's not as important as everything else, but sometimes it is. I mean, it [SRH] wasn't life or death threatening, but it could've changed my life a lot." Providers: We've been so focused on nutrition and liver disease and lung disease and diabetes, but now that […] quality of life continues to improve, this will be a big issue, a more important issue for everyone." Patient and provider discomfort around SRH is a major barrier to care:	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported. The relationship between the researchers and the respondents not clearly reported. Data collection: Data collection relied on the semi structured interviews. Structure of interview and topic guide reported. Description of how "themes" were arrived at was

Study details	Participants	Methods	Findings	Comments
Ref Id 469560 Study type Qualitative study Aim of the study To explore the attitudes, preferences, and experiences of patients with CF and CF providers toward sexual and reproductive health care for young women with CF. Country/ies where the study was carried out USA Study dates 2014-2014 Source of funding Not reported	Not reported	Data collection Women with CF completed semi-structured, individual in-person interviews investigating SRH (sexual and reproductive health) care experiences and attitudes toward SRH care in the CF setting. Interviews were structured by key questions and probes intended to guide conversation. All interviews were audio-recorded and transcribed. Thematic saturation was reached after the 13th interview. For program directors, semi-structured, individual phone interviews, exploring attitudes toward SRH care, timing and content of SRH discussions, and potential barriers and facilitators to female CF SRH care. Interviews were audio-recorded and transcribed. Thematic saturation was reached after the eighth interview.	Patients: "Sometimes women are afraid to speak up and they keep these things [SRH issues] personal to them… and might feel uncomfortable." Provider: "I think the number 1 [reason] is that a lot of the younger women are …embarrassed, especially because I'm a middle aged man, they're just a little embarrassed to bring it up." "You do what you're comfortable with. I'm not good at fielding questions about sexuality, so I probably don't bring it up as often as I should." Educational resources coupled with standardized provider discussions would facilitate SRH care: Patient: "Sometimes, if people were to feel uncomfortable… maybe be given a pamphlet. Or some papers that have Web sites that you can, you know, go on… or maybe there would be an online thing where you can actually ask questions, kinda like be anonymous because maybe some people are embarrassed." Providers: "…a concise booklet that was […] very accurate [with] all the different [SRH] subjects at a comprehensive level. Because some [patients] probably don't necessarily want to talk about it in the clinic, but … we could provide accurate information to them that they could access at their own convenience." Patients: "It's [SRH discussion] important. And, sometimes, [the CF provider] may have to be the initiator in these kinds of, you know, issues. Sometimes women are afraid to speak up and keep these things personal to them…and they [patients] might feel uncomfortable. The doctor should say, 'Hey, is there something – anything we could discuss about, you know, sexual development or things like that or pregnancy?'	discussed. Data saturation and full exploration of theme reported. Ethical approval process not reported. Data analysis: The analytical process was described with description of themes and categories. No critical review of the researchers' role in the process. Findings/results: Results were presented clearly (e.g., citation/data and the researchers' own input distinguished. Researchers' role and potential influences in the analytical process not critically reviewed. Overall quality: Other information The study did not described the ethical process of research. Study conducted by multiple researchers but the level of consistency between the researchers not reported. Findings cannot be generalized to all CF care providers (ie, those who are not directors).

Study details	Participants	Methods	Findings	Comments
		Data analysis Interview transcripts were analyzed through an iterative process of coding to identify themes. 1 initial set of codes for patient participants and 1 for providers were developed. By using a consensus coding approach, the coders reviewed their coding, discussed any discrepancies, and defined any new codes. A senior co-investigator (EM) adjudicated any differences in interpretation. ATLAS.ti 5.0 (Scientific Software Development GmbH, Berlin, Germany) was used to facilitate data management and coding.	” Providers: “[T]here’s definitely not a systematic approach. I think for us it’s very provider-dependent. It seems for our adult and adolescent providers, it’s part of what they’ve been trained to do…I think our paediatricians aren’t quite as systematic with it or as astute with how to approach it.” “I think one way [to improve SRH care provision] is to have clear transition topics that are brought up on a regular basis that need to be addressed. So that it [SRH] becomes a more routine part of annual visits and potentially even quarterly visits; it’s just part of the issues that need to be addressed with regularity. So, regularity becomes familiarity.” Women with CF prefer early, open-minded SRH discussions initiated by the CF team: Patients: “[SRH] was brought up in school when I was in 4th or 5th grade, so I was probably 9…I think between 8 and 10, depending on if puberty is starting, I think you should be informed.” “Honestly, for me, the easiest thing would be to just start [SRH discussions] young and have it be an expectation. We walk in here and know that people are going to talk to us about bowel movements, that’s just part of what we know is gonna be asked. So, if you start [SRH discussions] at a young age, I think it just becomes part of the routine and it doesn’t become as uncomfortable as it would be.” “I think that they should start talking about something to do with it [SRH] at a younger age. So then when you grow, and hopefully continue to see the same doctor as you grow up, you feel comfortable with that doctor and discussing the rest of the topics.” “I just think it would be good for the doctors to bring [SRH] up more because…when I was	

Study details	Participants	Methods	Findings	Comments
			younger, I never even thought to say anything about it. And then, by the time I was old enough, it was well past the age…of needing concern."	
Full citation Kirk, S., Milnes, L., An exploration of how young people and parents use online support in the context of living with cystic fibrosis, Health Expectations, 19, 309-21, 2016 Ref Id 473757 Study type Virtual observational study (Netnography or online ethnography) Aim of the study To explore how online peer support is used by young people and parents to support self-	Sample size 97 participants on young patient discussion forum and 182 participants on parent's discussion forum Characteristics Young adults with CF and parents Inclusion criteria Not reported Exclusion criteria Not reported	Setting Virtual. Based on discussion in online forum. Sample selection All postings made to the young people and parents over a random 4-month period Data collection Those relating to fundraising and non-CF issues (for example, favourite television programmes). Data analysis The discussion threads were downloaded into Word documents and imported into NVivo for analysis. The data were coded using an inductive grounded theory approach to identify themes and patterns emerging from the data. Through the constant comparison process, data were grouped	Themes/categories The online culture: communication styles and community While parents mainly used the site to seek specific advice or emotional support, young people use d it as a social networking site. "hey Tina welcome back! how did you get on with the exams? i'm good thanx, back on the IV's in June. how are you?" "aww i'm gd. on my Iv's atm. halfway there! yay! a week is too long though. i feel like pulling the needle out! glad to hear you're feeling good. i think i need a bronch to! havent had one in ages and sometimes you can just tell you need one! now is one of these times! (but don't tell the doctor!" Although the groups were a place where negative emotions could be expressed, it appeared that there were boundaries to this. Indeed, the online group was not always seen as being an appropriate place to discuss certain experiences and feelings: "This is a short post. I ashamed to say I often feel the same (perhapes manage it a little better though). I dont want to open up on this subject on here though. Feel free to email me on XXX" (Parent)	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported. Whether the sample is genuine representative of the CF population is unclear and it was based on a single online discussion forum. Data collection: Data collection relied on the discussion thread. Structure of study and topic guide not reported and might not be applicable as this is not a qualitative study. Description of how "themes" were arrived at was unclear or whether data saturation reached. Data analysis: The analytical process was described but was inadequate in description. No critical review of the researchers' role in the process. Use of NVivo for analysis Findings/results:

Study details	Participants	Methods	Findings	Comments
care in relation to CF. Country/ies where the study was carried out UK Study dates Not reported Source of funding NIHR's Health Services & Delivery Research programme, UK.		into codes and over-arching themes	Managing treatments Group sought advice and support about how to manage different treatments and therapies. "Have you tried going swimming together just the girls in yr family make exercise fun and then when she has done it go and have lunch together or buy her a treat, That has worked with my son 13." "We used to use straws – blowing cotton wool balls across the kitchen table – actually our physio who has retired showed us this one – it was great fun when we all joined in as a family. " Managing emotions Group discussion provided an outlet for parents and young adults to express their emotions. "Hey, You are certainly not alone! I think everyone with CF has felt like tha sometimes. I know for a fact I hve felt like why do I bother but I tend to do it when i'm well bcoz i cant see any difference when i take my tablet sna if i miss them but I've learnt now that i have to do my nebs and stuff" Managing identity Some parents tried to validate their identity and to justify that they were good parents	Results were presented clearly under different themes with generous use of quotes. Researchers' role and potential influences in the analytical process not critically reviewed. Overall quality: Moderate Other information As this is a virtual observational study of discussion thread, challengers and oppurtunities were discussed.. Ethical issues around online discussion is controversial and was addressed.

Study details	Participants	Methods	Findings	Comments
			"my daughter is 15 now but i remember like it was yesterday going through the stuff u r now and to be honest u sound like a great mum and my only advice is a mum knows best just listen to your heart and u wont go far wrong." Managing support from services and health-care professionals Participants advised parents to take an assertive stance and question medical decision making. "I just wanted to say that I think your attitude towards your son's care is fantastic. I know a lot of parents struggle to stand up to/question medical staff (including my mum when I was younger) so it's great that you have already managed to gain the confidence to do it when your son is still at such a young age."	
Full citation Lang, L., Duff, A. J., Brownlee, K. G., Introducing the need for lung transplantation in children with cystic fibrosis: parental experiences, Journal of Cystic Fibrosis,	Sample size N=8 parents of children with CF Characteristics Parents of children refered for lung transplant treatment. 7 female and 1 male. Age range = 35-50 years Married = 7, divorced = 1 Age of children with CF = 3-16 years	Setting Participants' home Sample selection 10 families of children undergoing lung transplant were asked to participate (mean time between referral and interview was 3 years and 4 months). Eight participant agreed. Data collection	Themes/categories Role of information in relation to lung transplantation Most of the participants thought information helped them to prepare: Distressing but facing reality Although upsetting, many parents felt discussion helped them face the reality of the situation (author's comment) "I wanted to be told everything (e.g. assessment criteria, procedures, complications and outcomes, including statistics, quality of life, drug-side effects and long-term progosis".	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported. The relationship between the researcher and the participants was not reported. Data collection: Data collection relied on the semi-structured interviews. Description of data

Study details	Participants	Methods	Findings	Comments
4, 259-62, 2005 Ref Id 473773 Study type Qualitative study with semi-structured interview Aim of the study To recruit the view of parents of children with CF on their actual experience, of how the flow of information should be managed and how the process of initial introduction by the refering centre could be improved Country/ies where the study was carried out UK Study dates No reported Source of funding	Inclusion criteria Not reported Exclusion criteria Not reported	Participants were interviewed at home via telephone there responses being transcribed verbatim at the time. Data analysis Content of transcript were analysed using well-validated qualitative research tool (Content Analysis). Coding and category identification were undertaken by two independent researchers and then aggregated with 90% inter-rater agreement	"Information makes you more aware and perpared" "I would have liked more information" Others were reluctant: "I didn't want information" "I didn't really want to deal with it" "Having the informatoin is depressing" Gradual introduction and support by the CF team A gradual and informal process of discussing CF and treatment options prior to crisis-point was recommended as a means of preparing and supporting families more effectively. (author's comment) Having a good relationship with the clinician introducing and discussing LTx was seen as essential. Parents felt the process would also be less formal and less distressing if the CF nurse, who knew the family and who had perhaps been previously emotionally supportive, was central to this. (author's comment) Availability of information, format and timing The majority of parents thought information was crucial to preparation, suggesting various formats (e.g., written material, videos, personal accounts, specific transplant group meetings and counselling). Parents wanted information at different times, either as soon as possible or when LTx became an option for their child. Therefore, it seems beneficial to have information available for parents to access as and when they wish.	collection method was vaguely described although validated qualitative research tool was used. Data analysis: The analytical process was reported vaguely. Description of emerging and overarching themes was reported, but saturation of data was not reported. Coding and category identification by two independent researchers suggest reliability of findings Findings/results: Results were presented clearly. Discussion of the finding was limited and cross reference to citation/data and the researchers' own input was not adequately presented Overall quality: Moderate Other information

Study details	Participants	Methods	Findings	Comments
Not reported			Referring for assessment When the time for lung transplant referral arrived, parents wanted to meet with the Consultant, the majority wanting to know all the facts at this point in order to make a decision. Some participants "only wanted to know the positive aspects" Several stated that following such discussions, they forgot some of what was said and said they "wanted written, bullet-point information or FAQs to refer back to". The majority of parents also wanted their partner/spouse to be involved. Parents felt that their child's age and ability to understand and make their own decision were important factors determining the extent to which their child was involved initially.	
Full citation Macdonald, K., Greggans, A., 'Cool friends': an evaluation of a community befriending programme for young people with cystic fibrosis, Journal of Clinical Nursing, 19, 2406-14, 2010 Ref Id 369281 Study type	Sample size N=17 participants of which n=10 were children or young people CF or their parents, n=3 were befrienders, n=2 play therapists, n=2 education liaison personnel Characteristics Age of people with CF: 8-18 FEV1: 27-101% Inclusion criteria Inclusion criteria for hospital and educational personnel: to be involved closely with the	Setting Setting of the befriending scheme: the Butterfly Trust Setting of the interview for children and parents: their own homes. Sample selection The Butterfly Trust approached all families in the befriending programme and sought permission for the researchers to contact them. Telephone contact was made and	Themes/categories Experiences of befriending Befrienders were mostly young people who were in transition between education and employment. Continuity in befriending with young adult with CF (befriendee) was thus difficult: Parent of a 16 year old befriendee: "They'd be better if the lassies were a wee bit older, ken they're away on holiday, I dunno what age, she can only be in her 20s, changing jobs, its months since we've seen her." Befriending – what's good about it? Befriending was seen as helpful by both parents and young adults. Young adult of 15 years was happy in the company of befriender	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported. The relationship between the researchers and the respondents not clearly reported. Data collection: Data collection relied on the semi structured interviews. Structure of interview and topic guide reported. Description of how

Study details	Participants	Methods	Findings	Comments
Qualitative logitudinal pilot study Aim of the study To evaluate the impact of a community youth befriending programme on a group of young people with CF and their carers. Country/ies where the study was carried out UK Study dates Not reported Source of funding Not reported	people with CF involved with the study. Exclusion criteria Not reported	then following verbal consent a visit was arranged to discuss the research and complete consent forms. Data collection Children and parents were interviewed individually (or together, according to their wishes) in their own homes. All interviews used a semi-structured format, with a topic guide. Half of the families were interviewed twice; once near the beginning of the befriending relationship and again if their befriending experience had extended to one year after the first interview. The three befrienders were interviewed via a focus group. Individual semi-structured interviews were conducted with the play therapists and education liaison personnel. Data analysis	"it's what I expected, going out having a wee bit of a laugh and when I come back my dad says I'm always happier than when I left home." Young adults understood that having a befriender took the pressure of parents. "when they first asked me if I wanted a befriender, I just wanted to go through it myself, saves my mum and dad having to do all that stuff." Parents also recognize that their children might share their emotion with befriender when they sometime struggle to share with parents. "… this is one of the reasons that the befriender … plays a role in it … that builds up a sort of friendship with (son) … that if he's got any fears like that, hopefully he'll speak tae the befriender." Befriending – what's not so good about it? Criticism of befriending was around the continuity. Young adult was unhappy about the lack of continuity "Don't know what happened to the first one……I thought it was me…. I could never get in touch with her. Parent shared the same concern "I feel let down and (son) has been let down because he was getting close to her." Befrienders also faced challenges in building and boundaries of the relationship "…It can take a while to get to that stage, I'm now totally comfortable with (child), we can talk about anything…"	"themes" were arrived at was discussed. Data saturation and full exploration of theme not reported. Data analysis: The analytical process was described with description of themes and categories. No critical review of the researchers' role in the process. Findings/results: Results were presented clearly with themes and quotes for robustness of findings. Researchers' role and potential influences in the analytical process not critically reviewed. Overall quality: Moderate Other information The study described the ethical process of research. Study conducted by multiple researchers but the level of consistency between the researchers and rigour of the process reported.

Study details	Participants	Methods	Findings	Comments
		Each interview was tape recorded and field notes recorded immediately after the interviews. Framework model previously reported in the literature was used to build a matrix of themes and codes from the four sets of data (children, parents, befrienders, others). Separate lists of themes, categories and concept maps were constructed for each participant group and peer reviewed by the second researcher to ensure congruence of findings.	"He doesn't understand why he can't come to my house, or I can't bring my child along and neither do I." Befrienders were also concerned about their lack of knowledge when discussing with parent or young adult about CF. "I would like more training about CF, the parents talk to you in jargon you don't understand – what's IV's?"	
Full citation Miller, A. R., Condin, C. J., McKellin, W. H., Shaw, N., Klassen, A. F., Sheps, S., Continuity of care for children with complex chronic health conditions: parents' perspectives,	Sample size Parents of 47 elementary school-aged children Characteristics Parents of elementary school-aged children with spina bifida, Down syndrome, attention-deficit/hyperactivity disorder, Duchenne muscular dystrophy or cystic fibrosis Inclusion criteria	Setting Most families (44 of 47) were interviewed in their homes, while three were interviewed at the hospital at their request. Sample selection Purposive sampling strategy to recruit parents or primary caregivers of elementary school-aged children. Participants were	Themes/categories Relational and informational continuity and their significance: Parents' believed that knowledge of the child, according to parents, developed through relationships with a consistent set of service providers, both in and outside of medical settings. "You need to see the regular faces, because they're the ones you feel at least know your child best," the mother said. "They know the history," the father added, "so you feel they have the whole story."	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported in detail including the process of recruitment of participants. The relationship between the researchers and the respondents not clearly reported.

Study details	Participants	Methods	Findings	Comments
BMC Health Services Research, 9, 242, 2009 Ref Id 473866 Study type Qualitative study Aim of the study Parent's perspectives on continuity of care for children with complex chronic health conditions and to identify the salient factors in the experience of, and factors contributing to, continuity in this population Country/ies where the study was carried out Canada Study dates Not reported Source of funding	Not reported Exclusion criteria Complex, multi-factorial clinical profile	contacted through specialized hospital clinics, physicians' offices, and patient support and advocacy organizations. These conditions were selected as representative of chronic conditions of childhood that have a significant and varied impact on child and family functioning and require a wide range of services. Data collection Semi-structured, open-ended interviews conducted by a trained member of the research team. Parents were encouraged to provide a spontaneous narrative about the various service providers with whom they and their child interacted over time, starting with their earliest contacts. Questions and probes were designed to provide an opportunity for parents to discuss how they perceived and experienced a	"It's nice when relationships do develop, you know. Kate knows the nurses [in the cystic fibrosis clinic] and she likes them, and ... she's not scared when she goes down there. Those faces are familiar to her, and if she is sick, it's not scary, it's not somebody she doesn't know." Continuity and communication: Parents identified communication as an integral feature of positive experiences of continuity of care. "I believe that's what [continuity] is. It's a relationship. A relationship is formed on communication, you know, and that's all that's happening between a doctor and patient, for example ..." Management continuity: seamlessness versus compartmentalization: Parents described high standards and even excellent management continuity provided by groups of service providers based in one location. "Most of her stuff is [cystic fibrosis] stuff and then there's the hearing thing, but that's not a doctor thing, that's more of a rehabilitation, audiology, speech therapy, and that kind of thing. The two aren't really related, except when her delayed language might interfere with what a child her age can do in terms of their own care, because you can't really explain it to them." Parents working to ensure continuity:	Data collection: Data collection relied on the semi structured interviews. Structure of interview process reported but no information on use of topic guide. Description of how "themes" were arrived at was discussed. Data saturation and full exploration of theme reported. Data analysis: The analytical process was described with description of themes and categories and use of specific technology. No critical review of the researchers' role in the process. Findings/results: Statements of the findings are clear. Reasoned and adequate discussion of the evidence. Researcher did not the credibility of their findings (e.g. triangulation, respondent validation). Overall quality: Moderate Other information The study did not describe the ethical process of research although ethical approval obtained. Interview conducted by single researcher but the level of consistency and accuracy not reported.

Study details	Participants	Methods	Findings	Comments
BC Medical Services Foundation and Michael Smith Foundation		number of aspects of their child's care Data analysis Interviews were transcribed and field notes were imported into ATLAS.ti for data management and anlysis of themes. Interview data underwent two major stages of coding and analysis. Some codes were developed inductively given their repeated appearance in the interviews; others were derived deductively based on the Reid and Haggerty continuity model.	Parent state that lack of continuity in management required parents to take initiative. "It was chaotic and frustrating, and nobody seemed to know what they were doing, and nobody was calling the specialized clinic at the Children's Hospital to find out what should be done...." Parent limiting continuity: Parent sometime want to limit or control the flow of information between different agencies. "I don't want them to send [reports from the hospital] to the school. The school doesn't need to know until I think they need to know, and then I can tell them." Systemic and organisational barrier to continuity: Parent reported lack of coordination between different organisations. "To me, it was like you were cut off from life. You turn six, that's it. You're gone. When they do it from zero to six, they coordinated. They stayed on top of it, they tell you what they need. As soon as they get into the school system ... I'm not even sure who coordinates it then."	
Full citation Roehrer, E., Cummings, E., Beggs, S., Turner, P., Hauser, J., Micallef, N.,	Sample size N=15 n=5 children n=5 adolescents n=5 adults Characteristics	Setting Sessions were conducted at the participant's residence whenever possible. Sample selection	Themes/categories Pre-pilot themes Awareness of symptoms and peer support: Participants expected that they would become more aware of their symptoms by being in the pilot.	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question

Study details	Participants	Methods	Findings	Comments
Ellis, L., Reid, D., Pilot evaluation of web enabled symptom monitoring in cystic fibrosis, Informatics for health & social care, 38, 354-65, 2013 Ref Id 333172 Study type Qualitative study with semi-structured interviews. Aim of the study To evaluate a pilot trial of an information system conceptualised and developed to assist people with CF, and their families, to enhance their skills and communication in relation to self-management for their condition.	Males=10; Females=4 Target recruitment age range: 0-10 years; 12-17 years; 18 years onwards Actual recruitment age range:19 months- 5 years; 11 years-14 years; 21 years-52 years Inclusion criteria Children, adolescents, and adults with CF. Exclusion criteria Not reported.	Participants were identified through attendance at one of the Tasmanian CF clinics. Recruitment was through random selection of participants in three groups to allow comparison within each age range group in their interaction and use of MyCF website. Data collection Data was collected at pre- and post- pilot, and sessions conducted in a structured manner. Data analysis Thematic analysis was used to analyse data. Codes were developed and similar themes grouped together.	Expected benefits included peer support for participants and parents (authors comment). Post-pilot themes Expectations: Participants reported that their expectations had been met by the pilot, but expected more interaction with the health care professional and peers (authors comment) Use of diary (MyCF website): Participants reported that using the diary daily was too great a burden (authors comment). Impact of negative and positive perspectives of MyCF website diary: Participants reported that there was no change to their management of CF as a result of using the diary (authors comment). However, Participants also reported that they felt a greater sense of involvement in their treatment, better understanding of symptoms (authors comment). Some participants felt that the diary was not useful or was limited (e.g., in times of illness).	Sample selection: Sample selection was clearly reported. The relationship between the researcher and the respondents not clearly reported Data collection: Data collection relied on the semi-structured interviews. Description of data collection method was described but limited in information provided Data analysis: The analytical process was reported. Description of emerging and overarching themes was reported, but saturation of data was not reported. Findings/results: Results were not presented clearly. (e.g., citation/data and the researchers' own input distinguished). Not supported by appropriate quote Overall quality: Low Other information The study looks at participant preferences (pre- and post-pilot) upon web-based use of a diary for managing their CF.

Study details	Participants	Methods	Findings	Comments
Country/ies where the study was carried out Australia Study dates June 2011 to September 2011. Source of funding Tasmanian Community Fund grant.				
Full citation Tipping, C. J., Scholes, R. L., Cox, N. S., A qualitative study of physiotherapy education for parents of toddlers with cystic fibrosis, Journal of Cystic Fibrosis, 9, 205-11, 2010 Ref Id 366981 Study type Qualitative study	Sample size N=11 n=5 physiotherapists n=6 parents of children or young people with CF Characteristics Age of children or young people: 2 to 16 Other characteristics not reported Inclusion criteria Physiotherapists were included if they were involved in CF care and education at Monash Medical Centre. Parents were included if they if they had a child with CF between 2-16 years of age and were involved with the CF	Setting CF clinic at Monash Medical Centre. Sample selection Participants were identified and recruited through purposeful sampling by the clinical co-researcher from the CF clinic. A variety of participants (in terms of age and gender) was used to gain a broader understanding of people experiences. Focus group sample size was determined based on the literature, which suggested 6–12 participants per group.	Themes/categories Physiotherapy treatment “I asked to see the physio at the time... it was just impossible to try and keep someone of that age still for 20 min to half an hour to finish the treatment... he started telling us about doing some bubble games” Physiotherapy education “They gave us a video as well, really outdated ... I didn't think it was the greatest video but anyway it was a bit old fashioned.” “I think firstly in that first week we felt information overload... to be told like especially with the physiotherapy...that you've got to do this every single day for your child's life it's just overwhelming.” Connectedness with health care professionals "I think they view it as a test if you ask them to demonstrate. Because often that first time that you're doing the education it is so	Limitations Aim(s): Aim of the study clearly reported, research method was appropriate for answering the research question. Sample selection: The recruitment strategy was appropriate for the aims of the research, because a variety of participants (in terms of age and gender) was used to gain a broader understanding of people's experiences. However, given that all the participants were from the Monash Medical Centre, the results obtained in this study may not be generalised to different CF population groups, for example families who are

Study details	Participants	Methods	Findings	Comments
Aim of the study To identify factors that impair the delivery and retention of physiotherapy education for parents of children with CF and factors that impair effective physiotherapy treatment in the home environment. Country/ies where the study was carried out Australia Study dates Not reported Source of funding Not reported	clinic at the Monash Medical Centre. Participants who fitted the study criteria and who appeared to the clinical co-researcher to be appropriate to interview as they would be willing to discuss the difficulties and challenges of having a child with CF. Exclusion criteria Participants were excluded if they did not speak English or were under 18 years of age.	Sample size for the interviews was determined by completing interviews until theoretical saturation of data was reached. Data collection One focus group of paediatric physiotherapists (1 h duration) and 6 semi-structured interviews of parents (25–55 min duration) were conducted guided by interview maps. Focus groups and interviews were digitally recorded and transcribed. The focus group and the first interview were conducted by an experienced facilitator, whilst the subsequent interviews were conducted by the principal researcher under the guidance of the experienced facilitator. Data analysis Grounded Theory principles were applied in the analysis. Each participant was	overwhelming" (from physiotherapists focus group) “I don't have any problem with people trying to tell me how to improve things. So yeah we thought it was really valuable.” Social support “I wasn't coping very well… the physio was very good. I don't know why, but for some reason I think the physio part of Cystic Fibrosis, not only is it huge because of what it does, I just think it's huge in terms of support. We just asked them so many questions … I've placed my baggage on them and they've taken that really well.” Family can be perceived as supportive by some people: “At the time we also had a bit of support unit with my mum and sister in law there and they were taught [physiotherapy techniques] as well for back up and a bit of emotional and moral support for me.” Or unsupportive by others: “My husband who is an angel, he is fantastic, he also wasn’t 100% support[ive] in that manner, he left most of it (physiotherapy) for me”	managed through different health care networks, thus limiting external validity. The relationship between the researcher and the respondents was not clearly reported. Data collection: Data collection was clearly reported, including the number of interviews, data saturation and the use of an interview map and digital recording. However, the authors did not explain why they chose a focus group for the physiotherapists and interviews for parents. Data analysis: The analysis process was described in detail, including details on how categories, sub-categories and themes were developed. Sufficient quotations were presented to support the findings. However, there was no mention of contradictory data and researchers did not critically examine their own role, potential bias and influence during analysis and data selection. Findings/results: The findings were explicit. Data analysis was completed independently by two researchers to enhance credibility. Moreover,

Study details	Participants	Methods	Findings	Comments
		assigned a code number and pseudonym for transcription and quotation. The audio and transcribed versions of data were reviewed multiple times to capture the full impression of the data. Line by line analysis was then completed to identify categories. The relationships between the categories were explored to develop sub categories and themes. Key quotations were identified and reviewed with the audio data for accuracy. The researchers met to discuss the emerging themes and were in agreement with themes and categories. Data analysis was completed independently by two researchers. The coding process was completed numerous times by each researcher to ensure clear development of		participants were asked to review the emerging themes and comment on their accuracy. There is adequate discussion of the evidence which takes into consideration studies with contrasting findings as well as studies with similar findings. Overall quality: Moderate Other information Ethics approval was obtained from the Southern Health and Monash University Ethics committees. All participants were required to give written informed consent. The authors noted that they outlined data collection and analysis clearly in order to allow completion of a similar study in other population groups. The authors also noted that by having children of participants spread across a wide age range they addressed recall bias of parents. Other information

Study details	Participants	Methods	Findings	Comments
		themes. Quotations were used to validate and reinforce key themes. Participant members were asked to review the emerging themes and comment on their accuracy.		
Full citation Tluczek, A., Koscik, R. L., Modaff, P., Pfeil, D., Rock, M. J., Farrell, P. M., Lifchez, C., Freeman, M. E., Gershan, W., Zaleski, C., Sullivan, B., Newborn screening for cystic fibrosis: parents' preferences regarding counseling at the time of infants' sweat test, Journal of Genetic Counseling, 15, 277-91, 2006 Ref Id 366982	Sample size N= 33 families Characteristics Families of infants with abnormal newborn results (8 with CF confirmed after sweat test) Inclusion criteria Not reported Exclusion criteria Not reported	Setting Qualittative interviews in families' homes and it lasted about 1 hr Sample selection Families were recruited from CF Centers during appointments for diagnostic sweat tests following abnormal CF NBS results. All participants provided written consent for this study. Data collection Semi structured interviews conducted by the principal investigator or 3 research assistants trained to conduct qualitative research. When both parents participated, they were interviewed together. Data analysis	Themes/categories Implication for child who is CF carrier Mother of carrier infant: "I think probably for his future. What is it going to mean for (him) when he gets married and has his own kids? How is that (being a CF carrier) going to play a role? How do we tell him about all this and explain it to him so that he understands? And I think more of how is it going to affect him then us, now? How in the future is it going to affect him?" Straight answers Father of carrier infant: "The lady who dealt with us, she didn't beat around the bush. If you ask her an open question, she would give us a straight answer to the best of her ability, and I appreciate that very much." Use simple language Mother of carrier infant: "We like to know that he does or he does not have this, instead of using all these big, giant words that make your head swim. It is confusing because one (test) could be a good thing that he's negative, another one could be a bad thing that he's negative." Information from a specialist Father of carrier infant: "It's a comparison between somebody who's a specialist in that area (genetic counselor), to somebody who, you	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection including process of recruitment was clearly reported. The relationship between the researchers and the respondents not clearly reported. Data collection: Data collection relied on the semi structured interviews. Structure of interview and topic guide not reported. Description of how "themes" were arrived at was discussed. Data saturation and full exploration of theme reported. Data analysis: The analytical process was described with description of themes and categories. No

Study details	Participants	Methods	Findings	Comments
Study type Qualitative study Aim of the study 1) understand parents' perceptions about genetic counselling received while awaiting their infant's sweat test results; 2) identify conditions that may affect the quality of their experience; 3) develop a model for genetic counselling under the conditions of new born screening (NBS) using CF as a prototype for NBS programs using gene technologies Country/ies where the study was carried out USA			know, is the initial person that you visit (primary care provider) and they don't have the expertise in that particular area ... the genetic counselor was more qualified, more prepared, and more comfortable." Wanted detailed explanation about CF before Sweat Test Results Father of carrier infant: "I want all the information. That way I know what I'm waiting to hear about. So it's not this black box that I don't know anything about and when I find out.. I think it was good that we had the information ahead of time. And, in fact, we were even seeking it out." Probability of CF diagnosis Mother of carrier infant: "She told us, based on the information she could see, there was a pretty low percentage, it was a very low percentage that, you know, this test was going to come back high (abnormal). And we felt pretty good after that, that, you know, we were going to be able to know for sure, and, and that it was going to be a good result, and we can put it behind us." Genetics of CF Mother of carrier infant: "She had the tools ...She started drawing out to show us 'if one of you is a carrier and one isn't,' ...she explained our chances of our child having the disease ...She had the statistics to back up what she was telling us. She could show us mathematically."	critical review of the researchers' role in the process. Findings/results: Results were presented clearly with appropriate use of quotes to support the findings (e.g., citation/data and the researchers' own input distinguished. Researchers' role and potential influences in the analytical process not critically reviewed. Overall quality: Moderate Other information The study did not described the ethical process of research or the ethical approval. Study conducted by multiple researchers but the level of consistency between the researchers not reported.

Study details	Participants	Methods	Findings	Comments
Study dates 2002-2004 Source of funding National Institute on Diabetes,Digestive,and Kidney Diseases and by the National Institute for Human Genome Research (R01 DK34108–16) and National Institute of Child Health and Human Development (K23HD42098-01)				
Full citation Tluczek, A., Orland, K. M., Nick, S. W., Brown, R. L., Newborn screening: an appeal for improved parent education, Journal of Perinatal & Neonatal	Sample size Unclear. N=193 parents of 100 infants diagnosed with CF (N=16), who were heterozygous Cystic fibrosis-Carrier (n=34), diagnosed with congenital hypothyroidism (N=23), or had normal screening results (N=27). Characteristics	Setting Interviews were conducted in parents' homes when infants were between 6-12 weeks of age. Sample selection Parents were recruited from 4 medical centres (paediatric primary care or specialty care clinics) in Wisconsin, USA. Convenience sampling was used to	Themes/categories Parental knowledge of new born screening: Fathers were more likely than mothers to be uninformed about new born screening, and obtained information from their wives, or by their infants' abnormal results: “We didn't know anything about the testing at all and then they called us a week after he was born saying that we need you to bring him in.”(mother, CF group) Misinformation: Parents reported that they had very little knowledge of NBS, and the lack of information increased emotional reactions to abnormal	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was unclear and it was mixed population with other chronic diseases. The role played by the researcher in sample selection was not clearly reported.

Study details	Participants	Methods	Findings	Comments
Nursing, 23, 326-34, 2009 Ref Id 366985 Study type Qualitative study with semi-structured interviews. Aim of the study To learn how parents were informed about new born screening and to obtain their suggestions for improving the process of educating parents about new born screening. Country/ies where the study was carried out USA Study dates Not reported. Source of funding National Institute on Diabetes, Digestive and	The sample was primarily of white European Americans (94.4%), and married couples (80%). Parents' age ranged from 18-59 years. Infant genders were equally divided. Inclusion criteria Families qualified for inclusion if their infants were less than 6 months and had an abnormal NBS in the State of Wisconsin and subsequent testing showed the infant to have (a) cystic fibrosis (CF group), (b) congenital hypothyroidism (CH group), (c) one CF mutation, considered to be a CF carrier (CF-C group), or (d) a normal NBS and healthy (H group). Exclusion criteria Infants with serious comorbid diagnoses or who were more than 8 weeks premature were excluded.	recruit parents on the basis of their infants' NBS results and subsequent diagnostic testing. Data collection Data was obtained through semi-structured interviews as a part of a larger research project conducted by the principle investigator (PI) or specially trained assistants. Interviews lasted for 20-30 minutes. All interviews were audiotaped and randomly checked by the PI. Data analysis Data was analysed by coding of the transcripts. Data was analysed for themes, labelled with descriptive codes, categorised by similarities in themes. Thematic codes were compared for differences or similarities based on participant's group membership. Codes and categories were reexamined and	results. They also expressed confusion about testing procedures: "They did not inform me in the hospital that 'we're doing the NBS'… . I had to ascertain when it was actually done because I was concerned, having some difficulty understanding the results. Which then begs the question 'why didn't I know when the NBS was done?' I think at the very least I should have been informed." (mother, CF group) Improving the educational process: Parents of infants who had abnormal results expressed the need for emphasis of the significance of NBS from health care providers to all new parents: "Make sure that they know how important it is. I mean it might not be important to the people who come out with perfectly healthy babies, but for people like us what a difference it made." (mother, CF group) Timing of parental education: Parents expressed that they would like NBS information at the hospital, at the time of the heel prick, or during pregnancy, in advance of parenthood, in the form of a pamphlet. However, one parent expressed that this information was not appropriate during labour or at the time of delivery: "In the pregnancy, explain 'when your child is born we're taking some of the blood and sending it here. Here's a pamphlet about what they're screening for." (father, CF group) Verbal and written communication: Parents expressed that there was a need of improved verbal and written information about NBS, what the test would involve and why the test was being done.	Data collection: Data collection relied on the semi-structured interviews. Description of data collection method was reported. Data analysis: The analytical process was reported in detail. Description of emerging themes was reported, but saturation of data was not reported. Direct and summative content analysis performed. Codes and categories were re-examined to ensure validity of the findings. Findings/results: Results were presented clearly. Findings were adequately supported with quotes and discussed in detail. (e.g., citation/data and the researchers' own input distinguished) Overall quality: Moderate Other information The population included parents of infants with: (1) a CF diagnosis, (2) one CF mutation and therefore CF carriers (CF-C), (3) congenital hypothyroidism (CH), and (4) normal screening results (H).

Study details	Participants	Methods	Findings	Comments
Kidney Diseases National Institute of Child Health and Human Development		refined to assure the descriptive, interpretive, theoretical, and evaluative validity. Finally, the frequencies were tabulated for each descriptive code and category across study groups. The PI cross-checked 20% of the coded data to assure at least 95% consistency among coders and checked all tabulations for 100% accuracy.		
Full citation Whyte, D. A., Baggaley, S., Rutter, C., Chronic illness in childhood: A comparative study of family support across four diagnostic groups, Physiotherapy, 81, 515-520, 1995 Ref Id 406577 Study type	Sample size N=4 families with a child with CF Characteristics Not reported Inclusion criteria Age of child: 4 years in 1993 Gender: male and female mix Parents: one single-parent family in the group if possible Severity of CF: At least one year after diagnosis; the illness not in a terminal stage Exclusion criteria	Setting Not reported (hospital setting?) Sample selection Convenient sample of four families were identified from hospital outpatients clinics living within 20 mile radius of hospital Data collection Data was collected through two interviews, one with the mother (only notes taken) and the second interview was conducted with both	Themes/categories Diagnosis of CF: Mothers reported variation of diagnosis of CF of their children and the stress of when they found out their diagnosis: "My husband and I were completely traumatised at first and only kept going on adrenalin for the first year. Now I grieve for the baby I wanted and didn't get. However, we still love Jane" (mother of infant diagnosed at birth) "we were told that she might die when she was in her teens-I shall always remember the doctor saying that, and the effect it had on us" (mother of an infant diagnosed at 15 months age, who had symptoms of loose stools) Informal support:	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported. The relationship between the researcher and the respondents not clearly reported Data collection: Data collection relied on the semi-structured interviews. Description of data collection method was very limited. No information on use of topic guide or the process to cover all the themes reported.

Study details	Participants	Methods	Findings	Comments
Qualitative study with semi-structured interviews Aim of the study To increase understanding of the needs of families caring for children with chronic illness To investigate the continuity, effectiveness and acceptability of care from the parents' perspective To identify commonalities and differences in the response of families to chronic childhood illness across four diagnostic and prognostic categories To inform the design of a questionnaire suitable for a large-scale survey of a	Not reported	parents (tape-recorded). A free flow of conversation was established around the areas of research interest although a schedule suggesting questions that should be addressed was included. Data analysis Interview transcripts were analysed and 28 major categories were identified. Hardcopies were made and analysed in detail alongside the interview transcripts.	A mother of twins with CF found that the help she received from the community support scheme was not helpful: "The help I got was not the same as help from the family. if only my mum had been around...we do miss a granny figure" Support groups: Some parents found that joining support groups was helpful, and parents considered volunteering to work with families who were newly-diagnosed with CF: "I would like to work with newly-diagnosed families. I needed much more help with the emotional side of things during the whole of the first year" (mother of a child with CF) Professional support (support at home, at school, and continued support and reassurance): Families considered the hospital as a primary source of professional support, for problems with their child adhering to physiotherapy: "the new physiotherapist came out to get the message over. 'If you won't let mum do it, someone else has to come'" (mother of a child with CF) Mothers reported that learning about physiotherapy in hospital was helpful: "we do it three times a day mostly-on different parts. We do front and back in the mornings, sides at lunch time and tops in the evening. We learnt that in hospital, it was helpful" (parent of a child with CF) Mothers reported that the visit of the physiotherapist to the school was helpful: "the physiotherapist went to the school and told them all about CF, and that helped the	Data analysis: The analytical process was not reported in detail. Description of methodology of emerging and overarching themes was not clearly reported, and saturation of data was not reported. Findings/results: Results were presented clearly (e.g., citation/data and the researchers' own input distinguished. Limited discussion of the results/findings. Overall quality: Low Other information Cystic fibrosis was one of the four groups of chronic diseases included in the study.

Study details	Participants	Methods	Findings	Comments
families caring for children with chronic illness Country/ies where the study was carried out United Kingdom Study dates January 1993-March 1994 Source of funding University of Edinburgh Development Trust			teachers to understand Rachel's problems" (mother of a child with CF, at school) Mothers reported that continued support from the physiotherapist was helpful in crisis situations: "I wasn't coping and I went to the hospital before my appointment was due and I just broke down in tears. The physiotherapist was very good, and said it wasn't a unique situation, and that I was coping well. I was happy that I had spoken to someone about it-it helped" (mother of a child with CF) Communication: Parents reported that there was a breakdown of communication between hospital and the community team that occurred on several occasions regarding changes in prescription: "communication between the hospital and the GP seems to have gone out of the window-John had his drugs changed and on-one told us, so the prescription was left lying" (parents of twins with CF)	
Full citation Widerman, E., Communicating a diagnosis of cystic fibrosis to an adult: what physicians need to know, Behavioral Medicine, 28, 45-52, 2002 Ref Id 367005	Sample size N=36 men and women diagnosed with CF. Male (N=15) and female (N=21) Characteristics Mean age of participants was 39.7 years (SD 10.6, range 20-69 years) Mean age of diagnosis was 26.5 years for men (SD 6.7) and 29.2	Setting Interviews were conducted face-to-face for participants (N=16) living within a 300-mile radius of the author's university, and by telephone (N=20) for other participants. Sample selection Participants were recruited by the author placing notices in CF	Themes/categories Information at diagnosis Diagnosis and communication For individuals suspected of CF, their physicians told them not to be concerned as they would probably test negative: "[My doctor] decided to have me tested for CF...He said, 'Don't worry, you're too old'. It can't be, blah, blah, blah, blah. And it came back positive. So they did it again. And it was positive again" (46 year old woman) Communication of diagnosis by physician	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported. The relationship between the researcher and the respondents clearly reported Data collection: Data collection relied on the semi-structured interviews. Data collection

Study details	Participants	Methods	Findings	Comments
Study type Qualitative study using semi-structured interviews Aim of the study To determine the extent to which the needs and issues of the CF adult are addressed by existing bad news and paediatric CF recommendations, and to develop and present recommendations to supplement them Country/ies where the study was carried out USA Study dates Not reported Source of funding Cystic Fibrosis Foundation	years (SD 8.5) for women Mean age of diagnosis was 9.9 years, SD 8.87, range 4 to 29 years) 50% of participants were married, or had a partner 75% participants attended or graduated from college 36% participants were employed full time Inclusion criteria Men and women in the US who had received a diagnosis of CF at 20 years age or older. Exclusion criteria Not reported.	patient publications, posting notices on a CF consumer list serve, and distributing flyers at selected CF centres in order to ensure diversity in gender and time since diagnosis (>3 or <3 years). Participants were continued to be recruited until no new perspectives emerged during data collection. Data collection Semi structured interviews, either face-to-face (n=16) or by telephone (n=20). Participants were asked to describe and reflect on their experiences when they received their diagnoses. Issues, experiences, and emerging themes were identified. Case notes were made from each interview. Data analysis Data were analysed by considering each individual's story and related case notes, highlighted words, experiences and	Physicians were tentative in communicating a positive result to the patient, as a result, participants reported that their initial diagnosis interview left them confused and questioning whether they actually had CF: "OK you tested positive for CF, but we wanted to make sure you really have the illness. So, therefore we are going to forward you another clinic for confirmation" (Participant's comment) Searching for information At first mention of CF, participants searched for information: "I immediately went to the library the next day and looked up CF. And, everything said you were going to die by the time you were 16. And here I was 40". Content of information at diagnosis: Physicians provided information about CF in even, unemotional, but not uncaring, tones: "[The doctor] was able to convey [the diagnosis] in such a manner as to keep me from getting overly excited about it". (Male participant diagnosed with CF previously) Participants reported that they were given educational materials during the diagnosis interview but they were directed to parents of young children and did not address issues associated with adult diagnosis: "I want to know about adult stuff. I want to know what to look for in symptoms, hints to better activities now, not to think I am going to die soon so often". (male participant) Directional or action-orientated content: Physicians provided information and answered questions, but the overall impression they communicated was one of doing something in	method was appropriately described Data analysis: The analytical process was reported but was unclear on use of analytical software. Authors' interpretation was checked independently. Unclear if saturation of themes was achieved Findings/results: Results were presented clearly (e.g., citation/data and the researchers' own input distinguished) Overall quality: Moderate Other information

Study details	Participants	Methods	Findings	Comments
and Solvay Pharmaceuticals		interpretations that were essential to the diagnosis experience. Data was reduced to identify essential characteristics and establish themes and categories. Interpretations were verified further for consistency.	response to the diagnosis, of taking control (authors comment) Life expectancy: Participants wanted to know how long they could expect to live and whether being diagnosed as an adult was associated with longer life expectancy (authors comment) Impact of CF: Participants wanted to know how CF would change their lives (whether they could or should have children), and what to expect in the future (authors comments) Questions about CF: Participants wanted to know what treatments would be effective, and signs to look out for as indicators of their health status, and if their symptoms could be controlled: "I wanted to know everything" (participants comment) Some participants questioned why they were diagnosed with a paediatric condition, why they had not experienced symptoms, and how many others are diagnosed as adults (authors comment) Participants were confused about what questions to ask at the time of diagnosis: "Because how can you ask questions about something you know nothing about? First you assimilate the disease, then you question it" (female participant) "I was confused. I didn't know what to ask" (male participant) What to do after diagnosis: Almost all participants asked about what they should do next:	

Study details	Participants	Methods	Findings	Comments
			"What do I do now?" or "how do I care for myself?" Coping with CF: Participants wanted to know how to have a "normal life" , and how to cope with CF emotionally, in addition to keeping their lifestyle patterns (e.g., job, exercise, travel) (authors comment) Support at diagnosis Participants preferred CF physicians as their primary source of treatment, information and support (authors comment) Most participants reported that they were satisfied with how the diagnosis was communicated to them either face-to-face or by telephone. Participants reported that they appreciated physicians who were optimistic, supportive, "straightforward", compassionate, and took their time in giving the news (authors comment) Participants reported that they reacted in a positive manner when their questions were answered, and given information about CF, as well as positive messages to promote hope (authors comment) Participants appreciated privacy, having other professionals available and a "warm" atmosphere (authors comment) Some participants expressed that their emotional needs were not met, and did not receive sufficient information, and were treated impersonally, and that they would have liked more privacy (authors comment) Recommendations made by participants: Participants expressed that physicians should consider the effect that a diagnosis of CF will have on patients and should appreciate that	

Study details	Participants	Methods	Findings	Comments
			learning of CF turns lives "upside down". They also felt that physicians must communicate with the patient in a way that acknowledges differences of experiences and learning of CF on an individual basis. Physicians should keep up to date about late CF diagnosis and have age specific educational materials at diagnosis (authors comment)	
Full citation Widerman, E., Knowledge, interests and educational needs of adults diagnosed with cystic fibrosis after age 18, Journal of Cystic Fibrosis, 2, 97-104, 2003 Ref Id 367006 Study type Quantitative and qualitative study Aim of the study To address evidence gap about the actual and self-perceived knowledge of	Sample size N=130 adults diagnosed with CF after age 18 Characteristics Male and female adults diagnosed with CF after age 18 Inclusion criteria Not reported Exclusion criteria Not reported	Setting Participant's home. Sample selection Notices posted on CF-related web pages, in CF newsletters, and through notices sent to CF centers with adult programs. To volunteer, individuals had to respond to an email address contained in the notices. 175 questionnaires were mailed to eligible male and female. The response rate was 74.3% (130) and represented: the continental US (92); the UK (5); Scandinavia (23); continental Europe (4); and other nations (6). Data collection	Themes/categories Evaluation of information provided at diagnosis Materials: Participants said most information materials were non specific and was not helpful with their particular concern. A women wrote "I got a booklet from the CF Foundation listing the median age of survival as 21. I was diagnosed at 24!" A man lamented, "None (of the materials) addressed social, economic, psychological, or political issues and obstacles." Some participants wanted information explaining their generally good health statuses and/or their atypical symptoms. A 39-year-old woman related, "My problems are associated with my sinuses and nasal cavity.... Much information did not know how to correctly treat this aspect of the disease." Another participant recalled, "We were given two books, but only one little paragraph really applied to me." Caregivers: Participants said that care givers should offer more information and show empathy. A 31 year-old woman wrote:"'Doctors need to have more information available. I had 15 min	Limitations Aim(s): Clearly reported Aim of the study clearly reported. Research method was not the most appropriate for answering the research question. Qualitative semi structured interview would have been better. Sample selection: Sample selection was unclear. The need for international sample solicited through email was not justified. Data collection: Data collection relied on the postal questionnaire with open ended question. Survey instrument described. There was no theme or topic guide or report of data saturation. Data analysis: The analytical process was poorly described and involved grouping information based on frequency.

Study details	Participants	Methods	Findings	Comments
people diagnosed with CF as adults in order to inform the development of educational materials for this sub-population and to guide caregivers in educating them. Country/ies where the study was carried out International Study dates Not reported. Source of funding Solvay pharm aceuticals, Belgium.		Data collected through pre-designed postal questionnaire and had both fixed response and open questionnaire for quantitative and qualitative information. Data analysis Grouping and counting responses to open-ended questions and assigning importance to them according to frequency of mention. Not all participants responded to all questions, but in most cases fewer than four cases were missing. Missing data were not included in analyses.	counsel with my diagnosis and that was it. I would call with a question. They would answer, but otherwise I have been on my own for information. It's scary to have a bomb dropped on you and then it's like here, deal with it." Another young woman recalled, "My physicians gave me no information. I actually supplied them with articles and I have continued my self-education once I realized that physicians often do not keep up on the literature." A 51-year-old man diagnosed 2 years previously said, "The concern for my emotional health by the medical professionals was almost non-existent." A 37-year-old male simply wrote, 'It seems like care is lacking.'	No further analysis of the qualitative information. Findings/results: Results were presented clearly but qualitative data was under-reported compared to quantitative data. Output were classified into sub-themes and categories. Researchers' role and potential influences in the analytical process not critically reviewed. Overall quality: Poor Other information Ethical approval not reported. Was sponsored by pharmaceutical company.
Full citation Widerman, E., The experience of receiving a diagnosis of cystic fibrosis after age 20: Implications for social work, Social Work in	Sample size N=36 participants with cystic fibrosis (male=15 & female=21 Characteristics Participant's age ranged from 20-69 years with a mean age of 28 years. Time since diagnosis ranged from 4 months to	Setting No reported Sample selection Participants recruited through newsletters or flyers. Purposive sampling was done according to time since diagnosis to ensure the exploration	Themes/categories Craving for information Timing of information Participants showed their frustration, as they wer not given information at time of diagnosis (authors' comment) Format	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was reported. The relationship between the

Study details	Participants	Methods	Findings	Comments
Health Care, 39, 415-433, 2004 Ref Id 474153 Study type Semi-structured qualitative study Aim of the study This study explores 1) the experience of receiving diagnosis of cystic fibrosis after age 20 & 2) adult's self-expressed educational and support needs, interests and preferences following a diagnosis of cystic fibrosis Country/ies where the study was carried out USA Study dates Not reported	29 years. Approximately 50% of them were married and in professional occupations, 75% attended or completed college, and almost approximately 33% worked full time outside of the home. Inclusion criteria Men and women living in the US who had received a diagnosis of cystic fibrosis at age 20 years or over. Exclusion criteria No reported	of cystic fibrosis experiences at different points in the illness trajectory in different individuals Data collection 20 telephone and 16 face to face interviews ranging from 45 minutes to 2 hours. A semi structured interview guide was developed for efficient collection of data. Data analysis Transcripts from interview and case notes from researcher were used for interpretation and for development of individual themes. To determine the accuracy of themes in capturing the experiences, participants were asked to comment on the developing themes. Similar themes were grouped together and data reduction done by eliminating repetitions. Themes were subdivided based on gender and self - perceived illness severity.	Participants said they were given information addressed to a paediatric audient. Few adult materials were available: "It seems there is not enough information for me to reseach on my own out there. I want to know about adult stuff" (man recently diagnosed with CF) A woman wanted directions on how to do chest percussions; she was given a booklet with illustrations of an infant (authors' comment) Content: general information, rather than illness-specific Participants were not particularly interested in biomedical descriptions of CF, or even in instructions on self-care (authors' comment). "We need more on everyday stuff" (man recently diagnosed with CF) A woman lamented her CD education involved "technical things" and "nothing about what life would be like". (woman diagnosed with CF as adult) Wanting sympathy Moderate or seriously ill participants admitted feeling self-pity and wanting sympathy, particularly from family members and caregivers (authors' comment). "Once in a while, I'd like someone to feel sorry for me" (woman diagnosed with CF as adult) Participants said they envied and resented the concern of the public for CF "poster children". But because CF is not outwardly apparent in most adults, participants felt their families, friends and coworkers understimated its impact (authors' comment).	researcher and the participants was not reported. Data collection: Data collection relied on the semi-structured interviews. Data collection method was vaguely described and needed further information on development of interview guide. Data analysis: The analytical process was reported but was unclear on use of analytical software. Authors' interpretation was checked independently which improved validity. Unclear if saturation of themes were achieved Findings/results: Results were presented clearly and discussed in detail (e.g., citation/data and the researchers' own input distinguished) Overall quality: Moderate Other information Ethical process not reported.

Study details	Participants	Methods	Findings	Comments
Source of funding Not reported				
Full citation Hodgkinson, R., Lester, H., Stresses and coping strategies of mothers living with a child with cystic fibrosis: implications for nursing professionals, Journal of Advanced Nursing, 39, 377-83, 2002 Ref Id 367043 Study type Qualitative study with semi-structured interview. Aim of the study To explore current stresses and coping strategies used	Sample size N=>100 (sampling cohort of mothers of children with CF) n=17 mothers interviewed Characteristics Maternal: Age ranged between 24-48 years Educational level: no GCSE, 4/17; GCSE/O level, 6/17; A levels/equivalent, 4/17; Degree, 3/17 Employment status: unemployed, 10/17; part-time employment, 6/17; full-time employment, 1/17 Family type: nuclear, 15/17; single parent, 2/17 SES: class I, 4/17; classII, 6/17; class IIIM, 3/17; class IV, 2/17; class V, 2/17 Children with CF: Age ranged between 2-13 years	Setting Interviews were conducted at the participant's home. Sample selection The sampling frame of this study was the cohort of over 100 mothers of children with CF attending the regional Birmingham (England) Children Hospital cystic fibrosis clinic. Data collection All semi-structured interviews were performed by RH, a third year medical student studying for an intercalating degree at Birmingham Medical School. Interviews lasted between 30 and 65 minutes. All interviews were audiotaped and fully transcribed. Interviewees were	Themes/categories Coping with CF (social support): Mothers found support from various sources including family, partner, friends, CF liason nurses and their primary health care team (authors comment) Mothers identified friends as an important source of support because they could talk about other things than CF: "If I visit my friend who lives round the corner, we don't sit there talking about S, you know, we can have a gossip and just things like that. CF isn't the centre of the conversation all the time, which like, it shouldn't have to be" . Relationship with health professionals (support from health care professional, nurse specialist, primary care) Most mothers considered recognition of responsibility for caring for a child with CF during consultations with nursing and medical healthcare professionals to be important and encouraging as well as achieving a mutual relationship with the healthcare professional: "He will always, without fail, give you praise…and he'll say Wonderful specimen mother. Well done, keep it up, wont you, you're doing marvellous', and it's what you need". Many mothers turned to nurse specialists for support and advice, and was critical in interpreting information and aiding understanding of treatment and compliance:	Limitations Aim(s): Clearly reported Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection was clearly reported. The relationship between the researcher and the respondents clearly reported Data collection: Data collection relied on the semi-structured interviews. Data collection method was appropriately described, including saturation of themes Data analysis: The analytical process was reported, but not in detail. Transparency of analysis was ensured by using two independent researchers who compared and extracting evidence from the transcripts. Saturation of themes was described in the data collection section. Findings/results: Results were presented clearly (e.g., citation/data and the researchers' own input distinguished

Study details	Participants	Methods	Findings	Comments
by mothers and to identify roles and strategies that nursing professionals could extend or adopt to support them and families of children with CF. Country/ies where the study was carried out United Kingdom Study dates January to May 2001. Source of funding Not reported.	Gender: female, 9/21; male, 12/21 Hospital stay in past year (number of stays): 0 stay, 7; 1 stay, 7; >2 stays, 3 Mean number of children with CF/household: range 1-3 Hospital visits in past year: range 5-21 GP visits in past year: range 0-4 Inclusion criteria Mothers of children with CF who attended the regional Birmingham Children Hospital CF clinic. Exclusion criteria Mothers of children who had been diagnosed within the previous 12 months and families known by the clinic nursing staff to be undergoing a period of crisis.	assured that any potentially identifying features would be removed from the transcripts. Themes were identified and developed from reading and re-reading transcripts. Themes were further refined and clarified using the Framework analytic approach. Interviews and analysis were conducted concurrently and continued until no new themes were emerging and data saturation was felt to be complete. Data analysis A grounded theory approach was used for data analysis. Ideas were read and compared and searched for disconfirming evidence during the analysis. All interviewees were also sent a copy of the primary analysis,	If we do have any worries or concerns [we] just contact the hospital straight away…we never bother going up to the doctors, we always just contact S, she's one of the nurses". Mothers reported that there was a need for a more involvement in their childrens treatment as their role was limited: "Well basically he [GP] just writes prescriptions for us…he hasn't played a big part in the cystic fibrosis part of it". Communication: Mothers described themselves as a conduit between the GP, practice nurse and specialist clinic as well as reporting poor communication in terms of co-ordinating drugs and change in treatments (Authors comment) Mothers reported that the primary care team's unfamiliarity with CF drugs, which contributed to distrust of primary care advice: "The GP says-'what do you normally have?' and it's sort of, well it would be nice if they could tell me what they think". Mothers felt that they could not escape discussions about CF with their health care professional, even if they had gone for unrelated problems: "I'm very aware if you need to go to the surgery that there must be this big label in my notes that says Child with CF. You could go with aningrown toe nail and it would be down to C, you know, you can never have a problem of your own, it'll be you're depressed becauseof C. I'm thinking, you know, I've lost, I'm never S, I'm never, I'm always C's mum".	Overall quality: Moderate Other information Mothers of Children with CF

Study details	Participants	Methods	Findings	Comments
		asked to comment on the themes and concepts, and these were then considered and incorporated in the subsequent phases of the analysis.		

G.3 Service delivery

G.3.1 Service configuration

Review question: Service configuration: What is the effectiveness of different models of care (for example, specialist centre, shared care [delivered by a Network CF Clinic which is part of an agreed designated network with a Specialist CF Centre], community, telehealth and/or home care for people with CF?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bosworth, D. G., Nielson, D. W., Effectiveness of home versus hospital care in the routine treatment of cystic fibrosis, Pediatric Pulmonology, 24, 42-7, 1997 Ref Id 330443 Country/ies where the study was carried out USA	Sample size N= 40 patients 19 home group 21 hospital group Subgroup: N=5 patients in the hospital+home group N= 59 courses 27 in home group 32 in hospital group Subgroup: N=12 courses in the hospital+home group 6 home group	Interventions Intervention Patients and families administered home IV antibiotics and chest physiotherapy at home. Prior to receiving home care, patients stayed in the hospital for up to 4 days. Nurses employed by a home care company visited the patients at home at least once a week.	Details Setting Inter mountain Cystic Fibrosis Centre at the University of Utah. Analysis Data was analysed using the t-test, paired sample t-test, and	Results FEV1 at 10-14 days: % change (mean (SEM)): Home (n=27) 13.7 (2.6) (p value=0.11) vs hospital (n=32) 23.3 (4.1) (p value <0.001) Subgroup hospital+home patients (Patients who received both home and hospital IV antibiotic therapy): Home (n=6) 11.2(11.0) (p value 0.12) vs hospital (n=6): 28.6 (2.7) (p value=0.007)	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: Low risk (Requirements for patients to receive home treatment included the availability of family members to deliver care, financial feasibility, and their demonstrated ability to perform care. This is likely to be representative of the home care population in the UK,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Comparative cohort study Aim of the study To compare the outcomes of home care with minimal supervision to outcomes of hospital care Study dates Study on patients attending the Intermountain CF Centre over 2 years covered by the study (dates not specified) Source of funding Not mentioned	6 hospital group Characteristics Confirmed diagnosis of CF Pulmonary exacerbation Age range: Home 7-31 vs hospital 8-29 Age (mean(SEM)): Home 18.8 (1.2) vs Hospital 17.5 (0.9), p value 0.35 Male/female (patients): Home 7/12 vs Hospital 13/8 Male/female (courses): Home 10/17 vs Hospital 20/12 FEV1 (% predicted): Home 40.6 (3.1) vs Hospital 46.0 (3.3), p value 0.24 Percent decrease in FEV1 from best measurement in the year preceding treatment: Home -18.4 (3.6) vs Hospital -21.7 (4.8) Weight (kg): Home 44.6 (2.3) vs Hospital 46.2 (2.0), p value 0.63 Inclusion criteria Care provided bythe Intermountain Cystic	Approved companies responded to any problems concerning the IV line or antibiotic preparations on a 24 hour basis. Weekly tobramycin serum concentrations were used to adjust the dose Patients were advised to continue physiotherapy at home with the same frequency as in the hospital. Comparison IV antibiotics administered at the hospital. Weekly tobramycin serum concentrations were used to adjust the dose Patients received chest physiotherapy four times a day while in the hospital.	Fisher's exact test as appropriate to each data set. Baseline characteristics were compared with a t-test. Changes in FEV1 between groups were compared with a paired t-test. Time to next exacerbations as a quantitative variable was compared between groups with a t-test. Time to next exacerbations as a categorical variable (did patients start the next course of IV antibiotics more than 12 weeks after completing the previous	Mortality: Not reported Patient and carer satisfaction Not reported LCI Not reported Time to next pulmonary exacerbation Quantitative variable (weeks between the end of the treatment course and the start of the next IV antibiotic course): Mean (SEM): home 15.1(3.3) vs hospital 23.1(3.0) (The difference did not achieve statistical significance) Categorical variable (did patients start the next course of IV antibiotics more than 12 weeks after completing the previous course: YES/NO): home (n=27) 13/14 vs hospital (n=32) 28/4, p<0.01 Subgroup hospital+home patients (YES/NO): home (n=6) 1/5 vs hospital (n=6) 6/0, p<0.01 Nutritional status Not reported Quality of life Not reported Frequency of cross-infections (pseudomonas, b.cepacia)	except perhaps for financial feasibility) Comparability: Low risk (The groups were matched by age and lung function) Outcome: Unclear for FEV1% pred and time to next exacerbation (Authors specify that patients were evaluation at the CF Clinic or the hospital before treatment but do not mention how evaluation after treatment was carried out). High risk for adherence (self-reported) Overall quality: moderate Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Fibrosis Centre at the University of Utah Sputum culture positive for Pseudomonas aeruginosa alone or in combination with S. aureus Patients able to perform spirometry Patients of comparable ages Exclusion criteria Patients with incomplete charts No one in the comparison group of similar age and similar lung function Cases in which the patients stayed in the hospital for more than 4 days and then finished their course of IV antibiotics at home		course: YES/NO) was compared between groups with a Fisher's exact test.	Not reported Staff experience Not reported Adherence to treatment Adherence (Mean (SEM)) (frequency of chest physiotherapy): home 2.4(1.2) days vs hospital 4.0(0.2) days, p<0.01	
Full citation Donati, M. A., Guenette, G., Auerbach, H., Prospective controlled study of home and hospital therapy of cystic fibrosis pulmonary disease, Journal of Pediatrics, 111, 28-33, 1987	Sample size 64 patents (82 treatments) home group: 26 patients (41 treatments) hospital group: 38 patients (41 treatments) Characteristics	Interventions Intervention Nurses made an initial visit within 24 hours of a patient's enrollment into the home IV program, and daily thereafter. During the visits, intravenous catheters were inserted when	Details Setting CF Clinic at the Children's Hospital in Boston, US. Data collection Spirometry was carried out with a 9 L	Results FEV1 (% predicted) at admission and on discharge (at 18 days): Mean +/- SEM: home (n=31) admission 43.5+/-4.0 discharge 50.2+/-4.2 (p value 0.005) vs hospital (n=32) admission 37.5+/-2.7 vs hospital 49.8+/-3.8 (p value <0.001)	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: Low risk (Eligibility criteria for home treatment included >= 1 hour drive form the hospital but this is unlikely to affect differences in

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 363900 Country/ies where the study was carried out USA Study type Controlled Prospective Clinical Trial Aim of the study To compare the efficacy and benefits of home and hospital treatment for patients with exacerbations of pulmonary disease caused by cystic fibrosis. Study dates 1984-1986: data collection 1987: publication date Source of funding Not reported	Age(yr) (Mean+-SEM): Home 23.3+-0.90 vs Hospital 23.3+-100 Inclusion criteria Confirmed diagnosis of CF ≥12 years or older Required IV antibiotic therapy for a pulmonary exacerbation Exclusion criteria Not reported	needed, clinical status was assessed, and patient/family competence and comfort with the home care regimen were evaluated. Medical backup was provided by the attending physician, and all home care cases were presented at weekly multidisciplinary rounds. Antibiotics were chosen on the basis of results of sputum cultures and sensitivities obtained prior to admission Comparison IV antibiotics administered at the hospital Antibiotics were chosen on the basis of results of sputum cultures and sensitivities obtained prior to admission	seal spirometer. All values were obtained at initiation of treatment and on discharge Data analysis The Student t tests for paired and independent samples were applied. In addition, the nonparametric Wilcoxon matched-pairs signed rank and Mann-Whitney U tests were applied. When no discrepancies were found, only those obtained from the Student t test for paired	Mortality Not reported Patient and carer satisfaction Not reported LCI Not reported Time to next exacerbation: Intervals between IV antibiotic treatments, months (Mean (SEM)): Home over 18 months before the study 5.9 (1.9) Home After 4.1(1.1), p <= 0.18; hospital over 18 months before the study 6.2 (1.3) hospital after 7.0 (1.0), p<= 0.48 Nutritional status at admission and on discharge (at 18 days): Weight (kg) Mean (SEM) (37 matched pairs): Home Admission 51.2 (1.9) Home Discharge 51.7 (1.9) vs Hospital Admission 50.4 (1.3) Hospital Discharge 52.0 (1.3) (p value comparing home vs hospital at admission NS, p value comparing home vs hospital on discharge NS) Quality of life Not reported Frequency of cross-infections (pseudomonas, b.cepacia) Not reported	outcomes between the home and hospital group) Comparablity: Low risk (Home and hospital patients were matched according to sex, age, pulmonary function tests and arterial blood gas values) Outcome: Low risk for weight: 37/41 matched pairs had results both on admission and discharge (90% follow up rate) Low risk for FEV1: 31/41 matched pairs in the home group and 32/41 matched pairs in the hospital group had data both on admission and discharge (76% and 78% follow up rate respectively) Overall quality: High Other information Patients meeting the same eligibility criteria for home treatment except distance to the hospital and who were admitted for IV therapy within 4 weeks of a home care patients served as controls. Home and hospital patients were matched according to sex, age, pulmonary function tests, and arterial blood gas values.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			samples are reported.	Staff experience Not reported Adherence to treatment Not reported	
Full citation Esmond, G., Butler, M., McCormack, A. M., Comparison of hospital and home intravenous antibiotic therapy in adults with cystic fibrosis, Journal of Clinical Nursing, 15, 52-60, 2006 Ref Id 330769 Country/ies where the study was carried out UK Study type Quasi-experimental, prospective study. Aim of the study To compare home and hospital treatment for clinical outcome and quality of life in adult cystic fibrosis patients receiving IV antibiotics for acute respiratory exacerbations. Study dates Six-month period. Dates not mentioned.	Sample size N= 28 patients (30 courses of treatments) 15 home courses if IV antibiotics 15 hospital courses of IV antibiotics 13 patients received a hospital course of antibiotics only 13 patients received a home course of antibiotics only 2 patients received both a home and hospital course of antibiotics Characteristics Mean(SD) Age: Home (n=15) 26.5 (6.3) vs Hospital (n=15) 22.5 (4.3), p value 0.61; Mean (SD) FEV1 (%predicted) on Day 0: Home (n=15) 33.8 (16.8) vs hospital (n=15) 32.3(16.9), p value 0.66; Mean (SD) BMI on Day 0: Home (n=15) 19.3 (3.0) vs hospital	Interventions Intervention IV antibiotic treatment administered at home. Patients received a combination of 2 IV antibiotics, which were chosen on the basis of the patient's latest sputum microscopy, culture and sensitivity Mean duration of treatment: 14 days (SD 1.5, range 10-18) The home group was asked to perform their own chest physiotherapy twice a day. Comparison IV antibiotic treatment administered at the hospital. Patients received a combination of 2 IV antibiotics, which were chosen on the basis of the patient's latest sputum microscopy, culture and sensitivity	Details Data collection Quasi-experimental design. The CFQoL questionnaire was used to measure quality of life. Analysis The samples were compared at time of entering the study (day 0) using the Mann-Whitney U-test. Statistical significance of change in FEV1, weight, BMI and quality of life during an antibiotic course was assessed	Results FEV1 % predicted at 15 days: Mean change (SD): Home (n=15) 2.0 (5.1) vs hospital (n=15) 5.1(5.6), p value 0.08; Post-treatment (post-Rx) Mean (SD): Home (n=15) 35.8 (19.1); hospital (n=15) 37.4 (19.7) p values (Wilcoxon signed rank test) home post-Rx vs Day 0: 0.16 hospital post-Rx vs Day 0: 0.005 Mortality Not reported Patient and carer satisfaction Not reported LCI Not reported Time to pulmonary exacerbation Not reported Nutritional status at 15 days: Mean change (SD) BMI: Home (n=15) 0.2 (0.3) vs hospital (n=15) 0.4 (0.8), p value 0.22.	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: Unclear (All CF patients over 18 years of age attending the adult cystic fibrosis centre over a six-month period who received IV antibiotics for an acute exacerbation who fulfilled the study criteria were asked to participate in the study once it had been decided if IV antibiotic therapy was going to be administered in hospital or at home. However, authors do not specify if they included in the analysis all the courses of treatment that these patients received over these six months). Comparability: High risk (The study does not control for any factor. The groups were not matched). Outcome: Unclear (Length of follow-up was adequate: one course of antibiotics. However, there was no description of how FEV1 (%

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not mentioned	(n=15) 18.9 (2.2), p value= 0.66 (In a different table BMI on Day 0 in hospital group is 19.0(2.3)) Inclusion criteria Confirmed diagnosis of cystic fibrosis Age 18 years and over Acute respiratory exacerbation Exclusion criteria Lung function < 30% predicted On active heart-lung transplant waiting list Pneumothorax Massive haemoptysis (>200 mls blood)	Mean duration of treatment: 15 days (SD 4.7, range 10-25) Chest physiotherapy performed by experienced respiratory physiotherapists twice a day. Input from a specialist CF dietician and availability of a supplements menu.	using the Wilcoxon signed rank test. The Mann-Whitney U-test was used to compare the change in home and hospital treatment groups.	Post-treatment (Post-Rx) BMI Mean (SD): Home (n=15) 19.5 (2.9); hospital (n=15) 19.4 (2.5) p values (Wilcoxon signed rank test) home post-treatment BMI post-Rx vs Day 0: 0.05 hospital post-treatments BMI post-Rx vs Day 0: 0.05 Mean (SD) quality of life at 15 days: Physical: Home (n=15): Day 0: 62.0 (14.0); Post-Rx: 72.0 (15.6), P=0.02 vs Hospital (n=15): Day 0: 55.5 (25.4); Post-Rx: 67.7 (21.0), P=0.07 Social: Home (n=15): Day 0: 74.0 (25.6); Post-Rx: 77.0 (22.2), P=0.22 vs Hospital (n=15): Day 0: 61.3 (32.7); Post-Rx: 67.7 (28.7), P=0.06 Treatment: Home (n=15): Day 0: 64.9 (31.2); Post-Rx: 71.1 (16.8), P=0.53 vs Hospital (n=15): Day 0: 62.0 (27.1); Post-Rx:70.2 (18.7) , P=0.21 Symptoms: Home (n=15): Day 0: 49.7 (21.9); Post-Rx: 68.8 (23.2), P=0.03 vs Hospital (n=15): Day 0: 47.0 (22.6); Post-Rx: 70.3 (15.2), P=0.006 Emotional: Home (n=15): Day 0: 66.0 (23.5); Post-Rx: 78.5 (17.6), P=0.01	predicted) or BMI were assessed, while QoL was self-reported with the CFQoL questionnaire). Overall quality: low Other information Patients at home All patients who chose home therapy had previously self-administered IV antibiotics at home. Intervention and comparison Patients treated at home were not asked about their adherence with physiotherapy. Patients at home are likely to have more flexibility around eating times and have more types of food available Power calculation The size of the sample was not based on a power calculation, as this was a pilot study. Analysis The article only gives the p values for a comparison of QoL scores on Day 0 vs QoL scores Post-Rx, for both home and hospital, but it does not compare with a statistical test the change in QoL scores during home treatment versus change during hospital treatment.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				vs Hospital (n=15): Day 0: 63.2 (26.1); Post-Rx: 71.5 (22.3), P=0.14 Future: Home (n=15): Day 0: 37.1 (23.5); Post-Rx: 40.9 (17.4), P=0.44 vs Hospital (n=15): Day 0: 42.3 (24.5); Post-Rx: 51.6 (21.3), P=0.04 Relationships: Home (n=15): Day 0: 45.9 (25.7); Post-Rx: 52.8 (22.0), P=0.049 vs Hospital (n=15): Day 0: 56.4 (2216*); Post-Rx: 55.9 (22.5), P=0.93 Body image: Home (n=15): Day 0: 44.0 (31.8); Post-Rx: 46.7 (27.8), P=0.19 vs Hospital (n=15): Day 0: 60.0 (23.0); Post-Rx: 61.8 (22.5), P=0.38 Career: Home (n=15): Day 0: 40.3 (29.4); Post-Rx: 50.3 (20.0), P=0.02 vs Hospital (n=15): Day 0: 51.3 (23.6); Post-Rx: 53.0 (23.4), P=0.65 *Mistake in the paper Frequency of cross-infections (pseudomonas, b.cepacia) Not reported Staff experience Not reported Adherence to treatment Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Finkelstein, S. M., Wielinski, C. L., Kujawa, S. J., Loewenson, R., Warwick, W. J., The impact of home monitoring and daily diary recording on patient status in cystic fibrosis, Pediatric Pulmonology, 12, 3-10, 1992 Ref Id 332667 Country/ies where the study was carried out US Study type Retrospective comparative study (follow-up of a RCT) Aim of the study To investigate the effectiveness of an experimental home monitoring system implemented at the University of Minnesota Cystic Fibrosis Center for assessing the progress and planning changes in the care of patients with cystic fibrosis (CF)	Sample size N= 50 patients 25 in the “intervention” group 25 in the control group Characteristics Age ranges: 6 -43 years (a. 6 -12 years = 24 patients; 13-18 years = 8 patients; older than 18 years =18 patients) Gender: N= 20 F; 30 M Inclusion criteria Patients who returned a minimum of 20% of the diary forms –with at least one of every 6 weeks over the study period Patients who were included in a previous RCT (N=271) Exclusion criteria Not reported	Interventions Intervention: One group of patients and families did daily recording of physical measurements and symptoms, and sent the diary to the data coordinating centre weekly for analysis. Self-measurement and daily recording took place in the absence of any therapeutic intervention. Comparison: No diary recording, no home monitoring	Details Setting This study was settled in the US and it consists of a follow up sturdy (4 years) of an RCT. In this trial patients were randomized by age and gender into either diary (n=173) or non-diary (n=98) groups. Data collection The medical records of the included patients were reviewed retrospectively over a period of 4 years (1983-1987). Pulmonary function and growth measures	Results FEV1 (% predicted): 1983: intervention=mean [+/-SEM]; control=mean [+/-SEM] 73.6 [6.0]; 72.3 [4.7] 1987 intervention=mean [+/-SEM]; control=mean [+/-SEM] 70.1 [5.2]; 60.8 [4.4] 1983-1987 dif. (over the 4-year period)= intervention=mean [+/-SEM]; control=mean [+/-SEM] 3.5 [2.3] p value=0.33, 95% CI= -2.3,8.1; 11.5 [3.0] p value=<0.01, 95% CI= 5.7,17.3 Intervention-control difference: p value=0.09, 95% CI= -15.5,0.03 Mortality Not reported Patient satisfaction Not reported LCI Not reported Time to next pulmonary exacerbation Not reported Nutritional status Not reported Quality of life Not reported	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: low risk of bias (clear sample size strategy, clear representativeness of the analysed cohort) Comparability: unclear risk bias (the authors did not control the analysis for none risk factors –relatively small sample size) Outcome: low risk of bias Overall quality: moderate Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Data collection date: 1983-1987 (4 years-follow-up) Publication date: 1992 Source of funding NIH grant 27355 and 37504			were obtained concurrently with clinical score component measures. The pulmonary function measures were performed in the paediatric function laboratory using standard instrumentation under computer control. Analysis Pulmonary changes were evaluated across groups over a period of 4 years. Comparability of the 2 groups at the beginning of the study was established	Frequency of cross-infections (pseudomonas, b.cepacia) Not reported Staff experience Not reported Adherence to treatment Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			via a t test. Differences for each participant of each group between the onset and endpoint of the study were calculated, and change over time were investigate by means of the t test		
Full citation Goldbeck, L., Fidika, A., Herle, M., Quittner, A. L., Psychological interventions for individuals with cystic fibrosis and their families, Cochrane Database of Systematic Reviews, 6, CD003148, 2014 Ref Id 406192 Country/ies where the study was carried out Wilkinson 2008: UK Study type	Sample size Wilkinson 2008 N randomised: 16 N completed the interventions: 7 4 on telemedicine 3 in the control arm N responses to the telemedicine satisfaction questionnaire: 5 * Of those who did not complete the study 4 patients died, 3 patients received a transplant, 1 withdrew following randomisation and 1	Interventions Wilkinson 2008 Intervention Telemedicine additional to standard care: the participants were provided with an ISDN line to their home and a videoconferencing unit was connected to their home television set. Participants were also given a micro-spirometer, pulse-oximeter and a supply of single use clinical thermometers. Contact was made, on a weekly basis, at a time agreed	Details Wilkinson 2008 Setting UK* Analysis RCT. Prospective pilot study. *Information extracted from primary study	Results Wilkinson 2008 FEV1 Not reported Mortality Not reported Patient satisfaction (% of responses) * : Q1 How did you find using the telemedicine equipment provided: "Very easy": 100% Q2: Did you find the link-up helpful in discussing health issues? Yes: 100% Q3 Did you feel a sense of security in seeing someone	Limitations Goldbeck 2014 AMSTAR score: 9/11 (Likelihood of publication bias not assessed; sources of support only reported for the systematic review, not for included studies) Wilkinson 2008 Random sequence generation (selection bias): Low risk (Participants were randomised by a physiotherapist distributing a pre-prepared sealed envelope, which was made by a third party not involved with recruitment)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Goldbeck 2014 Cochrane Systematic Review Wilkinson 2008 RCT Aim of the study Goldbeck 2014 To determine whether psychological interventions for people with cystic fibrosis provide significant psychosocial and physical benefits in addition to standard medical care. Wilkinson 2008 To investigate the feasibility of a video link to support patients on the transplantation waiting list and their families. Study dates Goldbeck 2014 Most recent search of the Cystic Fibrosis and Genetic Disorders Group's register: 19 December 2013. Most recent search of the Depression, Anxiety and Neurosis	was too unwell to continue. Characteristics Wilkinson 2008 Median age of the patients who were randomised: 27 (range 21-41) Inclusion criteria Wilkinson 2008 Patients on the transplantation list At least 16 years of age With a confirmed diagnosis of CF Willing to have an ISDN line installed in their home. Exclusion criteria Wilkinson 2008 Patients were excluded if they could not understand the implications of the study * *Information extracted from primary study	by the patient and assessor (senior physiotherapist or nurse consultant). The topics which were discussed included: non-invasive ventilation; haemoptysis; physiotherapy and amount of sputum; mobility; difficulties with any clinical procedures; appetite and weight; and any other problems as appropriate. Comparison Standard medical care		face to face from the CF team? Yes: 100% Q4 Does this type of service make you feel less isolated from the CF hospital team? Yes: 100% Q5: Did you find it intrusive with the assessor linking up with you in your home? No: 80%: No response: 20% Q6 Do you wish this service to be continued? Yes: 100%: Q7 Have you had any problems with the service? No: 60% Yes: 40% Q8: Do you think this is a good service? Yes: 100% Q9 on preference for the telephone, an extra clinic or telemedicine for clinical review: 1st choice: telephone: 20%, extra clinic: 0%, telemedicine: 80%; 2nd choice: telephone: 60%, extra clinic: 20%, telemedicine: 20%; 3rd choice: telephone: 20%, extra clinic: 80%, telemedicine: 0% LCI: Not reported Time to next pulmonary exacerbations Not reported	Allocation concealment (selection bias): Low risk (Participants and investigator could not foresee assignments because the authors reported that they used sequentially numbered sealed envelopes) Blinding (performance bias and detection bias) (all outcomes): Unclear risk (Due to the nature of the intervention the participants and teams providing the intervention could been blinded, but the authors provided no information on blinding of outcome assessment) Incomplete outcome data (attrition bias) (all outcomes): High risk (The authors reported a high number of dropouts. The number of dropoutsfor each group is unclear. Reasons for dropouts were reported: 4 patients died, 3 patients received transplant, 1 withdrew, and 1 was too unwell to continue) Selective reporting (reporting bias): High risk (Means and SDs for all outcome parameters for intervention and control group were not reported in the published article). Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Group's register: 12 November 2013. Wilkinson 2008 Data collection date: not reported (Authors only mention this was a "six-month prospective pilot study")* Source of funding Goldbeck 2014 Internal sources: Royal Liverpool Children's NHS Trust, UK. National Institutes of Health, USA. External sources: No sources of support supplied. Wilkinson 2008 Royal Brompton & Harefield Hospital Charitable Fund*				Nutritional status Not reported Quality of Life: Cystic Fibrosis Quality of Life Questionnaire (Gee 2000): Telemedicine group: a significant improvement in the subjects' perception of body image (p=0.02) Carer satisfaction: Not reported Frequency of cross-infections Not reported Staff experience Not reported Adherence to treatment Not reported *Information extracted from the primary study	Wilkinson 2008 Authors of the Cochrane review contacted the authors of the study for detailed quantitative data on outcome measures, but did not receive a response within the time of updating the review.
Full citation Riethmueller, J., Busch, A., Damm, V., Ziebach, R., Stern, M., Home and hospital antibiotic treatment prove similarly effective in cystic fibrosis,	Sample size N= 36 patients 19 patients in the hospital group 17 patients in the home care group N= 58 courses 28 hospital courses	Interventions Intervention IV antibiotic treatment at home 14-day therapy courses Ceftazidime (200 mg/kg body weight/day, 3 infusions per day) combined with	Details Setting: CF centre at the University Children's Hospital Tuebingen Data collection: Cl inical and	Results FEV1 Mean (SD) FEV1 (%)**: Home (n=29) Pre: 55(28) Post: 63 (29) vs Hospital (n=27) Pre: 66 (29) Post: 72 (30),Hospital vs Home n.s. Mortality Not reported	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: low risk (Inclusion criteria for participation in the study included good compliance and regular home physiotherapy - it seems

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Infection, 30, 387-91, 2002 Ref Id 331848 Country/ies where the study was carried out Germany Study type Prospective open study Aim of the study To compare home and and hospital IV antibiotic treatment in CF patients with chronic P. aeruginosa infection. Study dates Therapy courses were run between January 1996 and May 1997 Source of funding Financial support by Caremark Germany	30 home care courses. Characteristics Patients under the care of the CF centre at the University Children's Hospital Tuebingen Data of patients entering the study *: Mean (SD) Age: Home 16 (5) vs Hospital 15 (4), n.s., Mean (SD) FEV1 (%): Home 55 (28) vs Hospital 66 (29), n.s.; Mean (SD) weight for height (%): Home 86 (9) vs Hospital 94 (10), p <= 0.005. * Please note that authors write "clinical data of patients entering the study", however the data for FEV and weight for height is the same as the data given in the results table which refers to treatments, so it seems that the means were calculated based on treatments rather than patients. Inclusion criteria	tobramycin (10 mg/kg body weight/day, 3 infusions per day) except single cases of resistance when drugs were chosen according to resistogram Using intermateR containers 100 ml Tobramycin or colistin by inhalation High caloric nutritional intake Patients did their daily training and were supervised once per week by a physiotherapist specialized in CF. Patients were offered a visit by a specialized nurse if intravenous line or other problems occurred. Comparison IV antibiotic treatment in hospital 14-day therapy courses Ceftazidime (200 mg/kg body weight/day, 3 infusions per day) combined with tobramycin (10 mg/kg body weight/day, 3 infusions per day) except single cases of resistance when drugs	laboratory controls were done on days 1, 3 and 14. Analysis: Student's t-test and paired sample t-test were used for comparison of clinical and laboratory parameters before and after treatment. Analysis of variance was used for group comparison.	Patient and carer satisfaction Not reported LCI Not reported Nutritional status Mean (SD) Weight (kg): Home (n=29) Pre: 38(12) Post: 39.1(13) vs Hospital (n=28) Pre: 36.5 (9) Post: 37.6 (9), Hospital vs Home n.s. Mean (SD) Weight for Height (%): Home (n=29) Pre: 86(9) Post: 89(9) vs Hospital (n=28) Pre: 94 (10) Post: 98(10), Hospital vs Home n.s. Quality of life Not reported Frequency of cross-infections Mean (SD) Pseudomonas counts (log10) (cfu/ml sputum): Home (n=20) Pre: 7.1 (2.1) Post: 3.4 (2.8) vs Hospital (n=16) Pre: 6.4 (2.2) Post: 3.2 (2.9), Hospital vs Home n.s. Staff experience Not reported Adherence to treatment Not reported	reasonable that this might be required of patients eligible for home care). Comparability: high risk (The study does not control for any factor). Outcome: Low risk for weight, weight for height and FEV1 (Adequate length of follow up and small number of subjects lost to follow up - No. courses in results table: 29 in home group (97% follow up rate) vs 27 or 28 in hospital group (96% or 100% follow up rate)). High risk for Pseudomonas counts (High number lost to follow up and no description of those lost - No. courses in results table: 20 in home group vs 16 in hospital group - this means that follow up rate was 67% in home group and 57% in hospital group) Overall quality: Low Other information This study was planned as a prospective randomized cross-over study, however this could not be realized, because most of the adolescent patients refused hospital treatment. Therefore, the authors decided to open the study.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	P. aeruginosa in sputa over a time period of more than 6 months No changes in supportive therapy throughout treatment Good compliance and regular home physiotherapy. All patients had a positive antibody response towards P. aeruginosa measured by ELISA. Exclusion criteria Patients with pulmonary exacerbations Patients with lung transplantation Patients with Burkholderia cepacia infection First time antibiotic treatment Positive CRP (>10 mg/l)	were chosen according to resistogram Using conventional infusion pumps Tobramycin or colistin by inhalation High caloric nutritional intake Hospitalized patients had two daily courses of supervised physiotherapy (1 h). Diets were supervised by a dietician specialized in CF care.			
Full citation Thomas, C., Mitchell, P., O'Rourke, P., Wainwright, C., Quality-of-life in children and adolescents with cystic fibrosis	Sample size N= 162 (Specialist centre or CFC: 91; Shared care or CFOS: 71) CFQ-Teen: 34 (CFC: 24 vs CFOS: 10)	Interventions Intervention Cystic Fibrosis Centre (CFC): Children are reviewed at least 3 times a year and have full access to the MDT. (Similar to UK full	Details Setting The participants were treated by the Royal Children's Hospital CF team in a	Results FEV1 Not reported Mortality Not reported Patient and carer satisfaction Not reported	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: High risk (There was a significantly higher completion rate in the CFC

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>managed in both regional outreach and cystic fibrosis center settings in Queensland, Journal of Pediatrics, 148, 508-516, 2006
Ref Id
369582
Country/ies where the study was carried out
Australia
Study type
Cross-sectional
Aim of the study
To compare health-related quality of life (HRQOL) in children and adolescents with CF managed by CF Outreach Service (CFOS) with those treated in a CF centre (CFC).
Study dates
Data collection
The study does not mention when questionnaires were sent out.
Clinical data were collected retrospectively, from January 1, 2000 to December 31, 2002.
Source of funding</td>
<td>CFQ-Child: 83 (CFC: 46 vs CFOS: 37)
CFQ-Parent: 80 (CFC: 45 vs CFOS: 35)

Characteristics
Between 2 and 19 years of age

Inclusion criteria
Confirmed CF diagnosis
Exclusion criteria
Not mentioned</td>
<td>centre care, although in the UK routine appointments should be at least every 2-3 months)
Comparison
Cystic Fibrosis Outreach Service (CFOS): Children are managed by their local paediatrician or general practitioner and local hospital, and they also attend outreach clinics visited by CFOS. The CFOS varies, although it usually includes a paediatric respiratory physician, physiotherapist, dietician and CF nurse. Regional staff, such as paediatricians, physiotherapists, dieticians, and clinical nurses, are invited to attend the clinics. Outreach clinics occur twice per year except for one site, which has one clinic and two telehealth clinics per year.
(CFOS is similar to shared care in the UK as defined by the UK CF Trust Standards of</td>
<td>tertiary CFC or outreach setting (CFOS).
Data collection De mographic details were collected from medical records or available pathology databases. Two HRQOL surveys were administered : a generic HRQOL measure, PedsQL (TM), and a disease-specific HRQOL measure, the CFQ. Both have been previously validated and tested for reliability. The PedsQL (TM) was administered before the CFQ as per recommende</td>
<td>LCI
Not reported
Time to pulmonary exacerbation
Not reported
Nutritional status
Not reported
Quality of life
CFQ-Teen, Child and Parent: scale mean (SD) scores
<table>
<tr><th>Scales</th><th>CFC Teen</th><th>CFOS Teen</th><th>CFC Child</th><th>CFOS Child</th></tr>
<tr><td>Physical</td><td>72.6 (23.7)</td><td>90.4 (13.1)</td><td>76.0 (21.9)</td><td>77 (21)</td></tr>
<tr><td>Role</td><td>76.2 (21.4)</td><td>86.6 (21.9)</td><td>N/A</td><td>N/</td></tr>
<tr><td>Vitality</td><td>56.0 (25.9)</td><td>74.2 (15.9)</td><td>N/A</td><td>N/</td></tr>
<tr><td>Emotional</td><td>77.2 (18.4)</td><td>82.7 (17.0)</td><td>76.1 (14.8)</td><td>74 (14 9)</td></tr>
<tr><td>Social</td><td>76.4 (19.1)</td><td>94.0 (8.0)</td><td>70.2 (15.9)</td><td>71 (19 4)</td></tr>
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</td>
<td>population (88.4%, 91 of 103) compared with the CFOS population (62.28%, 71 of 114), p<.001. More females than males responded, p= .01. Of the 46 teens, participation was significantly higher for the CFC (24 of 27, 89.0%) compared with those from the CFOS (10 of 19, 53.0%), p=.006)
Comparability: High risk (The study does not mention controlling for any factor)
Outcome: High risk (Not all the p values are given for the statistical tests)
Overall quality: low
Other information</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Not mentioned</td>
<td></td>
<td>Care 2011. However, there are differences:
a UK Network CF Clinic should have an MDT separate to the specialist centre and a consultant with specialist interest and experience in CF;
MDTs in CFOS include less disciplines than the MDTs in UK CF Specialist CF centres.)</td>
<td>d administration guidelines. Questionnaires were self-administered for parents and for children aged 12 or over for the CFQ. Questionnaires were administered by interview for children aged 6-11 for CFQ. Interview surveys conducted in the waiting room were completed independently from parents. For the mailed surveys, instructions were included on how to complete the surveys.
Analysis One-way analysis of</td>
<td>
<table>
<tr><td>Body</td><td>72.2 (23.2)</td><td>76.7 (23.1)</td><td>78.3 (24.6)</td><td>81 (25 4)</td></tr>
<tr><td>Eating</td><td>80.6 (23.5)</td><td>94.4 (12.0)</td><td>76.1 (26.2)</td><td>76 (2(6)</td></tr>
<tr><td>TB</td><td>56.0 (21.1)</td><td>65.6 (26.4)</td><td>68.4 (25.2)</td><td>63 (2: 8)</td></tr>
<tr><td>Health</td><td>57.4 (21.4)</td><td>72.2 (23.6)</td><td>N/A</td><td>N/</td></tr>
<tr><td>Weight</td><td>59.7 (34.0)</td><td>66.7 (31.4)</td><td>N/A</td><td>N/</td></tr>
<tr><td>Respiratory</td><td>68.3 (18.3)</td><td>72.8 (12.7)</td><td>70.8 (20.5)</td><td>66 (2: 4)</td></tr>
<tr><td>Digestion</td><td>84.3 (16.4)</td><td>92.2 (10.5)</td><td>76.1 (26.9)</td><td>72 (2(9)</td></tr>
<tr><td>School function</td><td>N/A</td><td>N/A</td><td>N/A</td><td>N/</td></tr>
</table>
"In the CFQ surveys, teens from the CFOS group had a higher HRQOL score for all domains, but this difference was only significant for Social and Vitality scales (p<.05). CFOS children had better HRQOL scores for Physical, Social and Body
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<td></td>
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</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			variance was used to assess differences between CFC and CFOS groups for CFQ HRQOL scores.	Image but worse HRQOL scores for Emotional, Treatment Burden, Respiratory, and Digestion compared with CFC children, although these differences were not significant. There was no significant difference between any of the scale scores for the CFQ-Parent (proxy). Frequency of cross-infections (pseudomonas, b.cepacia) Not reported Staff experience Not reported Adherence to treatment Not reported	
Full citation Thomas, C. L., O'Rourke, P. K., Wainwright, C. E., Clinical outcomes of Queensland children with cystic fibrosis: a comparison between tertiary centre and outreach services, Medical Journal of Australia, 188, 135-9, 2008 Ref Id 333320	Sample size N= 273 (patients included in the study) Specialist centre: 131 Shared care review 3+ a year: 35 Shared care review 2+ a year: 72 Usual care: 35 6 patients died during the 3-year period (2 from LOC1, 3 from LOC 2, 1 from LOC 4). Analysis of changes in FEV1 was carried out on 150 patients	Interventions Intervention Specialist centre (Called Level of Care 1 (LOC1) in the study) All care is provided by the CFC Admission to the CFC when required Outpatient review at CFC three or more times per year Comparison 1 Shared care review 3+ a year (Called Level of	Details Setting Sites covered by the CF clinic at the Royal Children's Hospital, Brisbane Analysis Pulmonary function rate of change from 1 January 2000 to 31 December 2002 was	Results FEV1 (% predicted) Mean (95% CI) first to last FEV1 % predicted per year: Specialist centre -1.4 (-2.9 to 0.1) vs Shared care review 3+ a year 0.5 (-4.0 to 5.0) vs Shared care review 2+ a year 1.0 (-2.1 to 4.1) vs Usual care 4.3 (-1.5 to 10.1), p 0.09 Mean (95% CI) slope FEV1% per year: Specialist centre -1.5 (-2.9 to -0.1) vs Shared care review 3+ a year -1.4 (-5.0 to 2.2) vs	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: High risk (Children under different levels of care live in different geographical areas). Comparability: Unclear (Authors give the following information: “Potential confounding was checked using general linear models and adjustment was made where necessary for comparisons between LOC

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Australia Study type Retrospective study. Aim of the study To evaluate and compare the clinical outcomes of children with cystic fibrosis managed primarily at a tertiary cystic fibrosis centre (CFC) with those treated at regional centres by local health care professionals and the cystic fibrosis outreach service (CFOS). Study dates Clinical data between 1 January 2000 and 31 December 2002 Source of funding Not mentioned	Specialist centre: 74 Shared care review 3+ a year: 21 Shared care review 2+ a year: 37 Usual care: 18 Characteristics Characteristics of 273 children included in the study (authors give the following characteristics without specifying what year they refer to): Median age: 9 years (range 0-20, IQR: 5-13) Boys and girls 0-4 years: 64. Specialist centre: 28 vs Shared care review 3+ a year: 9 vs Shared care review 2+ a year: 21 vs Usual care: 6 Boys and girls 5-9 years: 76. Specialist centre: 38 vs Shared care review 3+ a year: 8 vs Shared care review 2+ a year: 23 vs Usual care: 7 Males >= 10 years: 71. Specialist centre: 35 vs Shared care review 3+ a year: 8 vs Shared	Care 2 (LOC2) in the study) Children living in regional centres and attending CFOS who also attend CFC regularly Admission to CFC or local hospital with local hospital care provided by local paediatrician Outpatient review by CFC or CFOS three or more times per year Comparison 2 Shared care review 2+ a year (Called Level of Care 3 (LOC3) in the study) Care is predominantly provided by the local paediatrician with consultation with CFC Admission to local hospital with care provided by local paediatrician Outpatient review by CFOS at least twice a year Comparison 3 Usual care (Called Level of Care 4 (LOC4) in the study)	calculated by simple linear regression using two methods: using all FEV1 % predicted measurements available for each child against time (slope FEV1 %) and using only the first and last FEV1 % predicted measurements available for each child against time (first to last FEV1 %). Associations between categorical variables were tested using the chi-squared test of association. Differences in patients' characteristics were assessed by	Shared care review 2+ a year 0.7 (-2.3 to 3.6) vs Usual care 1.8 (-1.0 to 4.7) Mortality Not reported Patient and carer satisfaction Not reported LCI Not reported Time to next pulmonary exacerbation Not reported Nutritional status Not reported Quality of life Not reported Frequency of cross-infections Not reported Staff experience Not reported Adherence to treatment Not reported	categories" without specifying what they adjusted for and when.) Outcome: High risk (Data on FEV1 were only available for 150 children (55% of the 273 children included in the study) and there was no description of those lost). Overall quality: low Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	care review 2+ a year: 15 vs Usual care: 13 Females >= 10 years: 62. Specialist centre: 30 vs Shared care review 3+ a year: 10 vs Shared care review 2+ a year: 13 vs Usual care: 9 p value for sex and age group: 0.59 Characteristics of 150 patients included in the analysis on the change from first to last FEV1: Mean (95% CI) maximum FEV1 % predicted measurement over two years: Specialist centre: 86.9 (82.1 to 91.7) vs Shared care review 3+ a year: 84.9 (75.0 to 94.8) vs Shared care review 2+ a year: 86.0 (80.7 to 91.2) vs Usual care: 84.2 (75.9 to 92.4), p 0.94 Inclusion criteria Children with confirmed diagnosis of CF born between 19 October 1982 and 19 February 2002	Involvement by CFC or CFOS once a year or no CFC/CFOS involvement Includes children seen by respiratory physicians but with no CFC or CFOS multidisciplinary health care involvement Alternatively, care provided by local paediatrician or general practitioner or unknown	one-way analysis of variance for pulmonary function and anthropometric measurements. Potential confounding was checked using general linear models and adjustment was made where necessary for comparisons between LOC categories.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Children with clinical data available between 1 January 2000 and 31 December 2002. Exclusion criteria Not mentioned				
Full citation Van Koolwijk, L. M. E., Uiterwaal, C. S. P. M., Van der Laag, J., Hoekstra, J. H., Gulmans, V. A. M., Van der Ent, C. K., Treatment of children with cystic fibrosis: Central, local or both?, Acta Paediatrica, International Journal of Paediatrics, 91, 972-977, 2002 Ref Id 406560 Country/ies where the study was carried out The Netherlands Study type Longitudinal, prospective Aim of the study To study the effects of the different levels of involvement of centralized care on	Sample size N= 105 Central care group: n=41 Shared care group: n=41 Local care group: n=23 Characteristics Males (%): central care 43.9 vs shared care 53.7 vs local care 52.2, n.s. Age (Mean (SEM): central 10.8 (0.5) vs shared 10.7 (0.5) vs local 9.4 (0.5), n.s. Age range: 5-17 Height (cm) (Mean (SEM): central 141.5 (2.7) vs shared 140.5 (3.0) vs local 134.9 (3.2), n.s. Weight (kg) (Mean (SEM): central 33.6 (1.8) vs shared 33.1 (1.9) vs local 29.9 (1.7), n.s. BMI, kg/m2 (Mean (SEM): central 16.2	Interventions Intervention Specialist centre (Called centralized care in the study) Patients receive their treatment completely in the Centre Regular visits at minimum intervals of 3 months Comparison 1 Shared care (also called shared care in the study) Includes a half-yearly visit to the Centre (annual check-up and an MDT outpatient clinic visit) combined with regular visits to the local paediatrician The local paediatrician comes to the centre during the annual check-up and participates in the multidisciplinary consultation	Details Data collection: A nnual data on FEV1, height and weight were obtained from the database of the CF Centre Utrecht. Spirometry was performed according to standards established by the American Thoracic Society. Pseudomon as colonization was studied throughout the whole study period at all	Results FEV1 (%predicted) FEV1 % pred (Annual change, Mean (SEM)): Central -2.9 (0.7) vs shared -2.4 (1.1) vs local -5.6 (1.5), none of the differences between groups was statistically significant Differences at the end of follow-up (3 years) between the three groups (I don't think we need this for our review): FEV1 % pred (Unadjusted mean difference (95% CI)): Shared-Central -7.1 (-17.6; 3.3) vs Local-Central 3.1 (-9.2;15.4) vs Local-Shared 10.2 (-2.1;22.5) FEV1 % pred (Mean difference adjusted for age, gender and corresponding baseline level (95% CI)) at 3 years: Shared-central 1.5 (-3.8, 6.7) vs Local-Central 2.2 (-1.2, 5.6) vs Local-Shared 12.5 (-11.5, 36.4) Mortality	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: Low risk (Different groups were drawn from the same community: although referral to any care model is predominantly based on the distance between the patient's home and the centre, on personal habituation of the referring paediatrician, and on the severity and complexity of the disease, authors excluded patients with well known factors for progressive disease because these patients often require specialized care) Comparability: High risk (The authors did not control for any factor when comparing annual changes across groups) Outcome: Unclear (Authors do not mention how they measured FEV1 or BMI. Authors mention that only patients from whom at least 2

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
the clinical conditions of children with CF. Study dates Patients attending the Cystic Fibrosis Centre Utrecht between January 1997 and January 2001. Source of funding Not mentioned	(0.3) vs shared 16.2 (0.3) vs local 16.2 (0.3), n.s. FEV1 % pred (Mean (SEM): central 87.5 (3.6) vs shared 81.7 (4.4) vs local 98.9 (3.9), p value 0.030 P. aeruginosa colonization (%): 53.7 vs 58.5 vs 39.1, n.s. Inclusion criteria Not mentioned Exclusion criteria Colonization with Burkholderia cepacia Allergic bronchopulmonary aspergillosis (ABPA) Diabetes mellitus Inability to perform lung function tests (because of young age or mental/physical handicap) Pulmonary exacerbation at time of the tests Lung transplantation during the time of follow-up Patients that did not have at least two years of follow-up data available	Regular visits at minimum intervals of 3 months Comparison 2 Usual care (Called "Local care" in the study) Patients visit the centre only once a year at the annual check-up, but remain fully treated at their local hospitals. The local paediatrician comes to the centre during the annual check-up and participates in the multidisciplinary consultation Regular visits at minimum intervals of 3 months	outpatient visits Analysis: Mean differences in baseline characteristics of the patients were assessed by one-way ANOVA or by the chi-squared test. Data on FEV1 % predicted, BMI collected 3 year before were subtracted from the most recent data on these parameters to derive the changes during the time of analysis. By dividing these changes by follow-up time, authors calculated	Not reported Patient and carer satisfaction Not reported LCI Not reported Time to pulmonary exacerbation Not reported Nutritional status BMI kg/m2 (Annual change, Mean (SEM)): Central care 0.42 (0.08) vs shared 0.54 (0.14) vs local 0.51 (0.15), none of the differences between groups was statistically significant Differences at the end of follow-up (3 years) between the three groups (I don't think we need this for our review): BMI kg/m2 (Unadjusted mean difference (95% CI)) at 3 years: Shared-Central 0.04 (-0.93;1.02) vs Local-Central -0.14 (-1.29; 1.01) vs local minus shared -0.19 (-1.34;0.97) BMI kg/m2 (Mean difference adjusted for age, gender and corresponding baseline level (95% CI)) at 3 years: Shared-Central -0.08 (-0.71;0.54) vs Local-Central 0.08(-0.30;0.46) vs Local-Shared 0.22(-0.53;0.96)	years of follow up data were available were included in the study, but do not say how many were excluded for this reason.) Overall quality: Low Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			the annual changes. The annual changes were compared between the groups using linear regression, with annual changes as dependent variables and a group indicator as independent variable. Similar models were also used to adjust differences in levels found at the end of follow-up for differences in levels at baseline. Effect measures are presented as linear regression coefficients indicating	Quality of life Not reported Frequency of cross-infections (pseudomonas, b.cepacia) Not reported Staff experience Not reported Adherence to treatment Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			mean group differences.		
Full citation Walters, S., Britton, J., Hodson, M. E., Hospital care for adults with cystic fibrosis: an overview and comparison between special cystic fibrosis clinics and general clinics using a patient questionnaire, Thorax, 49, 300-6, 1994 Ref Id 363517 Country/ies where the study was carried out UK Study type Cross-sectional study Aim of the study To assess the current pattern of medical service received by adults with cystic fibrosis and to compare the type of care between special cystic fibrosis and general clinics Study dates	Sample size N= 886 people with CF (59% of the total number of people with cystic fibrosis over 15 years of age in the UK at the time of the study). Characteristics N= 886 people with CF members of the Association of Cystic Fibrosis Adults N= 494 [62%] (All special cystic fibrosis clinics) N= 252 [33.8%] (All general clinics) Inclusion criteria Patients attending large special cystic fibrosis clinics and general clinics at local hospitals. Exclusion criteria Not reported	Interventions Intervention: Large special cystic fibrosis clinics Comparison: Non general clinics at local hospitals	Details Setting This study was placed In the UK, and it was basedf on a survey of the Association of Cystic Fibrosis Adults (ACFA) extends to approximatel y 68% of the UK population with cystic fibrosis aged over 16 years, and to over 80% of those over 25 years of age. Data collection Questionnair es were sent to all 1052 members of the Association of Cystic	Results FEV1 Not reported LCI Not reported Time to next pulmonary exacerbation Not reported Mortality Not reported Nutritional status Not reported Quality of life Not reporte patient and carer satisfaction: General clinics vs fibrosis general clinics [95% CI of mean difference between CF clinics and general clinics]; Hospital accommodation: 3.64 VS 3.74 [-0.26 to 0.06]; N = 636 Hospital food: 2.73 VS 2.76 [-0.22 to 0.16] ; N = 631 Consultant's knowledge of CF: 4.33 VS 4.74 [-0.53 to -0.29*]; N = 690 Consultant's understanding of your problems:3.93 VS 4.31 [-0.54 to – 0.23]; N = 687	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: low risk of bias (clear representativeness of the analysed cohort) Comparability: unclear risk bias (the authors did not control the analysis for none risk factors –relatively small sample size) Outcome: low risk of bias Overall quality: moderate Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Data collection date: Not explicitly stated (1990) Publication date: 1994 Source of funding Cystic Fibrosis Research Trust			Fibrosis Adults. 746 patients (494 patients were attending a cystic fibrosis clinic and 252 a general clinic). Analysis Data were analysed using, where appropriate, x2, Mantel-Haenszel, analysis of variance, and confidence intervals for single proportions and the difference between proportions. Not all respondents answered all questions, and analysis for each question is confined only to those who made	Junior doctors' understanding of CF: 3.13 VS 3.65 [-0.68 to -0.36*]; N = 645 Nurses' understanding of CF: 3.27 VS 3.93 [-0.81 to -0.51*]; N = 662 Physiotherapy advice you receive: 3.97 VS 4.27 [-0.47 to -0.13*]; N = 642 Dietary advice you receive: 3.23 VS 3.86 [-0.83 to -0-36*]; N = 694 Social work advice you receive: 2.24 VS 2.89 [-1.00 to - 0.30*]; N = 369 Overall rating of hospital care: 3.76 VS 4.20 [-0.58 to -0.29*]; N = 686*p<0.05 frequency of cross-infections (pseudomonas, b.cepacia) Not reported staff experience Not reported adherence to treatment Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			valid responses.		
Full citation Wilkinson, O. M., Duncan-Skingle, F., Pryor, J. A., Hodson, M. E., A feasibility study of home telemedicine for patients with cystic fibrosis awaiting transplantation, Journal of Telemedicine & Telecare, 14, 182-5, 2008 Ref Id 367007 Country/ies where the study was carried out See Cochrane SR Goldbeck 2014 Study type See Cochrane SR Goldbeck 2014 Aim of the study See Cochrane SR Goldbeck 2014 Study dates See Cochrane SR Goldbeck 2014 Source of funding See Cochrane SR Goldbeck 2014	Sample size See Cochrane SR Goldbeck 2014 Characteristics See Cochrane SR Goldbeck 2014 Inclusion criteria See Cochrane SR Goldbeck 2014 Exclusion criteria See Cochrane SR Goldbeck 2014	Interventions See Cochrane SR Goldbeck 2014	Details See Cochrane SR Goldbeck 2014	Results See Cochrane SR Goldbeck 2014	Limitations See Cochrane SR Goldbeck 2014 Other information See Cochrane SR Goldbeck 2014

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Wolter, J. M., Bowler, S. D., Nolan, P. J., McCormack, J. G., Home intravenous therapy in cystic fibrosis: a prospective randomized trial examining clinical, quality of life and cost aspects, European Respiratory Journal, 10, 896-900, 1997 Ref Id 363511 Country/ies where the study was carried out See Cochrane SR Balaguer 2015 Study type See Cochrane SR Balaguer 2015 Aim of the study See Cochrane SR Balaguer 2015 Study dates See Cochrane SR Balaguer 2015 Source of funding See Cochrane SR Balaguer 2015	Sample size See Cochrane SR Balaguer 2015 Characteristics See Cochrane SR Balaguer 2015 Inclusion criteria See Cochrane SR Balaguer 2015 Exclusion criteria See Cochrane SR Balaguer 2015	Interventions See Cochrane SR Balaguer 2015	Details See Cochrane SR Balaguer 2015	Results See Cochrane SR Balaguer 2015	Limitations See Cochrane SR Balaguer 2015 Other information See Cochrane SR Balaguer 2015
Full citation Balaguer, Albert, Gonzalez de Dios, Javier, Home versus hospital intravenous	Sample size Wolter 1997 17 participants 31 admissions	Interventions Wolter 1997 Intervention	Details Wolter 1997 Participants were initially randomized	Results Wolter 1997 FEV1 (% predicted) mean (SD*):	Limitations Balaguer 2015 Amstar score: 9/11 (The authors did not mention that publication bias could not be

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
antibiotic therapy for cystic fibrosis, Cochrane Database of Systematic Reviews, 2015 Ref Id 425672 Country/ies where the study was carried out Wolter 1997: Australia* Study type Balaguer 2015 Cochrane systematic review Wolter 1997 RCT and cross-over open study Aim of the study Balaguer 2015 To determine whether home intravenous antibiotic therapy in cystic fibrosis is as effective as inpatient intravenous antibiotic therapy and if it is preferred by individuals or families or both. Wolter 1997 To determine if home IV antibiotic therapy in	13 admissions: home therapy group * 18 admissions: control group * *Information extracted from individual paper Characteristics Wolter 1997 Agre range (median): 19-41 (22)* All patients had colonization of their sputum with P. aeruginosa* *Information extracted from individual paper Inclusion criteria Wolter 1997 Consenting adolescents and adults* With an infective exacerbation of cystic fibrosis Attending two Brisbane hospitals* *Information extracted from individual paper Exclusion criteria Wolter 1997 Unstable disease* Dwelling outside Brisbane*	Home therapy: Patients spent 2 - 4 days in hospital before discharge and were taught to prepare and administer their own IV antibiotics; Participants were discharged with medication and equipment for the duration of the proposed course of treatment; Home visits were conducted. All participants received the same antibiotic therapy with ceftazidime 2 g 12 hourly and tobramycin 4 to 6 mg/kg daily as a single bolus for a minimum of 10 days. Comparison Control group: Whole treatment was administered in the hospital. All participants received the same antibiotic therapy with ceftazidime 2 g 12 hourly and tobramycin 4 to 6 mg/kg daily as a single bolus for a minimum of 10 days.	in blocks of four by sealed envelopes, to home or hospital therapy. Participants experiencing recurrent episodes automatically alternated tr eatment arms after initial randomizatio n.	Day 0: Home 39 (17) vs hospital 44 (20) * Day 10: Home 45 (22) vs hospital 50 (21) Day 21 (post-treatment): Home 43 (19) vs hospital 51 (21) p value comparing magnitudes of overall changes in the home vs hospital arm: 0.27 Mortality Not reported Patient and carer satisfaction Not reported LCI Not reported Time to next pulmonary exacerbation Not reported Nutritional status Weight (kg)* mean (SD*): Day 0: Home 53.7 (8.6) vs hospital 52.5 (7.5) Day 10: Home 54.1 (8.9) vs hospital 53.4 (7.6) Day 21 (post-treatment): Home 53.9 (8.7) vs hospital 53.2 (7.6) p value comparing magnitudes of overall changes in the home vs hospital arm: 0.10 Quality of life Not reported	assessed because there were fewer than 10 included studies; Source of support or funding was mentioned for the systematic review, but not for the included study) Wolter 1997 Random sequence generation (selection bias): Low risk (Randomized in blocks of four) Allocation concealment (selection bias): Low risk (Randomization used sealed envelopes) Blinding (performance bias and detection bias), all outcomes: High risk (Participants and clinicians could not be blinded due to the nature of the treatment. No information given on whether outcome assessors were blinded) Incomplete outcome data (attrition bias), all outcomes: Low risk (Reasons for exclusions given) Selective reporting (reporting bias): Low risk (Authors were unable to detect any selective reporting) Other information The unit of analysis is the admission. 9 participants had 1 admission, 5 had 2 admissions, 1 had 3

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
adult patients with CF is a feasible, effective and less costly alternative to hospitalization, and to assess the impact of home therapy on quality of life. * *Information extracted from individual paper Study dates Balaguer 2015 Search date: The evidence is current to 23 November 2015. Wolter 1997 Not mentioned* *Information extracted from individual paper Source of funding Balaguer 2015 Internal sources: Universitat Internacional de Catalunya. Barcelona, Spain. External sources: National Institute for Health Research, UK. This systematic review was supported by the National Institute for Health	A history of noncompliance* Inability to learn treatment techniques, including home physiotherapy* Personal request* Patients with lung transplants* Patients on their first admission* * Information extracted from individual paper			Frequency of cross-infections Not reported Staff experience Not reported Adherence to treatment Not reported * Information extracted from individual paper	admissions, 1 had 4 admissions, and 1 had 5 admissions. It is not known whether admissions were different episodes or recurrences. All episodes, initial or recurrent, were analysed together. The statistical analysis considered recurrent episodes as independent events. Data on first randomized episodes are not currently available.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group. Wolter 1997 "The authors wish to acknowledge Glaxo Australia, Brisbane Teaching Hospitals Scholarship 1993, John P. Kelly Research Foundation, D. Battistutta from Medical Biostatistics Pty. Ltd" * *Information extracted from primary study					

G.3.2 Multidisciplinary teams

Review question: What is the clinical and cost-effectiveness of multidisciplinary teams of various compositions?

No clinical evidence was identified for this review.

G.4 Transition

Review question: What parts of the transition from children's to adult services are most important for young people with cystic fibrosis and their family members and carers?

Study details	Participants	Methods	Findings	Comments
Full citation	Sample size	Setting	Themes/categories Main Theme: Preparing for transition	Limitations

Study details	Participants	Methods	Findings	Comments
Al-Yateem, N., Child to adult: transitional care for young adults with cystic fibrosis, British Journal of Nursing, 21, 850-4, 2012 Ref Id 366753 Study type Qualitative study Aim of the study To explore and understand the experience of young people before and after their transitional care, and the factors that both contribute to and hinder that experience Country/ies where the study was carried out Ireland Study dates Not reported Source of funding Not reported	15 young adults with CF Characteristics Not reported Inclusion criteria Young adults with CF who were listed for transfer in the child setting, or who had been transferred to the adult setting within the last 2 years Exclusion Criteria Not reported	Two major children and adult hospital in Ireland. Sample selection Health professionals working in hospitals identified possible candidates and contacted through postal letters. Data collection In-depth interviews were carried out in the two hospitals during the data collection process, and followed the interview guide to ensure coverage of all the transition areas. Data analysis The phenomenological descriptions of experiences given by research participants, were carried out using the thematic analytical process.	Sub-themes Preparing for transition: sharing knowledge Participants noted a lack of adequate information about the transition process, especially about the different aspects of this process. One participant noticed a lack of detail "Ah, very little, almost nothing. I mean all they do is to tell you that you are transferring." Another participant was not aware of the hospital or CF service to which he would be referred. He said: "I don't really know, it might be either X hospital or Y hospital. I don't know we have to go and see. I don't know how they will be like?" One participant said that information is sometimes provided in a distracted environment and based on the judgment of health professionals which might not be relevant to CF patients. "Everyone [health professionals] will rush in the room and start doing their stuff and start talking … you are kind of distracted ... I don't really get much … after a while I kind of didn't even listen to what they are saying…"	The methodological limitations of the study were assessed using an adapted Critical Appraisal Skills Programme (CASP 2006) Aim(s): Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: The sample selection process was not clearly reported. The relationship between the researcher and the respondents clearly reported. The participants were appropriate to address the topic. Age of participants not reported, however, the criteria for inclusion was transition in the last 2 years from child to adult services. Data collection: Data collection relied on the in-depth interviews. Description of data collection method was vaguely described. Data analysis: The analytical process was reported vaguely. Thematic analysis reported, but description of how emerging and overarching themes was constructed and unclear on whether data saturation was reached.

Study details	Participants	Methods	Findings	Comments
			Lack of sharing knowledge led to unmet information need for CF patient. "Well the thing that they don't talk with us enough about CF, how it will be ... you know, and what it will be like in the future." Participants also stated that information should be provided at timely interval. "Actually, we haven't been told about the transfer yet, nobody talked to us about it…" "Yes, I know about transition…last month the CF nurse told me that I will be going to another hospital next year when I turn 18…" Preparing for transition: easing the process Transition from children to adult healthcare setting has created anxiety in the CF patients. "I am worried about the cutbacks in health and all when we move there (the new hospital), you know that with CF there are some cuts that you don't know when it's going to knock off…"	Findings/results: Results were presented clearly and was applicable to the aim. (e.g., citation/data and the researchers' own input distinguished) Overall quality: Low Other information: Ethical process reported. Study conducted by lone researcher as a part of PhD study and may lack some of the formal research vigour.

Study details	Participants	Methods	Findings	Comments
			The difference in quality of care was also raised as a major concern of CF patients. "We used to do it (sputum test) every month in x hospital, but they just do it every 3 months in here, so you kind of stay anxious for a long time ... you don't know when the infection is going to hit … it will be late…" One participant recommended visiting the adult hospital before transition to reduce anxiety: "They are going to take us over to the other hospitals, and talk to the other staff there, that would help, you will know them and they will know you…" Main Theme: Amorphous service Sub-themes No structured transition service CF patient stated that service provided were amorphous and appeared to lack a comprehensive and coherent structure to transitional programming. "There was no real discussion … it was just the CF nurse who told us last year that it would be when I finish the leaving cert. It would not be straight away when I turned 18, so it would be after."	

Study details	Participants	Methods	Findings	Comments
			This lack of structure created anxiety and negative feeling "I don't really like to come here…like, they don't do much for me…if they just listen I would have told them what I want to know…or how they can help…this is very annoying…" Focusing on the young adult The focus of some health professionals on clinic activities, rather than focusing on the actual individual needs of the young adult, was source of frustration in CF patients. "People need to be looked at and listened to …and then you make your diagnosis from there, but sometimes they are over reliant on paperwork that is obsolete and doesn't give any function. It doesn't solve problems..."	
Full citation Al-Yateem, N., Guidelines for the transition from child to adult cystic fibrosis care, Nursing Children and	Sample size Not reported Characteristics Healthcare professionals working with young adults.	Setting CF centre Sample selection All health care professionals in the environments where the group interviews took	Themes/categories An individualised comprehensive approach: Participants in the group suggested a systematic approach that considered every adolescent as an individual case.	Limitations The methodological limitations of the study were assessed using an adapted Critical Appraisal Skills Programme (CASP 2006) Aim(s): Aim of the study clearly reported, research method was

Study details	Participants	Methods	Findings	Comments
Young People, 25, 29-34, 2013 Ref Id 473328 Study type Qualitative survey with focus group interview Aim of the study To develop relevant and feasible guidelines for transition care, based on perspectives of stakeholders. Country/ies where the study was carried out Ireland Study dates 2012 Source of funding Self funded by researcher.	Inclusion criteria Healthcare professionals working with young adults with CF during their transition from child to adult health care, covering more than two years. Exclusion Criteria Not reported	place were invited to participate by postal letter Data collection The focus group interviews were held in conference rooms in both settings and were audio recorded. Each meeting lasted approximately 60 minutes. The transitional needs of adolescents with CF were discussed, contributions were analysed and proposed interventions were extracted. Data analysis The analysis of transcribed group interview data followed systematic approach based on literature. Relevant statements in the transcripts were highlighted. Similar statements were gathered and combined into categories and merged under one heading or theme	As one participant stated: "Absolutely, we should have an individualised comprehensive approach that cares about each individual separately and meets their needs" Assessment and care Planning of individual patient for transition was considered important by the group. One participant in the group: "The assessment will highlight to us what the adolescents actually need, and what might affect his or her transition in terms of information, family, or any other issues" Planning of care Care planning should include specific interventions targeted at the specific needs of the individual. As one participant suggested: "It will be good for everyone [planning] adolescent, parents, and even us… everybody will know what to do" Provision of information It should be appropriate to the person's age and developmental stage and supplemented with extra printed or digital material. "Anyway, providing information should be given extra attention, and possibly information sessions could solve this problem." Continuous evaluation and follow up mechanisms	appropriate for answering the research question. Sample selection: Sample selection was vague in detail. No actual number of interviewee in the focus group reported. The relationship between the researchers and the respondents not clearly reported. Data collection: Data collection relied on the focus group interview interviews for CF. No information on structure of interview or whether topic guide reported. Description of how "themes" were arrived at was discussed but information was not sufficient to conclude if data collection process was robust. No information on data saturation and full exploration of theme. Data analysis: The analytical process was described with description of themes and categories but lacks detail in data processing, checking validity or robustness of the data. No critical review of the researchers' role in the process. Findings/results: Results were presented in a confusing way with themes and categories overlapped. Themes were supported by quotes. Researchers' role and potential influences in the analytical process not critically reviewed.

Study details	Participants	Methods	Findings	Comments
			This according to group allows them to monitor and improve the care during transition One participant said: "Based on the transition plan you can later on evaluate whether the child has made any progress, or any further intervention might be needed" An approach that promotes independence One participant suggested that young adult should be more involved in decision making process "I think it is important to keep them involved … and take part in all decisions and activities during clinic and so on" Gradual handover to the adult service Group suggested that handover should be staggered overtime to make transition easier for young adults. "I think staff from the ... hospital can come over here and do their first few clinics with adolescents…this might help… and we can give them better information about our patients" Creating a suitable environment It was suggested that transition care should be provided taking account of developmental stage of young adults and their needs. One participant said: "Here, the adolescents do not feel attracted to the place… they sometimes tell us	Overall quality: Low Other information Ethical approval obtained for this study. Study conducted by lone researcher and may lack some of the formal research vigour involving multiple researchers.

Study details	Participants	Methods	Findings	Comments
			they feel like kids here… they are waiting to get out of here" Continuous training for health care Group advocated the continuous training and knowledge sharing among professional regarding transition care "I think we are used to dealing with kids more, and indeed adolescents, being in a different and unique developmental stage, may need another type of communication style, that we are not used to"	
Full citation Begley, T., Transition to adult care for young people with long-term conditions, British Journal of Nursing, 22, 506, 508-11, 2013 Ref Id 329512 Study type Qualitative study Aim of the study To evaluate how the transition from child to adult healthcare is managed in young people with CF or diabetes in Ireland. Country/ies where the study was carried out Ireland	Sample size N=132 healthcare professionals Characteristics Not reported Inclusion criteria All known consultants, clinical nurse specialists, advanced nurse practitioners caring for young people with CF and insulin dependent diabetes mellitus. Exclusion Criteria Not reported	Setting Healthcare centres across Ireland. Sample selection The study aimed to include all known healthcare professionals who from some adult and all children's services who looked for children before transition. As there was no centralized information on services, there were identified using the internet and personal information, and were confirmed by telephone calls. An anonymous questionnaire was sent to all HCPs with a comprehensive information sheet. Data collection	Themes/categories Criteria and age for transition Young people with CF and parents were also concerned about the lack of single rooms for people with CF, which lead to a fear of cross-infection: “Young people and their parents have real concern re cross-infection in mixed wards. They do not want to share wards with elderly patients” (healthcare professional) Age of transition Healthcare professionals found problematic for young people to be transferred at an “early age”. “Historically the age at which children attend adult services in this hospital is 14, which I consider too young and my training as an adult physician leaves me less able to deal with the	Limitations The methodological limitations of the study were assessed using an adapted Critical Appraisal Skills Programme (CASP 2006) Aim(s): Aim of the study clearly reported, research method was adequate for answering the research question, but a using interviews or focus groups would have been more useful to retrieve richer data. Sample selection: The sample selection process was not clearly reported, although the authors tried to involve all participants caring after young people before the transition process. The relationship between the researcher and the respondents clearly reported. The participants were appropriate to address the

Study details	Participants	Methods	Findings	Comments
Study dates Not reported Source of funding Not reported		4 weeks were allowed for questionnaires to be returned, after a reminder was sent. All data was anonymized. The response rate was 54%. Data analysis The open-ended questions were analysed using content analysis and constant comparison process (Glaser and Strauss 2008). This way each portion of data was compared to all other data to allow comparisons across respondents and information was merged to generate themes.	14-16 age group. I have difficulty in managing patients who in my mind are “children” and I find teenage/ adolescent emotional aspects of illness to be an unwelcome challenge” (healthcare professional)	topic. Age of young people was not reported. Only 56% response rate Data collection: Data collection relied on postal survey, with closed and open questions. Description of data collection method was vaguely described. Data analysis: The analytical process was reported vaguely. Content analysis reported, but description of how emerging and overarching themes was constructed. The authors do not explain whether data saturation was reached, but given the limited number of quotes presented in the study it is unlikely. Findings/results: Results were well presented and were applicable to the aim. Overall quality: Low Other information Conflict of interest: none This study includes healthcare professionals looking after young people with CF and diabetes. Only quotes relevant to CF have been extracted.
Full citation Brumfield, K., Lansbury, G., Experiences of adolescents with cystic fibrosis during their	Sample size N = 4 people with CF Characteristics	Setting Participants’ own home. Sample selection	Themes/categories Pediatric health care: Good paediatric care not only optimize the health of patients, but	Limitations The methodological limitations of the study were assessed using an adapted Critical Appraisal Skills Programme (CASP 2006)

Study details	Participants	Methods	Findings	Comments
transition from paediatric to adult health care: a qualitative study of young Australian adults, Disability & Rehabilitation, 26, 223-34, 2004 Ref Id 329552 Study type Qualitative study Aim of the study To explore the experiences of Australian adolescents with Cystic Fibrosis (CF) as they made the transition from paediatric to adult care. Country/ies where the study was carried out Australia Study dates Not reported Source of funding Not reported	Age 19 to 22 years No other characteristics reported Inclusion criteria No inclusion criteria. All CF patient who expressed interest were included in the research. Exclusion Criteria Not reported	Opportunistic sampling. Advertisement and word of mouth for recruitment of participants. Data collection The focused in-depth interview which allowed the interviewer to follow up and continue along a line of questioning raised by the informant to identify new themes and issues and to use probing questions and follow up ambiguous ideas. The topic guide was used which was adapted after the first interview as new issues were identified after analysis of previous information. Data analysis Data analysis was completed using a system after the completion of each interview, a dictating and transcribing system was used to create a written transcript of the entire interview. Thematic analysis, was applied to the transcripts of the interviews. Each interview was initially coded by the first named author according to issues which were raised as being significant by the informants and themes identified in the literature cited. The interviews were also read by the second named author	also to prepare them for a change to adulthood. "Sometimes it was like he (pediatric doctor) could read your mind . . . he always eased you, whatever your problem was, if you had a problem, you always went out feeling better." (22 year old with CF) Positive and supportive attitude helped in transition from children to adult health services. "He (pediatric doctor) really highly recommended Dr B. (adult doctor), which was good . . . the fact that he recommended him strongly would have helped." (21 year old with CF) Age appropriate treatment was considered and issue by CF patients "As I grew up, he (pediatric doctors) sort of treated me . . . as if I was older . . . he didn't start treating me like a little kid and stuff, so that was good." (19 year old with CF) However, another individual said that they were treated as children even when they were young adults ready for transition. "I thought . . . if only the (pediatric) doctors knew that we were becoming adults, you know, we were in our mid-teens thinking, they still treat us as if we were ten years old." (20 year old with CF) Elements of the transition programme:	Aim(s): Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample size was low (N=4). Opportunistic sampling and no inclusion and exclusion criteria reported. The relationship between the researchers and the respondents clearly reported. Data collection: Data collection relied on the in depth interviews for CF. Information on type of interview and topic guide was reported. Description of how "themes" were arrived at was discussed but information was not sufficient to conclude if data collection process was robust. No information on data saturation and full exploration of theme. Data analysis: The analytical process was described with description of themes and categories. No critical review of the researchers' role in the process. Findings/results: Results were presented clearly with themes supported by quotes. Researchers' role and potential influences in the analytical process not critically reviewed. Overall quality: Moderate

Study details	Participants	Methods	Findings	Comments
		who independently coded each one. The two authors then discussed the suggested coding and reconciled any differences.	Common element of transition was the inclusion of orientation tour of adult health centre. This helps them to make a more informed choice of the provider. "Oh, when I went to . . . (the first adult hospital) the Doctors were, sort of, a bit stand-offish . . . said something when they were asked, not . . . they didn't come out and . . . then we went over to . . . (the second adult hospital), they were giving us information about the clinic and how it was run and stuff like that which I thought was pretty good . . . I suppose if I went to . . . (the first hospital) they were a bit stand-offish then I'd feel uncomfortable even more than what I was at . . . (the second hospital)." (19 year old with CF) Having a familiar face around after transition to adult services was reassuring for the CF patients. "I knew her from before . . . even though it might not be a lot of contact with her, um, it was still a familiar face, and that was enough to give me reassurance in that regard." (20 year old with CF) Psycho-social factors that may affect transition: Support network for the CF patient was considered important for transition. CF patient are anxious and the lack of support	Other information Ethical approval process reported. Data collected by lone researcher and may lack some of the formal research vigour. Analysis was supported by one additional researcher.

Study details	Participants	Methods	Findings	Comments
			network does not help if fully utilising the services "I go to clinic, and I go in and I come out as quickly as I can." (22 year old with CF) Impact of transition experience: The bad transition experience created a negative impact and discouraged people in seeking care. "I always say to Mum that it's a waste of time going . . . I don't . . . I don't really trust them, because of the way they treat you, because you are a number . . . if it was up to me I probably wouldn't go back to clinic, but Mum has always told me that you've got to keep your foot in the door in case we need them (the clinic) . . . So I sort of go back on the off chance that I may need them." (22 year old with CF)	
Full citation Dupuis, F., Duhamel, F., Gendron, S., Transitioning care of an adolescent with cystic fibrosis: development of systemic hypothesis between parents, adolescents, and health care professionals, Journal of Family Nursing, 17, 291-311, 2011 Ref Id	Sample size N=26 participants 7 young people with CF; 7 mothers; 4 fathers; 8 members of the health care team Characteristics Age of young people with CF: 15 to 18 years	Setting Participant's home and principal investigator's office. Sample selection Recruitment took place over a 16-month period. Families were informed about the study by the nurse coordinator during a routine visit to the CF clinic. Those who agreed to receive more information were introduced to the first author (principal investigator) who remained	Themes/categories Suffering unrevealed to health care professionals: Health care professionals in adult services appeared to concern themselves mainly with giving information around clinical parameters rather than dealing with emotional factors in young adults associated with transition. As stated by one health care professional: "We talk to them about their medications, about physiotherapy, the respiratory	Limitations The methodological limitations of the study were assessed using an adapted Critical Appraisal Skills Programme (CASP 2006) Aim(s): Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Sample selection process was clearly dscribed. The relationship between the researcher and the participants was not reported

Study details	Participants	Methods	Findings	Comments
367032 Study type Qualitative study Aim of the study To explore the experience of parents and adolescents living with cystic fibrosis prior to the transfer of the adolescent's care from a pediatric to an adult health care facility. Country/ies where the study was carried out Canada Study dates Not reported Source of funding The Faculty of Nursing, University of Montreal, the Quebec Inter university Nursing Intervention Research Group, the Canadian Nurses Foundation (CNF), the Quebec Ministry of Education, Leisure and Sports (MELS).	No other characteristics reported. Inclusion criteria Not reported Exclusion Criteria Not reported	on site. The first author contacted the family 5 days later to confirm whether they wished to participate. Data collection On providing signed informed consent, each family completed a brief self administered questionnaire to describe family living arrangements, socioeconomic status and composition, including the number of children with CF in the family. Semi structured interviews were conducted separately with the young adults and their parents. The interview guides contained both linear and systemic questions to explore the relationships between individuals and events. Data analysis All data from interviews and the group discussion were recorded and transcribed verbatim. A content analysis based on five interrelated steps was conducted: (a) immersion in the data, (b) reconstitution of families' stories, (c) coding, (d) categorizing, and (e) modeling.	therapist sees them at every visit to go over the techniques. But other times, we show them that their X-ray has deteriorated. We show them the film, we explain that it's important for them to take control. We shake them up a bit."	Data collection: Data collection relied on the semi structured interviews for CF. No information on structure of interview or whether topic guide reported. Description of how "themes" were arrived at was discussed but information was not sufficient to conclude if data collection process was robust. No information on data saturation and full exploration of theme. Data analysis: The analytical process was described with description of themes and categories. Use of qualitative software not reported. No critical review of the researchers' role in the process Findings/results: Results were presented clearly (e.g., citation/data and the researchers' own input distinguished) Overall quality: Low Other information Most of the information was not relevant to process of transitions to adult health services. Ethical approval process reported and necessary consent obtained. Multiple researchers involved but the level of consistency between them not reported.
Full citation	Sample size	Setting	Themes/categories	Limitations

Study details	Participants	Methods	Findings	Comments
Iles,N., Lowton,K., What is the perceived nature of parental care and support for young people with cystic fibrosis as they enter adult health services?, Health and Social Care in the Community, 18, 21-29, 2010 Ref Id 168982 Study type Qualitative study Aim of the study This study examines how young people and staff perceive the nature of parental care and support for those with CF who have left paediatric services. Country/ies where the study was carried out UK Study dates Not reported Source of funding Burdett Trust for Nursing, Uk	N=50 young people and young adults with CF N=23 healthcare professionals Characteristics Age of young people and young adults: 13 to 24 years 32 out of 50 adults had already experienced transition Inclusion criteria Age 13 to 24 years Fuency in English Exclusion Criteria Near to death, or having experienced a recent bereavement, were excluded.	Participant's home, CF clinic or over the telephone. Sample selection Letters requesting participation were sent to 125 young people who were registered at either of two CF clinics in South-East London. Interested young people were asked to return a reply slip in a prepaid envelope to the researchers, who then contacted them to arrange an interview. Informed consent was obtained from all young people, with consent additionally obtained from the parents of those under 18 years. 23 health professionals were also interviewed. Staff were purposively sampled to include a range of team members from adult and paediatric services. Data collection Semi-structured interviews were conducted using a topic guide. To enable respondents to speak freely about their experiences and expectations, the interviewer had no clinical contact with any of the respondents and introduced herself as a researcher employed by the local University. All	Parent-as-partner: Young people preferred active involvement in their clinic appointments; and their desire for a confidential consultation. Many young people reported embracing opportunities to take the lead in adult clinic consultations, negotiating with their parents to facilitate this: "Since I went over to the adults' [clinic] it's been me more involved and she's just sat back and she'll take me if I want her to and she'll sit there and she won't say anything unless I ask her." (17 year old with CF) But some young adults did not want their parents to be involved during hospital consultations "My mum used to come with me to the clinic when I first transferred. I mean she'd come with me now if she could get time off work, if I'd let her, but sometimes I'd rather she wasn't there because there are obviously personal things you want to talk to the doctor about, like when I got my first boyfriend and stuff, I didn't want her to be there." (23 year old with CF) "I didn't tell my mum I was transferring. I didn't tell her, because my mum's a bit obsessive about the clinic and she feels she has to know everything, you know, even though I'm 17... I mean I know it's the duty of the parent, I know that's their job…But that's the good thing about	The methodological limitations of the study were assessed using an adapted Critical Appraisal Skills Programme (CASP 2006). Aim(s): Aim of the study clearly reported, research method was appropriate for answering the research question. Sample selection: Sample selection was clearly reported. The relationship between the researcher and the respondents was reported. Data collection: Data collection relied on the semi structured interviews for CF. Information on structure of interview or topic guide reported. Description of how "themes" were arrived at was discussed but information was not sufficient to conclude if data collection process was robust. No information on data saturation and full exploration of theme. Data analysis: The analytical process was described with description of themes, categories and use of qualitative software. No critical review of the researchers' role in the process. Findings/results: Results were presented clearly with themes supported by quotes. Researchers' role and potential influences in the analytical process not critically reviewed.

Study details	Participants	Methods	Findings	Comments
		participants were assured of confidentiality and that their data would remain anonymous. Issues covered with young people included their focusing on expectations and/or experience of transition to adult services. Interviews with staff focused on professional expectations and experiences of providing transition services. Interviews lasted between 15 to 60 minutes. Data analysis All interviews were audiotape recorded and transcribed verbatim. A thematic approach to analysis was taken. Transcripts were anonymised, checked against the original tapes and coded using the ATLAS-ti programme for qualitative data. Categories were generated inductively through identifying patterns of experiences recounted by respondents, which were grouped through codes into themes.	the adult clinic, is the parents don't have to be there, just the child or the patient's wishes. That's the good thing about being in the adult [service]." (17 year old with CF) Health professionals stressed the need for understanding the family dynamics but also recognised that young adults is a decision maker. "I think that when they move to the adult side we very much leave it up to the young person. Some of them leave their parents in the waiting room, others very firmly bring them in." (Specialist physician) "I make it very clear to the parents, when they come up, that I am quite happy to discuss anything with them that the patients want me to discuss with them, but that they are now adults and it's up to them if I speak to them. I mean I will ask my patients, 'Do you mind if I discuss your treatment options with your parents?' And nine times out of ten, they have no problem with it. But I make it very, very clear to the parents that I can't talk to them the way that I could do or [others] used to when they were children and it's really part of learning to let go for them." (CF Nurse Specialist) Parent as a protector: The main way in which young people perceived their parents to protect them was in withholding information	Overall quality: Moderate Other information Ethical approval process described. Participants assured of confidentiality and consent were obtained from the participants. Consistency between the researchers not reported.

Study details	Participants	Methods	Findings	Comments
			during childhood about the terminal nature of CF. "You know, I know a person [with CF], my mum knew him. And my mum never wanted to tell me [he had died] until I had turned 15." (16 year old with CF) Staff also acknowledged the difficulties communicating limited life expectancy with parents because of their protective nature, where it seemed that young people were perhaps more able than their parents to have these discussions with staff "We had to have a discussion whether to go on to mechanical ventilation would be the right thing ..... And she was able to have that discussion. And I asked her did she want me to let her mother know, if she wasn't going to tell her, that we had had that discussion? She asked me to tell her [mother]. And her mother was initially comfortable that we had had that discussion. Then over the space of about two or three hours, became very agitated and very upset that we'd had it… it was a huge stress for the mother, whereas her daughter, although finding it very difficult, was actually able to have [the conversation] and was – in the end, I think, glad she had had it." (Chest Physician) Some young adults had also started to protect their parents from knowing the extent of their deteriorating health	

Study details	Participants	Methods	Findings	Comments
			"Mum always used to sit in on consultations until, until I could get rid of her about three years ago. That made it really hard to talk about anything, because Mum obviously gets upset if you mention stuff like dying. So you have to be really careful. (23 year old with CF)	
Full citation Moola, F. J., Norman, M. E., 'Down the rabbit hole': enhancing the transition process for youth with cystic fibrosis and congenital heart disease by re-imagining the future and time, Child: Care, Health & Development, 37, 841-51, 2011 Ref Id 329912 Study type Qualitative study Aim of the study To explore how young people with CF and CHD and their parents understand their health in the future and the perspectives they bring towards the concept of time. Country/ies where the study was carried out	Sample size N=78 50 young people; 28 parents affected by CF and coronary heart disease Characteristics Age of young people: 11 to 17 years Age of parents: 35 to 55 years The severity of the condition ranged from mild to severe No other relevant characteristics reported Inclusion criteria Not reported Exclusion Criteria Not reported	Setting Clinic rooms Sample selection The study took place at the Hospital for Sick Children, a research/ teaching clinical care facility for children with acute and chronic conditions. No further details reported. Data collection 1 author conducted semi-structured interviews. A general interview guide was developed based on a review of the literature. Although interviews were semi-structured, participants' responses lead further lines of enquiry. Interviews lasted between 45 to 90 minutes. Data analysis All interviews were audio taped and transcribed verbatim. Field notes during data collection were also analysed.	Themes/categories The future as an uncertain terrain Young people in the study expressed they would want to get more actively involved in the future: My mum usually takes care of all the appointments and everything… it will probably change when I get older. When I'm an adult, I'll probably have to make all the appointments and everything" (young girl with CF, age 13) Time losses/ occupational restrictions Although they showed future aspirations, they contemplated if their health would deteriorate in the future, and the impact this would have on their lives. For example, they suggested it might be important to choose a school or work environment that is in close proximity to a hospital: "I will probably not live in the residence in the future and I will probably live at home with all the medicine near and staff right near me… It is easier to get all of the	Limitations The methodological limitations of the study were assessed using an adapted Critical Appraisal Skills Programme (CASP 2006) Aim(s): Aim of the study clearly reported, research method was appropriate for answering the research question. Sample selection: The sample selection process was vaguely reported. The relationship between the researcher and the respondents was not reported. The participants were appropriate to address the topic. Data collection: Data collection was done using semi-structured interviews, but allowing new questions depending on the responses of participants. The interview questions are not reported in the paper, and it is uncertain if they are relevant to the aim of the study. Interviews were recorded for analysis. Data analysis: The analytical process was well reported. All the

Study details	Participants	Methods	Findings	Comments
Canada Study dates Not reported Source of funding Not reported		The authors first engaged in multiple in-depth readings to familiarise themselves with the data (following Braun & Clarke 2006, and Byatziz 1998). Second, for the purpose of coding the raw data, the data were read again and coded. Commonly occurring words were coded. Third, the coded data were collated and organised into higher order themes. This process involves judgement about which themes are similar, and can be grouped together. Fourth, through a process of revision, the themes were collapsed and refined. Fifth, the themes were defined and named.	medicine and stuff; my mum is always driving down to get the medicine. And then I can just bring it home and get it right away. Instead of me living somewhere else and then having to get it. It would be so much more complicated" (young female with CF, age 15) Young women expressed sadness and resignation regarding the potential impact that illness could have on fertility. They were worried that illness would preclude them from being able to have a normal pregnancy: "I want to have a family, but I cannot have children because of CF" (young female with CF, age 16) Young people with CF and their parents described they feel threatened by CF, and expressed sadness for the lost time that would result in an early death: "I also know that I am not going to live as long as everybody else, so that is hard. I feel like it is out of my control, I feel helpless, how I used to be able to do it (physical activity), and now, I can't. It is kind of depressing. It makes me think that it is a progressive disease, and it makes me think that it is getting worse… it makes me worried" (young female with CF, age 15) "A parent never wants to have a kid die before her and what is what she (wife) was upset about. That is why I was trying to tell her to spend as	steps of the thematic analysis were reported, but it was unclear whether data saturation was reached. Findings/results: Results were presented clearly, but they were only partially applicable to the aim of the study, as very few themes referred to the transition from child to adult services. The citation/data and the researchers' own input distinguished. Overall quality: moderate Other information: Conflict of interest not reported This study includes a mixed population. Only quotes relevant to CF have been extracted.

Study details	Participants	Methods	Findings	Comments
			much time as you can, with her (CF child). And just think; every waking moment that you have, spend it with her. Even if you have both of them, of one by themselves, spend that time with her. I had her quit her job and that is why I work 16 hours a day. So that she can spend more time with them) (parent of a young person with CF). "It (CF) is part of who I am… I was thinking about life in general and how I knew that my disease was going to kill me off younger – I will probably not be able to see my grandchildren grow up, kind of thing… It really got to me that whole year and eventually, I just accepted the fact that everybody dies. It does not matter when you go, but you go. I just kind of got a positive attitude, that I might as well be happy and make the most of it" (young male with CF, age 17)	
Full citation Russell, M. T., Reinbold, J., Maltby, H. J., Transferring to adult health care: experiences of adolescents with cystic fibrosis, Journal of Pediatric Nursing, 11, 262-268, 1996 Ref Id 406459 Study type Qualitative study	Sample size N=17 participants N=7 young people and young adults with CF N=8 parents of young people and young adults with CF Characteristics Age of people with CF: 11 to 20 years Gender:	Setting At participant's home. Sample selection A convenience sample was selected. A letter was sent to the potential participants. As these subjects were all older than 18 years of age, direct telephone contact was made explaining the study and estimated length of time for involvement. Data collection	Themes/categories Adolescent Developmental Tasks: Adolescent wants to create their own identity and perform task to gain independence. To gain independence, the adolescents were in the process of developing autonomous and self-determined lives and separating from their parents. Many of the adolescents had begun attending clinic appointments on their own when they had acquired a driver's licence.	Limitations The methodological limitations of the study were assessed using an adapted Critical Appraisal Skills Programme (CASP 2006) Aim(s): Aim of the study clearly reported, research method was appropriate for answering the research question. Sample selection: Sample selection was clearly reported. Inclusion criteria process described in detail. The relationship between the

Study details	Participants	Methods	Findings	Comments
Aim of the study To investigate the experience of transferring to adult health care from the perspective of adolescents with CF and their parents. Country/ies where the study was carried out Australia Study dates Not reported Source of funding Not reported	5 females and 2 males with CF 7 mothers and 1 father Inclusion criteria 11 to 20 years of age; with a diagnosis of CF of at least 6 months duration; to have transferred health care management from the pediatric to adult hospital, and had either attended the respiratory medicine outpatient clinic of the adult hospital or had at least one admission to the adult hospital of 7 days or more, for treatment of CF. Exclusion Criteria Not reported	At the first interview, any questions the adolescents had pertaining to the study were answered, written consent obtained, and the demographic data collected. A second interview was then arranged to collect data using the Interview Guide. After completing the first interview with the adolescent, a parent of the adolescent was contacted for inclusion in the study. Parents were interviewed once using the same questions as the adolescents. All the interviews were tape-recorded with interview length ranging from 30 and 60 minutes. Data analysis All interviews were transcribed verbatim. Interview Guide data was categorised using the adaptive modes of Roy's Model. The data categorization was further refined using the subsections of each adaptive mode. Data was transcribed and coded and the data were clustered around emerging themes.	Parental Adaptive task: Even after the transfer of young adults to adult health services, the parents persisted in their attempts to be included until they were recognized as an integral part of the adolescent's care. One mother described this as, "I don't know whether they realized that we just weren't going to go away, that they would then have to get on with us and we were going to have to get on with them." Transition: Both the young adults and their parents are undergoing transition. During the transition phase, young adults start to feel more independence whereas parents start to relinquish responsibility. "I felt like an adult, I'd never felt like an adult before." (young adult) Preparation for the transfer was unplanned and in an ad hoc and for some young adults. Few parents were given the option of joining this visit, although they also would have liked to become acquainted with the adult hospital environment before the transfer.	researcher and the participants was not reported. Data collection: Data collection relied on the semi-structured interviews. Description of data collection method was well described with the use of topic guides and consistency in the interview process reported. Data analysis: The analytical process was reported vaguely. Description of emerging and overarching themes was reported, but saturation of data was not reported. Findings/results: Results were presented clearly (e.g., citation/data and the researchers' own input distinguished). Some of the themes were not supported by quotes from the participants. Overall quality: moderate Other information Ethical permission was obtained. Consistency between the researchers not reported.

Study details	Participants	Methods	Findings	Comments
Full citation Tierney, S., Deaton, C., Jones, A., Oxley, H., Biesty, J., Kirk, S., Liminality and transfer to adult services: a qualitative investigation involving young people with cystic fibrosis, International Journal of Nursing Studies, 50, 738-46, 2013 Ref Id 367061 Study type Qualitative study Aim of the study To explore young people's with cystic fibrosis experience of transferring to adult services. Country/ies where the study was carried out UK Study dates 2010 to 2011 Source of funding Manchester Academic Health Science Centre, UK	Sample size N=19 young people and young adults with CF Characteristics Age: 17 to 19 years Gender: 12 male participants Inclusion criteria Participants were eligible to take part if they had transferred to adult services no more than 12 months prior to interview and were not in the end stages of the disease. Exclusion Criteria Excluded for current acute psycho-social difficulties.	Setting One adult cystic fibrosis unit in the UK. Sample selection Young adults with CF were recruited through one adult CF unit in the north west of England that does not have an adolescent centre and is not based in the same hospital as paediatric clinics. All eligible pariticpants were requested to take part in this study. Young adults were purposefully sampled to ensure variation in terms of gender, children's hospital attended and severity of illness. Recruitment continued until data saturation occurred. Data collection Data collection from semi-structured interviews carried out face-to-face or by telephone, which were digitally recorded and transcribed verbatim. The option to respond via email was available. Responses provided through email were saved as a Word document. A topic guide was developed by the team prior to data collection, based on reading of relevant literature. Data analysis	Themes/categories Fracturing: Transfer involved the severing of bonds developed over several years with a trusted paediatric team. Some participants described their feelings about moving to adult services were superseded by procedural tasks, such as gathering relevant documents to forward to the adult team As one young adult with CF stated ''.. didn't seem to show interest in how you felt about moving over. It was more like we've sent your notes over to that side so we're just waiting for them to reply.'' Some interviewees believed their needs were neglected while they waited to move and described being uncertain about who was responsible for their care because they were straddled between two services: ".. they [paediatric staff] knew I was moving up so they'd gone a bit, put me last kind of thing, so I wasn't a priority because they knew I was going to be moving up soon that they'd lost interest but they were making sure that the younger ones were alright because they knew I was going soon" (young adult with CF). For young people , transition also meant that they had to take more responsibility	Limitations The methodological limitations of the study were assessed using an adapted Critical Appraisal Skills Programme (CASP 2006) Aim(s): Aim of the study clearly reported, research method was appropriate for answering the research question. Sample selection: Sample selection was clearly reported. Inclusion and exclusion of participants were clearly reported. The relationship between the researcher and the participants was not reported. Data collection: Data collection relied on the semi-structured interviews. Description of data collection method was well described. Option of email targeting young adults as data collection method was justified. Data analysis: The analytical process was reported in detail. Description of emerging and overarching themes was reported along with the use of specific software. Saturation of the data reached according to this study. Findings/results: Results were presented clearly (e.g., citation/data and the researchers' own input distinguished. More

Study details	Participants	Methods	Findings	Comments
		Preliminary interpretation of data was conducted in tandem with interviewing. Once all interviews had been completed, a systematic thematic analysis was carried out, using a recognised approach known as 'Framework'. First author coded data using the computer package NVIVO-9 and developed an indexing scheme. A summary of the analysis was passed to the remaining authors, who contributed to the refinement of themes.	.. I've never took it [CF] so serious. I've just always pushed it to one side and just tried to live a normal life but then you've got to, you can't always just put it to one side because at the end of the day it's a big part of your life... (Young CF patient). Acclimatising: Some interviewees welcomed a more direct approach and associated adult care with being listened to, making choices and playing a greater role in decision-making. ". . .as soon as the doctor started talking to me I was like, oh you're talking to me rather than me mum, which was good. . ."(CF patient) However, a few who had transferred very recently felt ill-equipped emotionally to cope with this change. ".. the doctor did ask me "what do you want to do?".. in childrens they wouldn't do that, they'd just say 'you need IVs, you should come in.' So it was quite a bit, it was a bit confusing because I didn't really know what to do myself. I was like, I don't know, you tell me what should I do" (CF patient). Presence of parents were reassuring especially during the early transition phase. ".. if my mum hadn't come, I wouldn't have asked half as many questions. I don't think I'd have been as open with the doctors talking to me.. I think	than one analyst checked the robustness of the findings. Overall quality: Moderate Other information Ethical approval granted and necessary consent obtained. Confidentiality and anonymity maintained.

Study details	Participants	Methods	Findings	Comments
			I'd have been a little bit more introvert and worried.. I know it sounds dead daft, me mum was there and I'm 19 but because me mum was there I was more confident in asking questions because I knew if I'd said something that had come out a funny way or the wrong way, mum would go well what she actually means is this" (CF patient) Online forums were a good source of information for young adults about to transfer to adult services as one CF patient stated. ".. since it was mentioned in the [adult] clinic about the forums.. I went on there and it's a big eye opener that there's loads of people going through it, been through it, and they can just offer you a lot more advice from a patient side of it.." Integrating: Integrating with the adult services was one of the challenges for young adults and was difficult to begin with. They believed that their issues would not be easily understood in adult health services. ".. I was with them for so long I got to know them really well and they knew I was a fussy person. But I'm sure it will all be the same with the adults." (CF patient) " .. he [paediatric consultant] could tell if I was ill. I've got like a problem	

Study details	Participants	Methods	Findings	Comments
			with my stomach and he could feel straight away if I was having, if it was worse or if it was manageable.. So he's known me for a long time. That's why I was worried about moving here.. he knew a lot of the problems that I've had..." Relocating to a new healthcare system is one of several transitions young people with a long-term condition. Hence, transfer takes place against a backdrop of additional pressures and might not be a top priority. "It was very busy actually because you know you've got to come in here at some point but then you've also just started at college, a new course, you don't want to miss all the beginning of your course. It's a new start both sides so you don't want to miss either one." (CF patient)	
Full citation Tuchman, L. K., Slap, G. B., Britto, M. T., Transition to adult care: experiences and expectations of adolescents with a chronic illness, Child: Care, Health & Development, 34, 557-63, 2008 Ref Id 367066 Study type	Sample size N=5 young people and young adults with CF Characteristics Age: 15 to 21 years Inclusion criteria Not reported Exclusion Criteria Not reported	Setting Tertiary care hospital. Sample selection Subset of the sample recruited for larger study voluntarily participated when requested in a hospital over an 18 month period. Data collection Data collected through individual semi structured interview Following each interview, interviewers completed a brief report	Themes/categories Feelings about timing of transfer: Participants with CF noted that the timing of transition seemed arbitrary and unfair. One young adult said: "And right now it's like, maybe in a year, but right now I'm, I've just gone off to college. It's like, I don't want to make that transition now. And they're like, well you need to. It's like, and you have patients here that are 30 years old and you're telling me I have to go?"	Limitations The methodological limitations of the study were assessed using an adapted Critical Appraisal Skills Programme (CASP 2006) Aim(s): Aim of the study clearly reported, research method was appropriate for answering the research question Sample selection: Mixed sample with other chronic diseases. Part of a much larger study. The

Study details	Participants	Methods	Findings	Comments
Qualitative study Aim of the study To describe expectations and concerns of adolescents with chronic illness regarding transition from subspecialty paediatric to adult-centred care during the transition process in order to guide effective programme design and implementation. Country/ies where the study was carried out USA Study dates Not reported Source of funding Robert Wood Johnson Foundation Generalist Physician Faculty Scholars Program, USA.		including a short free text summary of the interview, and indicated themes and topics discussed with the subject in a set of pre-coded boxes. Data analysis Two investigators independently reviewed each transcript, extracted portions related to transition, and independently identified all unique themes using an editing organizing style. An overall emergent coding scheme was developed based on these themes and data were coded using QSR N6, a qualitative data analysis software programme. Theoretical constructs were developed for content related to concerns of subjects before and after transition to adult care.	Another one said: "I think maybe if it wasn't just an all of a sudden strange situation. Slam the door behind you, you know. You're at university, you can't come back." Parent's changing role: Young adults appreciated the support of parents but also wanted independence in decision making. One young adult said: "My mom doesn't want to let go. She has flat out told me. You put 18 years into your child's health and it becomes your health as well" Another young with the similar view: "My mom has mixed emotions about it because she's not sitting back in the room with me anymore. She likes being able to put her two cents in. And I like being able to do it myself." Adolescents attitudes and concerns following transfer : Young adults appreciated the efficiency of adult services whereas others were concerned about the shorter appointment with less information which implied to them that people were less qualified than pediatric services. "It's just different. I mean I like how you kind of rush through it. It's not like where you have to talk to a million people. They don't seem as qualified there, it seems like the people that I talk to at Children's	relationship between the researchers and the respondents not clearly reported. Inclusion and exclusion criteria not reported Data collection: Data collection relied on the semi structured interviews for CF. Information on structure of interview or whether topic guide were vague. Description of how "themes" were arrived at was discussed but information was not sufficient to conclude if data collection process was robust. No information on data saturation and full exploration of theme Data analysis: The analytical process was described with description of themes and categories. No critical review of the researchers' role in the process Findings/results: Results were presented clearly with themes supported by quotes. Researchers' role and potential influences in the analytical process not critically reviewed. Credibility and robustness of findings not reported Overall quality: Low

Study details	Participants	Methods	Findings	Comments
			really knew what they were doing.Maybe it's because they don't talk to me as much." The main positive differences that subjects noted between paediatric and adult care were feeling greater control over and more involvement in decision making. One subject who was very resistant to transition was impressed with pulmonolgist: "She gave me this big talk about some of the new things [I'm] going to encounter as an adult with CF. And she just opened my eyes to a lot of things." Participant suggestions: Few young adults expressed ideas about how to smooth the transition process. One 18-year-old young adult with CF anticipating transition explained "I think it would have been easier if they would have really started pushing when I was younger. Like, even at 15 or 16, start really suggesting it. Really being like, you know you might want to look into this. You might want to start meeting some of the doctors over there."	Other information: Mixed population study with other chronic diseases. Appropriate approval for this study was obtained. Multiple researchers but consistency between them not reported.
Full citation van Staa, A. L., Jedeloo, S., van Meeteren, J., Latour, J. M., Crossing the transition chasm: experiences and	Sample size N=8 participants 3 young adults 3 parents	Setting At participant's home. Sample selection In each diagnostic group, three young adults were randomly selected from a list	Themes/categories Moving on to adult services Sub-themes Leaving paediatric care is a logical step:	Limitations The methodological limitations of the study were assessed using an adapted Critical Appraisal Skills Programme (CASP 2006)

Study details	Participants	Methods	Findings	Comments
recommendations for improving transitional care of young adults, parents and providers, Child: Care, Health & Development, 37, 821-32, 2011 Ref Id 330156 Study type Qualitative study Aim of the study This study has 2 objectives: to map experiences with the transfer to adult care of young adults with chronic conditions; to identify recommendations for transitional care of young adults, their parents and healthcare providers Country/ies where the study was carried out The Netherlands Study dates 2004 to 2007 Source of funding No external funding. Funded internally by Rotterdam University & Erasmus University Medical Center.	2 healthcare providers Characteristics Young adults with cystic fibrosis their parents and health care providers from tertiary care centre Inclusion criteria They were eligible for participation if they had no record of intellectual disabilities and had been transferred to adult care in the past 2 years. Exclusion Criteria Not reported	of patients officially in adult care for 2 years. Parents were approached after the young adults had given consent. When no consent was given or the young adults could not be reached, new patients were approached – until 3 in each group had consented in an interview. Data collection All interviews were carried out by a trained nursing or physiotherapy student after extensive training. The patient and parent interviews were conducted at home and lasted 45 to 120 min. Parents and young adults were interviewed separately with an interview guide developed by the researchers. Health care providers were interviewed at their workplaces and interviews lasted from 25 to 60 min. Data analysis Interviews were digitally recorded, transcribed verbatim and then imported into the qualitative software package ATLAS.ti 5.0. Thematic analysis was done. Initial codes (sub-themes) were formulated on the basis of the interview guide.	Young adults and their parents recognised the inevitability that they will be transferred to adult health care. "I'll need to get used to it. I've known my doctor awfully long,for 18 years.But I'll just see what's going to happen. [. . .] Actually, I'm getting too old now for a children's hospital. Seems to be the right age [for transfer] because I'm an adult now, aren't I?" (19-year-old male, CF) Health care providers recognised transfer as 'a natural process 'that is' age-appropriate. Transition is complicated by cultural gaps between paediatric and adult services: Some parents and young adults looked back at transfer as 'no big deal' and even as 'peanuts', when the process had been smooth or 'seamless'. But most young adults and especially parents said it had been more stressful and difficult than anticipated. Parents and young adults said that pediatric was more warm and friendly. On the other hand, they used metaphors like 'being lost', 'falling into a deep hole', 'feeling abandoned' and even 'waking up in a horror movie' for adult care. However, this was seen as temporary; transition was perceived	Aim(s): Aim of the study clearly reported, research method was appropriate for answering the research question. Sample selection: Sample selection was vaguely reported. The relationship between the researcher and the participants was not reported. Data collection: Data collection relied on the semi-structured interviews. Description of data collection method was described in detail. Data analysis: The analytical process was reported with the use of thematic analysis and qualitative software package. Description of emerging and overarching themes was reported, but saturation of data was not reported. Findings/results: Results were presented clearly but use of quotes to support the findings was inadequate. Use of citation/data and the researchers' own input distinguished in this study. Overall quality: moderate Other information Mixed population study with multiple chronic condition reported out of which CF sample and findings were extracted.

Study details	Participants	Methods	Findings	Comments
		Subsequently, these were modified, expanded or merged as new issues emerged during the analysis. The third step was collating subthemes to identify potential themes; emerging themes were checked iteratively in other interviews.	as a rite of passage:"you have to get used to it, that's all." Young adults noted that more independence and self-reliance was expected of them. Parents wondered whether their children could take up the full responsibility for their treatment. Health care providers recognized cultural differences between the paediatric and adult specialities that complicated transfer. The adult care had more 'business-like approach' which often contrasted with the paediatric 'holistic, system-oriented approach'.	Ethical process was adequate and confidentiality and anonymity of the data reported.

G.5 Complications of cystic fibrosis

Review question: What are the non-respiratory complications of cystic fibrosis in infants, children, young people and adults?

Study details	Participants	Methods	Outcomes and results	Comments
Full citation Bell, S. C., Bye, P. T., Cooper, P. J., Martin, A. J., McKay, K. O., Robinson, P. J., Ryan, G. F., Sims, G. C., Cystic fibrosis in Australia, 2009: results from a data registry, Medical Journal of Australia, 195, 396-400, 2011 Country/ies where the study was carried out Australia	Sample size N=2986 Characteristics People with CF Median age: 17.6 years Sex: Females: 48% Inclusion criteria People in the Australian CF Registry for 2009 Exclusion criteria	Details Register/Data source Australian CF Data Registry Definitions / thresholds. Not reported Data collection and measurements. All CF centres in Australia submitted data via a web-based form. Measurement tools not reported in the paper	Results Prevalence of insulin-dependent diabetes (chronic): 0-11 years: 0.5% (5/951) 12-17 years: 13.6% (61/448) ≥18 years: 20.7% (144/697) All age groups: 10.0% (210/2096)	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes, all people in the registry were included Was the sample size adequate? Yes, >250 as per protocol Were the study subjects and the setting described in detail? Yes

Study details	Participants	Methods	Outcomes and results	Comments
Study type Retrospective cross-sectional study Study dates 2009 data Source of funding Financial support from CFA; state CF organisations; Roche Pharmaceuticals and Solvay Pharmaceuticals.	Not reported in relation to outcomes of interest		Prevalence of insulin-dependent diabetes (intermittent): 0-11 years: 0% (0/951) 12-17 years: 1.1% (5/448) ≥18 years: 2.3% (16/697) All age groups: 1.0% (21/2096) All age groups: 1.0% (21) Prevalence of osteopenia: 0-11 years: 0.3% (3/951) 12-17 years: 3.3% (15/448) ≥18 years: 25.0% (174/697) All age groups: 9.2% (192/2096) Prevalence of osteoporosis: 0-11 years: 0.2% (2/951) 12-17 years: 1.3% (6/448) ≥18 years: 9.5% (66/697) All age groups: 3.7% (77/2096) Prevalence of fractures in 2009: 0-11 years: 0% (0/951) 12-17 years: 0.4% (2/448) ≥18 years: 1.1% (8/697) All age groups: 0.5% (10/2096)	Was the data analysis conducted with sufficient coverage of the identified sample? Yes, >250 people in each subgroup Were objective, standard criteria used for the measurement of the condition? Unclear - not reported Was the condition measured reliably? Unclear - not reported Was there appropriate statistical analysis? Yes - confidence intervals of percentages not provided however this is registry data so they are not needed Are all important confounding factors/subgroups/differences identified and accounted for? Yes, results disaggregated into age subgroups: children, adolescents and adults. Were subpopulations identified using objective criteria? Yes, age cut-offs Overall quality: moderate Other information None
Full citation	Sample size N=290	Details Register/data source.	Results	Limitations

Study details	Participants	Methods	Outcomes and results	Comments
Chavasse, R. J., Francis, J., Balfour-Lynn, I., Rosenthal, M., Bush, A., Serum vitamin D levels in children with cystic fibrosis, Pediatric Pulmonology, 38, 119-22, 2004 Country/ies where the study was carried out UK Study type Retrospective study Study dates Levels of 25-OHD measured between August 1999 and April 2001 Source of funding Not reported	Characteristics People with CF Age: 1-18 Sex: Males: 45% (131/290) Inclusion criteria All people aged 1–18 years, with confirmed diagnosis of CF under the care of specialist paediatric CF clinic who attended an annual assessment during the study period and had 25-OHD measured on at least one occasion. Exclusion criteria Not reported	Data from specialist paediatric CF clinic Definitions/thresholds. The laboratory reference range was 15–100 nmol/l. Authors also took into account that 25 nmol/l is generally regarded as the lower limit of normal. So the cut-off points were < 15 nmol/l and < 25 nmol/l. Measurement. 25-hydroxyvitamin D (25-OHD) was measured by an in-house, competitive protein-binding assay following extraction and chromatography of 25-OHD on silicic acid, performed at Charing Cross Hospital.	Prevalence of vitamin deficiency: 25-OHD < 15 nmol/l: 1% (4/290) 25-OHD < 25 nmol/l: 6% (17/290)	Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes, all people meeting inclusion criteria were included Was the sample size adequate? Yes, N>250 as per protocol Were the study subjects and the setting described in detail? Yes Was the data analysis conducted with sufficient coverage of the identified sample? N/A Were objective, standard criteria used for the measurement of the condition? Yes, both the laboratory reference range (15–100 nmol/l) and what is generally regarded as the lower limit of normal (25 nmol/l) were used to define cut-offs. Was the condition measured reliably? Yes Was there appropriate statistical analysis? Yes, no confidence interval provided however all the people in the clinic fitting inclusion criteria were included Are all important confounding factors/subgroups/differences identified and accounted for? No. Results were not disaggregated between infants, children, young people and adults. Were subpopulations identified using objective criteria? N/A

Study details	Participants	Methods	Outcomes and results	Comments
				Overall quality: moderate Other information None.
Full citation Heltshe, S. L., Borowitz, D. S., Leung, D. H., Ramsey, B., Mayer-Hamblett, N., Early attained weight and length predict growth faltering better than velocity measures in infants with CF, Journal of Cystic Fibrosis, 13, 723-9, 2014 Country/ies where the study was carried out United States Study type Retrospective study Study dates 1st January 2004 - 31st December 2009 Source of funding CFFT Grant BONUS11K0 and NIH NIDDK Grants R01 DK095738-01, and P30DK089507-01.	Sample size N=1992 infants and children Characteristics Infants and children with CF Age: 0-24 months Sex: Males: 50.6% Inclusion criteria Newborns diagnosed with CF who were born between Jan 1, 2004 and Dec 31, 2008, and entered in the registry before 4 months of age. Exclusion criteria Not reported	Details Data source/register. US CF Foundation National Registry Definitions/thresholds. The following thresholds were chosen as potential early markers of deficits at 24 months Guo et. al. US (Guo-US) velocity standards recommended by the CFF infant care guidelines: Guo-US 50th percentile for weight velocity and length velocity WHO standardized 2.5th, 5th, 10th, and 50th percentiles for weight and length velocity WHO standardized 2.5th, 5th, and 10th percentiles for weight and length for age Measurement. Encounter based weight and length measurements were derived from the registry and were used for calculating weight and length velocity as change in grams and centimeters per unit time, respectively. The velocities were then standardized to the WHO cohort and the Guo-US	Results Prevalence of inadequate attained weight or length for age or inadequate weight or length velocity: Age 12 months (N=374): weight for age <10th: 11% weight for age <5th: 8.3% weight for age <2.5th: 3.7% weight velocity (GUO-US) <50th: 48.1% weight velocity (WHO)<50th: 30.5% weight velocity <10th (WHO): 6.4% weight velocity<5th (WHO): 4.5% weight velocity<2.5th (WHO): 3.5% length for age <10th: 26.8% length for age <5th: 17.7% length for age <2.5th: 10.4% length velocity (GUO-US) <50th: 45.7% length velocity <50th (WHO): 38.4% length velocity <10th (WHO): 20.7%	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes, all people in the registry fitting inclusion criteria were included Was the sample size adequate? Yes, >250 as per protocol Were the study subjects and the setting described in detail? Yes Was the data analysis conducted with sufficient coverage of the identified sample? Yes. >250 people in each age subgroup Were objective, standard criteria used for the measurement of the condition? Yes, WHO and GUO-US standards Was the condition measured reliably? Yes Was there appropriate statistical analysis? No, no numerators provided. No confidence intervals provided for percentages however this is registry data so the CIs are not needed. Are all important confounding factors/subgroups/differences identified and accounted for? Yes,

Study details	Participants	Methods	Outcomes and results	Comments
		standards to generate age and sex specific percentiles. All analyses only included observations where a patient's weight or length was recorded at an age no more than ±9 days (30% of a month) from expected age at interval start (0–23 months), and follow-up measures of weight or length recorded at 1 or 2 or 3 months ±6 days later (20% of a month).	length velocity<5th (WHO): 13.4% length velocity<2.5th (WHO): 13.4% Age 24 months (N=317): weight for age <10th: 6.9% weight for age <5th: 2.8% weight for age <2.5th: 1.9% weight velocity (GUO-US) <50th: 59.3% weight velocity (WHO)<50th: 51.1% weight velocity <10th (WHO): 18.3% weight velocity<5th (WHO): 12.6% weight velocity<2.5th (WHO): 8.2% length for age <10th: 24.9% length for age <5th: 17% length for age <2.5th: 11.4% length velocity (GUO-US) <50th: 57.4% length velocity <50th (WHO): 58.7% length velocity <10th (WHO): 30.3% length velocity<5th (WHO): 24.3%	prevalence data are disaggregated by age groups Were subpopulations identified using objective criteria? Yes, age cut-offs Overall quality: moderate Other information None.

Study details	Participants	Methods	Outcomes and results	Comments
			length velocity<2.5th (WHO): 19.9%	
Full citation Lai, H. J., Shoff, S. M., Classification of malnutrition in cystic fibrosis: implications for evaluating and benchmarking clinical practice performance, American Journal of Clinical Nutrition, 88, 161-6, 2008 Country/ies where the study was carried out United States Study type Retrospective study Study dates 2002 Source of funding Not reported	Sample size N=14702 Characteristics Children, young people and adults with CF Age: <20 years Sex: Not reported Inclusion criteria Age: <20 years Exclusion criteria Missing height or weight or height, weight, or BMI values that deviated >4 SD from the reference mean (the authors specify that these height and weight values likely were outliers resulting from measurement or recording errors, and they were excluded)	Details Register / Data source US CF Foundation Patient Registry Definitions and thresholds 2002 CFF definition of nutritional failure: Age <2 y old: HTp <5th, %IBW <90%, or WHp <10th. For ages 2–20 y: HTp <5th, %IBW <90%, or BMIp <10th Corrected classification of nutritional failure: elimination of %IBW as an indicator of underweight Below BMI goal: Age<2 y old: WHp <50th. Ages 2-20 years: BMIp <50th. Measurements Not reported Analysis Age- and sex-specific HTp, WHp for ages <2 y, and BMIp for ages 2–20 y were calculated in a computerized program in SAS software (SAS Inc, Cary, NC) by using the Centers for Disease Control and Prevention reference values. The %IBW was calculated according to the method defined by Moore et al	Results Prevalence of "nutritional failure" using 2002 CFF definition: HTp<5th or BMIp<10th or %IBW<90): 33.0% Prevalence of "nutritional failure" using corrected classification: HTp<5th or BMIp<10th: 26.8% Prevalence of BMIp<50th: 56.8%	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes Was the sample size adequate? Yes, >250 as per protocol Were the study subjects and the setting described in detail? No. Unclear how many infants, children, young people and adults. Was the data analysis conducted with sufficient coverage of the identified sample? N/A Were objective, standard criteria used for the measurement of the condition? Unclear. Unclear why results do not take different definitions for infants into account. Was the condition measured reliably? Unclear. Not reported. Was there appropriate statistical analysis? Yes. No confidence intervals provided for prevalence at the national level however this is registry data so no confidence intervals are needed Are all important confounding factors/subgroups/differences identified and accounted for? No.

Study details	Participants	Methods	Outcomes and results	Comments
		in a computerized program in SAS, by using the Centers for Disease Control and Prevention reference values.		Data not disaggregated between infant, children, young people and adults. Were subpopulations identified using objective criteria? N/A Quality: very low Other information None.
Full citation Lewis, C., Blackman, S. M., Nelson, A., Oberdorfer, E., Wells, D., Dunitz, J., Thomas, W., Moran, A., Diabetes-related mortality in adults with cystic fibrosis. Role of genotype and sex, American Journal of Respiratory & Critical Care Medicine, 191, 194-200, 2015 Country/ies where the study was carried out United States Study type Retrospective study Study dates 2008-2012 Source of funding Supported in part by a grant from Pennsylvania Cystic Fibrosis Incorporated. One author was funded by National Institutes of Health grant T32DK66519. Another author was	Sample size N=462 Characteristics Age: ≥ 20 Sex: Not reported Inclusion criteria People attending the CF clinic between September 16, 2008 and December 31, 2012, who gave informed consent permitting their records to be reviewed for research purposes. Exclusion criteria Not reported	Details Register / Data source. University of Minnesota Cystic Fibrosis Database Definitions and thresholds. Not reported Data collection and measurements. Clinical information was reviewed from the database. Tests used not reported.	Results Prevalence of Cystic Fibrosis Related Diabetes (CFRD): 48% (221/462)	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes Was the sample size adequate? Yes, >250 as per protocol Were the study subjects and the setting described in detail? No, but age was reported Was the data analysis conducted with sufficient coverage of the identified sample? N/A Were objective, standard criteria used for the measurement of the condition? Unclear. Not reported Was the condition measured reliably? Unclear. Not reported Was there appropriate statistical analysis? Yes. Confidence interval for the percentage not provided however all the people from the centre were included so confidence intervals are not needed. Are all important confounding factors/subgroups/differences

Study details	Participants	Methods	Outcomes and results	Comments
funded by National Institutes of Health K23DK083551.				identified and accounted for? Yes, the study focused on adults only so there was no need to disaggregate by age subgroups Were subpopulations identified using objective criteria? N/A Overall quality: Moderate Other information Analyses were performed to build on previous study by Moran et al. (2009), which also used data from the University of Minnesota Cystic Fibrosis database, by adding data from the most recent time period.
Full citation Lucidi, V., Alghisi, F., Raia, V., Russo, B., Valmarana, L., Valmarana, R., Coruzzo, A., Beschi, S., Dester, S., Rinaldi, D., Maglieri, M., Guidotti, M. L., Ravaioli, E., Pesola, M., De Alessandri, A., Padoan, R., Grynzich, L., Ratclif, L., Repetto, T., Ambroni, M., Provenzano, E., Tozzi, A. E., Colombo, C., Growth assessment of paediatric patients with CF comparing different auxologic indicators: A multicentre Italian study, Journal of Pediatric Gastroenterology & Nutrition, 49, 335-42, 2009	Sample size N=892 Characteristics Age range: 0.1-18 Sex: Males: 50.7% (452/892) Inclusion criteria All people with a confirmed diagnosis of CF younger than 18 years on regular follow-up with one of the 10 CF centres during the period January 2005-December 2006 Exclusion criteria Not reported	Details Setting. 10 Italian CF centres Data collection and measurements. Height and weight were measured (when the patient was in a stable clinical condition) by specifically trained personnel and the values entered in a database that also contained demographic and clinical data of the patients. BMI was also calculated on the basis of weight in kilograms/(height in meters2) ratio. Reproducibility in anthropometric measurement was evaluated by comparing measures obtained with standard instruments in all centres with those obtained with reference	Results Prevalence of "nutritional failure" and risk of malnutrition by age group: 0-2 years (n=HAP: n=104; WLP: n=101) HAP<5th: 15.4% HAP 5th-25th: 18.3% WLP<10th: 12.9% WLP10th -25th: 22.7% 2-18 years (n=788) HAP<5th: 11.8% HAP 5th-25th: 29.3% BMIp<15th: 20.9% BMIp 15th-25th: 9.6% BMIp<50th: 54.4% 10-14 years (n=179) HAP<5th: 11.7% BMIp<15th: 20.1%	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes Was the sample size adequate? Yes, >250 as per protocol Were the study subjects and the setting described in detail? Yes Was the data analysis conducted with sufficient coverage of the identified sample? No - Some age subgroups included less than 250 people Were objective, standard criteria used for the measurement of the condition? Yes Was the condition measured reliably? Yes

Study details	Participants	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Italy Study type Prospective cross-sectional study Study dates Data from January 2005-December 2006 Source of funding Not reported		instruments in a sample of patients. Definitions and thresholds. The presence of nutritional failure was defined as: HAP <5th (all ages), WLP <10th (age <2 years), and BMIp <15th (age between 2 and 18 years). Risk of malnutrition: HAP <25th (all ages), WLP <25th (<2 years), BMIp <25th (2-18 years)	14-18 years (n=183) HAP<5th: 21.9% BMIp<15th: 27.9% 0-18 years (n=892) HAP<5th: 12.2% HAP 5th-25th: 28%	Was there appropriate statistical analysis? Yes, no confidence intervals for percentages however all the people in the centres fitting inclusion criteria were included so no confidence intervals are needed Are all important confounding factors/subgroups/differences identified and accounted for? Yes, age subgroups Were subpopulations identified using objective criteria? Yes, age cut-offs. Overall quality: moderate Other information None.
Full citation Moen, I. E., Nilsson, K., Andersson, A., Fagerland, M. W., Fluge, G., Hollsing, A., Gilljam, M., Mared, L., Pressler, T., Santi, H., Storrosten, O. T., Hjelte, L., Dietary intake and nutritional status in a Scandinavian adult cystic fibrosis-population compared with recommendations, Food and Nutrition Research, 55 (no pagination), 2011 Country/ies where the study was carried out Denmark, Norway and Sweden Study type	Sample size N=347 Characteristics Age: 18 years and over Sex: Females: 44% (152/347) Inclusion criteria Confirmed CF diagnosis. Age: at least 18 years of age Exclusion criteria Pregnancy People who had had a lung transplant	Details Setting. 7 of 8 centres in Denmark, Norway and Sweden. Definitions / thresholds. BMI < 19.0 and BMI < 18.5 Data collection and measurements. People were included consecutively in the study. Weight was measured in the morning wearing undergarments. Height was measured with no stockings or shoes and the means of 3 measurements were recorded	Results Prevalence of underweight: BMI<19.0 kg/m2: 18% (62/347) BMI<18.5 kg/m2: 13% (44/347)	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes, consecutively if fitting inclusion criteria Was the sample size adequate? Yes, >250 as per protocol Were the study subjects and the setting described in detail? Yes Was the data analysis conducted with sufficient coverage of the identified sample? N/A Were objective, standard criteria used for the measurement of the condition? Yes

Study details	Participants	Methods	Outcomes and results	Comments
Prospective cross-sectional study Study dates September 2003-May 2006 Source of funding This work was supported by Swedish Heart Lung Foundation, Stiftelsen Frimurare-Barnhuset i Stockholm, Karolinska Institutet, Norwegian and Swedish Cystic Fibrosis Associations and by an unrestricted grant from Solvay Pharma				Was the condition measured reliably? Yes Was there appropriate statistical analysis? Yes, no confidence intervals of percentages however all the people attending the centres and fitting inclusion criteria were included so no confidence intervals needed Are all important confounding factors/subgroups/differences identified and accounted for? Yes, the study population were adults only so there was no need to disaggregate data by age subgroup Were subpopulations identified using objective criteria?N/A Overall quality: High Other information People were defined as having CFRD if they used insulin or oral anti-diabetics. This definition was not relevant for the current systematic review so data on CFRD was not extracted.
Full citation Moran, A., Dunitz, J., Nathan, B., Saeed, A., Holme, B., Thomas, W., Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality, Diabetes Care, 32, 1626-31, 2009	Sample size N=872 Characteristics People with CF followed at the University of Minnesota Age: not reported Sex: not reported Inclusion criteria	Details Register / Data source. Minnesota Cystic Fibrosis Database Definitions / thresholds. CFRD was diagnosed by standard criteria including persistent random glucose levels>200mg/dl (11.1 mmol/l) and persistent fasting glucose levels >126 mg/dl (7.0 mmol/l) or by OGTT. People	Results Diabetes CFRD prevalence at the end of the interval (%): 1992-97: 20% +- 2% 1998-2000: 30% +-2% 2003-2008: 33% +-2% Prevalence of CFRD in September 2008	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes, all people in the database giving informed consent Was the sample size adequate? Yes, >250 as per protocol

Study details	Participants	Methods	Outcomes and results	Comments
Country/ies where the study was carried out United States Study type Retrospective study Study dates Prevalence at the end of three consecutive intervals: 1992-1997, 1998-2002, 2003-2008 Source of funding Not reported	All patients followed at the University of Minnesota Cystic Fibrosis Database who gave informed consent permitting their records to be reviewed for research purposes Exclusion criteria Not reported	with a fasting glucose ≥126 mg/dl (7.0 mmol/l) were diagnosed with CFRD with fasting hyperglycemia. People with a fasting glucose 126 mg/dl (7.0 mmol/l) and a 2-h glucose ≥200 mg/dl (11.1 mmol/l) were diagnosed with CFRD without fasting hyperglycemia. Data collection and measurements. Routine annual OGTT screening has been recommended at the University of Minnesota since the early 1990s for patients aged ≥6 years (1.75 g/kg glucose [maximum 75g]). OGTTs are performed when patients are in their usual baseline state of health.	Children < 11 years: 2% (2/93) (both without fasting hyperglycemia) Of 75 adolescents aged 11-17: 19% (14/75) (4 with fasting hyperglycemia) Population aged ≥18: 43% (155/359)* *Percentage calculated by the NGA technical team	Were the study subjects and the setting described in detail? Yes Was the data analysis conducted with sufficient coverage of the identified sample? No, there were less than 250 people in the children and young people subgroups Were objective, standard criteria used for the measurement of the condition? Yes Was the condition measured reliably? Yes Was there appropriate statistical analysis? No. No numerator or denominator provided for prevalence calculated at the end of the interval Are all important confounding factors/subgroups/differences identified and accounted for? Yes, age subgroups were provided for 2008. Were subpopulations identified using objective criteria? Yes, age cut-offs. Overall quality: Moderate Other information None.
Full citation Quon,B.S., Mayer-Hamblett,N., Aitken,M.L., Smyth,A.R., Goss,C.H., Risk factors for chronic kidney disease in adults with cystic fibrosis, American Journal of Respiratory and Critical	Sample size N=11912 Characteristics Adults with CF Age ≥ 18 Sex: Males: No CKD: 53.2% vs CKD: 45.6% Inclusion criteria	Details Register / data source. CF Foundation Registry Definitions and thresholds CKD was defined by eGFR measured less than 60 ml/min/1.73 m2 in two consecutive registry years. Based on National Kidney	Results Renal disease Mean annual prevalence: chronic kidney disease (stage 3 or greater): 2.3% Stage 3 or greater CKD amongst 18-25 years old: 0.6%	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes Was the sample size adequate? Yes, >250 as per protocol.

Study details	Participants	Methods	Outcomes and results	Comments
Care Medicine, 184, 1147-1152, 2011 Country/ies where the study was carried out United States Study type Retrospective study Study dates 2001-2008 Source of funding Supported by NIH/NIDDK (P30 DK089507–01). B.S.Q. was supported by a British Columbia Lung Association Fellowship Award.	Age ≥ 18 At least two estimated glomerular filtration rate (eGFR) measurements, not separated by more than 2 years, from January 1, 2001 to December 31, 2008. Exclusion criteria Not reported	Foundation KDOQI guidelines, this corresponds to stage 3 CKD severity and is the earliest stage that can be diagnosed using serum creatinine alone. More advanced stages of CKD were defined as follows: stage 4, eGFR less than 30 ml/min/1.73 m2; and stage 5, eGFR less than 15 ml/min/ 1.73 m2 or need for hemodialysis. Measurements. Renal function was estimated using the Cockcroft-Gault formula standardized for body surface area. Data on serum creatinine, age, weight, height, and sex were required for this calculation.	Stage 3 or greater CKD amongst those older than 55 years old: 19.2% stage 4 or greater CKD: 0.7% stage 5 CKD: 0.6%	Were the study subjects and the setting described in detail? Yes Was the data analysis conducted with sufficient coverage of the identified sample? N/A Were objective, standard criteria used for the measurement of the condition? Yes Was the condition measured reliably? Yes Was there appropriate statistical analysis? No. No numerators or denominators. Confidence intervals of percentages not provided however this is registry data. Are all important confounding factors/subgroups/differences identified and accounted for? Yes, age subgroups Were subpopulations identified using objective criteria? Yes, age cut-offs. Overall quality: moderate Other information None.
Full citation Rana, M., Wong-See, D., Katz, T., Gaskin, K., Whitehead, B., Jaffe, A., Coakley, J., Lochhead, A., Fat-soluble vitamin deficiency in children and adolescents with cystic fibrosis, Journal of Clinical Pathology, 67, 605-8, 2014	Sample size N=530 Characteristics People with CF Age: ≤18 years Sex: Males: 49.1% (260/530)* 301/470 children took fat soluble-vitamin supplementation	Details Register/data source. Data from 3 paediatric centres. The Children's Hospital at Westmead, Sydney, Sydney Children's Hospital, and John Hunter Children's Hospital Newcastle. Definitions/thresholds.	Results Prevalence of vitamin deficiency Vitamin A deficiency: 2007: 11.17% 2010: 13.13% Vitamin A levels on first vitamin level test in the study period:	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes, all people fitting inclusion criteria were included Was the sample size adequate? Yes, >250 as per protocol

Study details	Participants	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Australia Study type Retrospective audit Study dates 2007-2010 Source of funding Research scholarship received from the Royal College of Pathologists of Australasia.	*Percentage calculated by the NGA technical team Inclusion criteria People aged ≤18 years who lived in New South Wales, Australia and attended any of the following three paediatric CF centres from 2007 to 2010: The Children's Hospital at Westmead (CHW), Sydney, Sydney Children's Hospital (SCH), and John Hunter Children's Hospital (JHCH), Newcastle. Exclusion criteria Not reported	Vitamins A and E reference ranges varied in each laboratory due to historical reasons. The reference range at CHW was vitamin A (0.8–2.5 mmol/L), vitamin E (12–36 mmol/L); at JHCH, vitamin A (1.05–2.50 mmol/L), vitamin E (8–30 mmol/L). The reference range for vitamins A and E at SCH varied based on the child's age. 25-OHD was measured by radioimmunoassay (Diasorin, Stillwater, MN, USA). Deficiency of 25-OHD was defined as <50 nmol/L. Measurement. Vitamins A and E levels were performed using protein precipitation with high-performance liquid chromatography (HPLC) and ultraviolet detection (in-house method).	Abnormal:23.4% (123/526)* Low: 15% (80/526) Vitamin D deficiency: 2007: 22.11% 2010: 15.54% 25-OHD vitamin levels on first vitamin level test in the study period: Abnormal: 19.8% 65/328* Low: 19% (63/328) Vitamin E deficiency: 2007: 20.22% 2010: 13.89% Vitamin E levels on first vitamin level test in the study period Abnormal: 38.4% (201/523)* Low: 20% (105/523) Deficiency of one or more fat-soluble vitamins on their first vitamin level test: 45% (240/530) *Percentage calculated by the NGA technical team	Were the study subjects and the setting described in detail? Yes Was the data analysis conducted with sufficient coverage of the identified sample? N/A Were objective, standard criteria used for the measurement of the condition? No. The percentages for low vitamin levels at first vitamin test are different from the prevalence of vitamin deficiency in 2007 and it is unclear why. Was the condition measured reliably? No. The range for normal levels of vitamins differs between the laboratories taking part in the study. Was there appropriate statistical analysis? No. No numerators or denominators provided for vitamin deficiency. No confidence intervals provided however all the people attending the centres and fitted inclusion criteria were included so confidence intervals not needed Are all important confounding factors/subgroups/differences identified and accounted for? No, data was not disaggregated between infants, children, young people and adults. Were subpopulations identified using objective criteria? N/A Overall quality: Very low Other information None.

Study details	Participants	Methods	Outcomes and results	Comments
Full citation Somerville, R., Lackson, A., Zhou, S., Fletcher, C., Fitzpatrick, P., Non-pulmonary chronic diseases in adults with cystic fibrosis: analysis of data from the Cystic Fibrosis Registry, Irish Medical Journal, 106, 166-8, 2013 Country/ies where the study was carried out Ireland Study type Retrospective study Study dates All people alive on 31/12/2009. Data recorded from 2001. Source of funding Not reported	Sample size N=853 people in the analyis on prevalence of diabetes * N=859 people in the analysis on the prevalence of osteopenia or osteoporosis * * N calculated by the NGA technical team Characteristics Age: not reported Sex: not reported Inclusion criteria All people alive on 31/12/2009 Exclusion criteria Not reported	Details Register/data source CF Registry of Ireland Definitions/thresholds Authors considered osteopenia or osteoporosis present if documented in the medical notes in the last year. Measurement. Authors did not report what measurements were used for writing the medical notes.	Results Prevalence of osteopenia or osteoporosis: <18 years: 5.5% (25/454*) ≥18 years: 42.7% (173/405) * Denominator calculated by the NGA technical team	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes Was the sample size adequate? Yes, > 250 as per protocol. Were the study subjects and the setting described in detail? No. Baseline characteristics were provided for the adult population only. N used in the analysis was not reported and was different from N reported by the authors, however authors did not mention it and did not explain why. Was the data analysis conducted with sufficient coverage of the identified sample? Yes, N of each subgroup was >250 Were objective, standard criteria used for the measurement of the condition? Yes, authors considered osteopenia or osteoporosis present if documented in the medical notes. Was the condition measured reliably? Unclear if different medical personnel would have diagnosed osteopenia or osteoporosis using the same criteria. Was there appropriate statistical analysis? No. No denominator was provided for one age subgroup. Confidence intervals of percentages were not reported however this is

Study details	Participants	Methods	Outcomes and results	Comments
				registry data so the confidence intervals are not needed. Are all important confounding factors/subgroups/differences identified and accounted for? No. Age subgroups were <18 years and ≥18 years. Data for the former group was not disaggregated between infants, children and young people. Were subpopulations identified using objective criteria? Yes, 18 years old seems a reasonable cut-off. Overall quality: Low Other information Prevalence data on diabetes was not extracted from this study because it was based on whether a person was on insulin in the previous year - this definition is likely to underestimate prevalence
Full citation Stephenson, A. L., Mannik, L. A., Walsh, S., Brotherwood, M., Robert, R., Darling, P. B., Nisenbaum, R., Moerman, J., Stanojevic, S., Longitudinal trends in nutritional status and the relation between lung function and BMI in cystic fibrosis: a population-based cohort study, American Journal of	Sample size N= 909 Characteristics People with CF attending the Adult CF Clinic in Toronto Age: Not reported Sex: Not reported Inclusion criteria All people followed at St Michael's Hospital in Toronto from 1	Details Register / Data source. Toronto CF registry Data collection and measurements. Registry data are collected prospectively in all individuals attending the CF clinic in Toronto. Height (cm) and weight (kg) were recorded for each subject at each clinic visit. Height was measured by using a wall stadiometer, and weight was measured by using a calibrated balance beam scale. BMI was	Results Prevalence of underweight, overweight and obesity. Nutritional status of 651 subjects using their last available measurement between January 2000 and December 2011: Underweight: 17% Adequate weight: 60% Overweight: 18% Obese: 3.8%	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes Was the sample size adequate? Yes, >250 as per protocol Were the study subjects and the setting described in detail? No. Age not reported for each cohort. Only the most recent cohort was described in detail.

Study details	Participants	Methods	Outcomes and results	Comments
Clinical Nutrition, 97, 872-7, 2013 Country/ies where the study was carried out Canada Study type Retrospective study Study dates People followed at the clinic from 1 January 1985 to 31 December 2011 Source of funding Not reported	January 1985 to 31 December 2011 Confirmed diagnosis of CF Exclusion criteria Data obtained after lung transplantation Data obtained during pregnancy and in the 6 months of postpartum period Individuals older than 70 years	calculated by using weight (in kg)/height (in m2). Definitions. Subjects were classified into 1 of 4 BMI categories on the basis of WHO guidelines: Underweight(<18.5), adequate weight (18.5-24.9), overweight (25.0-29.9) or obese (≥30). Analysis. A random sample of 1000 measurements was taken for each of the 3 time intervals.	Underweight, with 1000 random measurements per time interval method: 1985-1990: 20.6% 1991-1999: 11.6%* 2000-2011: 11.1% Overweight, with 1000 random measurements per time interval method: 1985-1990: 7.0% 1991-1999: 15.8% 2000-2011: 18.4% *Percentage calculated by the NGA technical team	Was the data analysis conducted with sufficient coverage of the identified sample? N/A Were objective, standard criteria used for the measurement of the condition? Yes Was the condition measured reliably? Yes Was there appropriate statistical analysis? No, no numerators provided. No confidence intervals of percentages provided however all the people attending the clinic were included so confidence intervals were not needed. Are all important confounding factors/subgroups/differences identified and accounted for? No, no age subgroups. Were subpopulations identified using objective criteria? N/A Overall quality: Low Other information None.
Full citation Vieni, G., Faraci, S., Collura, M., Lombardo, M., Traverso, G., Cristadoro, S., Termini, L., Lucanto, M. C., Furnari, M. L., Trimarchi, G., Triglia, M. R., Costa, S., Pellegrino, S., Magazzu, G., Stunting is an independent predictor of mortality in patients with cystic	Sample size N=393 Characteristics People with CF, alive and deceased Age: > 6 years (193 "paediatric", 200 "adults" - age cut-off not reported)	Details Register / Data source. Data from Regional Centre in Palermo and Satellite Centre in Messina, Italy Definitions and thresholds. "Stunting": Height percentile <5th; "Wasting": BMI percentile <10th in paediatric patients and BMI<18.5 kg/m2 in adult patients	Results Prevalence of “stunting”: Height percentile <5th: 24.4% Prevalence of “wasting”: Either BMI percentile <10th or BMI < 18.5 kg/m2: 35.3%	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes Was the sample size adequate? Yes, >250 as per protocol Were the study subjects and the setting described in detail? No.

Study details	Participants	Methods	Outcomes and results	Comments
fibrosis, Clinical Nutrition, 32, 382-5, 2013 Country/ies where the study was carried out Italy Study type Retrospective study Study dates December 2007 Source of funding None of the authors had sources of support	Sex: Males: Alive: 52.3% vs Deceased: 44.2% Inclusion criteria People with CF who were followed up at the Regional Center in Palermo and at the Satellite Center in Messina with availability of clinical and anthropometric data up to December 2007 Exclusion criteria Not reported	Data collection and measurements. People were classified using the lowest height and weight values in the database. Weight and height in the study group were measured by nurses and dieticians by using precision balances and stadiometers, and CDC growth reference curves were used to obtain centiles from the raw measurements.		Although the number of paediatric and adult patients is given, age cut-off unclear. Was the data analysis conducted with sufficient coverage of the identified sample? N/A Were objective, standard criteria used for the measurement of the condition? Yes Was the condition measured reliably? Yes Was there appropriate statistical analysis? No. No numerators; no confidence intervals for percentages however all the people attending the centres were included so confidence intervals were not needed Are all important confounding factors/subgroups/differences identified and accounted for? No, data are not disaggregated by subgroup. Were subpopulations identified using objective criteria? Yes, age cut-offs. Overall quality: Low. Other information None.
Full citation Watts, K. D., Seshadri, R., Sullivan, C., McColley, S. A., Increased prevalence of risk factors for morbidity and mortality in the US Hispanic CF population,	Sample size N=22714 Characteristics Age: only reported for each ethnic subgroup Inclusion criteria Not reported Exclusion criteria	Details Register / Data source. CFF Patient Registry Definitions and thresholds. Bone and joint complications include arthritis, arthropathy, bone fractures, osteopenia, osteoporosis. Criteria to	Results Prevalence of bone and joint complications: 6.7% (1510/22714)* *Prevalence calculated by the NGA technical team summing up cases in the	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes

Study details	Participants	Methods	Outcomes and results	Comments
Pediatric Pulmonology, 44, 594-601, 2009 Country/ies where the study was carried out United States Study type Retrospective study Study dates Data from 2004 Source of funding The work was supported in part by a Cystic Fibrosis Foundation Clinical Fellowship Grant.	Not reported	diagnose these complications not reported.	Hispanic and in the non-Hispanic population	Was the sample size adequate? Yes, > 250 as per protocol Were the study subjects and the setting described in detail? Yes Was the data analysis conducted with sufficient coverage of the identified sample? N/A Were objective, standard criteria used for the measurement of the condition? Unclear, not reported Was the condition measured reliably? Unclear, not reported Was there appropriate statistical analysis? No, no separate data for each complication Are all important confounding factors/subgroups/differences identified and accounted for? No, no age subgroups Were subpopulations identified using objective criteria? N/A Overall quality: very low Other information None.
Full citation Wiedemann, B., Steinkamp, G., Sens, B., Stern, M., German Cystic Fibrosis Quality Assurance, Group, The German cystic fibrosis quality assurance project: clinical features in children and adults, European	Sample size N=4306 people in the registry who gave informed consent N=3448 people included in the analysis on the prevalence of medical complications Characteristics Mean age: 15.7 years	Details Register / data source. CF Quality Assurance Project registry Definitions. Not reported Data collection and measurements. Centres reported data for each person with CF once a year	Results Prevalence of DIOS Children: 3.0% Adults: 3.5% All ages: 3.2% Weight for height < 90% predicted in children and young people: 26.8%	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes, participating centres reported data for all people under their care. Was the sample size adequate? Yes, >250 as per protocol

Study details	Participants	Methods	Outcomes and results	Comments
Respiratory Journal, 17, 1187-94, 2001 Country/ies where the study was carried out Germany Study type Retrospective study Study dates Data from 1997 Source of funding This work was supported by Christiane Herzog Stiftung, Mukoviszidose e.V., and Niedersächsischer Verein zur Förderung der Qualität im Gesundheitswesen.	Age range: 0-58 Sex: Males: 53.1% Inclusion criteria People in the registry who gave informed consent Exclusion criteria Not reported	from a routine visit near the person's birthday when the person was in a stable clinical condition. Measurement tools were not reported.		Were the study subjects and the setting described in detail? Yes Was the data analysis conducted with sufficient coverage of the identified sample? Yes, N not reported but the authors specify that 35.8% of the people included in the study were older than 18 years, so the number of people in each age subgroup was >250 Were objective, standard criteria used for the measurement of the condition? Unclear. Not reported. Was the condition measured reliably? Unclear. Not reported Was there appropriate statistical analysis? No, numerator and denominator not provided. Confidence intervals of percentages not provided however this is registry data so confidence intervals were not needed. Are all important confounding factors/subgroups/differences identified and accounted for? No. Data was not disaggregated between children and young people. Were subpopulations identified using objective criteria? Unclear, age cut-offs, however cut-off to defined adults not reported. Overall quality: low Other information None.
Full citation	Sample size	Details	Results	Limitations

Study details	Participants	Methods	Outcomes and results	Comments
Wilcock, M. J., Ruddick, A., Gyi, K. M., Hodson, M. E., Renal diseases in adults with cystic fibrosis: a 40 year single centre experience, Journal of Nephrology, 28, 585-91, 2015 Country/ies where the study was carried out UK Study type Retrospective study Study dates 1969-2009 Source of funding Not reported	N=1532 Characteristics Adult CF department at the Royal Brompton Hospital Age: not reported Sex: not reported Inclusion criteria All people with details recorded in the database relating to 1969-2009, alive and deceased. Exclusion criteria Not reported	Register/Data source Database of adult CF department at the Royal Brompton Hospital. A search of the database from 1969 to 2009 was performed to identify patients with an entry in the ‘‘Renal Disease’’, ‘‘Renal Stones’’ or ‘‘Vasculitis’’ categories. All patients who had ever had a plasma urea greater than 10 mmol/l were also identified. Finally, a review of all entries in the ‘‘Other diseases’’ category was made to identify any remaining renal disease. The clinical notes for these patients were then studied for confirmation and to collect clinical data. Definitions AKI was defined as an acute rise in creatinine above the person's established baseline CKD as an abnormal creatinine level for greater than 3 months nephrotic syndrome as proteinuria (>3g/l), hypoalbuminaemia and peripheral oedema Cases were excluded if: isolated rise in plasma urea which resolved with no other evidence of renal impairment impaired renal function in the last few weeks of life	Prevalence of renal disease. Renal problem: 5.1% (78/1532) Acute kidney injury: 1.1%* (17/1532) (9 cases were presumed to be drug-induced; 2 were due to glomerular disease; others were miscellaneous; 3 cases required dyalisis) Chronic kidney disease: 0.9%* (13/1532) (4 cases were presumed to be drug-induced; the other most common aetiology was primary glomerular disease) Renal stone disease: 2.0% (30/1532) Isolated proteinuria: 0.1%* (2/1532) Isolated haematuria: 0.5%* (8/1532) Nephrotic syndrome: 0.1%* (2/1532) Miscellaneous disease: 0.5%* (8/1532) *Percentage calculated by the NGA technical team	Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes, all the people in the database fitting the inclusion criteria were included Was the sample size adequate? Yes, >250 as per protocol Were the study subjects and the setting described in detail? Study subjects were not described in detail. Only the cases were described in detail. Was the data analysis conducted with sufficient coverage of the identified sample? N/A Were objective, standard criteria used for the measurement of the condition? Yes Was the condition measured reliably? Yes Was there appropriate statistical analysis? No, percentages were not provided for some kinds of renal disease (only numerator and denominator were given). No confidence intervals of percentages provided however all the people attending the centre and fitting inclusion criteria were included so confidence intervals were not needed. Are all important confounding factors/subgroups/differences identified and accounted for? Yes.

Study details	Participants	Methods	Outcomes and results	Comments
		nephrotoxic immunosuppressant therapy before any episode of renal disease		The study focuses on a population from an adult centre so there is no need to disaggregate data by age. Were subpopulations identified using objective criteria? N/A Overall quality: Moderate Other information None.
Full citation Zhang, Z., Lindstrom, M. J., Lai, H. J., Pubertal height velocity and associations with prepubertal and adult heights in cystic fibrosis, Journal of Pediatrics, 163, 376-82, 2013 Country/ies where the study was carried out United States Study type Retrospective study Study dates PHV was calculated in relation to time interval 1994-2008. Registry records from 1986-2008 were used to identify participants. Source of funding Supported by the National Institutes of Health (R01DK072126)	Sample size N=1862 Characteristics People with CF Age: 10-18 years Sex: Males: 52.9% Inclusion criteria People with CF born in 1984-1987. Exclusion criteria People who had died by 2008; people lost to follow-up before age 18; people who had <3 height measurements per year during age 10-18 years.	Details Register/data source. Data retrieved from US CF Foundation Registry Definitions/thresholds. Longitudinal standard for peak height velocity for North American children developed by Tanner and Davies were used to define normal Peak Height Velocity (PHV). PHV was classified either as normal, delayed (PHV age at 2 SD later than average), attenuated (magnitude<5th percentile), or both delayed and attenuated (D&A). Measurement. Growth curve modeling was used to identify Peak Height Velocity (PHV). A semi-parametric shape-invariant model developed by Lindstrom was used. "Conceptually, this method assumes that all individuals of the same sex have a common shape for their	Results Prevalence of the following categories of pubertal peak height velocity (PHV): Normal: 60.3% (1123/1862)* Delayed: 9.4% (175/1862)* Attenuated: 20.8% (387/1862)* D&A: 5.3% (98/1862)* Unknown: 4.2% (79/1862)** *Percentage and denominator provided in the paper, numerator calculated by NGA technical team summing up numbers given for males and females ** Percentage and denominator provided the paper, numerator calculated by NGA technical team subtracting the numerators for the	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes. The authors specify that the study population did not differ significantly with regards to sex and pre-pubertal height percentile at age 7 from those excluded from the analysis. Were study participants recruited in an appropriate way? Yes, all people in the registry meeting inclusion and exclusion criteria were included. Was the sample size adequate? Yes, > 250 as per protocol. Were the study subjects and the setting described in detail? Yes Was the data analysis conducted with sufficient coverage of the identified sample? N/A Were objective, standard criteria used for the measurement of the condition? Yes Was the condition measured reliably? Yes

Study details	Participants	Methods	Outcomes and results	Comments
		age versus height curve, which is estimated using data from all children by a non-linear mixed effects model with regression spline that has 2 continuous analytical derivatives. Each child's individual height curve is then determined by shifting and scaling this common curve to obtain the best fit for his/her data. Once an individual's height curve is fitted, the calculated first derivatives of this curve are used to determine the HV curve. Using this approach, 4 measurements characterizing pubertal growth for each child are identified: age at take-off, height at take-off, age at PHV, and magnitude of PHV".	other categories from total number	Was there appropriate statistical analysis? Yes, no confidence intervals provided for prevalence data however this is registry data so confidence intervals were not needed Are all important confounding factors/subgroups/differences identified and accounted for? Yes, data for age subgroup 10-18. Were subpopulations identified using objective criteria? N/A Overall quality: high Other information None.
Full citation Zhang, Z., Shoff, S. M., Lai, H. J., Incorporating genetic potential when evaluating stature in children with cystic fibrosis, Journal of Cystic Fibrosis, 9, 135-42, 2010 Country/ies where the study was carried out United States Study type Retrospective study Study dates	Sample size N=3306 Characteristics People with CF Age: 2-18.5 years Sex: Males: 50% (1649/3306) Inclusion criteria Age: >2 years Self-reported parental heights available Exclusion criteria People with parental heights less than 100	Details Registry / Data source CFF Patient Registry Definitions / thresholds. Procedure to calculate CFF target height and range (lower bound method): 1. Average two parental heights to obtain mid-parental height. Calculate the child's target adult height by adding 6.5 cm to mid-parental height for a boy, or subtracting 6.5 cm for a girl. Apply ±10 cm for a boy or ±9 cm for a girl to define the target height range. 2. Plot target height and range	Results Prevalence of: Unadjusted height percentile <5th: 16% Unadjusted height percentile <10th: 26% Himes adjusted height percentile <5th: 18% Himes adjusted height percentile <10th: 31% CFF lower bound method: 24%	Limitations Critical appraisal using Munn et al 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes Was the sample size adequate? Yes, > 250 as per protocol Were the study subjects and the setting described in detail? Yes Was the data analysis conducted with sufficient coverage of the identified sample? N/A

Study details	Participants	Methods	Outcomes and results	Comments
Data from 1986-2005 Source of funding This work was supported by NIH grant R01-DK72126.	cm (likely due to inch-centimeter conversion or recording errors) were excluded from analysis.	at age 20 years on the 2000 CDC growth chart and estimate their respective percentiles. 3. Extrapolate the percentiles of target height and range at age 20 to the child's current age. 4. Plot the child's height on the 2000 CDC growth chart; if his/her height percentile is below the target height lower bound, he/she is considered to be below genetic potential. Procedure to calculate Himes adjusted height 1. Calculate mid-parental height. 2. Based on the child's sex, age, height and mid-parent height, find the adjustment value from the reference tables. 3. Apply the adjustment value to the child's height to obtain adjusted height. 4. Plot adjusted height on the 2000 CDC growth chart to obtain adjusted height percentile. Measurements. Not reported Analysis. The most recent height measurement between age 2 to 18.5 years for each patient was used for analysis.		Were objective, standard criteria used for the measurement of the condition? Yes Was the condition measured reliably? No. Self-reported parental heights. Was there appropriate statistical analysis? No. No confidence intervals of percentages. Are all important confounding factors/subgroups/differences identified and accounted for? No, data not disaggregated between children and young people. Were subpopulations identified using objective criteria? N/A Overall quality: Low Other information None.
Full citation Cystic Fibrosis Trust, Cystic Fibrosis Trust, UK Cystic Fibrosis Registry	Sample size 9587 Characteristics	Details Register/data source. UK CF registry Data collection.	Results Prevalence of the following complications: Kidney stones:	Limitations Critical appraisal using Munn et al 2014:

Study details	Participants	Methods	Outcomes and results	Comments
2015 Annual Data Report, 2016 Country/ies where the study was carried out UK Study type Registry report Study dates 2015 Source of funding The UK CF Registry has been sponsored and hosted by the Cystic Fibrosis Trust since 2007.	People with CF Median age: 19 Sex: Males: 53.0% Inclusion criteria Informed consent Complete data Exclusion criteria Not reported	CF care teams at every specialist centre and clinic across the UK filled in forms where they selected what complications (if any) each person with CF had. No definition of complications is provided in the form. Definitions. Detailed criteria for diagnosing complications not reported. Definitions are provided for the general public: Arthritis: "A condition causing pain and inflammation in the joints". Arthropathy: "A condition causing pain in the joints". Cirrhosis: "Chronic liver disease". Nasal polyps: "Small, sac-like growths of inflamed mucus caused by chronic inflammation of the nasal lining". Osteopenia: "A medical condition less severe than osteoporosis, where the mineral content of bone is reduced". Osteoporosis: "A condition where the bones become brittle from loss of tissue". Portal hypertension: "High blood pressure in the portal vein system, which is the blood system of the liver".	Overall: 1.0% (96/9587) <16 years: 0.3% (12/3845) ≥16 years: 1.5% (84/5742)Renal failure: Overall: 0.6% (57/9587) <16 years: 0% (<5) ≥16 years: 1.0% (55/5742) Renal failure: Overall: 0.6% (57/9587) <16 years: 0% (<5) ≥16 years: 1.0% (55/5742) Intestinal obstruction: Overall: 5.6% (539/9587) <16 years: 3.0% (116/3845) ≥16 years: 7.4% (423/5742) Treatment for CFRD: ≥10 years: 28.0% (1982/6970) 10-16 years: 10.0% (134/1624) ≥16 years: 32.2% (1848/5346) Nasal polyps requiring surgery: Overall: 2.3% (221/9587) <16 years: 1.1% (44/3845) ≥16 years: 3.1% (177/5742) Sinus disease Overall: 9.8% (939/9587) <16 years: 1.4% (53/3845)	Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes, all people fitting inclusion criteria were included Was the sample size adequate? Yes, >250 as per protocol Were the study subjects and the setting described in detail? Yes Was the data analysis conducted with sufficient coverage of the identified sample? Yes. >250 people in each age subgroup Were objective, standard criteria used for the measurement of the condition? Unclear. Criteria used to diagnose complications not reported Was the condition measured reliably? Unclear from the report, although diagnosis of relevant complications of CF would be consistent across the NHS. Was there appropriate statistical analysis? Yes, numerators and denominators provided. No confidence intervals provided for percentages however this is registry data so the confidence intervals are not needed. Are all important confounding factors/subgroups/differences identified and accounted for? No. Prevalence data is disaggregated into 2 age subgroups using 16 as cut-off, however data are not disaggregated by infants, children, young people and adults.

Study details	Participants	Methods	Outcomes and results	Comments
		Sinus disease: "When the sinuses, which are usually filled with air, are typically full of thick sticky mucus". Measurements. Not reported.	≥16 years: 15.4% (886/5742) Arthritis: Overall: 1.6% (158/9587) <16 years: 0.2% (7/3845) ≥16 years: 2.6% (151/5742) Arthropathy: Overall: 5.4% (517/9587) <16 years: 0.5% (18/3845) ≥16 years: 8.7% (499/5742) Osteopenia: Overall: 13.5% (1297/9587) <16 years: 0.9% (36/3845) ≥16 years: 22.0% (1261/5742) Osteoporosis: Overall: 5.3% (511/9587) <16 years: 0% (<5/3845) ≥16 years: 8.8% (507/5742) Bone fracture: Overall: 0.5% (46/9587) <16 years: 0.4% (14/3845) ≥16 years: 0.6% (32/5742) Raised liver enzymes: Overall: 11.6% (1116/9587) <16 years: 6.9% (264/3845) ≥16 years: 14.8% (852/5742)	Were subpopulations identified using objective criteria? Yes, age cut-offs Overall quality: moderate Other information None.

Study details	Participants	Methods	Outcomes and results	Comments
			Liver disease: Overall: 14.3% (1371/9587) <16 years: 8.8% (340/3845) ≥16 years: 18.0% (1031/5742) Cirrhosis with no portal hypertension: Overall: 1.2% (116/9587) <16 years: 0.7% (26/3845) ≥16 years: 1.6% (90/5742) Cirrhosis with portal hypertension: Overall: 1.7% (164/9587) <16 years: 0.7% (26/3845) ≥16 years: 2.4% (138/5742) Meconium ileus: Overall: 15.2% (1458/9587) <16 years: 16.7% (643/3845) ≥16 years: 14.2% (815/5742)	
Full citation Cystic Fibrosis Trust, UK CF Registry, BMI and BMI percentile in relation to the UK, year 2015. , [online; accessed 23 November 2016] Country/ies where the study was carried out	Sample size N=9084 Characteristics Age: 2 to 11: n=2498 12 to 16: n=885 >16: n=5701 Inclusion criteria	Details Register/Data source. UK CF Registry Definitions / thresholds. Please see results section for BMI cut-offs requested by the NGA technical team (and used by the registry team in providing the data)	Results Prevalence of malnutrition or impaired growth Data disaggregated using the cut-offs used in the Cystic Fibrosis Trust consensus document on nutritional management of cystic fibrosis (2016):	Limitations Critical appraisal using Munn et al. 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes Was the sample size adequate? Yes, >250 as per protocol

Study details	Participants	Methods	Outcomes and results	Comments
UK Study type Data obtained from the UK CF registry following a data request from the NGA technical team Study dates Data obtained on 23 November 2016 Source of funding The UK CF Registry is sponsored and managed by the Cystic Fibrosis Trust	People with CF in the UK with BMIp (BMI percentile) or BMI data recorded in the CF Registry in the year 2015 Exclusion criteria People not consenting to recording their data in the registry* *Information extracted from the UK Cystic Fibrosis Trust Registry 2015 Annual Data Report - which mentions that the registry is a database of consenting people	Data collection and measurements. CF care teams at every specialist centre and clinic across the UK entered data on weight, height and BMI for the registry.	Age 2-11 BMIp < 25th: 17.3% (432/2498)* BMIp >91st: 10.1% (253/2498)* Age 12-16: BMIp < 25th: 27.5% (243/885)* BMIp >91st: 5.9% (52/885)* Age 2-16: · BMIp < 25th: 20.0% (675/3383)* BMIp >91st: 9.0% (305/3383)* Age >16 years: BMI < 20 kg/m2: 24.5% (1398/5701)* BMI > 25 kg/m2: 22.2% (1266/5701)* *Numbers and percentages calculated by the NGA technical team based on the numbers below Data disaggregated by all cut-offs provided by the registry: Age 2-11: BMIp <2nd: 1.5% (38/2498) BMIp ≥2nd and <25th: 15.8% (394/2498) BMIp ≥25th and <50th: 22.9% (572/2498)	Were the study subjects and the setting described in detail? Yes, details available in the UK Cystic Fibrosis Trust Registry 2015 Annual Data Report Was the data analysis conducted with sufficient coverage of the identified sample? Yes, >250 in each age group Were objective, standard criteria used for the measurement of the condition? Unclear from the UK Cystic Fibrosis Trust Registry 2015 Annual Data Report how weight and height were measured Was the condition measured reliably? Unclear from the UK Cystic Fibrosis Trust Registry 2015 Annual Data Report how weight and height were measured Was there appropriate statistical analysis? Yes, numerators, denominators and percentages were provided; no confidence intervals for percentages however this is registry data so confidence intervals were not needed Are all important confounding factors/subgroups/differences identified and accounted for? Yes, data disaggregated into age subgroups: children; young people until 16; and young people older than 16 + adults. BMI is not recorded for infants so data for infants was not provided Were subpopulations identified using objective criteria? Yes, the 16 years

Study details	Participants	Methods	Outcomes and results	Comments
			BMIp ≥50th and ≤75th: 29.9% (748/2498) BMIp >75th and ≤91st: 19.7% (493/2498) BMIp >91st and ≤98th: 8.1% (203/2498) >98th BMIp: 2.0% (50/2498) Age 12-16 BMIp <2nd: 2.0% (18/885) BMIp ≥2nd and <25th: 25.4% (225/885) BMIp ≥25th and <50th: 28.4% (251/885) BMIp ≥50th and ≤75th: 24.6% (218/885) BMIp >75th and ≤91st: 13.7% (121/885) BMIp >91st and ≤98th: 5.4% (48/885) >98th BMIp: 0.5% (4/885) Age 2-16: BMIp <2nd: 1.7% (56/3383) BMIp ≥2nd and <25th: 18.3% (619/3383) BMIp ≥25th and <50th: 24.3% (823/3383) BMIp ≥50th and ≤75th: 28.6% (966/3383) BMIp >75th and ≤91st: 18.1% (614/3383) BMIp >91st and ≤98th: 7.4% (251/3383)	cut-off was used because BMI percentile is recorded in the registry until age 16, and BMI (kg/m2) is recorded for people older than 16. Overall quality: Moderate. Other information 107 people aged 2-16 did not have a record of BMIp in 2015

Study details	Participants	Methods	Outcomes and results	Comments
			>98th BMIp: 1.6% (54/3383) Age >16 years: BMI < 18.5 kg/m2: 8.1% (459/5701) BMI ≥ 18.5 and ≤20 kg/m2: 16.5% (939/5701) BMI ≥ 20 and ≤25 kg/m2: 53.3% (3037/5701) BMI > 25 kg/m2: 22.2% (1266/5701)	
Full citation Cystic Fibrosis Trust, UK CF Registry, Data on intestinal obstruction disaggregated by history of meconium ileus in relation to the UK, year 2015., [online; accessed 11 January 2017] Country/ies where the study was carried out UK Study type Data provided by the UK CF registry following a data request from the NGA technical team Study dates Data provided on 11 January 2017. Source of funding The UK CF Registry is sponsored and managed	Sample size N=9587 Characteristics People with CF Age <16: 3845 Age≥16: 5742 Males: 53%* *Information extracted from the UK Cystic Fibrosis Trust Registry 2015 Annual Data Report Inclusion criteria People with CF recorded in the UK CF registry during the year 2015. Exclusion criteria People not consenting to recording their data in the registry* *Information extracted from the UK Cystic	Details Register/Data source. UK CF Registry Definitions / thresholds. No definition given for intestinal obstruction or meconium ileus. Data collection and measurements. CF care teams at every specialist centre and clinic across the UK entered data on intestinal obstruction and meconium ileus for people with CF	Results Prevalence of intestinal obstruction. Prevalence of intestinal obstruction in age group <16: Among people with a diagnosis of meconium ileus: 6.4% (41/643)* Among people without diagnosis of meconium ileus: 2.3% (75/3202)* Prevalence of intestinal obstruction in age group ≥16: Among people with a diagnosis of meconium ileus: 13.9% (113/815)* Among people without diagnosis of meconium ileus: 6.3% (310/4927)* *Numbers and percentages calculated by the NGA technical team	Limitations Critical appraisal using Munn et al. 2014: Was the sample representative of the target population? Yes Were study participants recruited in an appropriate way? Yes Was the sample size adequate? Yes, >250 as per protocol Were the study subjects and the setting described in detail? Yes, details available in the UK Cystic Fibrosis Trust Registry 2015 Annual Data Report Was the data analysis conducted with sufficient coverage of the identified sample? Yes, more than >250 people in each age subgroup Were objective, standard criteria used for the measurement of the condition? Unclear from the UK Cystic Fibrosis Trust Registry 2015 Annual Data Report how DIOS and meconium ileus were diagnosed

Study details	Participants	Methods	Outcomes and results	Comments
by the Cystic Fibrosis Trust.	Fibrosis Trust Registry 2015 Annual Data Report - which mentions that the registry is a database of consenting people		based on the following numbers provided by the registry: Age group <16 (n=3845): Diagnosed with meconium ileus and 2015 intestinal obstruction: 41 Diagnosed with meconium ileus only: 602 Diagnosed with 2015 intestinal obstruction only: 75 Age group ≥16 (n=5742): Diagnosed with meconium ileus and 2015 intestinal obstruction: 113 Diagnosed with meconium ileus only: 702 Diagnosed with 2015 intestinal obstruction only: 310	Was the condition measured reliably? Unclear from the UK Cystic Fibrosis Trust Registry 2015 Annual Data Report how DIOS and meconium ileus were diagnosed Was there appropriate statistical analysis? Yes, numerators, denominators and percentages were provided; no confidence intervals for percentages however this is registry data so confidence intervals were not needed Are all important confounding factors/subgroups/differences identified and accounted for? No, prevalence data is disaggregated into 2 age subgroups using 16 as cut-off, however data are not disaggregated by infants, children, young people and adults. Were subpopulations identified using objective criteria? Yes, age cut-off Overall quality: Moderate. Other information

G.6 Pulmonary monitoring

Review question 1: What is the value of the following investigative strategies in monitoring the onset of pulmonary disease in people with CF without clinical signs or symptoms of lung disease?

- Non-invasive microbiological investigation- induced sputum samples, cough swab, throat swab, and nasopharangeal aspiration
- Invasive microbiological investigation- broncho-alveolar lavage
- Lung physiological function tests- Cardiopulmonary exercise testing, Spirometry and Lung Clearance Index
- Imaging techniques- Chest x-ray and CT scan

Review question 2: What is the value of the following investigative strategies in monitoring evolving pulmonary disease in people with established lung disease?

- Non-invasive microbiological investigation- induced sputum samples, cough swab, throat swab, and nasopharangeal aspiration
- Invasive microbiological investigation- broncho-alveolar lavage
- Lung physiological function tests- Cardiopulmonary exercise testing, Spirometry and Lung Clearance Index
- Imaging techniques- Chest x-ray and CT scan.

Review question 3: What is the added value of imaging and invasive microbiological testing in addition to non-invasive microbiological testing and lung function tests in monitoring the response to treatment following an acute exacerbation?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Sanders, D. B., Li, Z., Brody, A. S., Chest computed tomography predicts the frequency of pulmonary exacerbations in children with cystic fibrosis, Annals of the American Thoracic Society, 12, 64-69, 2015 Ref Id 371914 Country/ies where the study was carried out USA Study type Follow-up registry data of the Pulmozyme Early Intervention Trial	Sample size 60 children with CF Characteristics Not reported Inclusion criteria PEIT trial enrolled: children aged 6 to 10 years FVC% predicted ≥ 85 ability to perform reproductible pulmonary function test no dornase alpha use for 6 months before enrollment no pulmonary exacerbations before enrollment Exclusion criteria Not reported	Interventions Chest CT scans, scored using the Brody scoring system. PFTs	Details Procedure Baseline data Obtained from prospective PEIT study Follow-up data 10 years of data obtained during routine care CT scans were scored independently by 2 thoracic radiologist. Data from time of the chest CT in 1999 through 2009 were obtained from the CF Foundation Patient Registry (CFFPR) and linked to the original chest CT data Pulmonary exacerbation defined as hospitalizations treated with IV AB and/ or if the “pulmonary	Results Pulmonary exacerbations (rate ratio, 95% CI)* A 1-point increase in Brody chest CT score was associated with the rate of pulmonary exacerbations during the 10-year follow-up period: Rate Ratio =1.39 (95% CI: 1.15 to 1.67) A 5-point decrease in FEV1% predicted was associated with the rate of pulmonary exacerbations during the 10-year follow-up period: Rate Ratio =1.19 (95% CI: 1.10 to 1.30) A 1-point difference in the Brody chest CT score was more strongly associated with the rate of pulmonary exacerbations between 1999 and 2009 than a 5% predicted difference in	Limitations The quality of this study was assessed using the tool proposed by Hayden et al. (2006), as suggested by NICE methods manual (2014) (full citation: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37) 1. The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. UNCLEAR (follow up trial registry data) 2. Loss to follow-up is unrelated to key characteristics (that is,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
(PEIT) participants Aim of the study To determine whether chest CT scores and PFTs are associated with the rate of pulmonary exacerbations and pulmonary function over the next 10 years. Study dates 1999 to 2009 (PEIT trial 1997 to 2000) Source of funding Not reported (possible none)			exacerbation" box was checked in the CFFPR form Statistical analysis Multivariable Poisson regression models. Regression models were adjusted for important confounders Multivariable linear regression model were used to determine the association between the Brody chest CT scores in 1999 and FEV1% predicted in 2009 To compare whether chest CT scores were more strongly associated with the rate of pulmonary exacerbations than FEV1% predicted, the authors compared the magnitudes of the slopes of the chest CT score and FEV1% predicted in the multivariable Poisson regression model with a chi-square test Statistical significance was defined as a two-sided p-value ≤ 0.05	FEV1% predicted at the time of the chest CT (p=0.037 by chi-square test) Difference in FEV1% predicted (mean, 95% CI)** A 1-point increase in Brody chest CT score was associated with a reduction in FEV1% predicted at 10 years follow-up: MD=-4.76 (CI 95% -7.80 to -1.72) A 5-point decrease in FEV1% predicted was associated with a reduction in FEV1% predicted at 10 years follow-up: MD=-4.47 (CI 95% -6.48 to -2.46) No differences in the strengths of the association between the Brody chest CT score and FEV1% predicted in 1999 with FEV1% predicted in 2009 (p=0.04 by F test) * multivariate Poisson model adjusted for sex, genotype, and FEV1 and mucoid P aeruginosa status at the time of the chest CT	the study data adequately represent the sample), sufficient to limit potential bias. YES 3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. YES (CT scan is independently assessed by 2 radiologists. Measurement of FEV1% predicted is not reported) 4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. UNCLEAR (exacerbations are measured by number of hospitalizations requiring IV AB, but registry data is not always accurate. Measurement of FEV1% predicted is not reported) 5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. UNCLEAR (treatment is not controlled for, although it's not an easy factor to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				**multivariate linear regression model adjusted for sex, genotype, and FEV1 and mucoid P aeruginosa status at the time of the chest CT	control for in a long longitudinal study) 6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. YES OVERALL QUALITY: MODERATE Other information (+) DOI included (+) Only study found that evaluates CT scans and PFTs as predictors of later lung disease, measured as a true outcome measure (-) Relies on registry data (-) Study published in 2015 with data from 1999 to 2009 (??) (-) Study might not be representative of more recent birth cohort of children with CF
Full citation Wainwright, C. E., Vidmar, S., Armstrong, D. S., Byrnes, C. A., Carlin, J. B., Cheney, J., Cooper, P. J., Grimwood, K., Moodie, M., Robertson, C. F.,	Sample size N=170 infants diagnosed with CF through newborn-screening programs in 8 CF centres in Australia and New Zealand. BAL directed group: n=84 Standard monitoring: n=84 Characteristics	Interventions Infants received oral flucloxicillin as antistaphylococcal prophylaxis until their first birthday. Participants were seen every 3 months from enrolment until completion at age 5	Details Pulmonary exacerbations were defined as any change in respiratory symptoms from baseline. When unwell with upper respiratory symptoms, increased cough or wheeze, an oropharyngeal	Results Lung function - FEV1 Mean z score (SD) BAL-directed therapy group:-0.56 (1.25) (n=80) Standard therapy group: -0.41 (1.23) (n=77) Mean difference (95% CI) = -0.15 (-0.58 to 0.28); p=0.49 Lung function - LCI	Limitations The quality of this trial was assessed using the Cochrane risk of bias assessment tool. Random sequence generation: low risk of bias (computer generated codes)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Tiddens, H. A., Acfbal Study Investigators, Effect of bronchoalveolar lavage-directed therapy on Pseudomonas aeruginosa infection and structural lung injury in children with cystic fibrosis: a randomized trial, JAMA, 306, 163-71, 2011 Ref Id 332248 Country/ies where the study was carried out Australia and New Zealand Study type Multicentre randomised controlled trial Aim of the study To determine if BAL directed therapy for pulmonary exacerbations during the first 5 years of life provides better	BAL Therapy Group vs Standard Therapy Group Age mean (SD), months: 3.76 (1.62) vs 3.73 (1.69) Gender (Male): 44 (52) vs 44 (52) Pancreatic insufficiency: 73 (87) vs 71 (85) Meconium ileus: 17 (20) vs 16 (19) Presence of respiratory symptoms – Cough: 36 (43) vs 37 (44) Presence of respiratory symptoms – Wheeze: 11 (13) vs 6 (7) Inclusion criteria Infants younger than 6 months of age with a confirmed diagnosis of classic CF (two of the following: 2 CF mutations, sweat chloride level >60 mEq/L, pancreatic insufficiency or meconium ileus) Exclusion criteria Not stated	years, when anthropometric assessments, BAL, high resolution chest CT scan and pulmonary function testing was performed. The child's clinical stability was assessed based on these tests which were performed within 2 weeks. Visits for illness were scheduled as necessary. Standard therapy group Treatment decisions were on the basis of oropharyngeal specimens BAL-directed therapy group Participants also received BAL: a) before 6 months of age when well b) when hospitalised for pulmonary exacerbations c) if P. aeruginosa was cultured from oropharyngeal	specimen was obtained from participants and oral nonantipseudomonal antibiotics was started. Children were hospitalised if the specimen grew P aeruginosa or if the treating physician judged that hospitalisation was warranted because of symptom severity or failure to improve after 6 weeks of ambulatory treatment. Treatment in hospital was initially with IV tobramycin and ticarcillin-clavulanate (Australia) or cefuroxime (New Zealand). Further treatment was dependant on the results of BAL culture (BAL-directed therapy group) or oropharyngeal culture (standard therapy group). If no bacterial pathogens were grown from the BAL cultures, children in the BAL-directed therapy group were discharged receiving oral nonantipseudomonas antibiotics. For children	Not included in the study Lung function - oxygen saturation Not included in the study High-resolution computed tomography (CT) appearances Not included in the study Time to next exacerbation Not included in the study Clearance of the organism from the cultures Not included in the study Inflammatory markers Not included in the study Weight Mean z score (SD) BAL-directed therapy group:-0.15 (0.88) (n=80) Standard therapy group: -0.21 (0.82) (n=77) Mean difference (95% CI) = 0.06 (-0.21 to 0.32); p=0.68 Height Mean z score (SD) BAL-directed therapy group:-0.13 (0.83) (n=80) Standard therapy group: -0.19 (0.98) (n=77) Mean difference (95% CI)	Allocation concealment: low risk of bias (only revealed after confirmed recruitment) Blinding of outcome assessment: unclear (no blinding, but it is unlikely to affect the outcomes) Incomplete outcome data: low risk of bias (All groups were followed up for an equal length of time. In the BAL-directed group (n=80) 2 refused consent for BAL and 1 refused consent for P aeruginosa eradication. In the standard therapy group (n=77) 1 excluded from group by clinician and 3 refused consent for P aeruginosa eradication) Selective reporting: low risk (All groups were followed up for an equal length of time. The groups were comparable for treatment completion. Results not available for 14 participants in each group. The groups were comparable with respect to the availability of outcome data). Other bias: low risk (The groups were comparable

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
outcomes than current standard practice relying on clinical features and oropharyngeal cultures. Study dates 1 June 1999 and 31 December 2005 Source of funding National Health and Medical Research Council, the Royal Children's Hospital Foundation, Pathogenesis Corporation, Chiron Corporation, and Novartis Pharmaceuticals		specimens d) following P aeruginosa eradication therapy	in the BAL-directed therapy group, lower respiratory tract infection was diagnosed when BAL fluid cultures grew respiratory bacterial pathogens in concentrations of ≥ 103 CFUs/mL. If P aeruginosa infection was diagnosed children underwent full eradication treatment (initial 2 weeks tobramycin with either ticarcillin-clavulanate or cefazidime followed by two months of tobramycin inhalation solution and one month of oral ciprofloxacin. Children with <103 CFUs/mL of P aeruginosa in BAL fluid cultures were offered parenteral antipseudomonal antibiotics but not the full eradication course. At the end of treatment, another BAL was performed or an oropharyngeal swab was obtained to determine clearance. If P aeruginosa persisted, the eradication protocol was repeated. After the	= 0.06 (-0.23 to 0.35); p=0.69 BMI Mean z score (SD) BAL-directed therapy group:0.03 (0.93) (n=80) Standard therapy group: 0.01 (0.83) (n=77) Mean difference (95% CI) = 0.02 (-0.25 to 0.30); p=0.87 Quality of life Not included in the study Adverse events Substantial clinical deterioration during and within 24h of BAL 25/524 (4%) (During BAL: 7 children needed intervention for Hb desaturation <90% for duration>60s; 1 child had ventricular tachycardia associated with an anaesthetic protocol violation when halothane was used. Post BAL: 2 children had stridor; 6 children required supplemental O2 for>2hrs - one of whom was monitored in ICU; 2children had respiratory distress (no supplementary O2 required); 3 children were systemically unwell	at baseline, including all major confounding and prognostic. The comparison groups did not received the same care apart from the interventions studied, as the antibiotic choice varied according to best practice guidance for Australia and New Zealand, unlikely to affect relevant outcomes. The study had an appropriate length of follow-up. The study used a precise definition of outcome. The study used a valid and reliable method was used to determine the outcome) OVERALL QUALITY: LOW RISK OF BIAS Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			second cycle, repeat testing confirmed wither successful clearance of chronic infection. Successful clearance meant that future positive cultures were treated as new isolations, whereas chronic P aeruginosa infection was treated with inhaled and oral antipseudomonas antibiotics for respiratory exacerbations no requiring hospitalisation. Statistical Analysis Power calculations were based on the primary outcome of prevalence of P aeruginosa and in evidence of structural lung damage by the total CF-CT score. After an initial calculation indicated a sample size of 240 children would be necessary, subsequent published research indicated that a sample size of 160 children would provide 80% power for a mean difference of 1.5% (% maximum score) (0.45	Unplanned hospital admission post BAL 12/524 (2.3%) (6 children had high fevers and 6 children experienced substantial clinical deterioration) Contaminated bronchoscope 2/524 (0.4%) Fever within 24h post BAL ≥38.5C 40/524 (7.6%) Fever within 24h post BAL <38.5C 40/524 (9.9%) Transient worsening of cough post BAL (151/524 (29%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			SDs) and be adequate for prevalence of P aeruginosa. The study was designed as an intention to treat analysis. Continouous outcomes were compaed using t tests and corresponging confidence intervals for mean differences Weight, height and BMI z scores were calculated from the 2000 CDC Growth Reference Charts. Group comparisons are presented with 95% CIs and 2-sided p values; p<0.05 was used to define statistical significance.		

G.7 Airway clearance techniques

Review question: What is the effectiveness of chest physiotherapy in people with cystic fibrosis?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Braggion, C., Cappelletti, L. M., Cornacchia, M., Zanolla, L., Mastella, G., Short-term effects of three chest	Sample size See Cochrane SR Warnock 2013 Characteristics See Cochrane SR Warnock 2013 Inclusion criteria See Cochrane SR Warnock 2013	Interventions See Cochrane SR Warnock 2013	Details See Cochrane SR Warnock 2013	Results See Cochrane SR Warnock 2013	Limitations See Cochrane SR Warnock 2013 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
physiotherapy regimens in patients hospitalized for pulmonary exacerbations of cystic fibrosis: a cross-over randomized study, Pediatric Pulmonology, 19, 16-22, 1995 Ref Id 333496 Country/ies where the study was carried out Italy Study type RCT Aim of the study To compare short term efficacy of 3 different chest physiotherapy regimens: postural drainage (PD), PEP and high frequency chest compression.	Exclusion criteria See Cochrane SR Warnock 2013				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported. Source of funding Not reported.					
Full citation Darbee, J. C., Kanga, J. F., Ohtake, P. J., Physiologic evidence for high-frequency chest wall oscillation and positive expiratory pressure breathing in hospitalized subjects with cystic fibrosis, Physical Therapy, 85, 1278-89, 2005 Ref Id 333537 Country/ies where the study was carried out USA Study type RCT Aim of the study	Sample size See Cochrane SR Morrison 2014 Characteristics See Cochrane SR Morrison 2014 Inclusion criteria See Cochrane SR Morrison 2014 Exclusion criteria See Cochrane SR Morrison 2014	Interventions See Cochrane SR Morrison 2014	Details See Cochrane SR Morrison 2014	Results See Cochrane SR Morrison 2014	Limitations See Cochrane SR Morrison 2014 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To compare the effectiveness of HFCWO versus PEP mask in people with CF. Study dates Not reported Source of funding A grant from the Medical Centre Research Fund at the Kentucky University.					
Full citation Grzincich, G. L., Longo, F., Faverzani, S., Chetta, A., Spaggiari, C., Pisi, G., Short term effects of high frequency chest compression (HFCC) and positive expiratory pressure (PEP) in adults with cystic fibrosis [Abstract], European	Sample size See Cochrane SR Morrison 2014 Characteristics See Cochrane SR Morrison 2014 Inclusion criteria See Cochrane SR Morrison 2014 Exclusion criteria See Cochrane SR Morrison 2014	Interventions See Cochrane SR Morrison 2014	Details See Cochrane SR Morrison 2014	Results See Cochrane SR Morrison 2014	Limitations See Cochrane SR Morrison 2014 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Respiratory Society Annual Congress, Berlin, Germany, October, 2008 Ref Id 364197 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding					
Full citation Homnick, D. N., Anderson, K., Marks, J. H., Comparison of the flutter device to standard chest physiotherapy in hospitalized patients with cystic fibrosis: a pilot study, Chest, 114, 993-7, 1998 Ref Id	Sample size See Cochrane SR Morrison 2014 Characteristics See Cochrane SR Morrison 2014 Inclusion criteria See Cochrane SR Morrison 2014 Exclusion criteria See Cochrane SR Morrison 2014	Interventions See Cochrane SR Morrison 2014	Details See Cochrane SR Morrison 2014	Results See Cochrane SR Morrison 2014	Limitations See Cochrane SR Morrison 2014 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
333644 Country/ies where the study was carried out USA Study type RCT Aim of the study To compare the efficacy and safety of the flutter compared to manual chest physiotherapy. Study dates Not reported Source of funding Not reported					
Full citation McIlwaine, M. P., Alarie, N., Davidson, G. F., Lands, L. C., Ratjen, F., Milner, R., Owen, B., Agnew, J. L., Long-term multicentre randomised controlled	Sample size See Cochrane SR McIlwaine 2015 Characteristics See Cochrane SR McIlwaine 2015 Inclusion criteria See Cochrane SR McIlwaine 2015 Exclusion criteria See Cochrane SR McIlwaine 2015	Interventions See Cochrane SR McIlwaine 2015	Details See Cochrane SR McIlwaine 2015	Results See Cochrane SR McIlwaine 2015	Limitations See Cochrane SR McIlwaine 2015 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study of high frequency chest wall oscillation versus positive expiratory pressure mask in cystic fibrosis, Thorax, 68, 746-51, 2013 Ref Id 333735 Country/ies where the study was carried out Canada Study type RCT Aim of the study To compare the efficacy of HFCWO and PEP mask in people with CF. Study dates October 2008 and April 2012 Source of funding A grant from the Canadian CF Foundation.					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation McIlwaine, P. M., Wong, L. T., Peacock, D., Davidson, A. G., Long-term comparative trial of positive expiratory pressure versus oscillating positive expiratory pressure (flutter) physiotherapy in the treatment of cystic fibrosis, Journal of Pediatrics, 138, 845-50, 2001 Ref Id 333738 Country/ies where the study was carried out Canada Study type RCT Aim of the study	Sample size See Cochrane SR McIlwaine 2015 Characteristics See Cochrane SR McIlwaine 2015 Inclusion criteria See Cochrane SR McIlwaine 2015 Exclusion criteria See Cochrane SR McIlwaine 2015	Interventions See Cochrane SR McIlwaine 2015	Details See Cochrane SR McIlwaine 2015	Results See Cochrane SR McIlwaine 2015	Limitations See Cochrane SR McIlwaine 2015 Other information Notes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess the long term effects of chest physiotherapy with an oscillating device compared with PEP. Study dates Not reported Source of funding Supported by Telecon Funds.					
Full citation Moran,Fidelma , Bradley,Judy M., Piper,Amanda J., Non-invasive ventilation for cystic fibrosis, Cochrane Database of Systematic Reviews, -, 2013 Ref Id 319449 Study type Cochrane systematic review	Sample size and number of studies included in the Cochrane SR 7 trials, N=106 participants Characteristics of relevant studies Placidi 2006 Population: 17 participants with CF and severe lung disease. Acute participants. Young 2008 Population: 8 participants with CF and moderate lung disease. Mean age (SD) 37 (8) years; mean FEV1% predicted (SD) 35 (8) Inclusion criteria Placidi 2006* age > 15 yrs,	Interventions Placidi 2006 Interventions: direct cough, PEP mask, CPAP mask, NIV with IPAP. Order of intervention randomized: treatment twice daily for 70 minutes for 2 days per intervention. Young 2008 Intervention: 6 weeks of NIV Placebo (room air) 2-week washout period	Details Placidi 2006 Design: RCT, cross-over trial Outcomes. sputum weight, FEV1, SpO2, participants subjective impression of effectiveness Young 2008 Design: RCT, cross-over Outcomes: lung function, awake and sleep gas exchange, QoL (CF-QoL) Post treatment assessments carried out during a period of clinical stability i.e no need for hospitalisation or intravenous antibiotics*	Results Comparison: PEP vs control Sputum dry weight (follow-up mean 2 days (Placidi 2006) MD 0.03 lower (0.48 lower to 0.42 higher) Sputum wet weight (follow-up mean 2 days (Placidi 2006) MD 1.8 higher (1.72 lower to 5.32 higher) Lung function - FEV1 (follow-up mean 2 days (Placidi 2006) MD 0.01 higher (0.18 lower to 0.2 higher)	Limitations Quality of the Cochrane SR: Systematic review assessed using AMSTAR checklist. Total score: 11/11. Quality of the individual studies: Risk of bias assessment taken from the Cochrane systematic review Placidi 2006 Random sequence generation: low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To evaluate the effectiveness of NIV in people with CF. Study dates Last search: 01/03/2013 Source of funding Not reported	'best' value of the FEV1 in last 6 months < 40% of predicted, ability to expectorate sputum and reliably perform pulmonary function tests, ability to produce > 30 ml sputum volume expectorated per day, proficiency in PEP mask. Young 2008* FEV1 equal to or below 70% predicted, clinical stability, positive screening overnight oximetry SpO2 < 90% for >= 5% of night, impaired gas exchange on polysomnography, awake hypercapnia. Exclusion criteria Placidi 2006* severe respiratory failure with need of fraction of inspired oxygen > 31% and/or symptoms or signs of right heart failure, airway infection with B.cepacia complex and/or oxacillin-resistant S.aureus, need for > 2 physiotherapy sessions a day, gastroesophageal reflux, pneumothorax or massive hemoptysis,			Lung function - FVC (follow-up mean 2 days (Placidi 2006) MD 0.05 higher (0.35 lower to 0.45 higher) Oxygen saturation - Spo2 % (Placidi 2006) MD 0.3 higher (0.58 lower to 1.18 higher) Comparison: NIV vs control QoL - CF- QoL chest symptom score (Young 2008, n=8) MD (fixed, 95% CI): 7.00 (-11.73 to 25.73) QoL - CF- QoL traditional dyspnoea index score (Young 2008, n=8) MD (fixed, 95% CI): 2.90 (0.71 to 5.09) Lung function (while awake) - FEV1 (Young 2008, n=8) MD (fixed, 95% CI): 1.00 (-8.62 to 10.62) Lung function (while awake) - FVC (Young 2008, n=8) MD (fixed, 95% CI): 4.00 (-10.30 to 18.30)	Allocation concealment: unclear risk Blinding(all outcomes): unclear risk Incomplete outcome data (all outcomes): unclear risk Selective reporting: low risk Other bias: unclear risk Young 2008 Random sequence generation: low risk Allocation concealment: low risk Blinding: unclear risk Incomplete outcome data: low risk Selective reporting: low risk Other bias: low risk Other information The data presented in this section has been adapted from the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	need for surgical or endoscopic procedures during study period, symptons of asthma in the last year or FEV1 increase > 12% of predicted after inhalation of albuterol, known or suspected tympanic rupture or other middle-ear pathology, headache, earache or recurrent epistaxis associated with administration of positive airway pressure, inability to tolerate CPAP and NPPV via nasal mask. Young 2008* previous domiciliary oxygen or NIV, current sedative use, cardiac or neurological disease, obstructive sleep apnoea.			Oxygen saturation (nocturnal) (Young 2008, n=8) MD (fixed, 95% CI): 3.00 (-1.04 to 7.04)	Cochrane systematic review. We present the data that is relevant to the aims of this review. Individual studies where retrieved for accuracy and to check if other outcomes of interest where reported. Data extracted by the review team from the original study has been marked with an *.
Full citation Morrison, L., Agnew, J., Oscillating devices for airway clearance in people with cystic fibrosis, Cochrane Database of	Sample size and number of studies included in the Cochrane SR 35 trials, N=1050 participants Characteristics of relevant studies Darbee 2005 15 participants, 8 male, 7 female.	Interventions Darbee 2005 PEP versus HFCWO. Both treatments were alternated within 48 hours of hospital admission and then reversed prior to discharge.	Details Darbee 2005 Design: RCT, cross-over All participants performed HFCWO 1 - 3 times daily as outpatients before admission, but none had performed PEP Grzincich 2008 Design: RCT	Results Comparison: PEP mask vs oscillation Lung function - FEV1 (follow-up 2-4 weeks) % change from baseline Padman 1999: MD 4.08 higher (4.66 lower to 12.82 higher)	Limitations Quality of the Cochrane SR: Systematic review assessed using AMSTAR checklist. Total score: 11/11. Quality of the individual studies:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Systematic Reviews, 7, CD006842, 2014 Ref Id 361498 Study type Cochrane SR Aim of the study To determine if oscillatory devices are effective for airway clearance, and compare them to other airway clearance techniques. Study dates Last search 13/01/2014 Source of funding Not reported	Aged at least 7 years, mean (SD) age 17.5 (4.2) years. Participants were admitted to hospital for acute exacerbation. Grzincich 2008 23 participants. 12 female, mean age 25 years. Homnick 1998 22 participants enrolled into study, the data for 33 hospitalisations 20 male, 13 female. Mean (range) age: 12 (7- to 44) years. CF confirmed by sweat test and/or genetic testing. Oermann 2001 29 participants enrolled 14 male Aged 6 years or greater. Mean age 23 (9 to 39 range). Diagnosis of CF confirme d by sweat test. Required ability to reliably perform spirometry and lung volume measurements, to have baseline FVC of 50 - 80 %predicated and be clinically stable for 1 month prior toenrolment. Excluded if in concurrent study or history of massive haemoptysis within 1 month	Treatment lasted 30 minutes. Grzincich 2008 Use of HFCWO at setting of 20 Hz f or 30 minutes compared with 30 minutes of PEP; this occurred during the first 3 days of treatment Homnick 1998 Flutter or manual physiotherapy. Treatment was 4 times daily. CPT was carried out for 30 min and Flutter for 15 min. Oermann 2001 HFCWO and Oscillating PEP (Flutter) As prescribed previous to study - no mention whether this was 2 x daily etc. 4 weeks in each arm, 2-week lead-in/ wash out periods during which time they resumed their normal routine therapies which were not outlined Padman 1999 Flutter, PEP and manual physiotherapy.	Patients randomised to receive either HFCWO or PEP during the first 3 days of hospitalisation for an exacerbation Homnick 1998 Design: open label comparative trial, cross-over Oermann 2001 Design: RCT, cross-over 5 participants withdrew (4 exited due to illness and 1 due to non-compliance with clinic visits) Padman 1999 Design: RCT, cross-over 5 participants excluded due to hospital admission for acute exacerbation, 4 withdrew (no reason given). 6 participants completed the study van Winden 1998 Design: RCT, cross-over Outcomes were measured before and after each treatment intervention Warwick 2004 Design: RCT, cross-over 12 participants (all male) with CF. Mean (range) age 29.2 (19 - 50) years. Consistent sputum producers; all volunteers	Lung function - FEV1 (follow-up 2-4 weeks) % predicted van Winden: MD - 2 (4.36 lower to 0.36 higher) Lung function - FVC (follow-up 2-4 weeks) % predicted MD - 2 (4.09 lower to 0.09 higher) Comparison: PEP mask vs HFCWO Sputum volume (follow-up mean 1 weeks) ml Grzincich 2008: 1.8 (3 lower to 6.6 higher) Lung Function - FEV1 (follow-up 1-2 weeks) % predicted Darbee 2005: MD -3 (20.54 lower to 14.54 higher) FVC (follow-up 1-2 weeks) % predicted Darbee 2005: MD - 3 lower (16.6 lower to 10.6 higher) Comparison: oscillating device vs high frequency oscillation Lung function - FEV1 % predicted 2 to 4 weeks (1 study, =24) Oerman 2001: MD (fixed, 95% CI): -1.60 (-3.44 to 0.24)	Risk of bias assessment taken from the Cochrane systematic review Darbee 2005 Random sequence generation: low risk Allocation concealment: high Blinding(all outcomes): unclear risk Incomplete outcome data (all outcomes): unclear risk Selective reporting: unclear risk Other bias: unclear risk Grzincich 2008 Random sequence generation: unclear risk Allocation concealment: uncl ear risk Blinding(all outcomes): unclear risk Incomplete outcome data (all

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	or pneumothorax within 6 months of entrance. Padman 1999 15 participants aged 5 to 17 years with CF. Gender split was not stated. Participants were clinically stable and able to perform RFT's, no hospitalisations in the month prior to study. van Winden 22 participants 12 males Mean age 12 years; range 7 - 17 years. CF confirmed by sweat test or DNA mutation analysis, clinically stable for 2 weeks before study. Warwick 2004 12 participants (all male) with CF. Mean (range) age 29.2 (19 - 50) years. Consistent sputum producers; all volunteers with no illness within 6 weeks of study Inclusion criteria See characteristics of included studies Exclusion criteria See characteristics of included studies	Participants served as own controls, each therapy was performed for 15 min 3x daily for 1 month van Winden 1998 Flutter, PEP mask. Twice daily, 2 weeks in each arm, 1 week wash-in and wash-out period Warwick 2004 HFCC 5 minutes at 6 freque ncies, followed by 3 huffs and directed coughs at the end of each cycle. Manual physiotherapy10 hand positions. 3 huffs and directed cough afte r each position treatment lasting about 40 - 50 min. All treatments preceded by nebulisers and given daily for 4 weeks. Treatment times took approximately 36 - 50 min (standard CPT 45 - 50 min and HFCWO 36 - 40 min)	with no illness within 6 weeks of study	Lung function - FVC (% predicted) 2 to 4 weeks (1 study, =24) Oerman 2001: MD (fixed, 95% CI): -1.40 (-3.07 to 0.27) Comparison: manual chest physio vs oscillating device Lung function - FEV1 (% change from baseline) 2 to 4 weeks Padman 1999 (n=6) - Mean (SD): 3.66 (9.6) vs. 6.25 (5.6) Lung function - FEV1 (follow-up mean 8.8 days; % change from baseline Homnick 1998: MD 7.9 lower (31.04 lower to 15.24 higher) Lung Function - FVC (follow-up mean 2 weeks; % change from baseline) Homnick 1998: MD 2.9 higher (14.21 lower to 20.01 higher) Comparison: manual chest physio vs HFCWO Sputum weight, dry (g.) 1 to 2 weeks Warwick 2004 (n=12): MD 0.13 lower (0.42 lower to 0.16 higher)	outcomes): unclear risk Selective reporting: unclear risk Other bias: unclear risk Homnick 1998 Random sequence generation: unclear risk Allocation concealment: unclear risk Blinding(all outcomes): unclear risk Incomplete outcome data (all outcomes): high risk Selective reporting: unclear risk Other bias: low risk Oermann 2001 Random sequence generation: unclea r risk Allocation concealment: uncl ear risk Blinding(all outcomes): unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Sputum weight, wet(g.) 1 to 2 weeks Warwick 2004 (n=12): MD 4.04 lower (10.77 lower to 2.69 higher)	Incomplete outcome data (all outcomes): low risk Selective reporting: high risk Other bias: unclear risk Padman 1999 Random sequence generation: unclear risk Allocation concealment: unclear risk Blinding(all outcomes): unclear risk Incomplete outcome data (all outcomes): high risk Selective reporting: high risk Other bias: unclear risk van Winden 1998 Random sequence generation: unclear risk Allocation concealment: unclear risk Blinding(all outcomes): low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Incomplete outcome data (all outcomes): low risk Selective reporting: unclear risk Other bias: unclear risk Warwick 2004 Random sequence generation: unclear risk Allocation concealment: unclear risk Blinding(all outcomes): high risk Incomplete outcome data (all outcomes): unclear risk Selective reporting: unclear risk Other bias: high risk - paper also reports that a natural competition between two different therapists was created. In addition the hand positions used by

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					the therapist were not defined. Other information The data presented in this section has been adapted from the Cochrane systematic review. We present the data that is relevant to the aims of this review. Individual studies where retrieved for accuracy and to check if other outcomes of interest where reported. Data extracted by the review team from the original study has been marked with an *.
Full citation Newbold, M. E., Tullis, E., Corey, M., Ross, B., Brooks, D., The Flutter Device versus the PEP Mask in the	Sample size See McIlwaine 2015 Characteristics See McIlwaine 2015 Inclusion criteria See McIlwaine 2015 Exclusion criteria See McIlwaine 2015	Interventions See McIlwaine 2015	Details See McIlwaine 2015	Results See McIlwaine 2015	Limitations See McIlwaine 2015 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
treatment of adults with cystic fibrosis, Physiotherapy Canada, 57, 199-207, 2005 Ref Id 361522 Country/ies where the study was carried out Canada Study type RCT Aim of the study To evaluate the effectiveness of the flutter versus the PEP mask. Study dates Not reported Source of funding Not reported					
Full citation Oermann, C. M., Sockrider, M. M., Giles, D., Sontag, M. K., Accurso, F. J., Castile, R. G.,	Sample size See Cochrane SR Morrison 2014 Characteristics See Cochrane SR Morrison 2014 Inclusion criteria	Interventions See Cochrane SR Morrison 2014	Details See Cochrane SR Morrison 2014	Results See Cochrane SR Morrison 2014	Limitations See Cochrane SR Morrison 2014 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Comparison of high-frequency chest wall oscillation and oscillating positive expiratory pressure in the home management of cystic fibrosis: a pilot study, Pediatric Pulmonology, 32, 372-7, 2001 Ref Id 333781 Country/ies where the study was carried out USA Study type RCT Aim of the study To compare the effectiveness of high-frequency chest wall oscillation and oscillating positive expiratory	Exclusion criteria				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
pressure in the home management of cystic fibrosis. Study dates Not reported Source of funding Not reported					
Full citation Padman, R., Geouque, D. M., Engelhardt, M. T., Effects of the flutter device on pulmonary function studies among pediatric cystic fibrosis patients, Delaware Medical Journal, 71, 13-8, 1999 Ref Id 333786 Country/ies where the study was carried out Study type	Sample size See Cochrane SR Morrison 2014 Characteristics See Cochrane SR Morrison 2014 Inclusion criteria See Cochrane SR Morrison 2014 Exclusion criteria See Cochrane SR Morrison 2014	Interventions See Cochrane SR Morrison 2014	Details See Cochrane SR Morrison 2014	Results See Cochrane SR Morrison 2014	Limitations See Cochrane SR Morrison 2014 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Study dates Source of funding					
Full citation Placidi, G., Cornacchia, M., Polese, G., Zanolla, L., Assael, B. M., Braggion, C., Chest physiotherapy with positive airway pressure: a pilot study of short-term effects on sputum clearance in patients with cystic fibrosis and severe airway obstruction, Respiratory Care, 51, 1145-53, 2006 Ref Id 333804 Country/ies where the study was carried out	Sample size See Cochrane SR Moran 2013 Characteristics See Cochrane SR Moran 2013 Inclusion criteria See Cochrane SR Moran 2013 Exclusion criteria See Cochrane SR Moran 2013	Interventions See Cochrane SR Moran 2013	Details See Cochrane SR Moran 2013	Results Comparison: PEP versus control* Pulmonary function - FEV1 Before (mean±SD): 0.99±0.27 vs 0.96±0.26 After (mean±SD): 1.00±0.27 vs 0.99±0.25; p=0.19 Pulmonary function - FVC Before (mean±SD): 1.94±0.63 vs 1.87±0.57 After (mean±SD): 2.00±0.62 vs 1.95±0.58; p=0.99 Pulmonary function - FEF25-75 Before (mean±SD): 0.28±0.12 vs 0.28±0.11 After (mean±SD): 0.27±0.11 vs 0.28±0.12; p=0.20 Sputum dry weight (g) Mean±SD: 0.94±0.57 vs 0.97±0.76; p=0.29	Limitations See Cochrane SR Moran 2013 Other information The comparison PEP vs control was not included in the Cochrane review.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported (author correspondence in Italy). Study type RCT Aim of the study To evaluate short-term effects of directed cough combined with PEP, CPAP and NPPV on wet and dry sputum weight. Study dates Not reported Source of funding Not reported.				Sputum wet weight (g) Mean±SD: 15.78±5.49 vs 13.98±4.96; p<0.05 Oxygen saturation - Spo2 Before (mean±SD): 95.1±1.5 vs 94.8±1.7 After (mean±SD): 94.9±1.2 vs 94.6±1.4; p=0.007 Comparison: NIV (NPPV) vs control See Cochrane SR Moran 2013	
Full citation van Winden, C. M., Visser, A., Hop, W., Sterk, P. J., Beckers, S., de Jongste, J. C., Effects of flutter and PEP mask physiotherapy on symptoms and lung function in	Sample size See Cochrane SR Morrison 2014 Characteristics See Cochrane SR Morrison 2014 Inclusion criteria See Cochrane SR Morrison 2014 Exclusion criteria	Interventions See Cochrane SR Morrison 2014	Details See Cochrane SR Morrison 2014	Results See Cochrane SR Morrison 2014	Limitations See Cochrane SR Morrison 2014 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
children with cystic fibrosis, European Respiratory Journal, 12, 143-7, 1998 Ref Id 333902 Country/ies where the study was carried out Switzerland Study type RCT Aim of the study To compare the effectiveness of flutter and PEP mask in people with CF. Study dates Not reported Source of funding Not reported. Flutters were provided by VarioRaw.	See Cochrane SR Morrison 2014				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Warnock, L., Gates, A., van der Schans, C. P., Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis, Cochrane Database of Systematic Reviews, 9, CD001401, 2013 Ref Id 333912 Study type Cochrane SR Aim of the study To assess the effectiveness and acceptability of chest physiotherapy compared to no treatment in people with CF. Study dates Last search 05/09/2013	Sample size and number of studies included in the Cochrane SR 8 trials, N=96 participants Characteristics of relevant studies Braggion 1995 Population: 16 patients with CF 8 males, 8 females; mean age (SD): 20.3 (4) years; mean FEV1% 61.7% (17%) Interventions: breathing exercises, vibrations, manual percussion, PEP and control Inclusion criteria Age 14 yrs ability to expectorate sputum and reliably perform lung function tests more than 30 mL/day sputum volume expectorated mild/moderate airway obstruction profeciency in postural drainage and PEP CPT (manual technique). Exclusion criteria Need for > 2 physiotherapy sessions per day gastrooesophageal reflux, pneumothorax, massive haemoptysis	Interventions Braggion 1995 Interventions: breathing exercises, vibrations, manual percussion, PEP and control	Details Braggion 1995 Design: Cross-over study Outcomes: weight expectorated mucus; pulmonary function; subjective assessment	Results Comparison: PEP vs. control Lung function - FEV1 (Braggion 1995) mean (SD) before: 62.3±21.6 vs 60.8±19.9 mean (SD) after: 62.4±20.5 vs 60.3±19.4, ns Lung function - FVC (Braggion 1995) mean (SD) before: 82.8±21.1 vs 81.6±19.5 mean (SD) after: 83.6±19.8 vs 82.1±19.6, ns Lung function - FEF25-75 (Braggion 1995) mean (SD) before: 30.81±20.8 vs 27.8±17.2 mean (SD) after: 29.4±19.7 vs. 26.7±16.0, ns Expectorated secretions - wet weight of sputum (g) (Braggion 1995) mean (SD): 26.13±12.28 vs 5.98±6.21	Limitations Quality of the Cochrane SR: Systematic review assessed using AMSTAR checklist. Total score: 11/11. Quality of the individual studies: Risk of bias assessment taken from the Cochrane systematic review Braggion 1995 Random sequence generation: low risk Allocation concealment: unclear risk Blinding (all outcomes): unclear risk Incomplete outcome data (all outcomes): unclear risk Selective reporting: low risk Other bias: low risk Other information The data presented in this

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported	need for surgical or endoscopic procedures during the study period symptoms of asthma in the year before the study need for corticosteroid or bronchodilator therapy during study period.				section has been adapted from the Cochrane systematic review. We present the data that is relevant to the aims of this review. Individual studies where retrieved for accuracy and to check if other outcomes of interest where reported. Data extracted by the review team from the original study has been marked with an *.
Full citation Warwick, W. J., Wielinski, C. L., Hansen, L. G., Comparison of expectorated sputum after manual chest physical therapy and high-frequency chest compression, Biomedical Instrumentation & Technology,	Sample size See Cochrane SR Morrison 2014. Characteristics See Cochrane SR Morrison 2014. Inclusion criteria See Cochrane SR Morrison 2014. Exclusion criteria See Cochrane SR Morrison 2014.	Interventions See Cochrane SR Morrison 2014.	Details See Cochrane SR Morrison 2014.	Results See Cochrane SR Morrison 2014.	Limitations See Cochrane SR Morrison 2014. Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
38, 470-5, 2004 Ref Id 333916 Country/ies where the study was carried out USA Study type RCT Aim of the study To compare high frequency chest compression and manual chest physiotherapy in people with CF. Study dates Not reported Source of funding Not reported					
Full citation Young, A. C., Wilson, J. W., Kotsimbos, T. C., Naughton, M. T., Randomised placebo	Sample size See Cochrane SR Moran 2013. Characteristics See Cochrane SR Moran 2013. Inclusion criteria	Interventions See Cochrane SR Moran 2013.	Details See Cochrane SR Moran 2013.	Results See Cochrane SR Moran 2013.	Limitations See Cochrane SR Moran 2013. Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
controlled trial of non-invasive ventilation for hypercapnia in cystic fibrosis, Thorax, 63, 72-7, 2008 Ref Id 361764 Country/ies where the study was carried out Australia Study type RCT Aim of the study To study the effects of nocturnal NIV on quality of life, functional and physiological outcomes in CF subjects with awake hypercapnia. Study dates Not reported Source of funding National Health and Medical Research Council of	See Cochrane SR Moran 2013. Exclusion criteria See Cochrane SR Moran 2013.				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Australia, Monash University and The Australian Cystic Fibrosis Research Trust.					
Full citation McIlwaine, M, Button, B, Dwan, K, Positive expiratory pressure physiotherapy for airway clearance in people with cystic fibrosis, Cochrane Database of Systematic Reviews, CD003147, 2015 Ref Id 372830 Study type Cochrane SR Aim of the study To determine the effectiveness and the acceptability of	Sample size and number of studies included in the Cochrane SR 26 trials, N=733 participants Characteristics of relevant studies McIlwaine 2013 Participants: CF confirmed by sweat test or genotyping. 107 participants from 12 CF centres (57 males); age range 6 - 47 years; FEV1 over 40% predicted. Participants were excluded if they had been hospitalised within the past month for a pulmonary exacerbation, or if they were not stable on clinical evaluation, chest radiograph or pulmonary function. McIlwaine 2001 Participants CF confirmed by sweat test. 40 participants (24 male); age range 7 - 17 years;	Interventions McIlwaine 2013 Interventions: 2 interventions: 51 participants were randomised to PEP and 56 to HFCWO PEP - using a mask with pressures 10 - 20 cms H20, participants breathed through the device for 15 breaths followed by 2 -3 huffs and a cough; this was repeated for 6 cycles; HFCWO - using the InCourageTM system; 6 sets of 5-minute cycles were performed with frequencies between 6 - 15 Hz, this was interspersed with huffing and coughing. McIlwaine 2001 Interventions 2 interventions: 20 participants were	Details McIlwaine 2013 Design: Multi-centre RCT. Parallel design. Treatment for 1 year. On entering the study, participants performed a 2-month washout period before being allocated to an intervention Outcomes: Number of pulmonary exacerbations and time to first exacerbation. PFTs measuring FVC, FEV1 and FEF 25−75% in absolute change. Quality of life using the Cystic Fibrosis Questionnaire and patient satisfaction visual analogue scale Notes: There were 16 drop-outs during the washout period before participants commenced one of the two interventions being studied. These were not included in the results. A further 3 dropped out during the	Results COMPARISON: PEP VS OSCILLATING PEP (flutter and cornet) Lung function (FEV1) >6 to 12 months (1 study, n=30) MD (fixed, 95% CI): 9.71 (-2.12 to 21.54) Lung function (FEV1) >1 to 2 years (2 studies, n=72) MD (fixed, 95% CI): -2.34 (-6.86 to 2.18) Lung function (FVC) >6 to 12 months (1 study, n=30) MD (fixed, 95% CI): 8.68 (-0.54 to 17.90) Lung function (FVC) >1 to 2 years (1 study, n=42)	Limitations Quality of the Cochrane SR: Systematic review assessed using AMSTAR checklist. Total score: 11/11. Quality of the individual studies: Risk of bias assessment taken from the Cochrane systematic review McIlwaine 2013 Random sequence generation (selection bias): Low risk (Randomised was by an independent statistician using a computer-generated randomisation table. Participants were matched for age, sex and pseudomonas

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
positive pressure devices in people with CF. Study dates Last search 02/12/2014 Source of funding This SR is supported by the NIH.	FEV1 range 47 - 107% predicted; Schwachman score range 54 - 98 points. Participants were excluded if they had been hospitalised within the past month for a pulmonary exacerbation, or if they were not stable on clinical evaluation, chest radiograph or pulmonary function Newbold 2005 Participants CF diagnosed by St Michael's Hospital CF Clinic, Toronto. 42 participants (24 male). PEP Group: 21 participants (15 male); mean age 28, SD 8.1 years; mean FEV1 2.5, SD 1.2 litres; mean FEV1 66, SD 19.9% predicted. Flutter Group: 21 participants (9male); mean (SD) age 31 (8.7) years;mean (SD) FEV1 2.2 (0.7) litres; mean (SD) FEV1 69(18.5) % predicted. Participants were excluded if they had been hospitalised within the past month for a pulmonary exacerbation, had changed their medication within the past month, or did not have a daily cough or daily sputum	randomised to each group. The daily regimen for use of the devices is not described. 1. PEP treatment - participants inhaled and exhaled through the Astra Meditec PEP mask in sitting; the resistor which produced 10 to 20 cm H2O pressure during midexpiration was used. Over approximately 2 minutes, 15 tidal breaths with slightly active expiration were performed. Participants then removed themask, performed 2 or 3 forced expirations, and coughed, followed by 1 - 2 minutes of relaxed breathing. This sequence was repeated 6 times and these 20-minute sessions were repeated twice daily; 2. Oscillating PEP - participants exhaled through the flutter device which was angled to maximise the sensation of vibration in the chest. In sitting,	intervention period. These were included in analysis with intention to treat analysis. Published paper. McIlwaine 2001 Design: RCT. Parallel design. Treatment for 1 year. Outcomes: FEV1, FVC, and FEF25−75 and clinical assessment using Shwachman and Huang scores were measured at the beginning and at 3-monthly intervals throughout the study. Number of hospitalizations for pulmonary exacerbations were recorded throughout the study. Compliance with the interventions was recorded daily by the participants. A monthly questionnaire recorded physical activity, general well-being, cough, sputum production, subjective impression of the therapy, and adverse events. Chest radiographs were evaluated by a blinded radiologist at the beginning and end of the study	MD (fixed, 95% CI): -1.70 (-6.27 to 2.87) Lung function (FEF25-75%) >6 to 12 months (1 study, n=30) MD (fixed, 95% CI): 5.29 (-7.84 to 18.42) Lung function (FEF25-75%) >1 to 2 years (1 study, n=42) MD (fixed, 95% CI): -1.1 (-6.50 to 4.30) Hospitalizations for respiratory exacerbation (number per participant) >1 to 2 years (1 study, n=42) MD (fixed, 95% CI): -0.40 (-0.92 to 0.12) Patient preference: self-withdrawal due to lack of perceived effectiveness (6 to 12 months) (1 study, n=40) RR (M-H, fixed, 95% CI): 0.09 (0.01 to 1.54) COMPARISON: PEP VS. HFCWO	status. The statistician also attempted to block patients within each centre to control for any treatment differences between centres) Allocation concealment (selection bias): Low risk (The randomisation was performed by an independent statistician who provided the randomisation to the centre after the participant had enrolled in the study Blinding (performance bias and detection bias) - All outcomes: Low risk (Participants and person providing the therapy were not blinded - unclear risk; Outcome assessors were blinded - low risk) Incomplete outcome data

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Interventions 2 interventions: 21 participants were randomised to each group. Tannenbaum 2005 (abstract only) Participants 30 children with CF, age range 6 - 15 years, 20 females. Inclusion criteria See characteristics of included studies. Exclusion criteria See characteristics of included studies.	participants inhaled deeply through the nose, followed by a breath hold for 2 - 3 seconds, and exhaled through the device slightly into the expiratory reserve volume. After 10 - 15 breaths, participants huffed through the device, increasing the TV and speed of exhalation to precipitate coughing and expectoration. This sequence was repeated “until clear” and not for less than 15 minutes per session, twice daily Newbold 2005 Interventions 2 interventions: 21 participants were randomised to each group. PEP treatment - pressure 10 - 20 cm H2O using an Astra Meditec PEP mask; seated participants breathed 10 - 15 times through the mask, followed by huffing, coughing and relaxed breathing, this was repeated 5 - 6 times,	Notes: 3 participants were withdrawn due to non-compliance (< 85% of twice-daily sessions performed over 1 month) in the PEP group. 5 participants dropped out from the flutter group stating that subjectively the flutter did not appear to clear their secretions. Published paper. Newbold 2005 Design: RCT. Parallel design. Treatment for 13 months. Interventions 2 interventions: 21 participants were randomised to each group. Outcomes: Slope of change in FEV1, FVC, and FEF25−75 (absolute and % predicted), number of hospitalisations. Notes: 1 participant was withdrawn when he stopped attending the CF clinic. Published paper. Tannenbaum 2005 (abstract only) Design: RCT. Parallel design. Treatment period of 12 months.	Lung function (FEV1) 1 year (1 study, n=88) MD (fixed, 95% CI): -3.59 (-9.29 to 2.11) Lung function (FVC) 1 year (1 study, n=88) MD (fixed, 95% CI): -5.00 (-10.30 to 0.30) Lung function (FEF25-75) 1 year (1 study, n=88) MD (fixed, 95% CI): -0.34 (-12.54 to 11.86 Number of participants experiencing a respiratory exacerbation (1 study, n=91) RR (M-H, fixed, 95% CI): 0.73 (0.55 to 0.95) Patient preferences (1 study, n=36, single treatment) 18 participants preferred PEP 3 participants preferred HFCWO 13 participants had no preferences	(attrition bias) - All outcomes: Low risk (All outcomes in study design are reported. Dropouts prior to commencement of interventions being studies were not included in analysis. 3 dropouts during the intervention period were included in analysis with intention to treat approach) Selective reporting (reporting bias): Low risk (All outcomes in study design are reported). PFTs results were provided by the author Other bias: Low risk (Author of the study is one of this review’s authors, thus to eliminate bias, the study was assessed by the other two independent authors of this paper)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		over a 20-minute session, twice daily; Oscillating PEP - participants exhaled through the flutter device (Axcan Scandipharm) which was angled to maximise the sensation of vibration in the chest. In sitting, participants inhaled deeply through the nose, followed by a breath hold for 2 - 3 seconds, and exhalation through the device. After 5 - 10 breaths, participants increased the TV and speed of exhalation through the device, to precipitate coughing and expectoration. This sequence was repeated “until clear” or for approximately 20 minutes, twice daily Tannenbaum 2005 (abstract only) PEP (no further data provided); Oscillating PEP provided by the RC cornet (no further data provided)	Outcomes QWBS, FEV1, pulmonary exacerbations, LCI. Notes Information was provided from 3 abstracts, no further information obtained	(1 study, n=16, up to 7 days) No significant differences between interventions	McIlwaine 2001 Random sequence generation (selection bias): Low risk (Described as randomised. Randomised using a computer-generated block of numbers) Allocation concealment (selection bias): Unclear risk (Not described) Blinding (performance bias and detection bias) - All outcomes: Low risk (Participants and person providing the therapy were not blinded - unclear risk; Outcome assessors were blinded - low risk) Incomplete outcome data (attrition bias) - All outcomes: Low risk 3 participants were withdrawn due to noncompliance (<

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					85% of twice-daily sessions performed over 1month) in the PEP group. 5 participants dropped out from the flutter group stating that subjectively the flutter did not appear to clear their secretions, they also had a clinically significant deterioration in pulmonary function. intention to treat approach used) Selective reporting (reporting bias): Low risk (All outcome measures are reported in full) Other bias: Low risk (Both groups were reported to be similar at baseline regarding the most important prognostic indicators. Author of the study is one of the authors on this review, thus to eliminate bias, the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					study was assessed by the other two independent authors of this paper and by the previous authors) Newbold 2005 Random sequence generation (selection bias): Low risk (A random numbers table and block randomisation were used to ensure that groups would be of equal size) Allocation concealment (selection bias): Low risk (Allocation was sealed in opaque envelopes by an independent assistant. The envelopes were open in sequence after a participant was enrolled) Blinding (performance bias and detection bias) - All outcomes: Unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					(Participants and person providing the therapy were not blinded - unclear risk; Outcome assessors were blinded - low risk) Incomplete outcome data (attrition bias) - All outcomes: Low risk (1 participant was withdrawn when he stopped attending the CF clinic) Selective reporting (reporting bias): Low risk (Results are reported for all outcome measures) Other bias: Low risk (Groups similar at baseline regarding the most important prognostic indicators) Tannenbaum 2005 (abstract only) Random sequence generation (selection bias): Unclear risk (Randomisation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					was stratified by age, sex and FEV1. How randomisation was generated was not recorded) Allocation concealment (selection bias): Unclear risk (Not discussed) Blinding (performance bias and detection bias) - All outcomes: Unclear risk (Not discussed) Incomplete outcome data (attrition bias) - All outcomes: Low risk (2 dropouts are reported, one from each group. One found the cornet ineffective and difficult to clean. The other preferred a previously used device. Used Intention to treat approach) Selective reporting (reporting bias): Unclear risk (Not all outcome measures results

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					were provided in full. QWBS was reported as no significant changes over the year) Other bias: Low risk (Groups were similar at baseline regarding the most important prognostic indicators) Other information The data presented in this section has been adapted from the Cochrane systematic review. We present the data that is relevant to the aims of this review. Individual studies where retrieved for accuracy and to check if other outcomes of interest where reported. Data extracted by the review team from the original study has been marked with an *.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Tannenbaum, E, Prasad,SA, Main, E, Scrase, E, 374 Long term effects of positive expiratory pressure (PEP) or oscillatory positive pressure (RC cornet®) on FEV1 and perceived health in children with CF, Journal of Cystic Fibrosis, 4, S100, 2005 Ref Id 398314 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR McIlwaine 2015 Characteristics See Cochrane SR McIlwaine 2015 Inclusion criteria See Cochrane SR McIlwaine 2015 Exclusion criteria See Cochrane SR McIlwaine 2015	Interventions See Cochrane SR McIlwaine 2015	Details See Cochrane SR McIlwaine 2015	Results See Cochrane SR McIlwaine 2015	Limitations See Cochrane SR McIlwaine 2015 Other information None

G.8 Mucoactive agents

Review question: What is the effectiveness of mucoactive or mucolytic agents, including rhDNase, nebulised saline (isotonic and hypertonic) and mannitol?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Wilmott, R. W., Amin, R. S., Colin, A. A., DeVault, A., Dozor, A. J., Eigen, H., Johnson, C., Lester, L. A., McCoy, K., McKean, L. P., Moss, R., Nash, M. L., Jue, C. P., Regelmann, W., Stokes, D. C., Fuchs, H. J., Aerosolized recombinant human DNase in hospitalized cystic fibrosis patients with acute pulmonary exacerbations, American Journal of Respiratory & Critical Care Medicine, 153, 1914-7, 1996 Ref Id 333930	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Suri,R., Wallis,C., Bush,A., Thompson,S., Normand,C., Flather,M., Grieve,R., Metcalfe,C., Lees,B., A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis, Health Technology Assessment, 6, -, 2002	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 238945 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Gupta, S., Ahmed, F., Lodha, R., Gupta, Y. K., Kabra, S. K., Comparison of effects of 3 and 7% hypertonic saline nebulization on lung function in children with cystic fibrosis: a double-blind randomized, controlled trial,	Sample size N=31 were randomized. 30 completed the 28 days follow-up (15 in each group). Characteristics Children and young people with CF Mean (SD) age: 3% sodium chloride (n=15): 10.6 (2.87) vs 7% sodium chloride (n=15): 10.87 (3.64) Females: 3% sodium chloride (n=15): 6	Interventions Intervention: 3% sodium chloride BD 28 days Comparison: 7% sodium chloride BD 28 days (high dose)	Details Setting. Pediatric Chest Clinic of All India Institute of Medical Sciences, New Delhi, India. Randomization. The subjects were randomized to receive either 3 or 7% hypertonic saline nebulization. Random sequence was generated using a computer program by a person not involved	Results FEV1 Mean difference (95% CI) between % change in the 3% sodium chloride group (n=15) and the 7% sodium chloride group (n=15) at 2 weeks: -14.35 lower (-27.8 to -0.9)* Mean difference (95% CI) between % change in the 3% sodium chloride group (n=15) and the 7% sodium chloride group (n=15) at 2 weeks: -13 lower (-25.27 to -0.73)* *Calculated by the NGA technical team	Limitations Risk of bias assessed with the Cochrane risk of bias tool: Random sequence generation (selection bias): Low risk (Random sequence was generated using a computer program) Allocation concealment (selection bias): Low risk (Random sequence was generated using a computer program by a person not involved in the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Journal of Tropical Pediatrics, 58, 375-81, 2012 Ref Id 360188 Country/ies where the study was carried out India Study type Double-blind RCT, parallel design Aim of the study To compare the effects of 3 and 7% hypertonic saline administered by nebulization on lung function in children with cystic fibrosis. Study dates Not reported Source of funding Not reported. Baxter Pharmaceuticals Limited provided technical assistance for preparing the study drugs.	(40%) vs 7% sodium chloride (n=15): 2 (13.33%) Inclusion criteria Confirmed diagnosis of CF. Age between 6 and 16. On a regular follow-up for at least the previous 12 months. Able to perform reproducible pulmonary function test. Exclusion criteria Exclusion criteria: Fall in FEV1 by >15% following administration of bronchodilator and test dose of study drug by nebulization; required change in antibiotic treatment during the 4 weeks prior to enrollment; not performing regular chest physiotherapy at home. Children who were already receiving hypertonic saline nebulisation were eligible for the study after discontinuation of hypertonic saline nebulisation for 2 weeks.		in the study. The interventions solutions were sequentially numbered as per the random number list by another person not involved in the study. The collapsible bags were similar in appearance. The study was double-blinded. Data collection. Spirometry was performed according to the American Thoracic Society guidelines using Super Spiro Micromedics UK. Data analysis. T-tests were used to analyse if the mean FEV1 % predicted was significantly different between baseline, day 14 and day 28; t-tests were also used to compare percentage change in FEV1 in the 3% sodium chloride group vs the 7% sodium chloride group.		study. The interventions solutions were sequentially numbered as per the random number list by another person not involved in the study. The collapsible bags were similar in appearance.) Blinding (performance bias and detection bias): Low risk (The study was double-blinded, although it is unclear if both participants, clinicians and outcome assessors were blinded. The collapsible bags were similar in appearance.) Incomplete outcome data (attrition bias): Low risk (30 completed the study out of 31) Selective reporting (reporting bias): Low risk (FEV1 was reported both in the methods section as primary outcome and in the results section) Other bias: Low risk (None identified) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Suri, R., Metcalfe, C., Lees, B., Grieve, R., Flather, M., Normand, C., Thompson, S., Bush, A., Wallis, C., Comparison of hypertonic saline and alternate-day or daily recombinant human deoxyribonuclease in children with cystic fibrosis: a randomised trial, Lancet, 358, 1316-21, 2001 Ref Id 360190 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding See Yang 2016					
Full citation Minasian, C., Wallis, C., Metcalfe, C., Bush, A., Comparison of inhaled mannitol, daily rhDNase and a combination of both in children with cystic fibrosis: a randomised trial, Thorax, 65, 51-6, 2010 Ref Id 360191 Country/ies where the study was carried out See Nolan 2015 Study type See Nolan 2015 Aim of the study See Nolan 2015 Study dates See Nolan 2015 Source of funding See Nolan 2015	Sample size See Nolan 2015 Characteristics See Nolan 2015 Inclusion criteria See Nolan 2015 Exclusion criteria See Nolan 2015	Interventions See Nolan 2015	Details See Nolan 2015	Results See Nolan 2015	Limitations See Nolan 2015 Other information See Nolan 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Elkins, M. R., Robinson, M., Rose, B. R., Harbour, C., Moriarty, C. P., Marks, G. B., Belousova, E. G., Xuan, W., Bye, P. T., National Hypertonic Saline in Cystic Fibrosis Study, Group, A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis, New England Journal of Medicine, 354, 229-40, 2006 Ref Id 360204 Country/ies where the study was carried out See Wark 2010 Study type See Wark 2010 Aim of the study See Wark 2010 Study dates See Wark 2010 Source of funding See Wark 2010	Sample size See Wark 2010 Characteristics See Wark 2010 Inclusion criteria See Wark 2010 Exclusion criteria See Wark 2010	Interventions See Wark 2010	Details See Wark 2010	Results See Wark 2010	Limitations See Wark 2010 Other information See Wark 2010

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ratjen, F., Wonne, R., Posselt, H. G., Stover, B., Hofmann, D., Bender, S. W., A double-blind placebo controlled trial with oral ambroxol and N-acetylcysteine for mucolytic treatment in cystic fibrosis, European Journal of Pediatrics, 144, 374-8, 1985 Ref Id 360254 Country/ies where the study was carried out Germany Study type RCT Aim of the study To compare the effect of oral N-acetylcysteine and placebo in people with CF. Study dates Not reported Source of funding	Sample size N=21 N-acetylcysteine: n=10 Placebo: n=11 Characteristics People with CF. Age range: 6 to 21. Inclusion criteria Confirmed diagnosis of CF. People with mild to moderate lung disease were asked to participate when old enough to cooperate with pulmonary function tests. They had X-ray scores greater than 15 according to Schwachman and Kulczycki and less than 15 following the Chrispin-Norman score. Exclusion criteria Atopic patients and those receiving bronchodilators.	Interventions Intervention: Acetycysteine 200 mg, 3 times daily for 12 weeks Comparison: Placebo	Details Setting. Not reported. Randomization and blinding. 36 people were randomly assigned to 3 therapy groups with the help of a computer program, matched on the basis of Chrispin-Norman scores and age. Patients of the second group received acetylcysteine and patients in the third group received placebo. The drugs were given in granular presentation and could not be distinguished with regard to taste, colour and odour. Data collection. People were examined after a washout period of 14 days and after 6 and 12 weeks of trial. Lung function tests were performed exactly 2 hours after physiotherapy. The tests were always done between 11am and 2pm. Data analysis. Mean (SD)	Results Difference (95% CI) in FEV1 between mean change in acetylcysteine group (n=10) and mean change in placebo group (n=11): 5 (-10.84 to 20.84)	Limitations Assessed with the Cochrane risk of bias tool: Random sequence generation (selection bias): Low risk (People were randomly assigned to groups with the help of a computer program, matched on the basis of Chrispin-Norman scores and age) Allocation concealment (selection bias): Unclear risk (Not reported) Blinding (performance bias and detection bias): Low risk (Double-blinded, although unclear if both participants, personnel and outcome assessors were blinded. The drugs were given in granular presentation and could not be distinguished with regard to taste, colour and odour) Incomplete outcome data (attrition bias): Unclear risk (4/36 dropped out of the study: 2 due to irregular drug intake (unclear in which group), 1 due to missed appointments (unclear in which group), 1 in the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported			values of FEV1 were provided at baseline and after 12 weeks.		placebo group showed clinical impairment and deterioration of lung function tests after 4 weeks. No intention-to-treat analysis.) Selective reporting (reporting bias): Low risk (relevant outcome mentioned in methods and outcomes section) Other bias: Low risk (None detected) Other information
Full citation Fuchs, H. J., Borowitz, D. S., Christiansen, D. H., Morris, E. M., Nash, M. L., Ramsey, B. W., Rosenstein, B. J., Smith, A. L., Wohl, M. E., Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis,	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
New England Journal of Medicine, 331, 637-642, 1994 Ref Id 360261 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Amin,R., Subbarao,P., Lou,W., Jabar,A., Balkovec,S., Jensen,R., Kerrigan,S., Gustafsson,P., Ratjen,F., The effect of dornase alfa on ventilation inhomogeneity in patients with cystic fibrosis, European Respiratory	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Journal, 37, 806-812, 2011 Ref Id 310599 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Laube, B. L., Auci, R. M., Shields, D. E., Christiansen, D. H., Lucas, M. K., Fuchs, H. J., Rosenstein, B. J., Effect of rhDNase on airflow obstruction and mucociliary clearance in cystic fibrosis, American Journal of Respiratory & Critical Care Medicine, 153, 752-60, 1996	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 333688 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation McCoy, K., Hamilton, S., Johnson, C., Effects of 12-week administration of dornase alfa in patients with advanced cystic fibrosis lung disease. Pulmozyme Study Group, Chest, 110, 889-95, 1996 Ref Id 360298 Country/ies where the study was carried out	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Suri,R., Marshall,L.J., Wallis,C., Metcalfe,C., Bush,A., Shute,J.K., Effects of recombinant human DNase and hypertonic saline on airway inflammation in children with cystic fibrosis, American Journal of Respiratory and Critical Care Medicine, 166, 352-355, 2002 Ref Id 210686 Country/ies where the study was carried out See Yang 2016	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Ranasinha, C., Assoufi, B., Shak, S., Christiansen, D., Fuchs, H., Empey, D., Geddes, D., Hodson, M., Efficacy and safety of short-term administration of aerosolised recombinant human DNase I in adults with stable stage cystic fibrosis, Lancet, 342, 199-202, 1993 Ref Id 360317 Country/ies where the study was carried out See Yang 2016 Study type	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Ramsey, B. W., Astley, S. J., Aitken, M. L., Burke, W., Colin, A. A., Dorkin, H. L., Eisenberg, J. D., Gibson, R. L., Harwood, I. R., Schidlow, D. V., et al.,, Efficacy and safety of short-term administration of aerosolized recombinant human deoxyribonuclease in patients with cystic fibrosis, American Review of Respiratory Disease, 148, 145-51, 1993 Ref Id 360318	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Ballmann, M., von der Hardt, H., Hypertonic saline and recombinant human DNase: a randomised cross-over pilot study in patients with cystic fibrosis, Journal of Cystic Fibrosis, 1, 35-7, 2002 Ref Id 360356 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Ballmann, M., von der Hardt, H., Hypertonic saline and recombinant human DNase: a randomised cross-over pilot study in patients with cystic fibrosis [abstract], 22nd European Cystic Fibrosis Conference, 1998 Ref Id 360357 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Amin, R., Subbarao, P., Jabar, A., Balkovec, S., Jensen, R., Kerrigan, S., Gustafsson, P., Ratjen, F., Hypertonic saline improves the LCI in paediatric patients with CF with normal lung function, Thorax, 65, 379-83, 2010 Ref Id 360358 Country/ies where the study was carried out Canada Study type Crossover RCT Aim of the study To study the ability of lung clearance index (LCI) to detect a treatment response to hypertonic saline inhalation in paediatric patients with CF with normal spirometry.	Sample size N=20 randomized 19 participants were included in the analysis. 17 participants had complete crossover data available. Characteristics People with CF Mean (SD) age: 10.5 (3.1). Females: 12/19 Inclusion criteria Confirmed diagnosis of CF. Age range: 6 to 18. Ability to perform reproducible spirometry. Baseline FEV1% predicted ≥80% at screening visit. Oxyhaemoglobin saturation ≥90% on room air. Exclusion criteria Airway cultures yielding Burkholderia cepacia complex in the previous 2 years or non-tuberculous mycobacteria in the past year; oral corticosteroid use; oxygen supplementation; lung transplantation; intravenous antibiotics	Interventions Intervention: 7% sodium chloride 4ml BD 4 week Comparison: 0.9% sodium chloride 4ml BD 4 week	Details Setting. Hospital for Sick Children, Toronto, Canada. Randomization. Concealed, computer-generated randomisation performed by a research pharmacist not otherwise involved in the study. Clinicians and research personnel remained unaware of the treatment assignments throughout the study, including the primary efficacy analysis. Washout period. 4-week-long washout period between 4 week-long treatment periods. Data collection. At a screening visit, demographic characteristics, clinical data, physical examination and spirometry were recorded. Data analysis. Data were analysed using intention-to-treat analysis.	Results FEV1 % predicted Absolute difference for isotonic saline vs hypertonic saline, Mean (SD) [95% CI]: -1.8 (12.0) [-7.9 to 4.4] Quality of life (QOL) CFQ-R respiratory domain, Absolute difference for isotonic saline vs hypertonic saline, Mean (SD) [95% CI]: -5.2 (14.2) [-17.4 to 7.1] CFQ-R parent respiratory domain, Absolute difference for isotonic saline vs hypertonic saline, Mean (SD) [95% CI]: -5.9 (16.2) [-14.9 to 3.0]	Limitations Risk of bias assessed with the Cochrane risk of bias tool: Random sequence generation (selection bias): Low risk (Computer-generated randomisation) Allocation concealment (selection bias): Low risk (Concealed randomisation performed by a research pharmacist not otherwise involved in the study) Blinding (performance bias and detection bias): Low risk (Clinicians and research personnel remained unaware of the treatment assignments throughout the study, including the primary efficacy analysis) Incomplete outcome data (attrition bias): Low risk (Intention-to-treat analysis, 1/20 participants excluded from analysis) Selective reporting (reporting bias): Low risk (Relevant outcomes were reported both in the methods and results sections) Other bias: Low risk (None detected) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates All tests were performed between March and December 2008. Source of funding Canadian Institute of Health Research, the Canadian Cystic Fibrosis Foundation-Breathe Program and the Irwin (Arnold and Lynn) family donation.	or oral quinolones within 14 days of enrolment; or investigational drugs within 30 days of enrolment.				
Full citation Shah, P. L., Scott, S. F., Knight, R. A., Marriott, C., Ranasinha, C., Hodson, M. E., In vivo effects of recombinant human DNase I on sputum in patients with cystic fibrosis, Thorax, 51, 119-25, 1996 Ref Id 360384	Sample size 71 patients sampled and randomised. n=41 suitable for analysis. 30 patients excluded due to inadequate sputum samples for rheology analyses. Characteristics People with CF Age: not reported Sex: not reported No significant difference in baseline pulmonary function between treatment groups.	Interventions treatment: 2.5mg rhDNase BD for 10 days placebo: 150mmol NaCl + 1.5 mmol CaCl2 BD for 10 days Follow-up 42 days	Details Study drug delivered using Pulmo-Aide compressor and Acorn II jet nebuliser. PFTs performed at each study visit. Intrapatients variability accounted for by performing PFTs at same time of day and reproducibility assessed before administering study drug. Microlab 3000 series spirometer used for	Results Mean FEV1 (SE) (L) on day 10 of study: Dornase alfa (n=20): before treatment: 1.58 (0.2) ; after treatment: 1.78 (0.2) vs placebo (n=21): before treatment: 1.44 (0.13); after treatment: 1.46 (0.17) % change in FEV (SE): Dornase alfa (n=20): 13.32 (5.57) vs placebo (n=21): 0.15 (3.08) % change in FEV (SD): Dornase alfa (n=20): 13.32 (24.91)# vs placebo (n=21): 0.15 (14.11)# #SD calculated by the NGA technical team	Limitations Risk of bias assessed with Cochrane risk of bias tool: Adequate sequence generation (selection bias): Unclear risk (Method of randomisation not reported) Allocation concealment (selection bias): Unclear risk (Not mentioned) Blinding (performance bias and detection bias); Low risk (described as double blind, however unclear if both participants, personnel

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out United Kingdom Study type Phase II short-term double-blind placebo controlled trial Aim of the study To evaluate the effects of rhDNase on sputum rheology in vivo and to determine whether any changes produced are associated statistically with improvements in pulmonary function. Study dates Not reported Source of funding Genetech Inc supplied rhDNase	Inclusion criteria older than 15 years, with a FVC>40% predicted documented CF either by sweat Na+ concentration >70mmol/L by quantitative pilocarpine iontophoresis or homozygous for ΔF508 marker on genetic testing with clinica history indicative of CF Stable condition for 14 days prior to enrolment No changes to concomitant medications including oral steroids, antibiotics or bronchodilators. Exclusion criteria Not reported		PFTs using American Thoracic society guidelines. Standardised for age, sex and height using Knudson tables. Randomisation: method not described Allocation concealment: not described Statistics: PFTs presented as means and converted to percentage predicted values using Knudson tables.	FEV1 returned to baseline by day 42	and outcome assessors were blinded) Incomplete outcome data (attrition bias): Low risk (30 people excluded due to poor sputum samples; hwoever the authors state that the baseline characteristics of the 41 people included in the analysis were similar to those for the overall population of N=71. Moreover the authors state that the improvement in FEV1 in the group that received dornase alfa was similar to the improvement in FEV1 seen in patients who also received dornase alfa but were excluded from analysis due to inadequate sputum samples for rheology.) Selective reporting (reporting bias): Low risk (FEV1 mentioned in both the methods and results section) Other bias: Low risk (None detected) Other information
Full citation Bilton, D., Robinson, P.,	Sample size	Interventions See National Institute for Health	Details	Results See National Institute for Health and Clinical Excellence (2012)	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cooper, P., Gallagher, C. G., Kolbe, J., Fox, H., Jaques, A., Charlton, B., C. F. Study Investigators, Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study, European Respiratory Journal, 38, 1071-80, 2011 Ref Id 360399 Country/ies where the study was carried out See National Institute for Health and Clinical Excellence (2012) Study type See National Institute for Health and Clinical Excellence (2012) Aim of the study See National Institute for Health and Clinical Excellence (2012) Study dates	See National Institute for Health and Clinical Excellence (2012) Characteristics See National Institute for Health and Clinical Excellence (2012) Inclusion criteria See National Institute for Health and Clinical Excellence (2012) Exclusion criteria See National Institute for Health and Clinical Excellence 2012)	and Clinical Excellence (2012)	See National Institute for Health and Clinical Excellence (2012)		See National Institute for Health and Clinical Excellence (2012) Other information See National Institute for Health and Clinical Excellence (2012)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See National Institute for Health and Clinical Excellence (2012) Source of funding See National Institute for Health and Clinical Excellence (2012)					
Full citation Rosenfeld, M., Ratjen, F., Brumback, L., Daniel, S., Rowbotham, R., McNamara, S., Johnson, R., Kronmal, R., Davis, S. D., Isis Study Group, Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the ISIS randomized controlled trial, JAMA, 307, 2269-77, 2012 Ref Id 360408 Country/ies where the study was carried out USA and Canada	Sample size N= 321 were randomized: 7% sodium chloride: n=158 0.9% sodium chloride: n=163 15 participants withdrew from the 7% sodium chloride group and 14 from the 0.9% sodium chloride group. Characteristics Age < 6 years. Approx. 60% were <30 months at enrollment. Mean (SD) age: 7% sodium chloride (n=158): 2.2 (1.4) vs 0.9% sodium chloride (n=163): 2.3 (1.5) N (%) males: 7% sodium chloride (n=158): 84 (53%) vs	Interventions Intervention: 7% sodium chloride Twice daily for 48 weeks Comparison: 0.9% sodium chloride Twice daily for 48 weeks	Details Setting. 30 CF centres in the USA and Canada. Randomization. Participants were randomized 1:1 to 7% sodium chloride and 0.9% sodium chloride, base on random permuted blocks stratified by age (4 to 29 months, 30 to 60 months) and site, via a secure website. Participants, their families, health care providers and research personnel were blinded to treatment assignment. Data collection. The rate of pulmonary exacerbations (events per person-year) was defined as treatment with oral, inhaled or	Results Need for intravenous antibiotics for pulmonary exacerbations Total number of treatment days for a pulmonary exacerbation, adjusted mean difference (95% CI) 7% sodium chloride / 0.9% sodium chloride: 1.11 (0.89 to 1.37) (adjusted for age category and site) Time to next pulmonary exacerbation First pulmonary exacerbation, adjusted hazard ratio (95% CI) 7% sodium chloride / 0.9% sodium chloride: 0.94 (0.73 to 1.22) (adjusted for age category and site) Quality of life Adjusted mean difference (95% CI) for change in CFQ-R respiratory score between 7% sodium chloride group and 0.9% sodium chloride group: 3.3 (0.0 to 6.7) (adjusted by age category, site, and measure at randomization)	Limitations Risk of bias assessed with the Cochrane Risk of Bias tool: Random sequence generation (selection bias): Low risk (Participants were randomized 1:1, based on random permuted blocks stratified by age and site) Allocation concealment (selection bias): Unclear risk (Not reported) Blinding (Performance bias and detection bias): Low risk (Participants, their families, health care providers and research personnel were blinded to treatment assignment). Incomplete outcome data (attrition bias): Low risk (Withdrawals; 15/158 in 7% sodium chloride group and 14/163 in the 0.9%

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Multicentre double-blind RCT Aim of the study To determine if hypertonic saline reduces the rate of pulmonary exacerbations in people with CF <6 years of age. Study dates The study was conducted from April 2009 to October 2011. Source of funding Receipt of funding is reported for each author. Sources are: CF Foundation Therapeutics, Inc; the National Institutes of Health; CF Canada; Canadian Institute for Child Health; Inspire, Inc; NHLBI; CFFT.	0.9% sodium chloride (n=163): 92 (56%) Inclusion criteria Age < 6 years. Upper age limit of 60 months. Other inclusion criteria "detailed in the eMethods" Exclusion criteria Exclusion criteria "detailed in the eMethods".		intravenous antibiotics for 1 or more pre-specified signs and symptoms within the 3 days prior to antibiotic start date through antibiotic stop date. Quality of life was measured with CFQ-R. Data analysis. Pulmonary exacerbation rate was compared between groups according to intent-to-treat analysis using a Poisson log-linear regression model. The rate ratio was also analysed with adjustment for age category and site. The probability of remaining free of a pulmonary exacerbation was estimated by the Kaplan-Meier method and the hazard ratio for first pulmonary exacerbation with a proportional hazards regression model. The difference in mean change in CFQ-R was estimated by a linear regression model with and without		sodium chloride group. Intention to treat analysis). Selective reporting (reporting bias): Low risk (Relevant outcomes mentioned both in the methods and results section). Other bias: Low risk (None detected) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			adjustment for age category, site, and baseline measure.		
Full citation Jaques, A., Daviskas, E., Turton, J. A., McKay, K., Cooper, P., Stirling, R. G., Robertson, C. F., Bye, P. T., Lesouef, P. N., Shadbolt, B., Anderson, S. D., Charlton, B., Inhaled mannitol improves lung function in cystic fibrosis, Chest, 133, 1388-96, 2008 Ref Id 360418 Country/ies where the study was carried out See Nolan 2015 Study type See Nolan 2015 Aim of the study See Nolan 2015 Study dates See Nolan 2015 Source of funding	Sample size See Nolan 2015 Characteristics See Nolan 2015 Inclusion criteria See Nolan 2015 Exclusion criteria See Nolan 2015	Interventions See Nolan 2015	Details See Nolan 2015	Results See Nolan 2015	Limitations See Nolan 2015 Other information See Nolan 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See Nolan 2015					
Full citation Aitken, M. L., Bellon, G., De Boeck, K., Flume, P. A., Fox, H. G., Geller, D. E., Haarman, E. G., Hebestreit, H. U., Lapey, A., Schou, I. M., Zuckerman, J. B., Charlton, B., C. F. Investigators, Long-term inhaled dry powder mannitol in cystic fibrosis: an international randomized study, American Journal of Respiratory & Critical Care Medicine, 185, 645-52, 2012 Ref Id 360445 Country/ies where the study was carried out See National Institute for Health and Clinical Excellence (2012) Study type	Sample size See National Institute for Health and Clinical Excellence (2012) Characteristics See National Institute for Health and Clinical Excellence (2012) Inclusion criteria See National Institute for Health and Clinical Excellence (2012) Exclusion criteria See National Institute for Health and Clinical Excellence (2012)	Interventions See National Institute for Health and Clinical Excellence (2012)	Details See National Institute for Health and Clinical Excellence (2012)	Results See National Institute for Health and Clinical Excellence (2012)	Limitations See National Institute for Health and Clinical Excellence (2012) Other information See National Institute for Health and Clinical Excellence (2012)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See National Institute for Health and Clinical Excellence (2012) Aim of the study See National Institute for Health and Clinical Excellence (2012) Study dates See National Institute for Health and Clinical Excellence (2012) Source of funding See National Institute for Health and Clinical Excellence (2012)					
Full citation Conrad, C., Lymp, J., Thompson, V., Dunn, C., Davies, Z., Chatfield, B., Nichols, D., Clancy, J., Vender, R., Egan, M. E., Quittell, L., Michelson, P., Antony, V., Spahr, J., Rubenstein, R. C., Moss, R. B., Herzenberg, L. A., Goss, C. H., Tirouvanziam, R., Long-term	Sample size N=70 were enrolled and randomized. acetylcysteine group: n=36 placebo group: n=34 6 in the acetylcysteine group and 2 in the placebo group were withdrawn or lost to follow-up. Of these, only 1 in the placebo group was excluded from the analysis. Characteristics People with CF.	Interventions Intervention: Acetylcysteine 3 times a day for 24 weeks. Comparison: Placebo 3 times a day for 24 weeks.	Details Setting. 11 accredited CF Foundation care centres in the United States. Randomization and blinding. An adaptive randomization strategy was used to stratify according to baseline FEV1 % predicted (moderate: 40% ≤ FEV1 ≤ 60%; mild: 60%< FEV1 ≤ 85%); age (7 to 17 years vs ≥ 18 years), gender, and	Results FEV1 Difference (95% CI) between mean change in FEV1 % predicted Acetylcysteine group and mean change in placebo group at 24 weeks: 4.4 (0.83 to 7.9) Inflammatory markers Difference (95% CI) between mean change in sputum IL-8 (log10) in Acetylcysteine group and mean change in placebo group at 24 weeks:0.19 (-0.03 to 0.42) Pulmonary exacerbations	Limitations Risk of bias assessed with the Cochrane risk of bias tool: Random sequence generation (selection bias): Low risk (An adaptive randomization strategy was used to stratify according to baseline FEV1 % predicted; age; gender; and indicators for chronic oral and inhaled antibiotic and chronic ibuprofen use.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
treatment with oral N-acetylcysteine: affects lung function but not sputum inflammation in cystic fibrosis subjects. A phase II randomized placebo-controlled trial, Journal of Cystic Fibrosis, 14, 219-27, 2015 Ref Id 360447 Country/ies where the study was carried out USA Study type RCT Aim of the study To evaluate the effects of oral N-acetylcysteine (NAC), which replenishes systemic glutathione, on decreasing inflammation and improving lung function in CF airways. Study dates	Age range: 9 to 59. Females: 35/70 (50%) Inclusion criteria Confirmed diagnosis of CF. Clinically stable. Stable mild-moderate lung disease FEV1 ≥40% and ≤85% predicted. Ability to tolerate sputum induction with 3% hypertonic saline. Followed restrictions on consumption of anti-oxidants, antibiotics and anti-inflammatory medications. Exclusion criteria Not reported.		indicators for chronic oral and inhaled antibiotic and chronic ibuprofen use. Randomization assignments and a series of blinded drug kit numbers were generated by PPD, Inc. Kits were distributed to each centre and were assigned with the use of a centralized secure randomization system at the coordinating centre. All study personnel and participants were blinded to treatment assignment. The randomization codes for each participant were revealed to the researchers once recruitment, data collection and data analyses were completed. Data collection. Spirometry and sputum induction were obtained at the screening visit (day 0). The CFQ-R was administered to measure quality of life. If a patient discontinued the use of the study drug or	Incidence of pulmonary exacerbations at 24 weeks: Acetylcysteine group (n=36): 15 vs placebo group (n=34): 17. Quality of life Difference (95% CI) between mean change in CFQ-R respiratory domain in Acetylcysteine group and mean change in placebo group at 24 weeks: -0.34 (-6.3 to 5.67)	Allocation concealment (selection bias): Low risk (Randomization assignments and a series of blinded drug kit numbers were generated by PPD, Inc. Kits were distributed to each centre and were assigned with the use of a centralized secure randomization system at the coordinating centre) Blinding (performance bias and detection bias): Low risk (All study personnel and participants were blinded to treatment assignment. The randomization codes for each participant were revealed to the researchers once recruitment, data collection and data analyses were completed.) Incomplete outcome data (attrition bias): Low risk (6/36 in the acetylcysteine group and 2/34 in the placebo group were withdrawn or lost to follow-up. All but 1 in the placebo group, who was lost to follow-up, were included in the analysis -

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
The trial was conducted between 4th of November 2008 and 30th of June 2011. Source of funding Not reported.			withdrew for any reason, they were asked to undergo evaluation at an early termination visit and to complete all remaining scheduled visits and procedures. Data analysis. Intention to treat analysis. Differences were calculated between mean change in the intervention group and mea change in the placebo group.		intention-to-treat analysis.) Selective reporting (reporting bias): Low risk (Relevant outcomes mentioned both in the methods and outcomes section) Other bias: Low risk (None detected) Other information
Full citation Wark,Peter, McDonald,Vanessa M., Nebulised hypertonic saline for cystic fibrosis, Cochrane Database of Systematic Reviews, -, 2010 Ref Id 257227 Country/ies where the study was carried out Australia Study type Wark 2010	Sample size Elkins 2006 N=164. 2 people were excluded from the analysis: 1 person in each group voluntarily withdrew before first dose.* 17 people were lost to follow-up*: 7 in the hypertonic saline group (2 owing to time constraints, 2 owing to insufficient perceived benefit from trial solution, 2 owing to adverse reaction to	Interventions Elkins 2006 Intervention: 7% sodium chloride BD for 48 weeks Comparison: 0.9% sodium chloride BD for 48 weeks* *Information extracted from primary study	Details Randomised, double-blind, parallel group trial	Results Elkins 2006 Mean (SD) % change in FEV1 at 12 weeks: Hypertonic saline (n=76): 3.96 (15.13) vs isotonic saline (n=73): -0.14 (10.61). Mean difference [95% CI]: 4.10 [-0.08, 8.28] Mean (SD) % change in FEV1 at 24 weeks: Hypertonic saline (n=75): 4.46 (13.31) vs isotonic saline (n=65): -0.91 (12.85). Mean difference [95% CI]: 5.37 [1.03, 9.71] Mean (SD) % change in FEV1 at 36 weeks: Hypertonic saline (n=69): 5 (15.61) vs isotonic saline (n=65): 1.37 (15.05).	Limitations Wark 2010 AMSTAR score: 9/11 (Publication bias not mentioned; declarations of interest by authors of the systematic review are included but declarations of interest or sources of support related to included studies are not provided) Elkins 2006 Assessed with the Cochrane risk of bias tool based on primary study: Random sequence generation (selection bias): Low risk (Computer-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cochrane systematic review Elkins 2006 RCT, parallel design Aim of the study Wark 2010 The aim of the Cochrane systematic review was to investigate the effects of nebulised hypertonic saline in cystic fibrosis compared to placebo or other treatments for mucociliary clearance. Elkins 2006 To test the safety and efficacy of inhaled hypertonic saline in a long-term trial* *Information extracted from primary study Study dates Wark 2010 The most recent search for the Cochrane systematic review was 31 July 2008.	trial solution (cough), 1 provided no reason)* 10 in the control group (5 owing to time constraints, 3 owing to insufficient perceived benefit from trial solution, 1 failed to attend, 1 provided no reason)* 15 people stopped inhalation but continued visits*: 8 in the hypertonic saline group (4 had adverse reactions to trial solution (1 cough and vomiting, 1 pharyngitis and wheezing, 1 had voice changes, 1 had chest tightness), 2 could not tolerate taste of trial solution, 1 had insufficient benefit from trial solution, 1 lost interest)* 7 in the control group (3 owing to time constraints, 2 had adverse reaction to trial solution (1 tonsillitis and 1 lethargy), 1 had insufficient benefit from trial solution, 1 provided no reason)*			Mean difference [95% CI]: 3.63 [-1.56, 8.82] Mean (SD) % change in FEV1 at 48 weeks: Hypertonic saline (n=68): 4.75 (14.71) vs isotonic saline (n=66): 2.44 (14.97). Mean difference [95% CI]: 2.31 [-2.72, 7.34] Please note that % change in FEV1 at 2 to 4 weeks is provided in the Cochrane SR however it was not extracted because more specific follow-ups were prioritised. Mean (SD) change from baseline in quality of life measured with CFQ 14+ at 48 weeks: Hypertonic saline (n=46): 1.09 (10.92) vs isotonic saline (n=45): -6.68 (17.09). Mean difference [95% CI]: 7.77 [1.86, 13.68] Mean (SD) change from baseline in quality of life measured with CFQ parent at 48 weeks: Hypertonic saline (n=34): 0.9 (11.93) vs isotonic saline (n=33): 2.03 (14.48). Mean difference [95% CI]: -1.13 [-7.49, 5.23]	generated randomization. A minimization algorithm was used to balance the two groups with respect to age, FEV1, and presence or absence of long-term treatment with dornase alfa, use or non-use of physiotherapy, and study centre*). Allocation concealment (selection bias): Low risk (Concealed randomization performed by a person not otherwise involved in the study*). Blinding (performance and detection bias): Low risk (Described as double-blind*) Incomplete outcome data (attrition bias): Unclear risk (2 people excluded from the analysis, 17 lost to follow-up, 15 stopped inhalation but continued visits. Reasons for lost to follow-up or stopped inhalation included adverse reactions, insufficient perceived benefits, and "could not tolerate taste of trial solution" in addition to other reasons such as time constraints, failed to attend, lost interest, provided no reason*)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Elkins 2006 The study was conducted between September 2000 and November 2003.* *Information extracted from primary study Source of funding Wark 2010 Not reported Elkins 2006 Supported by the US CF Foundation, the National Health and Medical Research Council of Australia, and the Australian CF Research Trust. * *Information extracted from primary study	*Information extracted from primary study Characteristics Wark 2010 People of all ages and of both sexes with CF, including all degrees of disease severity. Elkins 2006 People with CF from 16 hospitals.* Males: 93. Females: 71. * Information extracted from primary study Inclusion criteria Elkins 2006 Age ≥6 years.* Clinically stable condition.* FEV1 at screening had to be within 10% of the best value obtain within the previous 6 months.* FEV1% predicted ≥40%.* *Information extracted from primary study Exclusion criteria Elkins 2006 Pregnant or breast-feeding women. Persons colonized with Burkholderia cepacia. Cigarette				Selective reporting (reporting bias): Low risk (Relevant outcomes mentioned both in the methods and results sections*) Other bias: Low risk (None detected) *Information extracted from primary study Other information Elkins 2006 Pfizer Pharmaceuticals provided hypertonic saline and normal saline but otherwise did not participate in the design and conduct of the study.* *Information extracted from primary study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	smokers. Use of hypertonic saline or non-routine antibiotics in the previous 14 days.* *Information extracted from primary study				
Full citation Shah, P. I., Bush, A., Canny, G. J., Colin, A. A., Fuchs, H. J., Geddes, D. M., Johnson, C. A., Light, M. C., Scott, S. F., Tullis, D. E., et al.,, Recombinant human DNase I in cystic fibrosis patients with severe pulmonary disease: a short-term, double-blind study followed by six months open-label treatment, European Respiratory Journal, 8, 954-8, 1995 Ref Id 333859 Country/ies where the study was carried out	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Quan, J. M., Tiddens, H. A., Sy, J. P., McKenzie, S. G., Montgomery, M. D., Robinson, P. J., Wohl, M. E., Konstan, M. W., Pulmozyme Early Intervention Trial Study, Group, A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities, Journal of Pediatrics, 139, 813-20, 2001 Ref Id	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
360681 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Nolan Sarah, J., Thornton, Judith, Murray Clare, S., Dwyer, Tiffany, Inhaled mannitol for cystic fibrosis, Cochrane Database of Systematic Reviews, 2015 Ref Id 431814 Country/ies where the study was carried out Nolan 2015: N/A Aitken 2012: See National Institute for Health and Clinical Excellence (2012)	Sample size Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 N=39 4 withdrawals. All 39 participants were included in the analysis. Minasian 2010 N=28 45 were recruited but only 28 were randomised. 8 participants withdrew	Interventions Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 Intervention Inhaled dry powder mannitol 420 mg 2x daily,14 x 30 mg capsules. Fine particle fraction > 40%. Children < 12 years: administered via low resistance	Details Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 Double-blind, randomised, cross-over study. Multicentre. Minasian 2010 Open-label, randomised, cross-over study. Multicentre: 2 centres.	Results Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 Mean (SD) change from baseline in FEV1% predicted at 2 weeks: Mannitol (n=36): 3.86 (6.48) vs Control (n=36): -0.09 (6.48) Adverse events: haemoptysis (mild) (n/N) at 2 weeks: Mannitol (n=38): 2/38 vs Control (n=36): 2/36 Adverse events: haemoptysis (severe) (n/N) at 2 weeks: Mannitol (n=38): 0/38 vs Control (n=36): 0/36 Minasian 2010	Limitations Nolan 2015 AMSTAR score: 11/11 Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 Random sequence generation (selection bias): Low risk (Randomisation code externally generated in small block design stratified to site and dornase alfa)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Bilton 2011: See National Institute for Health and Clinical Excellence (2012) Jaques 2008: Australia, New Zealand Minasian 2010: UK Study type Nolan 2015 Cochrane SR Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 Double-blind, randomised, cross-over study. Multicentre. Minasian 2010 Open-label, randomised, cross-over study. Multicentre: 2 centres. Aim of the study Nolan 2015	Characteristics Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 People with CF. Mean age: 19.1 years. Age range: 8 to 48. Females: 59% All participants clinically stable at start of study, mean (SD) baseline FEV1 % predicted 64.9 (13.6) for the mannitol group and 64.4 (11.8) for the control group. 46.2% received concomitant dornase alfa. Minasian 2010 People with CF. Considering randomised participants (results different from those who completed treatment in all arms and were analysed): 28 participants with CF: Mean (SD) age: 13.3 (2.24) years. Gender split: 36%	dry powder inhaler RS01 Plastiape, Osnago, Italy. Children >= 12 years and adults: administered via higher resistance dry powder inhaler, Inhalator, Boeringer-Ingelheim, Ingelheim, Germany. Control Non-respirable mannitol with afine particle fraction <2%. Identical in appearance and taste to mannitol capsules. 14 capsules 2x daily using same inhaler devices as for mannitol Minasian 2010 Pre-treated with participant's usual bronchodilator 15 minutes beforehand. Each intervention period lasted 12 weeks, with a 2-week washout period in between. Intervention 1		Mean difference (SE) [95% CI] in % change from baseline in FEV1 at 3 months, mannitol + dornase alfa (n=20) vs dornase alfa (n=20): -4.30 (5) [-14.10 to 5.50) Mean difference (SE) [95% CI] in % change from baseline in FEV1 at 3 months, mannitol (n=20) vs dornase alfa (n=20): 2.80 (3.88) [-4.80 to 10.40]	Allocation concealment (selection bias): Unclear risk (Not discussed) Blinding (performance bias and detection bias): Participants and clinicians: Low risk (Described as double-blind; mannitol and control capsules identical in taste and appearance. Same inhaler devices for mannitol and control). Outcome assessors: Low risk (Described as double blinded, it was stated that study staff and investigators were blinded. Same inhaler devices for mannitol and control. Pharmaxis confirmed the statistician is part of the study staff and therefore was blinded) Incomplete outcome data (attrition bias): High risk (56 days follow-up data not reported. 4 participants withdrew and one of these was due to "Unexplained withdrawal" by physician. Unclear how many participants were evaluated for each outcome) Selective reporting (reporting bias): Unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess whether inhaled dry powder mannitol is well tolerated, whether it improves the quality of life and respiratory function in people with cystic fibrosis and which adverse events are associated with the treatment. Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 To examine the efficacy and safety of therapy with inhaled mannitol over a 2-week period.* Minasian 2010 To compare inhaled mannitol with dornase alfa	male, 64% female. All participants clinically stable at start of study Characteristics of the 20 participants who completed treatment: Mean (SD) age: 13.2 (2.4) years. 70% female. Mean (SD) baseline FEV1: 1.67 (0.50) litres, 64 (10)% of predicted FEV1. Inclusion criteria Nolan 2015 Adults (18 years old and over) and children (under 18 years old) with CF (diagnosed clinically and by sweat or genetic testing and including all degrees of disease severity). Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 No hypertonic saline within 2 weeks of start of study. Clinical stability, defined as the absence of being	Mannitol 400 mg 2x daily, 10 x 40 mg capsules. Manufacturer of mannitol not reported but assumed to be Pharmaxis as study was sponsored by this company. Administered via breath-actuated device Osmohaler, Plastiape, Osnago, Italy Intervention 2 Dornase alfa alone - 2.5 mg Pulmozyme® 2x daily via participant's usual device Intervention 3 Mannitol (as above) plus dornase alfa (dose unclear).			risk (All outcomes specified were reported, but little detail). Other bias: High risk (Participants underwent a mannitol tolerance test at screening; those who failed the test or in whom the test was incomplete were not entered into the study and thus, the study population included only those with CF who passed the tolerance test and not all potential participants with CF. Sponsored by Pharmaxis; authors or study staff worked for Pharmaxis or had financial interest) Minasian 2010 Random sequence generation (selection bias): Low risk (Described as randomised, but details of randomisation process not discussed in paper. Dr Minasian provided additional information - participants were allocated a unique randomisation number and treatment schedule with equal probability for assignment to treatment sequences. Randomisation was carried out in balanced

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
in children and young people.* *Information extracted from primary study Study dates Nolan 2015 Date of the last search: 16 April 2015 Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 Not reported* Minasian 2010 Not reported* *Information extracted from primary study Source of funding Nolan 2015 No internal sources of support. External sources: National Institute for Health Research, UK	systematically unwell from any cause in the week leading up to study entry and the absence of additional antibiotic therapy in the 2 weeks before study enrollment.* Aged >8 years, with FEV1 between 41% and 91% predicted, and were capable of performing reproducible spirometry.* Minasian 2010 Age between 8 and 18 years.* Ability to perform repeatable reliable spirometry*. Either currently receiving dornase alfa or having an FEV1 >40% and <70% predicted (and therefore judged eligible to receive dornase alfa).* * Information extracted from primary study Exclusion criteria Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011				blocks with separate schedules created for each of the 2 recruiting centres) Allocation concealment (selection bias): Unclear risk (Not discussed) Blinding (performance bias and detection bias): High risk (open study) Incomplete outcome data (attrition bias): High risk (Results in the paper only reported for participants who completed all 3 arms of the study. The desired sample size was 48 participants: 45 were recruited but only 28 were randomised and 8 children withdrew) Selective reporting (reporting bias): Low risk (Limited information was reported in the study publication regarding outcomes of HRQoL, pulmonary exacerbations, sputum microbiology and no information reported on: time off work or school, nonroutine antibiotics, hospitalisations, tolerability or burden of treatment. Additional data were provided by Pharmaxis and primary

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 The study was sponsored by Pharmaxis. Minasian 2010 The study was sponsored by Pharmaxis.	See National Institute for Health and Clinical Excellence (2012) Jaques 2008 Pregnancy, breast feeding, current asthma, recent hemoptysis of >60mL, Burkholderia cepacia colonization, terminal illness, or the need for home oxygen.* No hypertonic saline within 2 weeks of start of study. Minasian 2010 Using hypertonic saline. Known hypersensitivity to mannitol, rhDNase or bronchodilators, sputum infection with methicillin-resistant Staphylococcus aureus (MRSA), or Burkholderia cepacia, portal hypertension or varices, significant haemoptysis (>60 ml) in the previous 12 months, breast feeding or pregnancy. Patients had to have no changes in treatment or new respiratory symptoms				investigator Dr Minasian on request for all primary outcomes of this review and many secondary outcome) Other bias: High risk (Participants underwent a mannitol tolerance test at screening; participants who failed the test or in whom the test was incomplete were not entered into the study and thus, the participant population included only those participants with CF who passed the tolerance test and not all potential participants with CF. Underpowered study, many dropouts (48%of required sample size were analysed in the published analysis). Actual dropout rate was 8/28 = 29%. Cross-over design - state that no carryover effect observed, but more details needed. Sponsored by Pharmaxis; authors or study staff worked for Pharmaxis or had financial interest) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	in the 2 weeks prior to the study.* *Information extracted from primary paper				
Full citation Dentice, R. L., Elkins, M. R., Middleton, P. G., Bishop, J. R., Wark, P. A., Dorahy, D. J., Harmer, C. J., Hu, H., Bye, P. T., A randomised trial of hypertonic saline during hospitalisation for exacerbation of cystic fibrosis, Thorax, 71, 141-7, 2016 Ref Id 425806 Country/ies where the study was carried out Australia Study type RCT, parallel design Aim of the study To determine the effects of hypertonic saline inhalation during	Sample size N=132 Intervention: 67 Control: 65 Characteristics Adults with CF Mean age (SD), range: Intervention: 28 (9), 17 to 62 years Control: 27 (9), 18 to 63 years Females, n/N (%) Intervention: 35/67 (52%) Control: 30/65 (46%) Inclusion criteria A confirmed diagnosis of CF. Admission for management of a pulmonary exacerbation for a minimum of 7 days. Exclusion criteria Major haemoptysis within the past year; thrombocytopenia; allergy to quinine sulfate; glucose 6-phosphate	Interventions Intervention: sodium chloride 4ml 7% 3 times daily throughout hospital admission (on average 12 days) Control: 0.12% sodium chloride 3 times daily throughout hospital admission (on average 13 days) Both groups received usual care.	Details Setting. Participants were recruited from Royal Prince Alfred Hospital, Westmead Hospital and John Hunter Hospital in New South Wales, Australia. Enrolment of participants occurred within 24 hours of hospital admission. Randomization. Participants were randomly allocated to the intervention or control group. The randomisation process used minimisation to adaptively balance the active and control treatment allocations at each enrolment site. This process also ensured that randomisation was stratified for deoxyribonuclease use, FEV1 (≥/<50% predicted on admission), gender	Results Lung function: FEV1, FVC Failed to regain pre-exacerbation FEV1 by discharge, n (%): Intervention (n=67): 17 vs Control (n=65): 28. RR: 0.59 (0.36 to 0.96) Time to next pulmonary exacerbation HR: 0.86 (CI 0.57 to 1.30) Quality of life (CFQ) Mean (SD) change in CFQ physical from admission to day 7:intervention (n=67): 11 (16) vs control (n=65): 9 (14). Between-group mean difference:2 (-4 to 7) Mean (SD) change in CFQ burden from admission to day 7:intervention (n=67): 0 (14) vs control (n=65): 0 (14). Between-group mean difference:-1 (-6 to 4) Mean (SD) change in CFQ health from admission to day 7:intervention (n=67): 12 (19) vs control (n=65):14 (17). Between-group mean difference: -2 (-8 to 4) Mean (SD) change in CFQ respiratory from admission to day 7:intervention (n=67): 13	Limitations Limitations assessed with Cochrane risk of bias tool: Random sequence generation (selection bias): Low risk (The randomisation process used minimisation to adaptively balance the active and control treatment allocations at each enrolment site. This process also ensured that randomisation was stratified for deoxyribonuclease use, FEV1, gender and fall in FEV1) Allocation concealment (selection bias): Unclear risk (Concealed randomisation, method unclear) Blinding (performance bias and detection bias): Low risk (All participants, clinicians and investigators remained blinded to treatment group allocation throughout the study)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
hospitalisation for exacerbation of CF on lung function, symptoms, time to next hospitalisation and other outcomes. Study dates Enrolment began in December 2005 and was completed in 6 years. Follow-up of hospital readmissions finished in February 2013. Source of funding The study was supported by the National Health and Medical Research Council Cooperative Centre for Research Excellence in Respiratory and Sleep Medicine postgraduate research scholarship and the US Cystic Fibrosis Foundation grant BYE04A0.	dehydrogenase deficiency; immune thrombocytopenic purpura; pregnancy; breastfeeding; Burkholderia cepacia or mycobacteria ever isolated from the sputum; or lung transplant.		and fall in FEV1 (≥/<25% fall from best outpatient FEV1 in the past 6 months. Data collection. FEV1 and FVC were measured by spirometry daily; quality of life was measured with SF36 and CFQ; time to next exacerbation was recorded with a minimum follow-up of 1 year. Data analysis. All analyses were by intention to treat.	(19) vs control (n=65): 12 (16). Between-group mean difference: 1 (-5 to 7) Mean (SD) change in CFQ physical from admission to discharge:intervention (n=67): 16 (19) vs control (n=65): 14 (17). Between-group mean difference: 3 (-4 to 9) Mean (SD) change in CFQ burden from admission to discharge:intervention (n=67): 1 (15) vs control (n=65): -1(20). Between-group mean difference: 1 (-4 to 7) Mean (SD) change in CFQ health from admission to discharge:intervention (n=67): 20 (21) vs control (n=65): 18 (20). Between-group mean difference: 2 (-5 to 10) Mean (SD) change in CFQ respiratory from admission to discharge:intervention (n=67): 19 (21) vs control (n=65): 21 (18). Between-group mean difference:-2 (-8 to 5)	Incomplete outcome data (attrition bias): Low risk (Intention to treat analysis, no withdrawals) Selective reporting (reporting bias): Low risk (Results for primary and secondary outcomes are reported) Other bias: Low risk (none identified) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Yang, C., Chilvers, M., Montgomery, M., Nolan, S. J., Dornase alfa for cystic fibrosis, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, 4, CD001127, 2016 Ref Id 537299 Country/ies where the study was carried out Please see methods section for countries where studies were conducted Study type Cochrane SR Aim of the study - Study dates - Source of funding -	Sample size Amin 2011 N:19 randomised 17 completed Ballmann 2002 (trial also reported in Ballmann 1998) N: 14 Withdrawals were not discussed within the paper. Fuchs 1994 N: 968 25 people withdrew from the study, 8 in the placebo group and once-daily group and 9 in the twice-daily group Laube 1996 N: 20 The published paper stated that there were no withdrawals. McCoy 1996 N: 320 40 participants withdrew from the trial, five due to adverse events, 10 withdrew consent, 1 did not comply with the study protocol, 15 died, 2 were unavailable for follow up and 7	Interventions Amin 2011. Treatment and control administered via PARI LC1 Star® nebuliser (Pari, Midlothian, VA, USA) Intervention: 2.5mg dornase alfa once daily Control: placebo once daily Ballmann 2002 (trial also reported in Ballmann 1998) Intervention: 2 puffs salbutamol via a spacer prior to nebulization of 2.5 mg dornase alfa od Comparison: 2 puffs salbutamol via a spacer prior to nebulization of 10 ml HS Fuchs 1994 Intervention: Nebulized dornase alfa 2.5 mg od (n=322) or bd (n=321) over 24 weeks	Details Amin 2011 Randomised, placebo controlled trial. Cross-over design. A 4-week washout period. Single centre. Ballman 2002 (trial also reported in Ballmann 1998) Open cross-over pilot trial 2 treatment periods of 3 weeks. A 3-week washout period. Participants were assessed before and after each period. Fuchs 1994 Randomised, double-blind parallel trial with 3 arms over 24 weeks. More participants aged 17 - 23 years were in the once daily dornase alfa arm. Measurements taken on days 7, 14 and every 14 days thereafter. Laube 1996	Results Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. Additional data extracted is marked with a *. All data for Amin 2011 was extracted from primary study as the Yang Cochrane SR was only idenfied during re-runs. Amin 2011 Mean (SD) FEV1 % predicted: Dornase alfa before treatment: 92.09 (6.57) and after treatment: 97.72 (9.96) vs placebo before treatment: 89.68 (10.68) and placebo after treatment: 90.44 (7.80)* Change in FEV1% predicted: Dornase alfa: -39 (140) vs placebo: -1 (135ml) * Mean (SD) CFQ-R: Dornase alfa before treatment: 80.56 (12.50) and after treatment: 70.07 (21.24) vs placebo before treatment: 79.17 (17.68) and placebo after treatment: 73.89 (16.98) * Mean (SD) CFQ-R parent: Dornase alfa before treatment: 80.95 (16.27) and after treatment: 76.39 (22.57) vs placebo before treatment: 75.42 (12.58) and placebo after treatment: 79.53 (21.30)*	Limitations Yang 2016 AMSTAR score: 10/11 (Sources of support or funding related to included studies not reported) Amin 2011 Random sequence generation (selection bias): Low risk (Concealed computer-generated randomisation) Allocation concealment (selection bias): Low risk (Randomisation performed by a research pharmacist not otherwise involved in the trial) Blinding (performance bias and detection bias): Low risk (All participants (solutions indistinguishable from each other), clinicians and outcome assessors blinded to treatment assignment) Incomplete outcome data (attrition bias): Unclear risk (Reported that data analysed according to the intention-to-treat principle, however, data only reported on 17 who completed trial compared to the 19 that were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	stopped for a medical procedure Quan 2001 239 participants randomized to dornase alfa and 235 to placebo. 410 completed the study, 60 participants withdrew from the study, 472 (out of 474) had follow-up data. The ITT population was 470. Ramsey 1993 N: 181 Data collected on all participants at the end of trial. The paper stated that there were no withdrawals. Ranasinha 1993 N: 71 Shah 1995a N: 70 participants allocate 70 participants allocated; 35 placebo, 35 dornase alfa. Specified 5 dropouts (2 died, 2 withdrew consent, 1 had a heart lung transplant) Suri 2001 (trial also reported in Suri 2002a and Suri 2002b)	Comparison: placebo (n=325) over 24 weeks Laube 1996 Intervention: 2.5 mg nebulized dornase alfa (n = 10) bd Comparison: placebo (n = 10) bd McCoy 1996 Intervention: Nebulized dornase alfa 2.5 mg od (n=158) over 12 weeks Comparison: Placebo (n=162) over 12 weeks Quan 2001 Intervention: 2.5 mg dornase alfa od Comparison: placebo Ramsey 1993 Intervention: nebulized dornase alfa * 0.6 mg (n = 45), 2.5 mg (n = 44) or 10 mg (n =44) bd for 10 days Comparison: placebo (n=48) Ranasinha 1993 Intervention: Nebulized dornase	Randomised, double-blind parallel design trial over 6 days. Measurements taken on day 6 only and reported in the paper. McCoy 1996 Randomised, double-blind, parallel trial over 12 weeks. Measurements taken on days 8, 15, 29, 57 and 85. Quan 2001 Randomised, double-blind parallel placebo controlled trial over 96 weeks, involving 49 CF centres. Measurements taken at week 4, 12 and every 12 weeks thereafter. Ramsey 1993 Randomised, double-blind, parallel trial with 3 treatment arms over 10 days. Participants were followed up for a further 32 days. Measurements taken on days 1, 3, 6, 10 with follow-up data on days 14, 21, 28 and 42.	Ballman 2002 (trial also reported in Ballmann 1998) FEVI increase (mean(SD)): dornase alfa 9.3% (11.7%) vs HS 7.7% (14%). Reported narratively. Adverse events not reported, salbutamol was given to prevent acute bronchospasm Fuchs 1994 Relative mean % change in FEVI at six months: N: 322; Mean(SD): 5.8(12.56) vs N: 325; Mean (SD): 0 (10.82). Mean number of days IV AB used at six months: Once daily N:322; Mean: 8.5. Twice daily: N: 321; Mean: 9.0. Placebo N: 325; Mean: 11.2 Please note the article reports this without SD. RhDNase od: 2.7 fewer days receiving parenteral antibiotics as compared with placebo (P<0.05). RhDNase bd: 2.2 fewer days receiving parenteral antibiotics (P<0.05) as compared with placebo. * Number of people experiencing exacerbations at six months (n/N): 71/322 vs 89/325 Adverse events: Haemoptysis at six months (n/N): 17/322 vs 21/325 Adverse events: Dyspnoea at six months (n/N): 37/322 vs 43/325 Adverse events: Pnemothorax at six months (n/N): 1/322 vs 1/325	randomised. Missing data from 2 participants: the LCI results of 1 participant failed to meet the quality control criteria for 1 of the 4 trial visits; 1 other participant dropped out of the trial after 2 visits because of a pulmonary exacerbation requiring IV antibiotics (protocol identified reason for withdrawal from trial), but not clear what treatment the participant had completed before withdrawal) Selective reporting (reporting bias): Low risk (All outcomes reported) Other bias: Low risk (Cross-over design with washout period of 4 weeks which should be adequate for lung function to return to baseline) Ballmann 2002 (trial also reported in Ballmann 1998) Adequate sequence generation: Unclear (Described as randomised, but method not clear) Allocation concealment: Unclear (Method unclear) Blinding (all outcomes): Unclear (Not blinded, due

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	N: 48 randomised. 45 completed first treatment period, 44 completed the second treatment period and 40 completed the third treatment period. 28 of the 48 patients produced sputum samples at the beginning and end of at least one of the treatment periods and were included in the analyses. * Wilmott 1996 N: 80 No withdrawals mentioned in the paper Characteristics Amin 2011 Mean age (SD): 10.1 (3.1) years* Female sex: 11* Ballmann 2002 (trial also reported in Ballmann 1998) Mean age: 13.3 With mild to moderate pulmonary involvement. Fuchs 1994 Age: Over 5.	alfa 2.5 mg bd (n = 36) for 10 days Comparison: placebo (n = 35) for 10 days Shah 1995a Intervention: 2.5 mg nebulised dornase alfa bd (n=35) for 14 days Comparison: Placebo (n=35) for 14 days Suri 2001 (trial also reported in Suri 2002a and Suri 2002b) Intervention: 2.5 mg dornase alfa od; alternate day 2.5 mg dornase alfa; 5 mL 7%hypertonic saline bd Comparison1: 2.5 mg dornase alfa od vs 5 mL 7%hypertonic saline bd. Comparison 2: 2.5 mg dornase alfa od vs alternate day 2.5 mg dornase alfa Wilmott 1996 Dornase alfa 2.5 mg bd (n = 43) nebulised over 15 days	Ranasinha 1993 Randomised, double-blind, parallel design safety and efficacy trial over 10 days with follow up to 42 days. Measurements taken at days 3, 6 and 10. Shah 1995a Randomised double-blind, parallel design trial over 14 days, with 6 month open follow up. ITT was not discussed. Suri 2001 (trial also reported in Suri 2002a and Suri 2002b) Open cross-over trial 3 treatment periods of 12 weeks A 2-week wash out period between each period. Measurements were taken at the start and end of each 12-week period Wilmott 1996. Randomised double-blind parallel designed trial over 15 days during a	Adverse events: Voice alteration at six months (n/N): 12/322 vs 7/325 Adverse events: Voice alteration (bd vs od treatment) (n/N): bd 16/321 vs od 12/322 Laube 1996 Relative mean % change in FEVI at one month: N: 10; Mean (SD): 9.4 (11.07) vs N: 10; Mean (SD): -1.8 (5.38) (Moderate disease severity subgroup) McCoy 1996 Relative mean % change in FEVI at three months: N: 158; Mean (SD): 9.4 (16.3) vs N: 162; Mean (SD): 2.1 (13.3). Mean number of days IV antibiotics used at three months: N: 158; Mean (SD): 25.35 (19.58) vs N: 162; Mean (SD): 28.31 (19.94) Mean number of days inpatient treatment at three months: N: 158; Mean (SD): 19.33 (15.91) vs N: 162; Mean (SD): 18.4 (12.31) There were no statistically significant differences in the risks of developing pulmonary exacerbations between the placebo and dornase alfa groups. The age-adjusted relative risk of one or more such events occurring over the study period in dornase alfa-treated patients, compared with the	to the taste of the hypertonic saline) Incomplete outcome data addressed (all outcomes): Unclear (No discussion of whether ITT analysis performed. Withdrawals were not discussed within the paper). Free of selective reporting: Unclear (None identified) Fuchs 1994 Adequate sequence generation: Unclear (Stated as randomised but no method was described). Allocation concealment: Unclear (Method unclear). Blinding (all outcomes): Unclear (Described as double blind, no further details). Incomplete outcome data addressed (all outcomes): Unclear (ITT principle was used. 25 people withdrew from the study, 8 in the placebo group and once-daily group and 9 in the twice-daily group) Free of selective reporting: Unclear (Measurements were taken on days 7, 14 and every 14 days

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Confirmed diagnosis of CF FVC: > 40% predicted Clinically stable Laube 1996 Age: Over 18 With stable stage CF FVC: 35%-75% predicted Non-smokers McCoy 1996 Confirmed CF diagnosis Age: 7-57 FVC: < 40% predicted. Baseline lung function in the treatment group was lower than that of the control group, P<0.05 Quan 2001 Age: 6-10 (mean age 8.4) FVC>85% predicted Ramsey 1993 Stable stage CF Age: 8-65 FVC>= 40% predicted Ranasinha 1993 Age: Adults Confirmed CF diagnosis All participants had stable disease	Placebo (n=37) ove r 15 days	respiratory exacerbation. Measurements taken on days 1, 8 and 15. Potential confounder; type of AB used. 8 of 36 placebo participants received oral AB versus 8 out of the 44 treatment group Country where studies were conducted Amin 2011: Canada* Ballmann 2002 (trial also reported in Ballmann 1998): Germany* Fuchs 1994: USA* Laube 1996: USA* McCoy 1996: USA* Quan 2001: (Australia, Belgium, Canada, Denmark, Germany, Ireland, Israel, Netherlands, Norway, Spain, Switzerland and the United States)* Ramsey 1993: Country not reported* Ranasinha 1993; Country not reported (however quality of copy available of primary study is	placebo group, was 0.925 (CI: 0.69;1.21. p=0.52) However, the adjusted power was 40%. * Adverse events: Dyspnoea at three months (n/N): 93/158 vs 97/162 Adverse events: Voice alteration at three months (n/N): 28/158 vs 10/162 Adverse events: The article states: Cf-related adverse events such as hemoptysis and chest pain occurred with similar frequency in both groups, as did dyspnea * Adverse events: In neither group was there an accelerated occurrence of pulmonary exacerbations * Quan 2001 Absolute mean % change in FEVI at two years: N: 204; Mean (SD): 0.04 (11.43) vs N: 206; Mean (SD): -3.2 (11.43) Number of people experiencing exacerbations at two years (n/N): 40/236 vs 56/234 Adverse events: Voice alteration at two years (n/N): 26/236 vs 27/234 Adverse events: Incidence of serious hemoptysis: 0% vs 0.4% * Ramsey 1993 Relative mean % change in FEVI at one month: N: 44; Mean (SD): 13.8 (13.27) vs N: 48; Mean	thereafter. The published trial reported the end of study results only) Laube 1996 Adequate sequence generation: Unclear (Stated as randomised but no method was described) Allocation concealment: Unclear (Method unclear) Blinding (all outcomes): Unclear (Described as double blind, no further details) Incomplete outcome data addressed (all outcomes): Unclear (ITT analysis was used in this study. The published paper stated that there were no withdrawals) Free of selective reporting: Unclear (None identified) McCoy 1996: Adequate sequence generation: Unclear (Stated as randomised but no method was described) Allocation concealment: Unclear (Method unclear) Blinding (all outcomes): Unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	FVC > 40% predicted Shah 1995a Age: 5 years or more Confirmed diagnosis of CF Severe (FVC < 40% predicted) lung disease Suri 2001 (trial also reported in Suri 2002a and Suri 2002b Age: 7.3-17 Baseline characteristics of these 28 children were comparable to that of the entire study population according to the authors: * F/M: 14/14 Age: Mean (SD): 12.1 (3.1) FEV1 % predicted: Mean (SD): 46.0 (16.0) Sputum inflammatory mediator levels: Total IL-8, ng/g: n: 25; Median: 102.4; 90% Range: 63.2 - 219.0 *, Free IL-8, ng/g: n: 28; Median: 1.6; 90% Range: 0.2 - 41.5 * Wilmott 1996 Age: Over 5		missing some rows)* Shah 1995a: USA, Canada, UK* Suri 2001 (trial also reported in Suri 2002a and Suri 2002b): UK* Wilmott 1996: USA* *Information extracted from primary study	(SD): -1.6 (9). Moderate disease severity subgroup Administration of rhDNase od reduced the use of parenteral antibiotics for protocol-defined respiratory tract infection relative to placebo by 22.5% (p=0.110) and twice daily reduced the use by 34.3% (p=0.012). If adjusted by age, rhDNase od reduced it by 28.4% (p=0.037) relative to placebo and rhDNase bd reduced it by 36.9% (p=0.006).* Adverse events Voice alteration at one month (n/N): 12/44 vs 0/48 Ranasinha 1993 Relative mean % change in FEVI at one month: N: 36; Mean (SD): 12.8 (18.6) vs N: 35; Mean (SD): -1.5 (11.24) (moderate disease severity subgroup) Adverse events: Haemoptysis at one month (n/N): 2/36 vs 0/35 Adverse events: Dyspnoea at one month (n/N): 15/36 vs 11/35 Adverse events: Pnemothorax at one month (n/N): 0/36 vs 0/35 Adverse events: Voice alteration at one month (n/N): 0/36 vs 0/35 Shah 1995a Relative mean % change in FEVI: N: 31; Mean(SD): 1.4 (11.7) vs N: 34; Mean(SD): 4.2 (12.8) (severe disease severity subgroup)	(Described as double blind, no further details) Incomplete outcome data addressed (all outcomes): Unclear (ITT principle used. 2 participants from the dornase alfa arm of the trial did not have lung function recorded. 3 participants inadvertently received dornase alfa instead of placebo (the results for these participants for lung function and respiratory exacerbations were analysed on an ITT basis, for safety data the results for these participants were published as if they had been randomised to dornase alfa). 40 participants withdrew from the trial, 5 due to adverse events, 10 withdrew consent, 1 did not comply with the study protocol, 15 died, 2 were unavailable for follow up and 7 stopped for a medical procedure) Free of selective reporting: Unclear (Measurements were taken on days 8, 15, 29, 57 and 85. The 85 day

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Admitted to hospital for at least 1 night for treatment of a chest exacerbation (protocol defined) with FVC > 35% predicted Confirmed CF diagnosis Both groups had analog dyspnea scores of 32 to 36, which represents a moderate clinical degree of dyspnea. * *Extracted from primary study Inclusion criteria - Exclusion criteria -			Adverse events: Haemoptysis at one month (n/N): 2/35 vs 3/35 Adverse events: Dyspnoea at one month (n/N): 11/35 vs 7/35 Adverse events: Pnemothorax at one month (n/N): 0/35 vs 1/35 Adverse events: Voice alteration at one month (n/N): 1/35 vs 3/35 Suri 2001 (trial also reported in Suri 2002a and Suri 2002b) Mean % change in FEVI (dornase alfa od vs hypertonic saline): Treatment difference (SE): 8 (3.06). Mean % change in FEVI (dornase alfa od vs dornase alfa on alternate days): Mean difference (SE): 2 (3.5714) Mean % change in quality of life score (dornase alfa od vs hypertonic saline): Treatment difference (SE): 0.03 (0.0205) Mean % change in quality of life score (dornase alfa od vs dornase alfa on alternate day): Treatment difference (SE): 0.01 (0.0153) Mean number of days of inpatient treatment (dornase alfa od vs hypertonic saline): Treatment difference (SE): -0.4 (0.9796) Mean number of days of inpatient treatment (dornase alfa od vs dornase alfa alternate day): Treatment difference (SE): -0.93 (1.1789)	mean was reported in the paper) Quan 2001 Adequate sequence generation: Yes (Adequate, done by computer stratifying by centre using a permuted block design) Allocation concealment: Yes (Adequate, carried out by a pharmacy) Blinding (all outcomes): Unclear (Described as double blind, no further details) Incomplete outcome data addressed (all outcomes): Unclear (ITT approach was used. 60 participants withdrew from the study, 472 (out of 474) had follow-up data. The ITT population was 470) Free of selective reporting: Unclear (Measurements taken at week 4, 12 and every 12 weeks thereafter. The end of study results were reported) Ramsey 1993: Adequate sequence generation: Unclear (State d as randomised but no method was described)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Number of children who experienced one or more pulmonary exacerbations . During the HS treatment period N: 15. During the daily rhDNase treatment period N: 18 During the alternate-day rhDNase treatment period N: 17 . (the numbers of treatment period where an individual had one or more pulmonary exacerbations were compared) (cross-over trial). There was no evidence of differences between treatments, as the exact McNemar significance probability was 1.00 when daily rhDNase was compared with alternate-day rhDNase and HS. * Adverse events: Number of patients with haemoptysis (n/N): dornase alfa od: 0/43; dornase alfa on alternate day: 2/43; HS: 0/40 * Adverse events: Number of patients with breathlessness (n/N): dornase alfa od: 1/43; dornase alfa on alternate day: 4/43; HS: 2/40 * Adverse events: There was not significant difference in the number of adverse effects between the groups in the trial. 3 participants receiving HS had significant bronchospasm with the initial dose (reported narratively)	Allocation concealment: Unclear (Method unclear) Blinding (all outcomes): Unclear (Described as double blind, no further details) Incomplete outcome data addressed (all outcomes): Unclear (Analysed on an ITT basis. The paper stated that there were no withdrawals) Free of selective reporting: Unclear (Measurements taken on days 1, 3, 6, 10 with follow-up data on days 14, 21, 28 and 42. Data were reported in the paper on days 3, 10, 21 and 42. Ranasinha 1993: Adequate sequence generation: Yes (Adequate. Participants were assigned a carton number based on a randomisation list generated by Genentech on a permuted block design) Allocation concealment: Yes (Adequate. Unidentifiable cartons of active drug and placebo were numbered and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Changes in inflammatory mediator levels (geometric mean ratios are of post over pretreatment values): Total IL-8, ng/g (geometric mean ratio (95% CI)): Daily rhDNase: 90% (73, 111%); Alternate Day dhDNase: 103% (77, 137%); Hypertonic Saline: 107% (83,186%) - No significant change. * Changes in inflammatory mediator levels (geometric mean ratios are of post over pretreatment values): Free IL-8, ng/g: (geometric mean ratio (95% CI)): Daily rhDNase: 116% (54, 247%); Alternate Day dhDNase: 192% (106, 346%) ; Hypertonic Saline: 98% (47, 204%) - There is a significant mean increase in free IL-8 with alternate-day rhDNase only (p=0.03). * Wilmott 1996 Relative mean % change in FEVI (in participants with acute exacerbations) up to one month: N: 43; Mean(SD): 20 (19.67) vs N: 37; Mean(SD): 19 (42.58). Adverse events: Pnemothorax (n/N): 1/43 vs 0/37 Adverse events: Voice alteration (in participants with acute exacerbations): 6/43 vs 2/37 Adverse events: Dyspnea *: the mean change in dyspnea measured on a visual analog scale improved in both groups of	provided to the pharmacist for dispensing) Blinding (all outcomes): Unclear (Described as double blind, no further details) Incomplete outcome data addressed (all outcomes): Unclear (ITT was not discussed) Free of selective reporting: Unclear (Measurements taken at days 3, 6 and 10, none were reported in the paper) Shah 1995a: Adequate sequence generation: Unclear (Stated as randomised but no method was described) Allocation concealment: Unclear (Method unclear) Blinding (all outcomes): Unclear (Described as double blind, no further details) Incomplete outcome data addressed (all outcomes): Unclear (ITT not possible for some outcomes. 5 out of 70 participants did not complete the 14-day trial period, 1 received a heart-lung transplant, 2 withdrew consent and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				patients (rhDNase 2.5 mg bd N:43; placebo N: 37). The mean percent change was significantly greater in the rhDNase-treated patients at Day 8 ($p<0.01$) but not significant at Day 15 ($p=0.10$) using an ANCOVA adjusted for baseline differences.* The improvement in the actively treated group was by 10% more than in the control group. This difference is of the order of 0.5 standard deviation, which is a moderate statistical effect size that is likely to to be of clinical significance. The dyspnea assessment by quality of life questionnaire improved in both groups of patients, but the change was not statistically significant. * * Information extracted from primary study	2 from the dornase alfa treated group died. Changes in lung function could therefore not be analysed on an ITT basis but adverse events and deaths were analysed on this basis.) Free of selective reporting: Unclear (None identified) Suri 2001 (trial also reported in Suri 2002a and Suri 2002b) Adequate sequence generation: Yes (Adequate (block randomisation was used). Randomisation carried out by telephone to an independent trials co-ordinating unit, and stratified by hospital and balanced after each group of 12 children). Allocation concealment: Yes (Adequate (independent trials co-ordinator). Blinding (all outcomes): Unclear (Not blinded, due to the taste of the hypertonic saline). Incomplete outcome data addressed (all outcomes): Unclear (48 children randomised, 45 completed 1st treatment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					period, 44 completed the 2nd treatment period and 40 completed the 3rd treatment period) Free of selective reporting: Unclear (none identified). Wilmott 1996: Adequate sequence generation: Unclear (Unclear). Allocation concealment: Unclear (Method unclear). Blinding (all outcomes): Unclear (Described as double blind, no further details) Incomplete outcome data addressed (all outcomes): Unclear (ITT. No withdrawals mentioned in the paper) Free of selective reporting: Unclear (Measurements taken on days 1, 8 and 15, no reported results, graph shown in the paper). Other information Fuchs 1994. The study compared od and bd to placebo *, Cochrane does not specify what it is reporting, but likely to be reporting od. Shah 1995a. 6-month open-ended

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					phase not included in the Cochrane review as no control group.
Full citation Mainz, J. G., Schumacher, U., Schadlich, K., Hentschel, J., Koitschev, C., Koitschev, A., Riethmuller, J., Prenzel, F., Sommerburg, O., Wiedemann, B., Staab, D., Gleiber, W., Fischer, R., Beck, J. F., Arnold, C., Cooperators,, Sino nasal inhalation of isotonic versus hypertonic saline (6.0%) in CF patients with chronic rhinosinusitis - Results of a multicenter, prospective, randomized, double-blind, controlled trial, Journal of Cystic FibrosisJ Cyst Fibros, 4, 4, 2016 Ref Id	Sample size N=69 Characteristics People with CF with chronic rhinosinusitis Mean age (SD): 22.8 (12) Females: 29/69 (42%) Inclusion criteria Age ≥6 years. Confirmed diagnosis of CF. Chronic symptoms of rhinosinusitis. Exclusion criteria Not reported.	Interventions Intervention: 6% sodium chloride once daily for 28 days Comparison: 0.9% sodium chloride once daily for 28 days	Details Setting. Participants were enrolled in 11 German CF outpatient clinics. Randomization. Participants were randomized to either hypertonic or isotonic saline. Wash-out period. After a wash-out period of at least 28 days, participants crossed over to the alternative treatment. Treatment with intravenous antibiotics within the wash-out period delayed the start of the second period for another 28 days. Data collection. Methods to measure FEV1 were not reported. Data analysis. Values of visit 1, day 1 (period 1) and visit 3, day 57 (period 2) were used as baseline values. The authors calculated change in	Results Mean (SD) change in FEV1 % predicted at day 29: 6% sodium chloride (n=62 at baseline and n=60 at day 29): 0.04 (6.73) vs 0.9% sodium chloride (n=63): -0.3 (6.9)	Limitations Assessed with risk of bias Cochrane tool: Random sequence generation (selection bias): Unclear risk (method not reported) Allocation concealment (selection bias): Unclear risk (not reported) Blinding (performance bias and detection bias): Low risk (Double-blinded study, although unclear whether double-blind refers to participants, clinicians or outcome assessors) Incomplete outcome data (attrition bias): Low risk (Intention-to-treat analysis was carried out, however 5/69 people were excluded from the analysis. The reasons were: diary not evaluable, study medication was taken too early, private reason, stopped medication and rejected inhalation because of vibration)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
542074 Country/ies where the study was carried out Germany Study type Multi-centre crossover RCT Aim of the study To compare 6% sodium chloride to 0.9% sodium chloride. Study dates The study was registered at ClinicalTrials.gov in March 2010. Participants were enrolled between April 2010 and June 2013. Source of funding The study was supported by a financial grant from "Association Luxemburgeoise de Lutte contre la Mucoviscidose a.s.b.l." in cooperation with Mukoviszidose Insitut gGmbH, Bonn, the research and development arm			FEV1 for each treatment sequence.		Selective reporting (reporting bias): Unclear risk (FEV1 not mentioned in the methods section but results were provided) Other bias: Low risk (None identified) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of German Cystic Fibrosis Association Mukoviszidose e.V (grant number: S03/09). The PARI GmbH provided the study centres with nebulizers and blinded medication.					
Full citation National Institute for Health and Clinical Excellence, Mannitol dry powder for inhalation for treating cystic fibrosis. Single technology appraisal, 2012 Ref Id 589512 Country/ies where the study was carried out NICE 2012: N/A CF-301 (Bilton 2011): Australia, New Zealand, UK, Ireland) CF-302 (Aitken 2012):	Sample size DPM-CF-301 (Bilton 2011) N=295 Mannitol: n=177 Control: n=118 DPM-CF-302 (Aitken 2012) N=305 Mannitol: n=184 Control: n=121 Characteristics DPM-CF-301 (Bilton 2011) Subjects with CF. Baseline characteristics: N (%) children aged 6 to 11: mannitol (n=177): 31 (1.75%) vs control (n=118): 17 (14.4%)	Interventions DPM-CF-301 (Bilton 2011) Intervention: dry powder mannitol for inhalation 400mg (in 40 mg capsules) BD for 26 weeks. Administered with a hand-held, breath activated device. Control: dry powder mannitol for inhalation 50mg (in 5 mg capsules) BD for 26 weeks. Administered with a hand-held, breath activated device. DPM-CF-302 (Aitken 2012) Intervention: dry powder mannitol for	Details DPM-CF-301 (Bilton 2011) Double-blinded multinational, multicentre RCT. People were from recruited from 40 sites. Subjects that were using rhDNase routinely prior to enrolment in this clinical trial continued to use rhDNase throughout the trial. FEV1 was measured at 6,14 and 26 weeks. Method of randomisation: All subjects from a site were given consecutive enrolment numbers in	Results DPM-CF-301 (Bilton 2011)* FEV1 % predicted Mean difference (SE) [95% CI] in change from baseline in FEV1 % predicted at 2 months, Mannitol (n=177) vs control (n=118): 2.588 (1.184) [0.27, 4.91] Mean difference (SE) [95% CI] in change from baseline in FEV1 % predicted at 4 months, Mannitol (n=177) vs control (n=118): 3.602 (1.2534) [1.15, 6.06] Mean difference (SE) [95% CI] in change from baseline in FEV1 % predicted at 6 months, Mannitol (n=177) vs control (n=118): 3.595 (1.3419) [0.96, 6.23] Time to next exacerbation at 26 weeks**	Limitations DPM-CF-301 (Bilton 2011)* Random sequence generation (selection bias): Low risk (Described as randomised using 3:2 ratio (mannitol versus control) and stratified according to current dornase alfa use. Pharmaxis confirmed participants were randomised to a treatment arm via an IVRS using the site-subject identification number, date of birth, initials and dornase alfa use as requisites. A master randomisation list, stratified by region (Australia and Europe) and dornase alfa use (yes/no), was prepared by an external company.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
USA, Canada, Argentina, Europe Study type NICE 2012 Technology appraisal DPM-CF-301 (Bilton 2011) Multi-centre RCT, parallel design DPM-CF-302 (Aitken 2012) Multi-centre RCT, parallel design Aim of the study DPM-CF-301 (Bilton 2011) To determine the effect of Bronchitol compared to control on FEV1 in patients with CF DPM-CF-302 (Aitken 2012) To determine whether inhaled Bronchitol compared to control improves FEV1 in patients with cystic fibrosis (CF). Study dates	N (%) young people aged 12 to 17: mannitol (n=177): 32 (18.1%) vs control (n=118): 25 (21.2%) N (%) people aged 18 and over: mannitol (n=177): 114 (64.4%) vs control (n=118): 76 (64.4%) Mean (SD) age: mannitol (n=177): 23.1 (11.7) vs control (n=118): 22.8 (10.8) N (%) females: mannitol (n=177): 71 (40.1%) vs control (n=118): 61 (51.7%) N (%) caucasians: mannitol (n=177): 169 (95.5%) vs control (n=118): 115 (97.5%) Mean (SD) BMI (kg/m2): mannitol (n=177): 21.1 (4.0) vs control (n=118): 20.4 (3.6) N (%) dornase alfa use: mannitol (n=177): 96 (54.2%) vs control (n=118): 67 (56.8%) FEV1 % predicted at baseline: mannitol (n=177): 62.4 (16.45)	inhalation 400mg (in 40 mg capsules) BD for 26 weeks. Administered with a hand-held, breath activated device. Control: dry powder mannitol for inhalation 50mg (in 5 mg capsules) BD for 26 weeks. Administered with a hand-held, breath activated device.	successive order of inclusion. Enrolment numbers were generatedelectronically and were correlated to one of two randomisation schedules. The randomisation schedules were independently generated in blocks of five, for a parallel study design and stratified according to region and rhDNase use. For every three subjects randomised to active treatment, two subjects were allocated to control. Method of blinding: The investigators, site staff, pharmacists, subjects, monitors, project managers and data managers remained blinded throughout the study. Sealed randomisation individual code break envelopes were kept with the study pharmacist. Both active and control treatments consisted of ten identical opaque capsules with	Hazard ratio [95% CI] for time to first protocol defined pulmonary exacerbation, Mannitol (n=177) vs control (n=118): 0.68 [0.42, 1.11]. log [hazard ratio] (SE): -0.3857 (0.25) Need for intravenous antibiotics for pulmonary exacerbations People needing additional IV antibiotics at 4 months follow-up (n/N): Mannitol: 63/177 vs control: 60/118. Risk ratio [95% CI]: 0.70 [0.54 to 0.91] People needing additional IV antibiotics at 6 months follow-up (n/N): Mannitol: 63/177 vs control: 60/118. Risk ratio [95% CI]: 0.70 [0.54 to 0.91] Quality of life Mean (SD) change in quality of life - respiratory at 4 months follow-up: Mannitol (n=128): 0.3 (16.3) vs control (n=101): 0.1 (15.62) . Mean difference [95% CI]: 0.20 [-3.95, 4.35] Mean (SD) change in quality of life - vitality at 4 months follow-up: Mannitol (n=92): -0.2 (17.56) vs control (n=74): -3.5 (18.71). Mean difference [95% CI]: 3.30 [-2.27, 8.87] Mean (SD) change in quality of life - physical at 4 months follow-up: Mannitol (n=127): -2.7 (16.55) vs control (n=100): -1.5	Randomisation numbers (for both mannitol and control) were generated for each stratum, in blocks of 5. The randomisation number was assigned sequentially within each stratum) Allocation concealment (selection bias): Low risk (Pharmaxis confirmed randomisation was managed via an IVRS, therefore the investigator was unaware prior to randomising the participant which specific blinded pack of treatment they would be allocated to) Blinding (performance bias and detection bias) - participants: Low risk (Participants blinded to treatment allocation through using a subtherapeutic does of mannitol and the same inhaler devices were used for both treatment arms (not specifically stated in the published paper but Pharmaxis confirmed use of same inhaler device with 10 capsules for both 400 mg mannitol and control (50 mg mannitol))

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
DPM-CF-301 (Bilton 2011) 5 April 2007 to 31 March 2009 DPM-CF-302 (Aitken 2012) 3 September 2008 to 12 April 2010 Source of funding NICE 2012 Technology appraisal submitted by Pharmaxis to NICE DPM-CF-301 (Bilton 2011) Pharmaxis DPM-CF-302 (Aitken 2012) Pharmaxis	vs control (n=118): 61.4 (16.13) DPM-CF-302 (Aitken 2012) Subjects with CF. N (%) children aged 6 to 11: mannitol (n=184): 35 (19.0%) vs control (n=121): 24 (19.8%) N (%) young people aged 12 to 17: mannitol (n=184): 56 (30.4%) vs control (n=121): 39 (32.2%) N (%) people aged 18 and over: mannitol (n=184): 93 (50.5%) vs control (n=121): 58 (47.9%) Mean (SD) age: mannitol (n=184): 19.6 (9.3) vs control (n=121): 20.4 (10.2) N (%) females: mannitol (n=184): 90 (48.9%) vs control (n=121): 58 (47.9%) N (%) caucasians: mannitol (n=184): 182 (98.9%) vs control (n=121): 119 (98.3%) Mean (SD) BMI (kg/m2): mannitol (n=184): 20.2 (4.12) vs		indistinguishable taste. Several strategies were put in place to minimize the subject's association between MTT and study drug. Addition of a second open label phase (the OLEP) which was added to ensure that a minimum of 100 subjects would receive 12 months of active treatment – this added two more safety visits to the open label phase. DPM-CF-302 (Aitken 2012) Double-blinded multinational, multicentre RCT. People were recruited from 53 sites. Subjects that were using dornase alfa routinely prior to enrolment in this clinical trial continued to use dornase alfa throughout the trial. Method of randomisation: Subje ct identification numbers were generated electronically when	(15.1). Mean difference [95% CI]: -1.20 [-5.33, 2.93] Mean (SD) change in quality of life - emotion at 4 months follow-up: Mannitol (n=128): -1.5 (15.4) vs control (n=100): -0.1 (13.94). Mean difference [95% CI]: -1.40 [-5.22, 2.42] Mean (SD) change in quality of life - eating at 4 months follow-up: Mannitol (n=128): 0.6 (15.1) vs control (n=99): 0.6 (14.23). Mean difference [95% CI]: 0.0 [-3.83, 3.83] Mean (SD) change in quality of life - health at 4 months follow-up: Mannitol (n=93): -0.1 (18.45) vs control (n=72): 2.3 (19.73). Mean difference [95% CI]: -2.40 [-8.30, 3.50] Mean (SD) change in quality of life - social at 4 months follow-up: Mannitol (n=128): -1.4 (15.6) vs control (n=98): -0.8 (11.54). Mean difference [95% CI]: -0.60 [-4.14, 2.94] Mean (SD) change in quality of life - body at 4 months follow-up: Mannitol (n=126): -1.2 (16.94) vs control (n=97): 1.6 (16.97). Mean difference [95% CI]: -2.80 [-7.29, 1.69] Mean (SD) change in quality of life - role at 4 months follow-up: Mannitol (n=92): 0.5 (18.05) vs control (n=72): -2.4 (15.66). Mean difference [95% CI]: 2.90 [-2.27, 8.07]	Blinding (performance bias and detection bias) - clinicians: Low risk (Study personnel blinded to treatment allocation. Pharmaxis confirmed that investigators and study staff including statisticians were blinded. Low-dose mannitol used as control which was identical in taste and appearance to the 400 mg mannitol Blinding (performance bias and detection bias) - outcome assessors: Low risk (Pharmaxis confirmed investigators and study staff, including statisticians and all outcome assessors at investigator sites e.g. spirometry technicians were blinded) Incomplete outcome data (attrition bias): Low risk (High dropout rates in blinded phase of study in both arms: 37% in mannitol arm and 28% in control arm. However, sensitivity analyses conducted by Pharmaxis (methods of imputation of missing data for withdrawals) showed a consistent treatment effect

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	control (n=121): 19.8 (3.70) N (%) dornase alfa use: mannitol (n=184): 137 (74.5%) vs control (n=121): 92 (76.0%) FEV1 % predicted at baseline: mannitol (n=184): 64.8 (15.7) vs control (n=121): 62.5 (16.0) Inclusion criteria NICE 2012 The TA focused on adults with CF. However neither study was powered to specifically show efficacy in this patient group, therefore the data from the total population is reported first. DPM-CF-301 (Bilton 2011) Age ≥6. FEV1 >30 and <90% predicted. Able to perform techniques necessary to measure lung function. Negative mannitol tolerance test (MTT). MTT was administered at the screening visit of the study. This MTT was necessary to assess bronchial		the subject's screening visit data were entered into the eCRF. The identification number was allocated sequentially and comprised a site number-subject number combination. Randomisation to treatment arm was carried out via Interactive Voice Response System (IVRS) using the site-subject identification number, date of birth, initials and rhDNase use as requisites. Randomisation was stratified by country and generated in paired blocks of five, one block for rhDNase users and one block for non-users. Within each block for every three subjects randomised to active treatment, two subjects were allocated to control. FEV1 was measured at 6,14 and 26 weeks. Method of blinding: The subjects,	Mean (SD) change in quality of life - weight at 4 months follow-up: Mannitol (n=92): 1.4 (26.11) vs control (n=73): 7.3 (29.53). Mean difference [95% CI]: -5.90 [-14.52, 2.72] Mean (SD) change in quality of life - digestion at 4 months follow-up: Mannitol (n=128): 0.8 (17.2) vs control (n=99):0.2 (17.75). Mean difference [95% CI]: -1.00 [-5.59, 3.59] Mean (SD) change in quality of life - respiratory at 6 months follow-up: Mannitol (n=114): 1.3 (15.95 vs control (n=87): -2.5 (17.55. Mean difference [95% CI]: 3.80 [-0.91, 8.51] Mean (SD) change in quality of life - vitality at 6 months follow-up: Mannitol (n=80): 2.1 (15.88) vs control (n=62): -5.1 (18.13). Mean difference [95% CI]: 7.20 [1.50, 12.90] Mean (SD) change in quality of life - physical at 6 months follow-up: Mannitol (n=113): -0.5 (16.22) vs control (n=87): -4.7 (17.56). Mean difference [95% CI]: 4.20 [-0.55, 8.95] Mean (SD) change in quality of life - emotion at 6 months follow-up: Mannitol (n=114): 0.3 (11.7) vs control (n=87): 0.5 (13.66) . Mean difference [95% CI]: -0.80 [-4.38, 2.78] Mean (SD) change in quality of life - eating at 6 months follow-	in favour of mannitol and no change to conclusions) Selective reporting (reporting bias): Low risk (Limited information was reported in the study publication; particularly HRQoL and lung function. Additional data were provided by Pharmaxis on request for all primary outcomes of this review and many secondary outcomes) Other bias: High risk (Participants underwent a mannitol tolerance test at screening; those who failed the test or in whom the test was incompletewere not entered into the study and thus, study population included only those with CF who passed the tolerance test and not all potential participants with CF. Sponsored by Pharmaxis; authors or study staff worked for Pharmaxis or had financial interest) DPM-CF-302 (Aitken 2012)* Random sequence generation (selection bias): Low risk (Further

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	responsiveness to Bronchitol and was necessary to exclude patients with airway hyperresponsiveness. The MTT assessment entails 6 steps where incremental doses of dry powder Bronchitol are administered in cumulative doses and lung function measurements are performed. Only patients who passed the MTT were randomised to treatment. DPM-CF-302 (Aitken 2012) Age ≥6. FEV1 >40% and <90% predicted. Negative Bronchitol tolerance test (MTT). MTT was administered at the screening visit of the study. This MTT was necessary to assess bronchial responsiveness to Bronchitol and was necessary to exclude patients with airway hyperresponsiveness. The MTT assessment entails 6 steps where incremental doses of		investigators, pharmacists and Pharmaxis clinical and statistical staff were blinded to treatment allocations. The study pharmacist could access the allocation using the IVRS if necessary to unblind a subject. Both active and control treatments consisted of ten identical opaque capsules with indistinguishable taste. Several strategies were put in place to minimize the subject's association between MTT and study drug. Change in % predicted FEV1 was not in protocol however was included in the statistical analysis plan.	up: Mannitol (n=114): 2.3 (15.47) vs control (n=87): 1.9 (13.89). Mean difference [95% CI]: 0.40 [-3.67, 4.47] Mean (SD) change in quality of life - health at 6 months follow-up: Mannitol (n=79): 1.4 (17.47) vs control (n=62): 1.1 (18.3). Mean difference [95% CI]: 0.30 [-5.67, 6.27] Mean (SD) change in quality of life - social at 6 months follow-up: Mannitol (n=113): 0.3 (13.75) vs control (n=87): -0.7 (13.74). Mean difference [95% CI]: 1.00 [-2.84, 4.84] Mean (SD) change in quality of life - body at 6 months follow-up: Mannitol (n=111): 1.6 (16.26) vs control (n=86): 1.8 (15.14). Mean difference [95% CI]: -0.20 [-4.60, 4.20] Mean (SD) change in quality of life - role at 6 months follow-up: Mannitol (n=80): -0.4 (16.66) vs control (n=62): -1.6 (15.15). Mean difference [95% CI]: 1.20 [-4.05, 6.45] Mean (SD) change in quality of life - weight at 6 months follow-up: Mannitol (n=80): 3.7 (23.72) vs control (n=62): 6.5 (31.85). Mean difference [95% CI]: -2.80 [-12.28, 6.68] Mean (SD) change in quality of life - digestion at 6 months follow-up: Mannitol (n=114): -0.7 (19.46) vs control (n=87): 0	details were provided by Pharmaxis: the master randomisation list, stratified by country and dornase alfa user (yes/no) for a parallel design was prepared usingSAS Version 8.1 by an external company. 300 randomisation numbers (180 active and 120 control) were generated for each country and each dornase alfa user/non user group. Randomization blocking by country was done in paired blocks of 5, 1 block for dornase alfa users and 1 block for non users)) Allocation concealment (selection bias): Low risk (Pharmaxis confirmed randomisation managed via an IVRS, therefore the investigator was unaware prior to randomising the participant which specific blinded pack of treatment they would be allocated to. This provided an extra level of security (over and above the blinded nature of the study) against selection bias)) Blinding (performance bias and detection bias) - participants: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	dry powder Bronchitol are administered in cumulative doses and lung function measurements are performed. Only patients who passed the MTT were randomised to treatment. Exclusion criteria DPM-CF-301 (Bilton 2011) Considered "terminally ill", listed for or had lung transplant Use of nebulised hypertonic saline was an exclusion criterion assessed at screening (visit 0). Significant episode of haemoptysis (>60mL) in the three months prior to enrolment Have had a myocardial infarction, cerebral vascular accident, major ocular, chest or brain surgery in the 3 months prior to enrolment Known cerebral, aortic or abdominal aneurysm			(21.63). Mean difference [95% CI]: -0.70 [-6.48, 5.08 Adverse events Adverse events: haemoptysis (mild) (n/N) at 6 months: Mannitol: 3/177 vs control: 2/118. Risk ratio: 4.62 [0.10, 224.14] Adverse events: bronchospasm (mild) (n/N) at 6 months: Mannitol: 0/177 vs control: 0/118. Risk ratio: Not estimable. Adverse events: haemoptysis (moderate) (n/N) at 6 months: Mannitol: 9/177 vs control: 1/118. Risk ratio: 6.00 [0.40, 89.09] Adverse events: bronchospasm (moderate) (n/N) at 6 months: Mannitol: 1/177 vs control: 0/118. Risk ratio: 2.01 [0.03, 133.11] Adverse events: haemoptysis (severe) (n/N) at 6 months: Mannitol: 1/177 vs control: 1/118. Risk ratio: 0.67 [0.02, 25.14] Adverse events: bronchospasm (severe) (n/N) at 6 months: Mannitol: 1/177 vs control: 0/118. Risk ratio: 2.01 [0.03, 133.11] DPM-CF-302 (Aitken 2012)* Need for intravenous antibiotics for pulmonary exacerbations	(Described as double blind - mannitol and low-dose mannitol control administered and capsules identical in taste and appearance with identical methods of administration) Blinding (performance bias and detection bias) - clinicians: Low risk (Described as double blind - mannitol and low-dose mannitol control administered as capsules identical in taste and appearance and with identical methods of administration Pharmaxis confirmed investigators and study staff, including statisticians and all outcome assessors at investigator sites e.g. spirometry technicians were blinded. Both Bilton 2011 and Aitken 2012 used the same low-dose mannitol control that identical in taste and appearance to the 400mg mannitol active intervention) Blinding (performance bias and detection bias) - outcome assessors: Low risk (Described as double blind - mannitol and low-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Female subjects currently breast feeding or pregnant or using unreliable form of contraception if at risk of pregnancy) Participation in another investigative drug study parallel to, or within 4 weeks of study entry Known allergy to Bronchitol Use of beta-blockers Uncontrolled hypertension – systolic BP >190 and/or diastolic BP >100 Condition or situation which in the Investigator's opinion may put the subject at significant risk, may confound results or may interfere significantly with the subject's participation in the study MTT test positive DPM-CF-302 (Aitken 2012) Considered "terminally ill", listed for or had lung transplant Using nebulised hypertonic saline - can be eligible if 4 week			People needing additional IV antibiotics at 4 months follow-up (n/N): Mannitol: 63/177 vs control: 60/118. Risk ratio [95% CI]: 0.70 [0.54 to 0.91] People needing additional IV antibiotics at 6 months follow-up (n/N): Mannitol: 102/184 vs control: 74/121. Risk ratio [95% CI]: 0.91 [0.75 to 1.10] FEV1 % predicted Mean difference (SE) [95% CI] in change from baseline in FEV1 % predicted at 2 months, Mannitol (n=184) vs control (n=121): 3.89 (1.81) 3.89 [0.34, 7.44] Mean difference (SE) [95% CI] in change from baseline in FEV1 % predicted at 4 months, Mannitol (n=184) vs control (n=121): 2.34 (2.04) [-1.66, 6.34] Mean difference (SE) [95% CI] in change from baseline in FEV1 % predicted at 6 months, Mannitol (n=184) vs control (n=121): 4.55 (2.03) [0.57, 8.53] Time to next exacerbation at 26 weeks** Hazard ratio [95% CI] for time to first protocol defined pulmonary exacerbation, Mannitol (n=184) v s control (n=121): 0.74 [0.41, 1.32]. log [hazard ratio] (SE): -0.3011 (0.2953) Quality of life	dose mannitol control administered as capsules identical in taste and appearance and with identical methods of administration. Pharmaxis confirmed blinding of investigators and study staff including statisticians and all outcome assessors. Incomplete outcome data (attrition bias): Low risk (Higher dropout rate with mannitol, 17% versus 12% for control, for adverse events and other reasons e.g. withdrawal of consent. However, paper provides flow diagram with timing and reasons for drop out and which group the participants were in. Sensitivity analyses conducted by Pharmaxis (methods of imputation of missing data for withdrawals) showed a consistent treatment effect in favour of mannitol andno change to conclusions)) Selective reporting (reporting bias): Low risk (Limited information was reported in the study publication; particularly HRQoL and lung function)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	washout between screening and baseline visits Significant episode of haemoptysis (>60mL) in the three months prior to enrolment Have had a myocardial infarction, cerebral vascular accident, major ocular, chest or brain surgery in the 3 months prior to enrolment Known cerebral, aortic or abdominal aneurysm Female subjects currently breast feeding or pregnant or using unreliable form of contraception if at risk of pregnancy) Participation in another investigative drug study parallel to, or within 4 weeks of study entry Known allergy to Bronchitol Use of beta-blockers Uncontrolled hypertension – systolic BP >190 and/or diastolic BP >100 Condition or situation which in the			Mean (SD) change in quality of life - respiratory at 4 months follow-up: Mannitol (n=164): -0.1 (17.58) vs control (n=114): 3.8 (21.89). Mean difference [95% CI]: -3.90 [-8.74, 0.94] Mean (SD) change in quality of life - vitality at 4 months follow-up: Mannitol (n=115): -1.9 (17.94) vs control (n=80): 5.4 (15.81). Mean difference [95% CI]: 3.50 [-1.27, 8.27] Mean (SD) change in quality of life - physical at 4 months follow-up: Mannitol (n=164): -0.1 (18.17) vs control (n=114): 2.3 (16.53). Mean difference [95% CI]: -2.40 [-6.52, 1.72] Mean (SD) change in quality of life - emotion at 4 months follow-up: Mannitol (n=164): 0.3 (14.35) vs control (n=114): 2.9 (12.64). Mean difference [95% CI]: -2.60 [-5.79, 0.59] Mean (SD) change in quality of life - eating at 4 months follow-up: Mannitol (n=164): -1.6 (17.29) vs control (n=114): -3.3 (16.39). Mean difference [95% CI]: 1.70 [-2.31, 5.71] Mean (SD) change in quality of life - health at 4 months follow-up: Mannitol (n=115): -0.1 (16.22) vs control (n=80): -1 (17.52). Mean difference [95% CI]: 0.90 [-3.95, 5.75] Mean (SD) change in quality of life - social at 4 months follow-	Additional data were provided by Pharmaxis on request for all primary outcomes of this review and many secondary outcomes Other bias: High risk (Participants underwent a mannitol tolerance test at screening; those who failed the test or in whom the test was incomplete were not entered into the study and thus, the participant population included only those with CF who passed the tolerance test and not all potential participants with CF. Sponsored by manufacturer of mannitol (Pharmaxis); authors or study staff worked for Pharmaxis or had financial interest). *Information on risk of bias extracted from Nolan 2015 Cochrane SR Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Investigator's opinion may put the subject at significant risk, may confound results or may interfere significantly with the subject's participation in the study MTT test positive or incomplete			up: Mannitol (n=164): -1.6 (13.66) vs control (n=114): 0.2 (15.55). Mean difference [95% CI]: -1.80 [-5.34, 1.74] Mean (SD) change in quality of life - body at 4 months follow-up: Mannitol (n=164): -2 (21.75) vs control (n=113): 1.5 (21.39). Mean difference [95% CI]: -3.50 [-8.66, 1.66] Mean (SD) change in quality of life - role at 4 months follow-up: Mannitol (n=115): -0.9 (13.93) vs control (n=79): -0.8 (17.33). Mean difference [95% CI]: -0.10 [-4.69, 4.49] Mean (SD) change in quality of life - weight at 4 months follow-up: Mannitol (n=115): 2 (32.23) vs control (n=80): 4.6 (27.94). Mean difference [95% CI]: -2.60 [-11.10, 5.90] Mean (SD) change in quality of life - digestion at 4 months follow-up: Mannitol (n=164): 0.1 (16.58) vs control (n=114): 2.1 (21.36). Mean difference [95% CI]: -2.00 [-6.67, 2.67] Mean (SD) change in quality of life - respiratory at 6 months follow-up: Mannitol (n=154): -1.4 (20.16) vs control (n=110): 5.6 (22.51). Mean difference [95% CI]: -7.00 [-12.28, -1.72] Mean (SD) change in quality of life - vitality at 6 months follow-up: Mannitol (n=107): -1.6 (20.48) vs control (n=76): -4.2	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(17.72). Mean difference [95% CI]: 2.60 [-2.96, 8.16] Mean (SD) change in quality of life - physical at 6 months follow-up: Mannitol (n=155): -1.7 (18.85) vs control (n=110): 1.1 (18.2). Mean difference [95% CI]: -2.80 [-7.31, 1.71] Mean (SD) change in quality of life - emotion at 6 months follow-up: Mannitol (n=155): 0.4 (15.34) vs control (n=109): 2.1 (12.84). Mean difference [95% CI]: -1.70 [-5.11, 1.71] Mean (SD) change in quality of life - eating at 6 months follow-up: Mannitol (n=155): 155 -0.4 (18.37) vs control (n=110): -1.4 (17.3). Mean difference [95% CI]: 1.00 [-3.34, 5.34] Mean (SD) change in quality of life - health at 6 months follow-up: Mannitol (n=107): -1.5 (17.61) vs control (n=77): -0.9 (18). Mean difference [95% CI]: -0.60 [-5.82, 4.62] Mean (SD) change in quality of life - social at 6 months follow-up: Mannitol (n=155): 3.3 (16.99) vs control (n=110): 0.9 (16.23). Mean difference [95% CI]: -4.20 [-8.24, -0.16] Mean (SD) change in quality of life - body at 6 months follow-up: Mannitol (n=155): 0.4 (20.29) vs control (n=109): 2.9 (20.86). Mean difference [95% CI]: -2.50 [-7.55, 2.55]	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Mean (SD) change in quality of life - role at 6 months follow-up: Mannitol (n=106): -2.3 (17.35) vs control (n=76): 1.1 (13.83). Mean difference [95% CI]: -3.40 [-7.94, 1.14] Mean (SD) change in quality of life - weight at 6 months follow-up: Mannitol (n=106): 4.1 (33.71) vs control (n=77): 7.8 (29.07). Mean difference [95% CI]: -3.70 [-12.83, 5.43] Mean (SD) change in quality of life - digestion at 6 months follow-up: Mannitol (n=154): 1.4 (20.47) vs control (n=110): 2.8 (23.48). Mean difference [95% CI]: -1.40 [-6.85, 4.05] Adverse events: Adverse events: haemoptysis (mild) (n/N) at 6 months: Mannitol: 3/184) vs control: 0/121. Risk ratio: 1.00 [0.10, 10.29] Adverse events: haemoptysis (moderate) (n/N) at 6 months: Mannitol: 1/184) vs control: 0/121. Risk ratio: 1.98 [0.03, 131.35] Adverse events: haemoptysis (severe) (n/N) at 6 months: Mannitol: 2/184) vs control: 0/121. Risk ratio: 3.30 [0.06, 176.31]	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				*Results extracted from Nolan 2015 Cochrane SR. ** Follow-up identified from primary study	
Full citation Skov, M., Pressler, T., Lykkesfeldt, J., Poulsen, H. E., Jensen, P. T., Johansen, H. K., Qvist, T., Kraemer, D., Hoiby, N., Ciofu, O., The effect of short-term, high-dose oral N-acetylcysteine treatment on oxidative stress markers in cystic fibrosis patients with chronic P. aeruginosa infection - A pilot study, Journal of Cystic Fibrosis, 14, 211-218, 2015 Ref Id 360293 Country/ies where the study was carried out Denmark	Sample size N=21 Characteristics Gender: 12 males and 9 females Median age: 39 years (range 25–61 years) Baseline lung function of the patients in the NAC group was FEV1 (% predicted) mean (95% CI) 58.36% (46.26; 70.46) and of the patients in the control group 53.7% (37.6; 69.8). Inclusion criteria Adult patients with confirmed CF with chronic P. aeruginosa lung infection, at the end of a two-week intravenous antibiotic treatment. Exclusion criteria Hypersensitivity to N-acetyl cysteine, prior lung transplantation or	Interventions NAC in a mean dose of 36 mg/kg/day (max 59 mg/kg/day and min 25.8 mg/kg/day). Duration: 4 weeks Comparison: Control group (no placebo)	Details Design: open-label, controlled, RCT Method of randomization: not reported Allocation concealment: not reported Blinding: open trial Procedure: the control group did not receive placebo medication and was therefore aware of the group to which they were assigned. Patients in the NAC group received oral treatment with N-acetylcysteine, tablets of 600 mg effervescent (Mucolysin ®600 produced by Sandoz A/S), 2 tablets twice a day (a total daily dose of 2400 mg) for 4	Results Change in FEV1 % predicted mean (95% CI) Intervention: +2.11 (−1.44; 5.66) Control: −1.4 (−4.7; 1.9)	Limitations Assessed with risk of bias Cochrane tool: Random sequence generation (selection bias): Unclear risk (method not reported) Allocation concealment (selection bias): Unclear risk (not reported) Blinding (performance bias and detection bias): high risk (open trial) Incomplete outcome data (attrition bias): Low risk (Intention-to-treat analysis was carried out) Selective reporting (reporting bias): low risk Other bias: Low risk (None identified) Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Open-trial RCT Aim of the study This study was intended as a pilot study enabling proper power calculations necessary for number of CF patients to be included in a larger phase II clinical study in CF patients. Study dates March 2011 to August 2013 Source of funding The Mucolysin tablets were kindly provided by Sandoz A/S. The Novo Nordisk Foundation supported HKJ as a clinical research stipend.	if on lung transplant waiting list Patients who received NAC in the last 30 days, patients with recent hemoptysis or an abnormal liver function test (ALAT) more than twice the normal range (10–70 U/L).		weeks. All other medication was continued, including inhalation with pulmozyme, bronchodilators with β2 agonists and colistin and per oral treatment with ciprofloxacin and azithromycin. Analysis: not reported. Two of the patients belonging to the NAC group did not complete the trial (1 due to adverse events 1 due to lack of compliance). These two patients were excluded from the final analysis, thus the effect of the treatment with NAC was evaluated in 9 CF patients compared to 10 CF controls.		

G.9 Pulmonary infection - prophylaxis

Review question: What is the effectiveness of long-term antimicrobial prophylaxis to prevent pulmonary bacterial colonisation with Staphylococcus aureus in people with CF?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Beardsmore,C.S., Thompson,J.R., Williams,A., McArdle,E.K., Gregory,G.A., Weaver,L.T., Simpson,H., Pulmonary function in infants with cystic fibrosis: the effect of antibiotic treatment, Archives of Disease in Childhood, 71, 133-137, 1994 Ref Id 104558 Country/ies where the study was carried out Study type See Smyth 2014, Cochrane systematic review Aim of the study See Weaver 1994 Study dates - Source of funding -	Sample size See Cochrane SR Smyth 2014 Characteristics See Cochrane SR Smyth 2014 Inclusion criteria See Cochrane SR Smyth 2014 Exclusion criteria See Cochrane SR Smyth 2014	Interventions See Cochrane SR Smyth 2014	Details See Cochrane SR Smyth 2014	Results See Cochrane SR Smyth 2014	Limitations See Cochrane SR Smyth 2014 Other information This study provides additional information for Weaver 1994.
Full citation Smyth, A. R., Walters, S., Prophylactic anti-staphylococcal antibiotics for cystic fibrosis, Cochrane Database of Systematic Reviews, 11, CD001912, 2014 Ref Id 367815 Country/ies where the study was carried out Study type	Sample size This review includes 4 trials. Characteristics Chatfield 1991 Infants with CF (diagnosed by	Interventions This review includes any oral antibiotic prophylactic intervention used continuously for a long period of time	Details All the studies included in the review are RCTs.	Results Data has been taken from the Cochrane SR where possible. Additional data has been extracted from	Limitations Limitations Quality of the systematic review AMSTAR score: 10 out of 11 Quality of the individual studies Data has been taken from the Cochrane SR where possible. Additional data has been extracted from studies if needed.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cochrane systematic review Includes 4 RCTs: Chatfield 1991, Schlesinger 1984, Stutman 2002, Weaver 1994 NOTE: data has been extracted directly from the Cochrane SR where possible. Individual studies have been retrieved for completeness. Aim of the study This review aims to assess the effectiveness and safety of oral antibiotic prophylaxis to prevent the acquisition of S. Aureus versus no prophylaxis in people with CF. Study dates Searches up to 04.09.2014 Source of funding Not reported.	neonatal screening or clinically) N = 122 (2 withdrew, n = 120, prophylaxis = 54, 'as required' = 66) Mean age at enrollment: 18 weeks for prophylaxis & 22 weeks for 'as required'. Followed up to age three years. Data available at one, two & three years Stutman 2002 Children under 2 years 209 enrolled, and 119 completed the study (90 withdrew) n=68 in prophylaxis group and n=51 in placebo group	(> 1 year), compared with no prophylactic intervention to prevent the acquisition of S. aureus. Participants in both groups could receive intermittent courses of antibiotics if needed, on the basis of symptoms and organisms found in respiratory secretions. Interventions included in the individual studies: Chatfield 1991 Intervention: continuous oral Flucloxacillin Comparison: intermittent antibiotics 'as required'		studies if needed. Time to identification of the pathogen (S aureus) in sputum culture Not reported Number of positive pathogen cultures (S aureus) identified during study period, measured as number of children from whom S. aureus was isolated at least once by year of age (n/N) 1 year Chatfield 1991* Flucloxacillin group: 9/45 "as required" group: 19/51 Stutman 2002*	Chatfield 1991 Sequence generation: unclear risk (judgement: method not described, unclear) Allocation concealment: unclear risk (judgement: not described) Blinding - all outcomes: high risk (judgement: unbllinded, no placebo) Incomplete outcome data - all outcomes: unclear risk (judgement: ITT analysis not possible. Infants with meconium ileus not randomised and therefore excluded from analysis. One participant lost to follow up and one infant died) Selective outcome reporting: unclear risk (judgement: study reported outcomes up to three years of age. Only summary statistics have been presented in abstracts, and full paper describes the methodology, but does not present results by antibiotic groups) Other sources of bias: low risk (judgement: no other potential source of bias identified) Stutman 2002 Sequence generation: low risk (judgement: participant stratified by respiratory culture status. Permuted block design: blocks of 6, with 3 participants in each block randomised to cephalexin or placebo) Allocation concealment: low risk (judgement: treatment allocation known only to the study pharmacist. The pharmacist was responsible for

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Weaver 199 Infants with CF diagnosed by neonatal screening 42 participants enrolled, 4 withdrew (n = 38 prophylaxis = 18, 'as required' = 20) Similar mean ages at enrollment (7 weeks for prophylaxis, 5 weeks for 'as required') Followed up to age 2 years. Inclusion criteria See characteristics of included studies Exclusion criteria See characteristics of included studies	Stutman 2002 Intervention: continuous oral Cephalexin Comparison: placebo Weaver 1994 Intervention: continuous oral Flucloxacillin Comparison: intermittent antibiotics 'as required'		Cephalexin group: 11/75 "as required" group: 36/77 2 years Chatfield 1991* Flucloxacillin group: 10/51 "as required" group: 22/60 Stutman 2002* Cephalexin group: 19/87 "as required" group: 52/79 Weaver 1994* prophylaxis group: 3/18 "as required" group: 12/20 3 years Chatfield 1991* Flucloxacillin group: 12/54 "as required" group: 28/65 Stutman 2002* Cephalexin group: 25/77	increasing the dose of the prophylactic antibiotic as the children grew) Blinding - all outcomes: low risk (judgement: double-blinded, placebo-controlled) Incomplete outcome data - all outcomes: unclear risk (judgement: formal ITT analysis was not possible, however, analysis was performed for children completing treatment per protocol (n = 119) and those completing at least 1 year of the trial (n = 165)) Selective outcome reporting: low risk (judgement: measured and reported stated outcome variables yearly up to 6 years of age) Other sources of bias: low risk (judgement: no other potential source of bias identified) Weaver 1994 (Beardsman) Sequence generation: low risk (judgement: described as randomised in the published paper. Authors confirmed treatment was allocated on the basis of block randomisation and allocation was given by telephone from the co-ordinating centre) Allocation concealment: low risk (judgement: allocation of treatment was concealed from the local investigator until the participant was enrolled) Blinding - all outcomes: high risk (judgement: unblinded, no placebo)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				"as required" group: 50/64 4 years Stutman 2002* Cephalexin group: 25/71 "as required" group: 47/56 5 years Stutman 2002* Cephalexin group: 20/58 "as required" group: 34/40 6 years Stutman 2002* Cephalexin group: 7/25 "as required" group: 14/18 Lung function, measured as FEV1 at 6 years (mean±SD) Stutman 2002* Cephalexin group:	Incomplete outcome data - all outcomes: unclear risk (judgement: ITT analysis was not possible) Selective outcome reporting: low risk (judgement: the study reported outcome variables at one and two years following study entry) Other sources of bias: low risk (judgement: no other potential source of bias identified) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				1.1±0.25; N=68 "as required" group: 1.1±0.18; N=51 Lung function, measured by LCI Not reported Evidence of inflammation in CT scan (only for < 5 yrs) Crispin-Norman score at 1.3 years (mean±SD) Chatfield 1991* Flucloxacillin group: 5.71±1.84; N=48 "as required" group: 5.98±2.32; N=61 Time to next pulmonary exacerbation	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Number of children requiring admission (annualised rates) Chatfield 1991* Flucloxacillin group: 10/40 "as required" group: 14/46 Stutman 2002* Cephalexin group: 5/68 "as required" group: 4/51 Weaver 1994* Flucloxacillin group: 7/18 "as required" group: 8/20 Pulmonary exacerbations (mean±SD) Stutman 2002** Cephalexin group: 61.8±48.6; N=68 "as required" group: 66.7±47.1; N=51	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				QOL, measured by: o CFQoL (Gee 2000) o CFQ-R (Quittner 2009) Not reported Adherence to treatment (or patient preference) Not reported Adverse events, minor events Generalised rash (mean±SD) Stutman 2002* Cephalexin group: 0.6±1.7; N=68 "as required" group: 0.2±0.9; N=51 Nappy rash (mean±SD) Stutman 2002* Cephalexin group: 4±5.8; N=68	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				"as required" group: 3.1±5.1; N=51 Increased stool frequency (mean±SD) Stutman 2002* Cephalexin group: 4.3±6.1; N=68 "as required" group: 4.1±6.9; N=51 Adverse events, major events Not reported Number of children from whom P. Aeruginosa isolated at least once 1 year Chatfield 1991* Flucloxacillin group: 6/44 "as required" group: 3/51 Stutman 2002*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Cephalexin group: 27/75 "as required" group: 24/77 2 years Chatfield 1991* Flucloxacillin group: 7/51 "as required" group: 8/60 Stutman 2002* Cephalexin group: 38/87 "as required" group: 40/79 Weaver 1994* prophylaxis group: 2/18 "as required" group: 6/20 3 years Chatfield 1991* Flucloxacillin group: 9/54 "as required" group: 14/66 Stutman 2002* Cephalexin group: 45/77	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				"as required" group: 38/64 4 years Stutman 2002* Cephalexin group: 46/71 "as required" group: 33/56 5 years Stutman 2002* Cephalexin group: 41/58 "as required" group: 20/40 6 years Stutman 2002* Cephalexin group: 22/25 "as required" group: 12/18 Emergence of resistant organisms Not reported	
Full citation Stutman, H. R., Lieberman, J. M., Nussbaum, E., Marks, M. I., Antibiotic prophylaxis in	Sample size	Interventions	Details See Cochrane	Results	Limitations See Cochrane SR Smyth 2014 Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
infants and young children with cystic fibrosis: a randomized controlled trial, Journal of Pediatrics, 140, 299-305, 2002 Ref Id 332098 Country/ies where the study was carried out UK Study type RCT Aim of the study To evaluate the effects of prophylactic treatment in infants born with CF. Study dates Source of funding Medical Research Council, the CF research trust, and the East Anglia health authority.	See Cochrane SR Smyth 2014 Characteristics See Cochrane SR Smyth 2014 Inclusion criteria See Cochrane SR Smyth 2014 Exclusion criteria See Cochrane SR Smyth 2014	See Cochrane SR Smyth 2014	SR Smyth 2014	See Cochrane SR Smyth 2014 The study also reports the following outcomes: Adherence to treatment: 85% vs 80% (statistical significance not reported)	None.
Full citation Weaver,L.T., Green,M.R., Nicholson,K., Mills,J., Heeley,M.E., Kuzemko,J.A., Austin,S., Gregory,G.A., Dux,A.E., Davis,J.A., Prognosis in cystic fibrosis treated with continuous flucloxacillin from the neonatal period, Archives of Disease in Childhood, 70, 84-89, 1994 Ref Id 81026 Country/ies where the study was carried out USA Study type See Smyth 2014, Cochrane systematic review Aim of the study	Sample size See Cochrane SR Smyth 2014 Characteristics See Cochrane SR Smyth 2014 Inclusion criteria See Cochrane SR Smyth 2014 Exclusion criteria	Interventions See Cochrane SR Smyth 2014	Details See Cochrane SR Smyth 2014	Results See Cochrane SR Smyth 2014	Limitations See Cochrane SR Smyth 2014 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To determine if anti-SA prophylaxis is effective in preventing or delaying the infection with S. Aureus in infants with CF. Study dates 1987 to 1998 Source of funding The National Institute for Allergy and Infectious disease, the CF Trust foundation, and the Memorial Medical centre foundation.	See Cochrane SR Smyth 2014				

G.10 Pulmonary infection – acute

Review question: What is the effectiveness of antimicrobial treatment for acute pulmonary infection or those with an exacerbation in children and adults with cystic fibrosis?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Blumer, J. L., Saiman, L., Konstan, M. W., Melnick, D., The efficacy and safety of meropenem and tobramycin vs ceftazidime and tobramycin in the treatment of acute pulmonary exacerbations in patients with cystic fibrosis, Chest, 128, 2336-46, 2005 Ref Id	Sample size See Cochrane SR Hurley 2015 Characteristics See Cochrane SR Hurley 2015 Inclusion criteria See Cochrane SR Hurley 2015 Exclusion criteria See Cochrane SR Hurley 2015	Interventions See Cochrane SR Hurley 2015	Details See Cochrane SR Hurley 2015	Results See Cochrane SR Hurley 2015	Limitations See Cochrane SR Hurley 2015 Other information See Cochrane SR Hurley 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
330421 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding					
Full citation Conway, S. P., Pond, M. N., Watson, A., Etherington, C., Robey, H. L., Goldman, M. H., Intravenous colistin sulphomethate in acute respiratory exacerbations in adult patients with cystic fibrosis, Thorax, 52, 987-93, 1997 Ref Id 330612 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Hurley 2015 Characteristics See Cochrane SR Hurley 2015 Inclusion criteria See Cochrane SR Hurley 2015 Exclusion criteria See Cochrane SR Hurley 2015	Interventions See Cochrane SR Hurley 2015	Details See Cochrane SR Hurley 2015	Results See Cochrane SR Hurley 2015	Limitations See Cochrane SR Hurley 2015 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation De Boeck, K., Smet, M., Eggermont, E., Treatment of Pseudomonas lung infection in cystic fibrosis with piperacillin plus tobramycin versus ceftazidime monotherapy: preliminary communication, Pediatric Pulmonology, 7, 171-3, 1989 Ref Id 330669 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Hurley 2015 Characteristics See Cochrane SR Hurley 2015 Inclusion criteria See Cochrane SR Hurley 2015 Exclusion criteria See Cochrane SR Hurley 2015	Interventions See Cochrane SR Hurley 2015	Details See Cochrane SR Hurley 2015	Results See Cochrane SR Hurley 2015	Limitations See Cochrane SR Hurley 2015 Other information None
Full citation Gold, R., Overmeyer, A., Knie, B., Fleming, P. C., Levison, H., Controlled trial of ceftazidime vs. ticarcillin and tobramycin in the	Sample size See Cochrane SR Hurley 2015 Characteristics See Cochrane SR Hurley 2015 Inclusion criteria See Cochrane SR Hurley 2015	Interventions See Cochrane SR Hurley 2015	Details See Cochrane SR Hurley 2015	Results See Cochrane SR Hurley 2015	Limitations See Cochrane SR Hurley 2015 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
treatment of acute respiratory exacerbations in patients with cystic fibrosis, Pediatric Infectious Disease, 4, 172-7, 1985 Ref Id 330910 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Exclusion criteria See Cochrane SR Hurley 2015				
Full citation Hurley, M. N., Prayle, A. P., Flume, P., Intravenous antibiotics for pulmonary exacerbations in people with cystic fibrosis, Cochrane Database of Systematic Reviews, 7, CD009730, 2015 Ref Id 398614 Country/ies where the study was carried out	Sample size 13 randomised control trials (RCTs) from this Cochrane SR were included: Blumer 2005 Conway 1997 De Boeck 1989 Elborn 1992 Gold 1985 Macfarlane 1985 Master 2001 McCarty 1988 Richard 1997 Salh 1992 Schaad 1987 Schaad 1989	Interventions Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Blumer 2005 Intervention 1: IV meropenem 40 mg/kg up to a maximum dose of 2 g and IV tobramcyin(given for a mean of 13.5 days) Intervention 2: IV ceftazidime 50 mg/kg up to a maximum dose of 2 g and I V	Details Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Blumer 2005 Multicentre (16 centres from the US) investigator-blinded RCT with an expected duration 14 days, follow up 2 - 4 weeks after discontinuation of therapy. Conway 1997	Results Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. Additional data extracted is marked with a * Blumer 2005 Lung function (FEV1) N: 47; Mean (SD): 13.8 (9.52) VERSUS N: 50; Mean (SD): 11.1 (7.68) Eradication of specific pathogen Not reported Time to next pulmonary exacerbation Not reported	Limitations Quality of the SR AMSTAR score: 11/11 Quality of the individual primary studies The risk of bias assessment has been taken from the SR. Blumer 2005 Random sequence generation: unclear risk of bias (Described as randomised but no detail given) Allocation concealment: unclear risk of bias (Not described) Blinding of participants and personnel: unclear risk of bias ("Investigator" Blinded)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Cochrane SR Aim of the study The SR aims to establish if IV antibiotics for the treatment of pulmonary exacerbations in people with CF improve short- and long-term clinical outcomes. Study dates Searches up to 27 July 2015. Source of funding Wellcome Trust, UK. MH was funded by a Wellcome Trust Clinical Research Training Fellowship (Grant number WT092295AIA). National Institute for Health Research, UK. AP is funded by an NIHR Doctoral Research Fellowship (Grant number DRF-2009-02-112).	Wesley 1988 Characteristics Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Blumer 2005 121 participants with a recent (usually < 1 month) culture of P. aeruginosa or B. cepacia complex recruited at a protocol-de fined exacerbation. 102 participants with P. aeruginosa infection susceptible to meropenem and ceftazidime recruited to randomised trial and stratified according to disease severity 19 participants with B. cepacia or ceftazidime-resistant P. aeruginosa recruited to	tobramycin(given for a mean of 14.1 days) Tobramycin dose adjusted to give a peak serum concentration of>= 8 µg/mL and trough concentration of < 2 µg/mL Conway 1997 Intervention 1: IV colistin (2 MU 3x daily). Intervention 2: IV colistin (2 MU 3x daily) and a second anti-pseudomonal antibiotic De Boeck 1989 Intervention 1: IV ceftazidime 50 mg/kg 3x daily. Intervention 2: IV piperacillin 75 mg/kg 4x daily and IV tobramycin 10 mg/kg/day in3 doses Elborn 1992 Intervention 1: IV ceftazidime 2 g 3x daily. Intervention 2: IV aztreonam 2 g 3x daily. Gold 1985 Intervention 1: IV ceftazidime 200	Single centre (from the UK) single-blind RCT with a duration of 12 days. De Boeck 1989 Single centre (from Belgium) RCT with a duration of 14 days. Elborn 1992 Single centre (from UK) RCT with a duration of 14 days. Gold 1985 Single centre (from Canada) RCT with a duration of 10-14 days. Macfarlane 1985 Single centre (from Australia) double-blind placebo-controlled RCT with a duration of 14 days Master 2001 Single centre (from Australia) double-blind RCT with a duration of 10 days. McCarty 1988 Single centre (from US) open-label RCT with a duration of at least 10 days. Richard 1997 Multicentre (from France, Germany,	Resolution of infection/exacerbation or measure of treatment failure Not reported Duration of the acute episode Not reported Quality of life (QOL) Not reported Mortality Not reported Adverse events Not reported Conway 1997 Lung function (FEV1) N: 36; Mean (SD): 140 (312.5) VERSUS N: 35; Mean (SD): 300 (330.6) Eradication of specific pathogen Not reported Time to next pulmonary exacerbation Not reported Resolution of infection/exacerbation or measure of treatment failure Not reported Duration of the acute episode Not reported Quality of life (QOL) Not reported Mortality n/N: 0/36 VERSUS n/N: 1/35	Blinding of outcome assessment: unclear risk of bias (The report indicates that the 'investigator' was blinded but that this did not include assessing all the outcomes) Incomplete outcome data: high risk of bias (Some 'evaluable' data for lung function and microbiology data are missing. 2 'clinically evaluable' participants (1 from each group) withdrew) Selective reporting: unclear risk of bias (Insufficient evidence). Other bias: unclear low of risk of bias (None identified). Conway 1997 Random sequence generation: unclear risk of bias (Described as randomly assigned but no detail given) Allocation concealment: unclear risk of bias (No detail given) Blinding of participants and personnel: high risk of bias (Single blind - outcome assessor) Blinding of outcome assessment: unclear risk of bias (Laboratory and radiology were blinded - unclear if

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
National Institute for Health Research, UK. This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.	openlabel study - the open label study is analysed separately Age: > = 5 years of age Age:>= 5 years of age Conway 1997 53 participants with CF and chronic P. aeruginosa experiencing a protocol-defined exacerbation. Intervention 1: 36 participants; mean (SD) age 21.7 (4.2) years; 17 females, 19 males; mean (SD) FEV1 % predicted 43.3 (16.6). Intervention 2: 35 participants; mean (SD) age 21.2 (4.25) years; 12 females, 23 males; mean (SD) FEV1 % predicted 45.8 (21.8). De Boeck 1989 21 participants with CF and a protocol-defined pulmonary exacerbation, chronically infected with P. aeruginosa	mg/kg/day in 4 doses. Intervention 2: IV ticarcillin 300 mg/kg/day in 4 doses and IV tobramycin 10 mg/kg/day in 3 doses Macfarlane 1985 Intervention 1: IV piperacillin 50 mg/kg 4-hourly. Intervention 2: IV placebo 5% dextrose 4-hourly. Intervention 3: IV piperacillin 100 mg/kg 8-hourly. Intervention 4: IV placebo 5% dextrose 8-hourly. All participants received IV tobramycin 2.5 mg/kg 3x daily, oral flucloxacillin 25 mg/kg/day in 4 doses and oral probenecid (suggested to increase antibiotic concentrations)250 - 500 mg 3x daily Master 2001 Intervention 1: IV ceftazidime 50 mg/kg/dose 3x daily and IV tobramycin 3 mg/kg/dose 3x daily	Greece, Hungary, Israel, Italy, Portugal, South Africa and Switzerland) open-label RCT with a duration of 14 days. Salh 1992 Single centre (from UK) double-blind RCT with a duration of at least 10 days. Schaad 1987 Single centre (from Switzerland) RCT with a duration of at least 15 days. Schaad 1989 Single centre (from Switzerland) RCT with a duration of 2 weeks IV treatment, with oral treatment extended for a further 4 weeks in 1 group. Wesley 1988 Single centre (from New Zeland) RCT with a duration of at least 14 days.	Adverse events (neurological adverse events) n/N: 33/35 VERSUS n/N: 36/36 De Boeck 1989 Lung function (FEV1 % predicted - absolute change) N: 11; Mean (SD): 16 (11.75) VERSUS N: 10; Mean (SD): 15 (11.28) Eradication of specific pathogen Not reported Time to next pulmonary exacerbation N: 9; Mean (SD): 8 (5.66) VERSUS N: 10; Mean (SD): 9 (4.2) Resolution of infection/exacerbation or measure of treatment failure Not reported Duration of the acute episode Not reported Quality of life (QOL) Mortality n/N: 1/10 VERSUS n/N: 1/11 Adverse events Not reported Elborn 1992 Lung function (FEV1 litres - absolute change) N: 12 Mean (SD): 0.38 (0.33) VERSUS N: 12; Mean (SD): 0.27 (0.26)	physiological outcome assessors were blinded) Incomplete outcome data: low risk of bias (9 withdrawals described and analysed as ITT.) Selective reporting: unclear risk of bias (Insufficient evidence) Other bias: high risk of bias (Unit of Analysis issues - 18 participants enrolled 2x) De Boeck 1989 Random sequence generation: unclear risk of bias (Randomisation stated but not described) Allocation concealment: unclear risk of bias (No information given) Blinding of participants and personnel: high risk of bias (Participants and clinicians were not blinded) Blinding of outcome assessment: low risk of bias (Lung function undertaken by a technician blinded to regimen) Incomplete outcome data: low risk of bias (No withdrawals) Selective reporting: unclear risk of bias (None identified) Other bias: low risk of bias (None identified) Elborn 1992

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	that was sensitive to piperacillin, tobramycin and ceftazidime. Mean age 14.8 years. Intervention 1: 10 participants. Intervention 2: 11 participants. Elborn 1992 24 participants with CF and chronic P. aeruginosa infection experiencing exacerbations. Mean (range) age 20 (14 - 48) years. Gender split: 12 male, 12 female. Gold 1985 30 participants with CF and P. aeruginosa infection present at the previous clinic visit, experiencing an acute respiratory exacerbation. Intervention 1: 17 participants; mean (SE) age 18.9 (1.1) years; 15 males, 2 females	Intervention 2: IV tobramycin 9 mg/kg/day 1x daily. Duration: at least 10 days. McCarty 1988 Intervention 1: IV piperacillin 600 mg/kg/day (regimen not detailed) Intervention 2: IV piperacillin 600 mg/kg/day and tobramycin 8 - 10 mg/kg/day(regimen not detailed Duration: at least 10 days. Richard 1997 Intervention 1: oral ciprofloxacin 15 mg/kg 2x daily. Intervention 2: IV ceftazidime 50 mg/kg 3x daily and IV tobramycin 3 mg/kg 3x daily Duration: 14 days. Salh 1992 Intervention 1; IV aztreonam 8 g/day in 4 doses. Intervention 2: IV ceftazidime 8 g/day in 4 doses. Duration: 2 weeks		Eradication of specific pathogen Not reported Time to next pulmonary exacerbation Not reported Resolution of infection/exacerbation or measure of treatment failure Not reported Duration of the acute episode Not reported Quality of life (QOL) Not reported Mortality Not reported Adverse events Not reported Gold 1985 Lung function (FEV1 % - relative change) N: 17; Mean (SD): 13.7 (23.09) VERSUS N: 13; Mean (SD): 33.3 (27.76) Eradication of specific pathogen Not reported Time to next pulmonary exacerbation Not reported Resolution of infection/exacerbation or measure of treatment failure Not reported Duration of the acute episode	Random sequence generation: unclear risk of bias (Desccribed as randomised but no method detailed) Allocation concealment: unclear risk of bias (No detail given) Blinding of participants and personnel: unclear risk of bias (No detail given) Blinding of outcome assessment: unclear risk of bias (No detail given) Incomplete outcome data: unclear risk of bias (No withdrawals described) Selective reporting: unclear risk of bias (Insufficient information) Other bias: low risk of bias (No other bias identified) Gold 1985 Random sequence generation: low risk of bias (Randomised using a table of random numbers used) Allocation concealment: unclear risk of bias (No detail) Blinding of participants and personnel: high risk of bias (Unblinded) Blinding of outcome assessment: low risk of bias (Outcome assessor blinded)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Intervention 2: 13 participants; mean (SE) age 17.8 (0.8) years; 9 males, 4 females Macfarlane 1985 19 participants aged over 8 years with CF with P. aeruginosa in sputum admitted to hospital for worsening respiratory status. Mean age 13.7 to 15.6 years Intervention 1: 4 participants; mean (SD) age 15.3 (3) years Intervention 2: 5 participants; mean (SD) age 12.5 (2.9) years Intervention 3: 4 participants; mean (SD) age 13.7 (2.6) years Intervention 4: 5 participants; mean (SD) age 15.6 (3.4) years Master 2001 51 participants with CF experiencing a protocol-defined exacerbation with	Schaad 1987 Intervention 1: IV ceftazidime 250 mg/kg/day in 4 doses and IV amikacin 33 mg/kg/day in 3 doses Intervention 2: IV ceftazidime 250 mg/kg/day in 4 doses and IV amikacin 33 mg/kg/day in 3 doses and nebulised amikacin 100 mg 2x daily Duration: 15 days Schaad 1989 Intervention 1: IV aztreonam 300 mg/kg/day in 4 doses and IV amikacin 36 mg/kg/day in 3 doses Intervention 2: IV ceftazidime 300 mg/kg/day in 4 doses and IV amikacin 36 mg/kg/day in 3 doses for 2 weeks followed by oral ciprofloxacin 30 mg/kg/day for 4 weeks Duration: 2 weeks IV treatment, with oral treatment extended for a further 4 weeks in1 group Wesley 1988		Not reported Quality of life (QOL) Not reported Mortality Not reported Adverse events (Proteinuria) N/n: 1/17 VERSUS N/n: 1/17 Macfarlane 1985 Lung function (FEV1 % predicted - relative change). COMPARISON 1Single IV antibiotic in combination with placebo (IV placebo 5% dextrose 4-hourly and IV tobramycin) VERSUS combination IV antibiotics (IV piperacillin 50 mg/kg 4-hourly and IV tobramycin) N: 4; Mean (SD): 8 (18.7) VERSUS N: 5; Mean (SD): 12.2 (14.5) COMPARISON 2Single IV antibiotic in combination with placebo (IV placebo 5% dextrose 8-hourly and IV tobramycin)VERSUS combination IV antibiotics (IV piperacillin 100 mg/kg 8-hourly and IV tobramycin) N: 4; Mean (SD): 9.75 (9.7) VERSUS N: 5; Mean (SD): 1.8 (15.7)Mean Difference IV, Fixed, 95% CI: 7.95 [-8.78, 24.68] Eradication of specific pathogen	Incomplete outcome data: low risk of bias (No withdrawals) Selective reporting: unclear risk of bias (Insufficient information) Other bias: low risk of bias (No other bias identified) Macfarlane 1985 Random sequence generation: unclear risk of bias (Described as randomly as signed but no method given) Allocation concealment: unclear risk of bias (No method described) Blinding of participants and personnel: low risk of bias (Described as double-blind. Identities of infusions known only to pharmacy personnel) Blinding of outcome assessment: low risk of bias (Described as double-blind) Incomplete outcome data: high risk of bias (2 participants withdrew and did not contribute data to the analysis) Selective reporting: unclear risk of bias (Insufficient information) Other bias: high risk of bias (Unit of Analysis issues - 1

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	P. aeruginosa isolated from sputum. Participants with an FVC lower than 40%predicted were excluded Intervention 1: 21 participants; mean (SD) age 16 (7) years. Intervention 2: 23 participants; mean (SD) age 15 (5) years. McCarty 1988 17 children with CF admitted for treatment of pulmonary exacerbations Intervention 1: 8 participants. Intervention 2: 9 participants. Age: range 2 - 12 years. Richard 1997 108 children with CF and P. aeruginosa infection and experiencing a protocol-defined pulmonary exacerbation	Intervention 1: IV ceftazidime 150 mg/kg/day (regimen not detailed) Intervention 2: IV tobramycin 7.5 mg/kg/day and IV ticarcillin 300 mg/kg/day (regimen not detailed) Duration: 14 days		Not reported Time to next pulmonary exacerbation Not reported Resolution of infection/exacerbation or measure of treatment failure Not reported Duration of the acute episode Not reported Quality of life (QOL) Not reported Mortality Not reported Adverse events (sensitivity reaction) N/n: 0/8 VERSUS N/n: 3/10 Odds Ratio (M-H, Fixed, 95% CI): 0.13 [0.01, 2.86] Master 2001 Lung function (FEV1 % predicted - absolute change). N: 47; Mean (SD): 10.6 (8.5) VERSUS N: 14; Mean (SD): 13.21 (9.92) Eradication of specific pathogen Not reported Time to next pulmonary exacerbation Not reported Resolution of infection/exacerbation or measure of treatment failure Not reported	participant received 2 treatment courses) Master 2001 Random sequence generation: unclear risk of bias (Described as randomised, stratified for age and disease progression, but no method detailed) Allocation concealment: unclear risk of bias (No detail given) Blinding of participants and personnel: low risk of bias (Described as double blind with medical and nursing staff and participants blinded with identical syringes and placebos) Blinding of outcome assessment: low risk of bias (Described as double blind) Incomplete outcome data: low risk of bias (Withdrawals were described and those participants who completed 10 days treatment but excluded for other reasons were in included in an ITT analysis. The ITT analysis is described as not changing the effect of the short-term analysis, but no data provided)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Intervention 1: oral ciprofloxacin - mean age 10.2 years; 32 males, 23 females Intervention 2: IV ceftazidime and IV tobramycin - mean age 11.0 years; 27 males, 26 Females Salh 1992 22 participants with CF and P. aeruginosa sensitive to the study drugs who were admitted to hospital due to an infective exacerbation Age: 16 - 32 years. Gender split: aztreonam - 6 females, 8 males; ceftazidime - 4 females, 8 males Schaad 1987 62 participants with CF admitted with an acute pulmonary exacerbation who had P. aeruginosa isolated on admission. Those who had been admitted to hospital			Duration of the acute episode Not reported Quality of life (QOL) Not reported Mortality Not reported Adverse events (Tinnitus) N/n: 2/47 VERSUS N/n: 2/51 McCarty 1988 Lung function (FEV1) Results reported in a narrative way (pag. 203)* Eradication of specific pathogen* n/N: 12/19 VERSUS n/N: 5/19 Time to next pulmonary exacerbation Not reported Resolution of infection/exacerbation or measure of treatment failure Not reported Duration of the acute episode Not reported Quality of life (QOL) Not reported Mortality n/N: 0/8 VERSUS n/N: 0/9 Adverse events (Rash) n/N: 0/8 VERSUS n/N: 1/9 Richard 1997 Lung function Not reported	Selective reporting: unclear risk of bias (Insufficient information) Other bias: high risk of bias (Unit of Analysis issues - each participant contributed multiple treatment episodes) McCarty 1988 Random sequence generation: unclear risk of bias (Described as randomly assigned but no details given) Allocation concealment: low risk of bias (Sequentially numbered en velopes were used, although it is not clear if these were opaque and sealed. On balance, considered low risk) Blinding of participants and personnel: high risk of bias (Unblinded) Blinding of outcome assessment: high risk of bias (Unblinded) Incomplete outcome data: low risk of bias (No withdrawals) Selective reporting: unclear risk of bias (Insufficient information) Other bias: high risk of bias (Unit of Analysis issues - 3 participants were included twice)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	in the recent 6 months were excluded Age: range 3 - 24 years. Intervention 1: 24 participants. Intervention 2: 30 participants. Schaad 1989 42 participants with CF admitted with a protocol-defined pulmonary exacerbation and P. aeruginosa isolated at admission. Those who had been admitted to hospital in previous 4 months were excluded Age: mean (SD) 15.4 (6) years (range 2.3 - 25.4 years). Intervention 1: 28 participants. Intervention 2: 28 participants. Wesley 1988 13 children with CF and severe chest disease. Age range 9 - 15 years.			Eradication of specific pathogen* n/N: 30/48 VERSUS n/N: 12/49 Time to next pulmonary exacerbation Not reported Resolution of infection/exacerbation or measure of treatment failure Not reported Duration of the acute episode Not reported Quality of life (QOL) Not reported Mortality Not reported Adverse events (Treatment-related events) n/N: 10/53 VERSUS n/N: 9/55 Salh 1992 Lung function (litres -absolute change) N: 11 Mean (SD): 0.26 (0.356) VERSUS N: 11; Mean (SD): 0.54 (0.497) Eradication of specific pathogen Not reported Time to next pulmonary exacerbation Not reported Resolution of infection/exacerbation or measure of treatment failure	Richard 1997 Random sequence generation: unclear risk of bias (Described as randomised, but no detail given) Allocation concealment: unclear risk of bias (No detail given) Blinding of participants and personnel: high risk of bias (Unblinded) Blinding of outcome assessment: high risk of bias (Unblinded) Incomplete outcome data: low risk of bias (The efficacy and safety analysis were described as analysed on an ITT basis) Selective reporting: unclear risk of bias (Insufficient information) Other bias: unclear risk of bias (An author on the paper is affiliated to Pharma Research Center, Bayer AG. Bayer produced ciprofloxacin) Salh 1992 Random sequence generation: unclear risk of bias (Randomised in pharmacy using 'simple random allocation')

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Intervention 1: 13 participants. Intervention 2: 10 participants. Inclusion criteria Exclusion criteria			Not reported Duration of the acute episode Not reported Quality of life (QOL) Not reported Mortality Not reported Adverse events Not reported Schaad 1987 Lung function Not reported Eradication of specific pathogen P. aeruginosa eradication at completion of therapy ceftazidime and amikacin with inhaled amikacin: 30/43 (70%) vs ceftazidime and amikacin alone: 18/44 (41%) Time to next pulmonary exacerbation Not reported Resolution of infection/exacerbation or measure of treatment failure Not reported Duration of the acute episode Not reported Quality of life (QOL) Not reported Mortality Not reported	Allocation concealment: low risk of bias (Sealed opaque envelopes but unclear whether sequentially numbered) Blinding of participants and personnel: low risk of bias (Described as double-blind infusions prepared in pharmacy and labelled with trial number) Blinding of outcome assessment: low risk of bias (Unclear, but as the physicians and participants were blinded it is likely the outcome assessors were also blinded) Incomplete outcome data: unclear risk of bias (4 withdrew -3 of whom were treatment failures-, it is unclear if these contributed to the analysis) Selective reporting: unclear risk of bias (Insufficient evidence) Other bias: high risk of bias (Unit of Analysis issues - 4 participants contribute multiple treatment episodes) Schaad 1987 Random sequence generation: unclear risk of bias (Described as randomly allocated but no details given)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Adverse events (Raised liver transaminases) n/N: 5/30 VERSUS n/N: 6/24 Schaad 1989 Lung function (FEV1 % predicted - absolute change). N: 24; Mean (SD): 13 (6.8) VERSUS N: 25; Mean (SD): 9 (8.3354664) Eradication of specific pathogen* n/N: 17/28 VERSUS n/N: 16/28 Time to next pulmonary exacerbation Not reported Resolution of infection/exacerbation or measure of treatment failure Not reported Duration of the acute episode Not reported Quality of life (QOL) Not reported Mortality Not reported Adverse events (A- Thrombocytopenia; B- Liver transaminases - AST/SGOT % ALT/SGPT; C- Rash) Thrombocytopenia n/N: 3/28 VERSUS n/N: 0/28 Liver transaminases n/N: 4/28 VERSUS n/N: 2/28	Allocation concealment: unclear risk of bias (No detail given) Blinding of participants and personnel: unclear risk of bias (No information on blinding given) Blinding of outcome assessment: low risk of bias (Clinical evaluator blinded to treatment allocation) Incomplete outcome data: low risk of bias (No withdrawal) Selective reporting: unclear risk of bias (Insufficient evidence) Other bias: unclear high risk of bias (Unit of Analysis issues - 13 participants enrolled 2x and 6 participants enrolled 3x) Schaad 1989 Random sequence generation: unclear high risk of bias (Randomised but no detail given) Allocation concealment: unclear high risk of bias (No detail given) Blinding of participants and personnel: unclear risk of bias (Unclear - no detail given) Blinding of outcome assessment: low risk of bias (Clinical evaluation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Rash n/N: 0/28 VERSUS n/N: 2/28 Wesley 1988 Lung function Not reported Eradication of specific pathogen Not reported Time to next pulmonary exacerbation (Proportion readmitted, requiring IV antibiotics or death in subsequent 3 months-proxy outcome) n/N: 7/12 VERSUS n/N: 19/32 Not reported Resolution of infection/exacerbation or measure of treatment failure Not reported Duration of the acute episode Not reported Quality of life (QOL) Not reported Mortality Not reported Adverse events (Liver transaminase enzyme elevation) n/N: 0/12 VERSUS n/N: 0/10	undertaken by 2 investigators without knowledge of allocation) Incomplete outcome data: high risk of bias (Clinical outcomes available for about 50% of participants only. Some participants are young children (and so would be able to perform lung function tests) but the mean age is 15.4 years and so there are data missing for many participants for whom lung function testing would have been possible) Selective reporting: unclear risk of bias (Insufficient evidence) Other bias: high risk of bias (Unit of Analysis issues - 42 participants received 56 courses of treatment) Wesley 1988 Random sequence generation: unclear risk of bias (Described as randomised but no details given) Allocation concealment: unclear risk of bias (No detail given) Blinding of participants and personnel: unclear risk of bias (Described as double blind but no details given)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Blinding of outcome assessment: unclear of bias (Described as double blind but no details given) Incomplete outcome data: unclear risk of bias (No detail available) Selective reporting: unclear high risk of bias (Insufficient information) Other bias: high risk of bias (Unit of Analysis issues - 13 participants received 23 courses of treatment) Other information
Full citation Langton Hewer, S. C., Smyth, A. R., Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis, Cochrane Database of Systematic Reviews, 11, CD004197, 2014 Ref Id 363031 Country/ies where the study was carried out Study type	Sample size Two randomised control trials (RCTs) were included from this Cochrane SR: Proesmans 2013 Taccetti 2012 Characteristics Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Proesmans 2013	Interventions Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Proesmans 2013 Treatment (n = 29): Inhaled TSI (300 mg 2x daily for 28 days) Control (n = 29): 3 months combination therapy with inhaled colistin (2 MU 2x daily) + oral ciprofloxacin (10 mg/kg 3x daily) Taccetti 2012	Details Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Proesmans 2013 Single centre (based in Europe) RCT with a duration of 3 months. Taccetti 2012 Multicentre (13 centres - based in Italy) RCT with a duration of 28 days.	Results Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. Additional data extracted is marked with a * Proesmans 2013 Lung function Not reported Eradication of specific pathogen Not reported Time to next pulmonary exacerbation Not reported Resolution of infection/exacerbation or measure of treatment failure	Limitations Quality of the SR AMSTAR score: 10/11 Quality of the individual primary studies The risk of bias assessment has been taken from the SR Proesmans 2013 Random sequence generation: unclear risk of bias (Randomised in blocks of 10. No description given of method of randomisation, nor of any stratification) Allocation concealment: unclear risk of bias (Did not report how allocation was concealed) Blinding: high risk of bias (Blinding not possible for

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cochrane SR Aim of the study The objectives of this review are: 1) To determine whether antibiotic treatment of early Pseudomonas aeruginosa infection in children and adults with cystic fibrosis eradicates the organism, delays the onset of chronic infection, and results in clinical improvement. 2) To evaluate whether there is evidence that a particular antibiotic strategy is superior to or more cost-effective than other strategies and to compare the adverse effects of different antibiotic strategies (including respiratory infection with other micro-organisms). Study dates	58 children with CF, all with new isolation of P. aeruginosa (sputum or cough swabs). Age: median age 9 years, interquartile range (4.7 - 13.1 years) Gender: 31 male, 27 female. Lung function: median FEV1 at inclusion 98% predicted. Taccetti 2012 223 participants with first ever or new P. aeruginosa infection. New infection defined as P. aeruginosa isolation following bacterial clearance documented by 3 negative cultures within the previous 6 months Age: over 1 year. Gender: 116 male, 107 female. Inclusion criteria Exclusion criteria	Group A (n = 105; 52 male and 53 female): 28 days 2x daily inhalation of 2 MU colistin with 2x daily doses of ciprofloxacin 15 mg/kg/dose Group B (n = 118; 64 male and 54 female): 28 days therapy with TSI (300 mg 2x daily) with 2x daily doses of ciprofloxacin 15 mg/kg/dose		Not reported Quality of life (QOL) Not reported Adverse events (Severe cough) n/N: 0/29 VERSUS n/N: 1/29 Taccetti 2012 Lung function (FEV1) N: 60; Mean (SD): 2.15 (8.5) VERSUS N: 68; Mean (SD): 4.55 (11.54) Eradication of specific pathogen Not reported Time to next pulmonary exacerbation Not reported Resolution of infection/exacerbation or measure of treatment failure Not reported Quality of life (QOL) Not reported Adverse events (A-vomiting; B- Photosensitivity; C-Wheeze; D- Pulmonary exacerbation during early eradication treatment; E- Lack of compliance) Vomiting n/N: 1/105 VERSUS n/N: 2/118 Photosensitivity n/N: 1/105 VERSUS n/N: 0/118 Wheezen/N: 0/105 VERSUS n/N: 1/118	participants and clinicians as treatments compared were inhaled versus inhaled and oral. No details regarding whether outcome assessors were blinded) Incomplete outcome data: low risk of bias (ITT analysis on all 58 randomised participants) Selective reporting: high risk of bias (Protocol published on ClinicalTrials.gov -identifier: NCT01400750. All pre-specified outcomes reported BMI z score, weight z score and frequency of exacerbations were reported not to have changed significantly for trial participants, but numerical data are not reported) Other bias: unclear risk of bias (Primary outcome was assessed at end of treatment which was different for the 2 treatment groups 28 days for TSI participants versus 3 months for colistin/ciprofloxacin participants) Taccetti 2012 Random sequence generation: low risk of bias (Randomisation sequence generated by statistical software within permuted

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Searches up to 08 September 2014. Source of funding No details given.				Pulmonary exacerbation during early eradication treatment n/N: 4/105 VERSUS n/N: 5/118 Lack of compliance n/N: 11/105 VERSUS n/N: 13/118	blocks of size 10, stratified according to age and FEV1) Allocation concealment: low risk of bias (Separation of individuals responsible for randomisation and treatment assignment) Blinding: high risk of bias (Open-label trial so no blinding of participants nor researchers) Incomplete outcome data: low risk of bias (38 of 223 randomised participants -17%- dropped out of the trial. The biggest reason for dropping out was lack of compliance with follow up protocol -11 from Group A and 13 from Group B- and identification of a pulmonary exacerbation during early eradication therapy -4 from Group A and 5 from Group B. Analysis was by ITT) Selective reporting: unclear risk of bias (We have been unable to locate a published protocol for this trial. The details published on the EudraCT database -number 2008-006502-42; describe objectives but not outcomes. In the main paper, the methods section does not describe all the trial objectives. Only eradication, time free of P. aeruginosa

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					and spirometry are described in the methods section. These outcomes plus the additional outcomes of isolation of other organisms and adverse events are described in the results) Other bias: low risk of bias (No evidence of other bias identified) Other information
Full citation Lo, D. K., Hurley, M. N., Muhlebach, M. S., Smyth, A. R., Interventions for the eradication of meticillin-resistant Staphylococcus aureus (MRSA) in people with cystic fibrosis, Cochrane Database of Systematic Reviews, 2, CD009650, 2015 Ref Id 398687 Country/ies where the study was carried out Study type Cochrane SR Aim of the study	Sample size Children and adults diagnosed with CF clinically and by sweat or genetic testing with a confirmed positive microbiological isolate of MRSA on clinically relevantCF respiratory cultures (bronchoalveolar lavage (BAL), cough or oropharyngeal swab, spontaneous or induced sputum culture) specimen prior to enrolment into the trial. The authors included all disease severities.	Interventions Intervention Any combinations of topical, inhaled, oral or intravenous antimicrobials with the primary aim of eradicating MRSA once detected on clinically relevantCF respiratory cultures Comparison Placebo Standard treatment No treatment.	Details	Results No randomised control trials (RCTs) were identified for inclusion.	Limitations Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To evaluate the effectiveness of treatment regimens designed to eradicate MRSA and to determine whether the eradication of MRSA confers better clinical and microbiological outcomes for people with cystic fibrosis. Study dates Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 2, 2015. Review content assessed as up-to-date: 18 February 2015. Source of funding	They did not include patients with nasal carriage of MRSA alone in this review. Characteristics Inclusion criteria Exclusion criteria				
Full citation Macfarlane, P. I., Hughes, D. M., Landau, L. I., Olinsky, A., The role of piperacillin	Sample size See Cochrane SR Hurley 2015 Characteristics See Cochrane SR Hurley 2015	Interventions See Cochrane SR Hurley 2015	Details See Cochrane SR Hurley 2015	Results See Cochrane SR Hurley 2015	Limitations See Cochrane SR Hurley 2015 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
therapy in pulmonary exacerbations of cystic fibrosis: a controlled study, Pediatric Pulmonology, 1, 249-55, 1985 Ref Id 331397 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Inclusion criteria See Cochrane SR Hurley 2015 Exclusion criteria See Cochrane SR Hurley 2015				
Full citation Master,V., Roberts,G.W., Coulthard,K.P., Baghurst,P.A., Martin,A., Roberts,M.E., Onishko,C.R., Martin,A.J., Linke,R.J., Holmes,M., Jarvinen,A., Kennedy,D., Colebatch,K.A., Hansman,D., Parsons,D.W., Efficacy of once-daily tobramycin monotherapy for	Sample size See Cochrane SR Hurley 2015 Characteristics See Cochrane SR Hurley 2015 Inclusion criteria See Cochrane SR Hurley 2015 Exclusion criteria See Cochrane SR Hurley 2015	Interventions See Cochrane SR Hurley 2015	Details See Cochrane SR Hurley 2015	Results See Cochrane SR Hurley 2015	Limitations See Cochrane SR Hurley 2015 Other information See Cochrane SR Hurley 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
acute pulmonary exacerbations of cystic fibrosis: a preliminary study, Pediatric Pulmonology, 31, 367-376, 2001 Ref Id 310452 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding					
Full citation McCarty, J. M., Tilden, S. J., Black, P., Craft, J. C., Blumer, J., Waring, W., Halsey, N. A., Comparison of piperacillin alone versus piperacillin plus tobramycin for treatment of respiratory infections in children with cystic fibrosis, Pediatric Pulmonology, 4, 201-4, 1988 Ref Id	Sample size See Cochrane SR Hurley 2015 Characteristics See Cochrane SR Hurley 2015 Inclusion criteria See Cochrane SR Hurley 2015 Exclusion criteria	Interventions See Cochrane SR Hurley 2015	Details See Cochrane SR Hurley 2015	Results See Cochrane SR Hurley 2015	Limitations See Cochrane SR Hurley 2015 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
331472 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding					
Full citation Proesmans, M., Vermeulen, F., Boulanger, L., Verhaegen, J., De Boeck, K., Comparison of two treatment regimens for eradication of Pseudomonas aeruginosa infection in children with cystic fibrosis, Journal of Cystic Fibrosis, 12, 29-34, 2013 Ref Id 331777 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Langton 2014 Characteristics See Cochrane SR Langton 2014 Inclusion criteria See Cochrane SR Langton 2014 Exclusion criteria See Cochrane SR Langton 2014	Interventions See Cochrane SR Langton 2014	Details See Cochrane SR Langton 2014	Results See Cochrane SR Langton 2014	Limitations See Cochrane SR Langton 2014 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Richard, D. A., Nousia-Arvanitakis, S., Sollich, V., Hampel, B. J., Sommerauer, B., Schaad, U. B., Oral ciprofloxacin vs. intravenous ceftazidime plus tobramycin in pediatric cystic fibrosis patients: comparison of antipseudomonas efficacy and assessment of safety with ultrasonography and magnetic resonance imaging. Cystic Fibrosis Study Group, Pediatric Infectious Disease Journal, 16, 572-8, 1997 Ref Id 331843 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Hurley 2015 Characteristics See Cochrane SR Hurley 2015 Inclusion criteria See Cochrane SR Hurley 2015 Exclusion criteria See Cochrane SR Hurley 2015	Interventions See Cochrane SR Hurley 2015	Details See Cochrane SR Hurley 2015	Results See Cochrane SR Hurley 2015	Limitations See Cochrane SR Hurley 2015 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Salh, B., Bilton, D., Dodd, M., Abbot, J., Webb, K., A comparison of aztreonam and ceftazidime in the treatment of respiratory infections in adults with cystic fibrosis, Scandinavian Journal of Infectious Diseases, 24, 215-8, 1992 Ref Id 331916 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Hurley 2015 Characteristics See Cochrane SR Hurley 2015 Inclusion criteria See Cochrane SR Hurley 2015 Exclusion criteria See Cochrane SR Hurley 2015	Interventions See Cochrane SR Hurley 2015	Details See Cochrane SR Hurley 2015	Results See Cochrane SR Hurley 2015	Limitations See Cochrane SR Hurley 2015 Other information None
Full citation Schaad, U. B., Wedgwood-Krucko, J., Guenin, K., Buehlmann, U., Kraemer, R., Antipseudomonal therapy in cystic fibrosis: aztreonam	Sample size See Cochrane SR Hurley 2015 Characteristics See Cochrane SR Hurley 2015 Inclusion criteria	Interventions See Cochrane SR Hurley 2015	Details See Cochrane SR Hurley 2015	Results See Cochrane SR Hurley 2015	Limitations See Cochrane SR Hurley 2015 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and amikacin versus ceftazidime and amikacin administered intravenously followed by oral ciprofloxacin, European Journal of Clinical Microbiology & Infectious Diseases, 8, 858-65, 1989 Ref Id 331932 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	See Cochrane SR Hurley 2015 Exclusion criteria See Cochrane SR Hurley 2015				
Full citation Schaad, U. B., Wedgwood-Krucko, J., Suter, S., Kraemer, R., Efficacy of inhaled amikacin as adjunct to intravenous combination therapy (ceftazidime and amikacin) in cystic fibrosis, Journal of	Sample size See Cochrane SR Hurley 2015 Characteristics See Cochrane SR Hurley 2015 Inclusion criteria See Cochrane SR Hurley 2015 Exclusion criteria See Cochrane SR Hurley 2015	Interventions See Cochrane SR Hurley 2015	Details See Cochrane SR Hurley 2015	Results See Cochrane SR Hurley 2015	Limitations See Cochrane SR Hurley 2015 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pediatrics, 111, 599-605, 1987 Ref Id 331933 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding					
Full citation Taccetti, G., Bianchini, E., Cariani, L., Buzzetti, R., Costantini, D., Trevisan, F., Zavataro, L., Campana, S., Italian Group for, P. aeruginosa Eradication in Cystic Fibrosis, Early antibiotic treatment for Pseudomonas aeruginosa eradication in patients with cystic fibrosis: a randomised multicentre study comparing two different protocols,	Sample size See Cochrane SR Langton 2014 Characteristics See Cochrane SR Langton 2014 Inclusion criteria See Cochrane SR Langton 2014 Exclusion criteria See Cochrane SR Langton 2014	Interventions See Cochrane SR Langton 2014	Details See Cochrane SR Langton 2014	Results See Cochrane SR Langton 2014	Limitations See Cochrane SR Langton 2014 Other information Nonw

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Thorax, 67, 853-9, 2012 Ref Id 332108 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding					
Full citation Elborn, S., Colville, A., Cordon, S., Hiller, E. J., Shale, D., A comparison of intravenous ceftazidime and aztreonam in the treatment of respiratory exacerbations in cystic fibrosis [abstract], 11th International Cystic Fibrosis Congress, 1992 Ref Id 419093 Country/ies where the study was carried out Study type Aim of the study Study dates	Sample size See Cochrane SR Hurley 2015 Characteristics See Cochrane SR Hurley 2015 Inclusion criteria See Cochrane SR Hurley 2015 Exclusion criteria See Cochrane SR Hurley 2015	Interventions See Cochrane SR Hurley 2015	Details See Cochrane SR Hurley 2015	Results See Cochrane SR Hurley 2015	Limitations See Cochrane SR Hurley 2015 Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding					
Full citation Wesley, A. W., Quested, C., Edgar, B. W., Lennon, D. R., A double-blind comparison of ceftazidime with tobramycin and ticarcillin in the treatment of exacerbations of pseudomonas chest infection in children with cystic fibrosis [abstract], 10th International Cystic Fibrosis Congress. R, 1988 Ref Id 363310 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Hurley 2015 Characteristics See Cochrane review Hurley 2015 Inclusion criteria See Cochrane SR Hurley 2015 Exclusion criteria See Cochrane SR Hurley 2015	Interventions See Cochrane SR Hurley 2015	Details See Cochrane SR Hurley 2015	Results See Cochrane SR Hurley 2015	Limitations See Cochrane SR Hurley 2015 Other information None
Full citation Horsley, A., Jones, A. M., Lord, R., Antibiotic treatment for	Sample size Individuals with CF, of any age, diagnosed on the basis of clinical	Interventions Intervention Any antibiotic treatment regimen for treating an	Details	Results No relevant trials were identified.	Limitations Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Burkholderia cepacia complex in people with cystic fibrosis experiencing a pulmonary exacerbation, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, 1, CD009529, 2016 Ref Id 537684 Country/ies where the study was carried out Study type Cochrane Systematic review Aim of the study To assess the effectiveness and safety of different antibiotic regimens in people with cystic fibrosis experiencing an exacerbation and chronically infected with organisms of the Burkholderia cepacia complex. Study dates	evidence of CF-lung disease and either genotype analysis or sweat testing, or both. Participants were also required to have evidence of pulmonary infection with organisms of the Burkholderia cepacia complex (Bcc), defined as at least two positive sputumor bronchoalveolar lavagemicrobiology specimens within the last sixmonths, grown on specialist media and confirmed by conventional molecular and microbiological techniques. Characteristics Inclusion criteria Exclusion criteria	exacerbation of CF-lung disease Comparison Placebo Different antibiotic regimen, regardless of frequency of administration, treatment duration, route of delivery or use of additional therapies			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Date of latest search: 28 August 2015. Source of funding					
Full citation Regan, K. H., Bhatt, J., Eradication therapy for Burkholderia cepacia complex in people with cystic fibrosis, Cochrane Database of Systematic Reviews, 11, CD009876, 2016 Ref Id 567004 Country/ies where the study was carried out Study type Cochrane systematic review Aim of the study This review has 2 aims: To identify whether treatment of Burkholderia cepacia complex infections can achieve eradication, or if	Sample size Any person with a clinical diagnosis of CF that has been confirmed by sweat testing or genetic analysis, or both, who acquires a new infection or a re-infection with BCC. People of all ages and disease severity will be included. Characteristics Inclusion criteria Exclusion criteria	Interventions Intervention Any antibiotic or antibiotic adjuvant therapy used alone or in combination to eradicate BCCinfection. Comparison Alternative antimicrobial agent Pacebo No treatment (excluding the participant's usual therapeutic regimen). The mode of delivery of the intervention may be inhaled, oral or intravenous and there is no limit to the duration of therapy or dosage used.	Details	Results No trials were identified for inclusion in this review.	Limitations Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
treatment can prevent or delay the onset of chronic infection. To establish whether following eradication, clinical outcomes are improved and if there are any adverse effects. Study dates Date of last search: 14 July 2016 Source of funding This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.					
Full citation Waters, Valerie, Ratjen, Felix, Antibiotic treatment for nontuberculous mycobacteria lung	Sample size Adults and children (ages 0 to 18 years) diagnosed with CF (with all levels of disease severity),	Interventions Intervention The intervention was antibiotics to treat NTM pulmonary infections. The authors planned	Details	Results No trials were identified for inclusion in the review.	Limitations Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
infection in people with cystic fibrosis, Cochrane Database of Systematic Reviews, 2016 Ref Id 589511 Country/ies where the study was carried out Study type Cochrane systematic review Aim of the study The objective of the review was to compare antibiotic treatment to no antibiotic treatment, or to compare different combinations of antibiotic treatment, for nontuberculous mycobacteria lung infections in people with cystic fibrosis. The primary objective was to assess the effect of treatment on lung function and pulmonary exacerbations and to quantify adverse	confirmed with sweat test or genetic testing, or both, who have NTMpulmonary infection (defined as at least two respiratory specimens positive by culture for NTM - post hoc change) will be included. Individuals with a respiratory tract specimen that is positive on stain for acid-fast bacilli (AFB) but culture negative for NTM will not be included. Respiratory tract specimens will include sputum, lung biopsy or bronchoalveolar lavage specimens. Individuals with CF who have received a lung transplant will be excluded. Characteristics Inclusion criteria Exclusion criteria	to compare NTM antibiotics to no antibiotic treatment as well as compare different NTM antibiotic regimens. Antibiotics included single or multiple antibiotics, oral, inhaled or intravenous antibiotics.			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
events. The secondary objectives were to assess treatment effects on the amount of bacteria in the sputum, quality of life, mortality, nutritional parameters, hospitalizations and use of oral antibiotics. Study dates Date of last search: 03 November 2016. Source of funding					

G.11 Pulmonary infection – chronic

Review question: What is the effectiveness of antimicrobial regimens in suppressing chronic pulmonary infection in children and adults with cystic fibrosis with any of the following pathogens: Pseudomonas Aeruginosa, Burkholderia Cepacia Complex, Staphylococcus Aureus and Aspergillus Fumigatus?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Aaron, S. D., Vandemheen, K. L., Freitag, A., Pedder, L., Cameron, W., Lavoie, A., Paterson, N., Wilcox, P., Rabin, H., Tullis, E., Morrison, N., Ratjen, F., Treatment of Aspergillus	Sample size N=35 (another 32 patients declined to participate)	Interventions Intervention Treatment: itraconazole Formulation: capsules	Details Randomization Central allocation schedule for	Results Lung function - % change in FEV1 predicted	Limitations The Risk of bias was assessed using the Cochrane Risk of Bias tool. Sequence generation: low risk Allocation concealment: unclear risk (the process is not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
fumigatus in patients with cystic fibrosis: a randomized, placebo-controlled pilot study, PLoS ONE [Electronic Resource], 7, e36077, 2012 Ref Id 398320 Country/ies where the study was carried out Canada Study type RCT, placebo-controlled Aim of the study To evaluate if treatment directed against A. Fumigatus improves pulmonary function and clinical outcomes in patients with CF. Study dates Jan 2008 - May 2010 Source of funding Not reported	Itraconazole n=18 placebo n=17 Characteristics Age (mean±SD): 25.3±10.5 vs. 25.2±9.1 Male (%): 56% vs 53% FEV1 % predicted (mean±SD): 63.4%±22.2 Coinfections S. Aureous: 39% vs 47% P. Aeruginosa: 39% vs 59% Inclusion criteria 9 Canadian CF clinics	Duration: 24-weeks Dosing: daily dose of 5 mg/kg, as per CF Consensus Guidelines Timing of administration: once daily; if the dose exceeded 200 mg/day it was given twice daily Patients were advised to take the medication with orange juice of cola to maximise oral absorption All patients continued with standard CF medication as prescribed by their physicians Comparison Placebo	randomization through computer generated list, in variable blocks of 2 or 4. Allocation concealment Not reported Blinding Study medication given by site research pharmacist.Research and medical staff were blinded. Data collection Patients underwent study assessments at baseline, 4, 12, 24 and 48 weeks.	from baseline 24-week follow-up period: -4.62% (decline) vs 0.32% (improvement); MD: -4.94% (95% CI: -15.33 to 5.45); adj MD (age, gender, baseline FEV1): -4.85%; p=0.34 48-week follow-up period: MD: -3.71% (95% CI: -13.26 to 20.68) Time to next pulmonary exacerbation Median to 1st exacerbation: 77 vs 134	Blinding: low risk Incomplete data: low risk Selective reporting: unclear risk (the assessments were taken at 4, 12, 24 and 48h and data is only reported for 24 and 48h. Also some results are poorly reported, and cannot be imputed in RevMan) Other: high risk (the sample size is quite small and 32 patients declined to participate) OVERALL QUALITY: moderate risk of bias Other information (+) first prospective RCT (+) ITT analysis (-) pilot study small sample size, authors failed to recruit more patients to extend the study (-) Failure to achieve therapeutic levels of Itraconazole in many patients

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Confirmed CF diagnoses ≥ 6 years of age Chronically colonised with A, Fumigatus, defined as at least 2 positive sputum cultures within the last 12 months Clinically stable at the time of randomization, with no acute treatment for acute CF pulmonary exacerbation allowed for at least 14 days prior randomization Exclusion criteria Patients were	Same as above	Data analysis Changes in FEV1 were compared using Student t-test. The proportion of patients that experience exacerbations was calculated with Chi-Square. Kaplan Meier survival curves were used to calculate time to first exacerbation.	days; p=0.35 AdjHR (age, gender, baseline FEV1): 1.34 (95% CI: 0.57 to 3.14; p=0.50) proxy outcome: number of patients that experienced pulmonary exacerbations requiring oral or IV AB 24-week follow-up - 67% (n=12) vs. 44% (n=7); p=0.18 48-week follow-up - 83% (n=15) vs. 69% (n=11); p=0.43 proxy outcome:	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	excluded if they had: History of renal insufficiency, defined as serum Cr > 1.5 times normal) Liver disease, defined as serum AST or ALT ≥2.5 times higher the upper limit of normal History of billiary cirrhosis Portal hypertension Allergic brochopulmonary aspergillosis (ABPA) B. Cepacia infection Lung transplantation Were on any antifungal			number of patients that experienced pulmonary exacerbations requiring hospitalization 24-week follow-up - 17% (n=3) vs. 19% (n=3); p=0.99 48-week follow-up - 22% (n=4) vs. 19% (n=3); p=0.99 Eradication of the specified organism from sputum/airway cultures Not reported Nutritional status Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	agents within 6 months before randomization			Quality of life (CFQ-R) (better represented by higher outcomes) 24-week follow-up - No significant differences in any of the 12 domains 24-week follow-up - Respiratory domain: 3.76 vs 4.77 points increase; MD -1.01 (p=0.87) Adverse events during the 24-week study period increased dyspnea: 2/18 vs 2/16 rash: 2/18 vs 1/16 hemoptysis: 2/18 vs 1/16	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				hyperglycaemia: 1/18 vs 0/16 flu-like illness: 3/18 vs 0/16 diarrhea: 0/18 vs 1/16 conjunctivitis: 0/18 vs 1/16 spontaneous pneumothorax: 1/18 vs 0/17 Emergence of resistant organisms/ antibiotic resistance Not reported	
Full citation Assael, B. M., Pressler, T., Bilton, D., Fayon, M., Fischer, R., Chiron, R., LaRosa, M., Knoop, C., McElvaney, N., Lewis, S. A., Bresnik, M., Montgomery, A. B., Oermann, C. M., Azli Active Comparator Study Group, Inhaled aztreonam lysine vs. inhaled tobramycin in cystic fibrosis: a comparative efficacy trial, Journal	Sample size N=273 randomized patients N=268 received treatment AZLI: n=136 TNS: n=132	Interventions Intervention Treatment: Inhaled aztreonam lysine (AZLI) Duration: 28 days Dose: 75 mg, (3 times/day)	Details Randomisation Method not reported Allocation concealment Open-label Blinding	Results Lung function (% change in FEV1 predicted from baseline) Across 3 treatment courses,	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: randomisation methods not reported, but group characteristics appear to be balanced Allocation concealment and blinding: open label study - patients and investigators were not blinded to treatment allocation Incomplete data: low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of Cystic Fibrosis, 12, 130-40, 2013 Ref Id 398353 Country/ies where the study was carried out Belgium, Denmark, France, Germany, Ireland, Italy, UK, USA Study type Open-label, randomised, parallel-group trial Aim of the study To compare the efficacy and safety of AZLI to TNS, across three 28-day treatment courses. Study dates August 2008 to May 2010 Source of funding Gilead Sciences	233 patients (85.3%) completed the active-comparator period Mean use of distributed vials was 94.0% (AZLI) and 94.2% (TNS) Of 169 eligible patients, 133 (78.7%) entered the open-label extension period (AZLI: 68; TNS: 65), and 118 patients completed 3 AZLI courses (88.7%). Characteristics Patient characteristics were balanced between	Comparison Treatment: Inhaled tobramycin (TNS) Duration: 28 days Dose: 3000 mg (2 times/day) Control No treament Duration: 28 days	An independent, blinded data adjudication committee determined respiratory hospitalisations and respiratory events requiring additional antipseudomonal antibiotics. No further details reported. Data collection Collected at weeks 4, 12 and 20. No further details reported. Data analysis Statistical analyses were performed on the intent-to-treat (ITT) population:	mean actual change (SE): Aztreonam 2.05% (0.69) TNS -0.66% (0.72) Mean difference, aztreonam - TNS: Across 3 treatment courses: 2.70 (95% CI 0.98% to 4.43%, p=0.002) Mean difference at day 28 (week 4): 7.80 (95% CI 3.86% to 11.73%, p<0.001) Mean change from baseline at day 28 (week 4) (aztreonam 4.367, TNS 0.287) calculated	Selective reporting: supported by Gilead Sciences and continuous endpoints reported as the mean of weeks 4, 12 and 20 - final endpoint values are not reported Other: Other information Patients receiving additional antipseudomonal antibiotics at any point after randomisation could continue study treatments Included in SR Maiz 2013

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	treatment groups and reported separately for each group, overall: Mean age 25.5 years (SD 9.0) 50% male Mean FEV1% predicted 52.3 (SD 15.1) Inhaled colistin use in previous year 38.4% Aztreonam use at baseline 64.9% Dornase alfa use at baseline 68.3% Inhaled tobramycin use in previous year: >83 days, 85.1%		randomized patients receiving ≥1 dose of AZLI/TNS The primary non-inferiority endpoint (change in FEV1%) was assessed with an analysis of covariance (ANCOVA) model with terms for treatment, baseline FEV1% predicted (continuous variable), and inhaled tobramycin use in previous year (≥84, b84 days) The primary superiority endpoint was the average least- square means from	from relative change from baseline Time to next pulmonary exacerbation Not reported Proxy outcome: number of patients that experienced pulmonary exacerbations requiring oral or IV AB Aztreonam 52/136 (38.2%) TNS 76/132 (57.6%) p=0.002 Proxy outcome: number of patients that experienced pulmonary exacerbations requiring hospitalization	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria ≥6 years of age documented CF diagnosis PA-positive sputum culture within the previous 3 months FEV1 ≤75% predicted at screening Additional antipseudomonal AB could be administered for symptoms consistent with the diagnosis of acute pulmonary exacerbation Patients receiving additional antipseudomonal antibiotics at any point		Weeks 4, 12, and 20 visits, based on a mixed-effect model repeated measures (MMRM) analysis method outlined by Siddiqui, which included terms for treatment, baseline FEV1% predicted (continuous variable), inhaled tobramycin use (≥84, b84 days), visit, and treatment/visit interaction	Aztreonam 40/136 TNS 58/132 p=0.044 Eradication of the specified organism from sputum/airway cultures Not reported Nutritional status Weight, relative change from baseline at Week 24 (end of active-comparator period), b %, adjusted mean (SE): Aztreonam 0.58 (0.41) TNS 0.06 (0.43) p=0.289 Quality of life CFQ-R respiratory	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	after randomization could continue study treatments Exclusion criteria Patient using additional TNS during the active-comparator period			symptoms scale, change from baseline score, b adjusted mean (SE): Week 4 (after course 1; AZ: n= 131; TNS: n= 131): aztreonam: 8.2 (1.7) TNS 2.6 (1.7) p= 0.005 Average across 3 courses (Weeks 4, 12, 20; Aztreonam: n= 131; TNS: n= 131) Aztreonam 6.3 (1.5) TNS 2.2 (1.5) p= 0.019 Adverse events	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Chest discomfort Aztreonam 14/136 (10.3%) TNS 13/132 (9.8%) Cough aztreonam 96/136 (70.6%) TNS 104/132 (78.8%) Headache aztreonam 29/136 (21.3%) TNS 27/132 (20.5%) Vomiting aztreonam 14/136 (10.3%) TNS 14/132 (10.6%) Dyspnoea aztreonam 31/136 (22.8%) TNS 21/132 (15.9%) Haemoptysis	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				aztreonam 31/136 (22.8%) TNS 21/132 (15.9%) Emergence of resistant organisms/ antibiotic resistance Log10 PA CFU/g sputum, change from baseline, b adjusted mean (SE) Week 4 (after course 1; AZLI: n= 88; TNS: n= 94) Aztreonam −0.60 (0.23) TNS −0.34 (0.23) p= 0.330 Average across 3 courses (Weeks 4, 12, 20; AZLI: n= 97; TNS: n= 97)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				aztreonam −0.55 (0.19) TNS 0.32 (0.19) p= 0.295	
Full citation Chuchalin, A., Csiszer, E., Gyurkovics, K., Bartnicka, M. T., Sands, D., Kapranov, N., Varoli, G., Monici Preti, P. A., Mazurek, H., A formulation of aerosolized tobramycin (Bramitob) in the treatment of patients with cystic fibrosis and Pseudomonas aeruginosa infection: a double-blind, placebo-controlled, multicenter study, Paediatric Drugs, 9 Suppl 1, 21-31, 2007 Ref Id 330572 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Ryan 2011 Characteristics See Cochrane SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria See Cochrane SR Ryan 2011	Interventions See Cochrane SR Ryan 2011	Details See Cochrane SR Ryan 2011	Results See Cochrane SR Ryan 2011	Limitations See Cochrane SR Ryan 2011 Other information None.
Full citation Elphick, H. E., Southern, K. W., Antifungal therapies for allergic bronchopulmonary aspergillosis	Sample size na Characteristics	Interventions Intervention Antifungal treatments,	Details na	Results No studies were identified for	Limitations AMSTAR score: 11/11 Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
in people with cystic fibrosis, Cochrane Database of Systematic Reviews, 11, CD002204, 2014 Ref Id 365540 Country/ies where the study was carried out Study type Cochrane SR Aim of the study To evaluate the effectiveness of antifungal interventions for the treatment of allergic bronchopulmonary aspergillosis (ABPA) in people with CF Study dates Most recent search 17 March 2014 Source of funding Not reported	na Inclusion criteria na Exclusion criteria na	including major treatments such as: oral azoles nebulised amphotericin Comparison No treatment Placebo Different dosages		inclusion in this review.	
Full citation Galeva,I., Konstan,M.W., Higgins,M., Angyalosi,G., Brockhaus,F., Piggott,S., Thomas,K., Chuchalin,A.G., Tobramycin inhalation powder manufactured by improved process in cystic fibrosis: the randomized EDIT trial, Current Medical Research and Opinion, 29, 947-956, 2013 Ref Id	Sample size TIP vs. placebo ITT efficacy population: 32 vs. 30 safety population: 30 vs. 32 (2 patients in TIP were	Interventions TIP 112mg or placebo twice daily, as capsules administered via the T-326 dry powder inhaler	Details Randomisation Using a validated autmated system and startified by age and screening FEV1% predicted	Results Lung function (% change in FEV1 predicted from baseline) Mean absolute change (SE) from	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: low risk Allocation concealment: low risk Blinding: low risk Incomplete data: low risk Selective reporting: sponsored by Novartis Other: small sample size leading to an under powered study Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
310612 Country/ies where the study was carried out Bulgaria, Estonia, Latvia, Lithuania, Romania, Russia, Egypt, India Study type Double-blind, placebo-controlled randomised phase III trial Aim of the study To evaluate the efficacy and safety of tobramycin inhalation powder (TIP) in people with CF aged 6 to 21 years. Study dates June 2009 to May 2011 Source of funding Sponsored by Novartis Pharma AG, who were responsible for the design of the study and analysis of the data and in collaboration with the authors, interpreted and presented the data for this report	misallocated) completed: 29 vs. 30 Characteristics TIP vs. placebo female 70.0% vs. 59.4% mean (SD) FEV1% predicted 61.8 (17.5) vs. 63.1 (18.7) mean age (SD), years 12.9 (4.3) vs. 12.9 (4.7) The most frequently used medications were mucolytics (80% vs. 81%) and enzyme preparations (70% vs. 91%)		Allocation concealment Blinding details provided Blinding Blinding was maintained through matched packaging, laeling, schedule of administration and outer appearance of drug and device Data collection During each visit, lung function was measured using at least 3 acceptable forced expiratory maneuvers Spirometry data was transferred to a central site where an over-read was	baseline to day 29 analysed as randomised: TIP 4.9 (1.6) placebo 0.5 (1.7) p= 0.0496 Time to next pulmonary exacerbation Not reported Proxy outcome: number of patients that experienced pulmonary exacerbations requiring oral or IV AB Not reported Proxy outcome: number of patients that experienced pulmonary exacerbations requiring	If patients requiring treatment with antipsedudomonal antibiotics other than the study drug for signs and/or symptoms of a pulmnary exacerbation, they were required to withdraw from the study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria Males and females aged 6 to 21 years with a diagnosis of CF confirmed by at least 1 clinical feature of CF plus sweat chloride test >60mEq/L, known mutations in each CF transmembrane conductance regulator (CFTR) gene or abnormal nasal transepithelial potential difference FEV1 at screening >24 and <81% of normal predicted		conducted to ensure inclusion only of acceptable data where quality standards were met Sputum and serum samples were collected on days 1 and 29 Supplementary appendix provides more details on data collection including that for safety assessments for the incidene and severity of adverse events Data analysis Aample size of 100 estimated to provide 90%	hospitalisation Hospitalistion due to respiratory events occurred in on patient in the placebo arm Eradication of the specified organism from sputum/airway cultures Clearance rates for PA at day 29 TIP 41.4% placebo 0% Supression, change in PA sputum density log10 CFU/G TIP 1.2 (0.3) n=29 placebo 0.0 (0.3) n=26 p= 0.002	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	values for age, sex and height positive sputum or throat culture for P.A within 6 months of screening positive sputum culture for P.A at the screening visit Exclusion criteria Any previous exposure to TIP Any inhaled antipseudomonal antibiotics within 4 months prior to screening Any systemic antipsedomonal antibiotics within 28 days prior to		power to detect a treatment difference of 11% mean relative change in FEV1% predicted from baseline to day 29 at a 2 sided 5% significance level, assuming a SD of 16% and dropout rate <10% All efficacy analysis performed on ITT population and safety analysis on safety population Missing day 29 values were imputed with discontinuation visit measurement or the	Nutritional status Not reported Quality of life Not reported Adverse events Minor any TIP 8/29 (27.6%) placebo 11/26 (42.3%) Auditory impairment TIP 3/29 (10.3%) placebo 2/26 (7.7%) Cough TIP 5/29 (17.2%) placebo 0/26 (0%) Major, any TIP 1/29 (3.4%) placebo 1/26 (3.8%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	study drug administration Loop diurectics within 7 days of first study drug admiistration Positive cultures for B.cepacia within 2 years prior to screening or at screening hemoptysis >60ml at any time within 30 days of study drug administration aminoglycoside hypersensitivty or adverse reaction to inhaled antibiotics serum creatine ≥2 mg/dl		baseline value (hence a change of 0 if no post baseline measure existed) ANCOVA was used to analyse the primary endpoint (relative change in FEV1% predicted from baseline to day 29) using screening FEV1% (<50 and ≥50 predicted) and age (<13 and ≥13 years) as factors, ANCOVA methods also used for change in sputum density of PA and absolute FEV1%	Emergence of resistant organisms/ antibiotic resistance Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	blood urea nitrogen ≥40 mg/dl abnormal urinalysis		predicted change		
Full citation Hodson, M. E., Gallagher, C. G., Govan, J. R., A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis, European Respiratory Journal, 20, 658-64, 2002 Ref Id 331052 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Ryan 2011 Characteristics See Cochrane SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria See Cochrane SR Ryan 2011	Interventions See Cochrane SR Ryan 2011	Details See Cochrane SR Ryan 2011	Results See Cochrane SR Ryan 2011	Limitations See Cochrane SR Ryan 2011 Other information None.
Full citation Jensen, T., Pedersen, S. S., Garne, S., Heilmann, C., Hoiby,	Sample size See Cochrane	Interventions See Cochrane SR Ryan 2011	Details See Cochrane	Results See Cochrane	Limitations See Cochrane SR Ryan 2011 Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
N., Koch, C., Colistin inhalation therapy in cystic fibrosis patients with chronic Pseudomonas aeruginosa lung infection, Journal of Antimicrobial Chemotherapy, 19, 831-8, 1987 Ref Id 331175 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	SR Ryan 2011 Characteristics See Cochrane SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria See Cochrane SR Ryan 2011		SR Ryan 2011	SR Ryan 2011	None.
Full citation Konstan,M.W., Flume,P.A., Kappler,M., Chiron,R., Higgins,M., Brockhaus,F., Zhang,J., Angyalosi,G., He,E., Geller,D.E., Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial, Journal of Cystic Fibrosis, 10, 54-61, 2011 Ref Id 239390	Sample size See Tappenden 2013 Characteristics See Tappenden 2013 Inclusion criteria	Interventions See Tappenden 2013	Details See Tappenden 2013	Results See Tappenden 2013	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: unclear risk Allocation concealment: unclear risk Blinding: unclear risk Incomplete data: low risk Selective reporting: low risk Other: study funded by Novartis OVERALL: Moderate risk of bias , Risk of bias (Cochrane Risk of Bias tool) Sequence generation: unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	See Tappenden 2013 Exclusion criteria				Allocation concealment: unclear risk Blinding: unclear risk Incomplete data: low risk Selective reporting: low risk Other: study funded by Novartis OVERALL: Moderate risk of bias Other information
Full citation Konstan, M. W., Geller, D. E., Minic, P., Brockhaus, F., Zhang, J., Angyalosi, G., Tobramycin inhalation powder for P. aeruginosa infection in cystic fibrosis: the EVOLVE trial, Pediatric Pulmonology, 46, 230-8, 2011 Ref Id 361387 Country/ies where the study was carried out 38 centres: Bulgaria, Lithuanua, Serbia, Argentina, Brazil, Chile, Mexico, US Study type Randomised, double-blind, placebo-controlled trial Aim of the study To assess the efficacy and safety of tobramycin inhalation powder formulation for treating CF patients with P.aeruginosa infection	Sample size TIP vs. placebo Randomised: 46 vs. 49 Completed cycle 1: 39 vs. 40 Modified intention-to-treat: 29 vs. 32 (18 patients excluded due to results of sensitivity interim analysis, see other information for details) Characteristics	Interventions cycle 1 (of 3) was double-blind and placebo-controlled with patients randomised 1:1 to tobramycin inhalation powder (TIP, 112mg) or placebo both administered twice daily via the T-326 inhaler during cycle 1 (28 days) patients received TIP (4 capsules 28mg inhaled twice daily) or matching	Details Randomisation Method not reported Allocation concealment Placebo drug described in detail, but no further details provided Blinding Described as double-blind, but no further details provided	Results Lung function (% change in FEV1 predicted from baseline) TIP vs Placebo: 13.3 (95% CI: 5.31, 21.28) Time to next pulmonary exacerbation Not reported Eradication of the specified organism from	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: unclear risk Allocation concealment: unclear risk Blinding: high risk Incomplete data: high risk Selective reporting: low risk Other: study funded by Novartis OVERALL: High risk of bias Other information After cycle 1, based on fulfilment of the pre-defined stopping criteria (statistically significant benefit of TIP over placebo) the Data Monitoring Committee recommended the trial be terminated early After reviewing spirometry data, the Data Monitoring Committee recommended the trial be terminated early again as 10 TIP treated and 8 placebo treated patients should be excluded from the interim analysis due to unacceptable calibration of the spirometer or unacceptable FEV1 data quality

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates September 2005 to February 2007 Source of funding Funded by Novartis	TIP (n=46) vs. placebo (n=49) mean (SD) age, years 13.4 (4.42) vs. 13.2 (3.91) male n(%) 19 (41.3%) vs. 23 (46.9%) caucasian n(%) 37 (80.4%) vs. 43 (87.8%) mean (SD) FEV1% predicted* 54.7 (18.89) vs. 58.5 (20.03) * excluding patients from Latin America sites with potential spirometry quality concerns (n=32 vs. n=37) Inclusion criteria	placebo capsules after completing cycle 1, all patients received open-label TIP for 2 additional cycles (2x 28 days)	Data collection Planned interim analysis discussed in detail. Spirometry measurements and susceptabilty also described. No further detail on data collection methods reported. Data analysis sample size of 140 patients (70 per group) was estimated to provide 90% power at 2-sided 0.05 significance level to detect a treatment difference of	sputum/airway cultures Not reported Nutritional status Not reported Quality of life Not reproted Adverse events During cycle 1 (TIP vs. placebo) cough 6 (13.0%) vs. 13 (26.5%) productive cough 1 (2.2%) vs. 4 (8.2%) hemoptysis 1 (2.2%) vs. 1 (2.0%) headache 1 (2.2%) vs. 3 (6.1%) any serious adverse event 6.5% vs. 14.3%	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	CF patients aged 6 to 21 years FEV1 25 to 80% predicted based on Knudson criteria Positive sputum or throat culture for P.aeruginosa within 6 months of screening and a positive sputum culture for P.aeruginosa at the screening visit Exclusion criteria Positive cultures for B.cepacia within 2 years prior to screening or at screening		11% in mean (20% SD) relative change in FEV1% predicted in cycle 1 primary efficacy measure (relative change in FEV1% from baseline to day 28) was based on the MITT population primary measure assessed using ANCOVA with factors of treatment, baseline FEV1% predicted, age and region included in the model all other efficacy measures used the all-	Emergence of resistant organisms/ antibiotic resistance Sputum density of both non-mucoid and mucoid phenotypes of P.aeruginosa TIP vs. placebo: mean decrease (SD) non-mucoid: 1.91 (2.54) vs. 0.15 (0.68) log10CFU/g mucoid: 2.61 (2.53) vs. 0.43 (1.05) log10CFU/g Mortality 1 placebo patient died, they took their last	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	hemoptysis >60 cc at any time within 30 days of study drug administration aminoglycoside hypersensitivity or adverse reaction to inhaled antibiotics serum creatine ≥2 mg/dl blood urea nitrogen ≥40 mg/dl or abnormal urinalysis (≥2+ proteinuria) received inhaled antipseduomonal antibiotics within 28 days prior to study drug administration and loop		treated population all final analysis based on observed data with no imputation performed for missing data	treatment on day 8 during cycle 1 and discontinued due to a pulmonary exacerbation the next day	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	diuretics within 7 days of study drug administration Note: if patients required treatment with antipseudomonal antibiotics other than study drug for signs and/or symptoms of a pulmonary exacerbation, they were required to withdraw from the study				
Full citation Lenoir, G., Antypkin, Y. G., Miano, A., Moretti, P., Zanda, M., Varoli, G., Monici Preti, P. A., Aryayev, N. L., Efficacy, safety, and local pharmacokinetics of highly concentrated nebulized tobramycin in patients with cystic fibrosis colonized with	Sample size See Cochrane SR Ryan 2011 Characteristics See Cochrane	Interventions See Cochrane SR Ryan 2011	Details See Cochrane SR Ryan 2011	Results See Cochrane SR Ryan 2011	Limitations See Cochrane SR Ryan 2011 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pseudomonas aeruginosa, Paediatric Drugs, 9 Suppl 1, 11-20, 2007 Ref Id 331327 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria See Cochrane SR Ryan 2011				
Full citation Lo, D. K., Hurley, M. N., Muhlebach, M. S., Smyth, A. R., Interventions for the eradication of meticillin-resistant Staphylococcus aureus (MRSA) in people with cystic fibrosis, Cochrane Database of Systematic Reviews, 2, CD009650, 2015 Ref Id 398687 Country/ies where the study was carried out Study type Cochrane SR Aim of the study To evaluate the effectiveness of antimicrobial treatment regimens	Sample size na Characteristics na Inclusion criteria na Exclusion criteria na	Interventions Intervention Any combination of topical, inhaled, oral or IV antimicrobials to eradicate MRSA Comparison Placebo Standard treatment No treatment	Details na	Results No trials were identified for inclusion in this review.	Limitations AMSTAR: 11/11 Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
to eradicate meticillin-resistant S. Aureus (MRSA) in people with CF and all disease severities. Study dates Searches up to 4 September 2014 Source of funding National Institute for Health Research, UK					
Full citation McCoy, K. S., Quittner, A. L., Oermann, C. M., Gibson, R. L., Retsch-Bogart, G. Z., Montgomery, A. B., Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis, American Journal of Respiratory & Critical Care Medicine, 178, 921-8, 2008 Ref Id 331480 Country/ies where the study was carried out Study type Aim of the study THIS STUDY GOES IN THE NMA. DO I NEED TO EXTRACT DATA IN STAR? Study dates Source of funding	Sample size See Cochrane SR Ryan 2011 Characteristics See Cochrane SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria See Cochrane SR Ryan 2011	Interventions See Cochrane SR Ryan 2011	Details See Cochrane SR Ryan 2011	Results See Cochrane SR Ryan 2011	Limitations See Cochrane SR Ryan 2011 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Murphy, T. D., Anbar, R. D., Lester, L. A., Nasr, S. Z., Nickerson, B., VanDevanter, D. R., Colin, A. A., Treatment with tobramycin solution for inhalation reduces hospitalizations in young CF subjects with mild lung disease, Pediatric Pulmonology, 38, 314-20, 2004 Ref Id 361511 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Ryan 2011 Characteristics See Cochrane SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria See Cochrane SR Ryan 2011	Interventions See Cochrane SR Ryan 2011	Details See Cochrane SR Ryan 2011	Results See Cochrane SR Ryan 2011	Limitations Other information
Full citation Ramsey, B. W., Dorkin, H. L., Eisenberg, J. D., Gibson, R. L., Harwood, I. R., Kravitz, R. M., Schidlow, D. V., Wilmott, R. W., Astley, S. J., McBurnie, M. A., et al.,, Efficacy of aerosolized tobramycin in patients with cystic fibrosis, New England Journal of Medicine, 328, 1740-6, 1993	Sample size See Cochrane SR Ryan 2011 Characteristics See Cochrane	Interventions See Cochrane SR Ryan 2011	Details See Cochrane SR Ryan 2011	Results See Cochrane SR Ryan 2011	Limitations See Cochrane SR Ryan 2011 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 331798 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria See Cochrane SR Ryan 2011				
Full citation Ramsey, B. W., Pepe, M. S., Quan, J. M., Otto, K. L., Montgomery, A. B., Williams-Warren, J., Vasiljev, K. M., Borowitz, D., Bowman, C. M., Marshall, B. C., Marshall, S., Smith, A. L., Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group, New England Journal of Medicine, 340, 23-30, 1999 Ref Id 331799 Country/ies where the study was carried out Study type	Sample size See Cochrane SR Ryan 2011 Characteristics See Cochrane SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria	Interventions See Cochrane SR Ryan 2011	Details See Cochrane SR Ryan 2011	Results See Cochrane SR Ryan 2011	Limitations See Cochrane SR Ryan 2011 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Study dates Source of funding	See Cochrane SR Ryan 2011				
Full citation Remmington, T., Jahnke, N., Harkensee, C., Oral anti-pseudomonal antibiotics for cystic fibrosis, Cochrane Database of Systematic Reviews, 7, CD005405, 2016 Ref Id 537710 Country/ies where the study was carried out Study type Cochrane SR Aim of the study To determine the benefits or harms, or both, of oral anti-pseudomonal antibiotic therapy for people with CF who are colonised with P. aeruginosa in two clinical settings: treatment of a pulmonary exacerbation: and long-term treatment of chronic respiratory tract infection Study dates Date of last search: 08 July 2016. Source of funding No sources of support supplied	Sample size Sheldon 1993 40 randomised 31 completed the trial Characteristics Sheldon 1993 Mean age (sd) of 15 participants in the active treatment group: 28.3 years (6.06 years) Mean age (sd) of 16 participants in the placebo group: 24.9 years (5.15 years) Sex: active treatment	Interventions Sheldon 1993 Ciprofloxacin (500 mg) tds or an identical placebo for 10 days every 3 months for 4 courses	Details Sheldon 1993 Double-blind RCT (generation of allocation sequence & allocation concealment both graded as 'adequate') Parallel design Single centre The trial had a power of 80%for detecting a real difference of 200ml in the improvement of FEV1 between the groups significant at the 5% level.	Results Sheldon 1993 Ciprofloxacin vs. placebo Lung function (% change in FEV1 predicted from baseline) Not reported Time to next pulmonary exacerbation Not reported Eradication of the specified organism from sputum/airway cultures Not reported Nutritional status,	Limitations Sheldon 1993 Adequate sequence generation? Yes. On enrolment into the trial participants were given consecutive trial numbers, which corresponded to the treatment group randomised before the study. Randomisation of treatment courses was arranged prior to the start of the trial in blocks of 4: 2 each for treatment and placebo Allocation concealment? Yes. Treatment courses were prepared by Bayer, none of the staff involved with the trial had knowledge of the treatment allocated to each participant Blinding? Unclear. Clinician/person delivering treatment: yes. Participants: yes Outcome assessor: unclear (see below). Described as double-blinded "None of the staff involved in the study had knowledge of the treatment allocated to each patient" Incomplete outcome data addressed? Unclear. 9 withdrawals, all described. 5 participants receiving CPX were withdrawn for the following reasons: poor compliance (2), heart-lung transplant (1), death (1), nausea & anorexia (1) 4 participants receiving placebo were withdrawn for the following reasons: poor compliance (2), death (1), desire to become pregnant (1) Free of selective reporting? No. Study protocol not available. All outcomes listed as beingmeasured at clinic visits were described in full in the results section of the paper for baseline and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	group: 13 males, 2 females; placebo group: 10 males, 6 females Country: UK Inclusion criteria Cochrane criteria: Ran domised or quasi-randomised controlled trials comparing any dose of oral anti-pseudomon al antibiotics, to other combination s of inhaled, oral or intravenous antibiotics, or to placebo or usual treatment for pul monary exacerbation s and long-			mean (SD) weight kg 55.7 (11.4) N=15 vs. 51.3 (11.6) N=16 MD 4.4 (95% CI -3.7 to 12.5) Quality of life Not reported Adverse events, n/N Gastrointest inal 2/20 vs. 0/20, RR 5.00 (95% CI 0.26 to 98.00) Emergence of resistant organisms/ antibiotic resistance Isolation of antibiotic resistant strains P.aeruginos a 10/15 vs. 5/16, RR 2.13 (0.95 to 4.80)	12 months. However, no data were presented for intermediate clinic visits Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	term treatment. Criteria applied in the included trials: Sheldon 1993 Eligible if over 18 years of age and chronically infected with P. aeruginosa Participants were excluded from the trial if they had P. aeruginosa resistant to CPX in their sputum culture immediately prior to entering the trial, renal insufficiency, an intention to become pregnant,			Isolation of antibiotic resistant strains S.aureus 4/15 vs. 6/16, RR 0.71 (0.25 to 2.03) Mortality 1/20 vs. 1/20, 1.00 (0.07 to 14.90)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	current treatment with theophyllines or a past history of poor compliance Exclusion criteria See inclusion criteria.				
Full citation Retsch-Bogart, G. Z., Quittner, A. L., Gibson, R. L., Oermann, C. M., McCoy, K. S., Montgomery, A. B., Cooper, P. J., Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis, Chest, 135, 1223-32, 2009 Ref Id 331839 Country/ies where the study was carried out Australia, Canada, New Zealand and USA Study type Randomised, double-blind, placebo-controlled trial Aim of the study	Sample size Randomised: aztreonam 80, placebo 84 Completed to day 28: aztreonam 73, placebo 65 Characteristics Placebo; aztreonam mean age (range): 31.7 (11-74); 27.4 (7-54) male: 45/84 (53.6%);	Interventions 75mg aztreonam, 52.5mg of lysine monohydrate, or placebo (5mg lactulose) both administered with an eFlow Electronic nebuliser (PARI) patients self-administered a short acting beta2-agonist before administering	Details Randomization Randomized 1:1. Web-based system using a central computer-generated randomization schedule, and stratified by baseline disease severity (FEV1 ≤ or ≥ 50%) and a block size of 4.	Results Lung function - FEV1 (L) change from baseline At week 4: aztreonam - placebo 0.102; calculated from relative change from baseline assuming baselines are same Time to next pulmonary	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: low risk Allocation concealment: unclear, the process is not reported Blinding: unclear, the study indicates that it is double-blinded, but the process is not reported Incomplete data: high number of people discontinued treatment for a short trial: placebo 19/84, aztreonam 7/80 Selective reporting: supported by Gilead Sciences Other: none Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To evaluate the efficacy and safety of inhaled aztryonam lysine (AZLY) in patients with CF and chronic P. Aeruginosa infection. Study dates June 2005 to April 2007 Source of funding Gilead Sciences	48/80 (60.0%) dornase alfa use: 64%; 66% mean (SD) FEV1% predicted: 54.8 (14.0); 54.4 (13.4) mean (SD) CFQ-RRS: 60.9 (18.9); 60.5 (18.1) Inclusion criteria ≥6 years of age Confirmed CF diagnosis Moderate-to-severe lung disease (FEV1 ≥25% to ≤75% predicted) PA airway infection (documented at screening or twice within previous year,	the study medication at home	Allocation concealment Not reported Blinding Double-blinded, no details provided Data collection Physical examination at baseline; spirometry at every visit, before and 30' after any treatment. FEV1% predicted Knudson. Data analysis Sample size of 40 estimated to provide 77% power to detect an 8-point difference for change in	exacerbation Not reported Proxy outcome: number of patients that experienced pulmonary exacerbations requiring hospitalisation At 42 days: aztreonam 4/80; placebo 12/84 Eradication of the specified organism from sputum/airway cultures Adjusted MD in sputum PA density log10 CF/g at day 28: -1.453 (95%CI -2.1 to -0.8); p<0.001	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	including once within the previous 3 months) without regard to PA susceptibility to aztreonam Ability to perform reproducible pulmonary function tests Exclusion criteria recent (ie, day -28 to screening) administration of inhaled, IV, or oral antipseudomonal antibiotics, azithromycin, or aerosolized hypertonic saline solution current oral corticosteroid use		CFQ-RRS assuming a SD of 20 and >90% power to detect a 9% difference in FEV1 assuming a SD of 12 with a two sided alpha 0.05 CFQ-R analysis used last observation carried forward Efficacy and safety analysis included all randomly assigned patients receiving one or more doses of aztreonam/placebo Continuous variables were analysed using	Nutritional status Weight, mean change %, at day 28: 1,1 (n=80) vs 0,1 (n=84); (95%CI 0.33 to 1.69); p=0.004 Quality of life (CFQ-R) (better represented by higher outcomes) AZLI group (n=80) vs placebo (n=84) Body Image:3.2 vs 1.0; p=0.327 Digestion: 2.2 vs 1.9; p=0.889 Eating: -3.6 vs 4.7; p=0.001	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	equivalent to >10 mg of prednisone daily airway cultures yielding Burkholderia cepacia complex (previous 2 years) daily continuous oxygen supplementation or >2 L/min at night monobactam antibiotic hypersensitivity intolerance to inhaled short-acting beta2-agonists recent changes in antimicrobial, bronchodilator, antiinflammatory, or		analysis of covariance models with treatment as the fixed effect, disease severity ad baseline values were covariates	Emotional Functioning: 3.9 vs 1.3; p=0.005 Health Perceptions: 5.0 vs -4.8; p=0.001 Physical Functioning: 2.3 vs 6.9; p=0.001 Respiratory Symptom: -7.1 vs 2.6; p=0.001 Role/School: 2.1 vs 4.2; p=0.014 Social Functioning: 1.2 vs -3.6; p=0.248 Treatment Burden: 0.2 vs 3.1; p=0.177 Vitality: 3.6 vs 4.4; p=0.005 Weight: 4.7 vs 1.4; p=0.376	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	corticosteroid medications, or physiotherapy technique/schedule lung transplantation new findings on chest radiograph at screening or in the previous 90 days aspartate aminotransferase or alanine aminotransferase levels more than five times the upper limit of normal (at screening), or serum creatinine levels more than two times the upper limit of			Minor adverse events Cough, at 28 days (n/N): 28/80 vs. 25/84 Headache, at 28 days (n/N): 5/80 vs 10/84 Chest discomfort, at 28 days (n/N): 5/80 vs 4/84 Abdominal pain, at 28 days (n/N): 2/80 vs 6/84 Major adverse events Hemoptysis, at 28 days (n/N): 2/80 vs 6/84 Dyspnea, at 28 days (n/N): 5/80 vs 8/84	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	normal (at screening) pregnancy lactation in the opinion of the investigator, medical or psychiatric illness interfering with study participation. Patients were not permitted to use other antipseudomonal antibiotics or azithromycin during the study or during the 14-day follow-up period, unless required for the treatment of worsening symptoms.			Emergence of resistant organisms/ antibiotic resistance proxy: treatment-emergent persistent isolation of other organisms, 42 days follow-up S aureus (n/N): 2/74 vs 5/81 B cepacia (n/N): 0/74 vs 0/81 S maltophilia (n/N): 2/74 vs 0/81 A xylosoxidans (n/N): 1/74 vs 2/81	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ryan, G., Singh, M., Dwan, K., Inhaled antibiotics for long-term therapy in cystic fibrosis, Cochrane Database of Systematic Reviews, CD001021, 2011 Ref Id 331888 Country/ies where the study was carried out Study type Cochrane SR Aim of the study The aim of this review is to identify the most effective inhaled antibiotic for long-term therapy in people with CF. Study dates Searches up to 31 January 2011 Source of funding Clinical Staff Education Fund, Sir Charles Gairdner Hospital (Australia)	Sample size 8 trials were included from this review 1 trial (McCoy 2008) evaluates Aztreonam 2 trials (Hudson 2002, Jensen 1987) evaluate Colistin 6 trials (Chuchalin 2007, Hudson 2002, Lenoir 2007, Murphy 2004, Ramsay 1993, Ramsay 1999) evaluate Tobramycin Characteristics	Interventions Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. Chuchalin 2007 Intervention: Tobramycin 300mg (Bramitob®. Used a Pari LC Plus jet nebuliser and Pari Turbo Boy air compressor Comparison: placebo (saline solutionwith quinine hydrochloride solution) Study duration: 24 weeks (4 weeks 'on treatment'	Details Chuchalin 2007 Randomised Multicentre (21 sites across Hungary, Poland and Russia, parallel study Placebo-controlled Double-blind A 2:1 (tobramycin: placebo) allocation used Hodson 2002 Random allocation, stratified by age and centre Parallel design Open label Jensen 1987 Random allocation Parallel design	Results Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. Additional data extracted is marked with a * COMPARISON: AZTREONAM VS PLACEBO McCoy 2008 FEV1 FEV1% change from baseline to day 28: AZLI vs placebo	Limitations Quality of the SR AMSTAR score: 11/11 Quality of the individual studies The RoB assessment has been taken from the SR. Chuchalin 2007 Adequate sequence generation: unclear (Randomised, but method not stated. Ratio tobramycin to placebo 2:1) Allocation concealment: unclear (not stated, multicentre) Blinding (all outcomes): yes (Double-blind, quinine hydrochloride added to placebo to mask taste) Incomplete data outcome (all outcomes): yes (247 randomised, 245 ITT analysis, 215 PP analysis. 232 completed the study, 6.1% drop out rate (tobramycin group 7 dropouts (4.3%), placebo group 8 dropouts (9.3%)). Reasons given) Free selective reporting: Unclear (Not clear if results formicrobiology are ITT or PP) Other bias: no (Supported by Chiesi Famaceutici SpA (Italy), MDS Pharma Services (France)) Hudson 2002 Adequate sequence generation: Unclear (Described as 'randomised'. Stratified by age groups in each centre) Allocation concealment: Unclear (Not stated) Blinding (all outcomes): No (Not used) Incomplete outcome data addressed (all outcomes): Yes (Figure of screened, randomised, treated, withdrawn, analysed ITT stated. 94% completed. Attrition rate 6%. Reasons given) Free of selective reporting: Yes (Outcome stated in methods section have been reported, although no

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Chuchalin 2007 N: 247 randomised 245 included in ITT population M/F: 135 males, 110 females Diagnosis of CF + P. Aeruginosa Hodson 2002 N: 143 people screened, 17 screening failures 126 people randomised, 11 withdrew before treatment, 115 treated Gender: 45% males Age range: 7 - 50 years Exclusion: any anti-pseudomonal antibiotics within the	followed by 4 weeks 'off treatment') Hodson 2002 Intervention: Tobramycin 300 mg in 5 ml twice daily Comparison: Colistin 1MU in 3 ml in saline twice daily Duration: 28 days Pari LC plus (tobramycin) or Ventstream (colistin) nebuliser with CR50 compressor. Jensen 1987 Intervention: Colistin (1 million units), twice daily, raindrop nebuliser with 3.0 ml of solution. Comparison: placebo (normal	Double-blinded Placebo control Lenoir 2007 RCT Parallel design Multicentre (13 sites, 4 countries) Double-blind Placebo-controlled McCoy 2008 RCT Parallel design Multicentre (56 centres in USA) Double-blind Placebo controlled Ramsey 1993 Random allocation Cross-over design: 3-period cross-over design Double blinded	(6.3% (95% CI: 2.5-10.1)) Time to next exacerbation proxy outcome: frequency of one or more hospital admissions at 1 to 3 months: placebo 1/76; AZLI 6/135 Eradication of the organism Nutritional status Not reported Quality of life CFQ-R at 1 month (MD, SE): 5.01 (2.14) Adverse events minor AE - Voice alteration, at the end of	protocol was available for a more thorough assessment) Other bias: Unclear (Sponsor Pathogenesis Limited.) Jensen 1987 Adequate sequence generation: Unclear (Described as randomised, but method not stated) Allocation concealment? Unclear (Not stated) Blinding (all outcomes): Unclear (Reported as double-blind, but not stated who was blinded) Incomplete outcome data addressed (all outcomes): Yes (29/40 completed. Attrition rate 28%. Reasons given) Free of selective reporting: No (Tolerance, FEF, Shwachman score and nocturnal cough are partially reported so that data could not be included in a meta-analysis i.e. 'no significant difference'. No protocol was available for a more thorough assessment) Free of other bias: No (Uneven withdrawals; 2/20 in colistin group and 9/20 in placebo group. Mean baseline FEV1 71% predicted (colistin) and 79% predicted (placebo) in participants analysed) Lenoir 2007 Adequate sequence generation: Yes (Randomly assigned to 1 of 2 treatments according to randomisation list prepared in blocks of 4 participants) Allocation concealment: Unclear (Not stated. Multi-centre) Blinding (all outcomes): Yes (Double-blind, quinine hydrochloride added to placebo. Report stated investigators, co-investigators and nursing staff were blinded to the treatment randomized; participants presumed to be blinded. Tobramycin and matching placebo supplied in unit dose vials) Incomplete outcome data addressed (all outcomes): Yes (59 randomised, 59 ITT analysis, 56 PP analysis.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	previous 14 days. Criteria for diagnosis abnormal sweat electrolytes, gene mutation Jensen 1987 N: 40 Gender: 20 males Age range: 7 - 35 years Diagnostic criteria for CF: not stated Chronic P. aeruginosa infection. Mean baseline FEV1 71% (SD 25) and 79% (SD 29) predicted in 2 treatment groups Lenoir 2007 N: 59 participants Gender: 32 males	saline), twice daily Duration of treatment: 3 months Lenoir 2007 Intervention: Tobramycin 300 mg (Bramitob®, t wice dail. Used Pari LC Plus nebuliser and Pari TurboBoy compressor. Comparison: placebo, twice daily Duration: 4 weeks followed by a 4-week run-out phase 4 weeks. McCoy 2008 Intervention: Aztreonam 75 mg, 2 or 3 times per day for 28 days Comparison: placebo (5mg lactose in 1 ml. 0.17%	Placebo control Ramsey 1999 Random allocation Parallel design Double blinded Placebo control Murphy 2004 Randomised Parallel group Open label Stratified by age and sex	the study (n/N): 2/135 vs 4/76 minor AE - Cough (n/N), at the end of the study: 43/135 vs 26/76 major AE - Haemotypsis, at the end of the study (n/N): 13/135 vs 7/76 major AE - Anaphylaxis, at the end of the study: none reported in any of the groups* Deaths: no deaths* Emergence of resistant organisms/ AB resistance Not reported	51 completed, 13.6% drop out rate (tobramycin group 1 drop out (3.4%), placebo group 7 dropouts (23.3%). Reasons given) Free of selective reporting: No (Some outcomes stated in the methods section were not reported in the results section, for example blood pressure, heart rate) Other bias: Unclear (Study sponsored & funded by Chiesi Farmaceutici (Italy)) McCoy 2008 Adequate sequence generation: unclear (states "randomly assigned" only) Allocation concealment: unclear (not stated) Blinding: unclear (indicates double blind, but not clear who's blinded) Incomplete data outcome: yes (211 participants started the study after the open-label phase started, and 173 finished the study, Reasons provided in the flowchart) Free selective reporting: no Other bias: unclear (authors used a composite endpoint "the need (symptoms) for additional AB") Ramsey 1993 Adequate sequence generation:Unclear (Described as randomised, stratified FEV1 groups in each centre) Allocation concealment: Unclear (Not described) Blinding (all outcomes): Unclear (Described as double blind, but not stated who. Used quinine to mask nebulised solutions adequately) Incomplete outcome data addressed (all outcomes): Yes (Intention-to-treat analysis stated with random exclusion to match numbers for crossover analysis. 66/71 completed. 5 withdrew from study. Attrition rate 6%. Reasons given) Free of selective reporting: No (Serum creatinine and auditory acuity only partially reported. 'The levels of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Age range: 6 to 30 years Diagnosed CF + P. aeruginosa McCoy 2008 N: 246 participant Gender: 121 males Age range: 7 to 65 years Documented diagnosis of CF + P. aeruginosa, 3 or more courses of tobramycin in previous year, FEV1 between 25 and 75% predicted. Ramsey 1993 N: 71 participants Gender: 37 male Mean age: 17.7 years, SD 1.25 years and	NaCl), 2 or 3 times per day Duration: 4 weeks Ramsey 1993 Intervention: Tobramycin 600 mg, 3-times daily Comparison: Placebo. 0.5 normal saline, 3-times daily Duration: 28 days, then cross-over for two 28-day periods Ultrasonic (Ultraneb 100/99) nebuliser with 30 ml solution and 200 inhalations Ramsey 1999 Intervention: Tobramycin 300 mg, twice daily. Pari LC plus nebuliser with 5 ml of solution and		COMPARISON: COLISTIN VS PLACEBO Jensen 1987 FEV1 mean (SD) % change in FEV1 (% predicted) at 1 to 3 months (90 days): placebo - 17.00 (11.00); nebulised colistin - 11.00 (6.00) mean (SD) final FEV1 (% predicted) at day 60: placebo 62.00 (25.00); nebulised colistin 63.00 (24.00) Time to next exacerbation	serum creatinine in all patients remained in the normal range throughout the study. No clinically important or statistically significant change occurred in auditory acuity in either study group') Other bias: No (Cross-over design. They examined for carry-over or period effects and a carry-over effect for FEV1 was reported. When tobramycin was used intermittently, an improvement in FEV1 did not return to baseline during four weeks off treatment. Sponsor CFF) Ramsey 1997 Adequate sequence generation: Unclear (Described as adaptive randomisation procedure, stratified by 7 criteria) Allocation concealment: Unclear (Not stated) Blinding (all outcomes): Unclear (Described as double blind, but not stated who. Used quinine to attempt to mask nebulised solutions adequately) Incomplete outcome data addressed (all outcomes): Yes (ITT analysis stated, 90%completed. Attrition rate 10%. 56 participants did not complete the study.) Free of selective reporting: No (FVC is only partially reported in the many journal articles for this study. Other results seemto be reported. No protocol was available for a more thorough assessment and there were multiple publications from this study) Other bias: Unclear (Some investigators are patent holders. Support NIH, CFF, FDA.) Murphy 2004 Adequate sequence generation? Unclear risk. Described as randomised, but no method described Allocation concealmnt? Unclear risk. Not described Blinding? High risk. Open label study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	16.6 years, SD 1.24 years CF diagnosed by sweat test Sputum culture of P. aeruginosa susceptible to tobramycin. Mean baseline FEV1 55% (SE 3.7) and 60% (SE 3.2) predicted in 2 treatment arms Ramsey 1999 N: 520 participants Gender: 54% male Age from six years, 54% 18 years or older Criteria for CF were CFF clinical	Pulmo-aide compressor. Comparison: placebo, 0.225 normal saline and 1.25 mg quinine, twice daily Duration: three 28-day on-off cycles Murphy 2004 Tobramycin 300 mg twice daily, alternating 4-weekly cycles for 56 weeks Method of nebulisation: Pari LC Plus jet nebulizer and Pulmo-Aide compressor		Not reported Eradication of the organism P. Aeruginosa was not eradicated from the sputum of any patient during 3-month the trial* Nutritional status Not reported Quality of life Not reported Adverse events Not explicitely reported Emergence of resistant organisms/ AB resistance No superinfecti on with with other colistin-	Incomplete outcome data addressed? Low risk. Planned sample size 400, 184 randomised, 63 completed 56 weeks. Attrition rate 65%. 88 sponsor requested withdrawals. Reasons given Free of selective reporting? High risk. Many outcomes were not fully reported, only stating a non-significant difference between groups, including number of missed school days and weight. Also for lung function measurements, although these were also shown graphically Free of other bias? High risk. Early termination for benefit. 63 of 181 randomised participants completed 56 weeks. Sponsor tobramycin manufacturer Chiron Corporation Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	practice guidelines All infected with P. aeruginosa. Baseline FEV1 25-75% predicted Murphy 2004 N: 184 52% male age 6-15 years 2 or more cultures of P.aeruginosa Inclusion criteria Chuchalin 2007 Diagnosis of CF + P. aeruginosa Hodson 2002 Exclusion included any anti-pseudomonal antibiotics within the			resistant microorganisms, including Ps. Cepacia, Serratia marcescens, Proteus mirabilis, Gram-positive organisms or fungi during 3-month the trial* Resistance to Colistin did not develop in any strain during 3-month the trial* No change in resistance pattern to other commonly used anti-pseudomonas treatments during 3-	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	previous 14 days Criteria for diagnosis abnormal sweat electrolytes, gene mutation Jensen 1987 Diagnostic criteria for CF not stated Chronic P. aeruginosa infection Lenoir 2007 Diagnosed CF + P. aeruginosa McCoy 2008 Documented diagnosis of CF + P. aerugi nosa, 3 or more courses of tobramycin in previous yea r, FEV1 betwe en 25 and			month the trial* COMPARIS ON: TOBRAMY CIN VS PLACEBO Chuchalin 2007 FEV1 mean (SD) FEV1% predicted at 24 weeks (adjusted for baseline): placebo 62.27 (1.42); tobi neb 68.65 (1.03) Time to next exacerbatio n proxy outcome: frequency of one or more hospital admissions over 3 months and up to 12	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	75% predicted Ramsey 1993 CF diagnosed by sweat test Sputum culture of P. aeruginosa susceptible to tobramycin Ramsey 1999 Criteria for CF were CFF clinical practice guidelines All infected with P. aeruginosa Baseline FEV1 25-75% predicted. Murphy 2004 2 or more cultures of P. aeruginosa			months: placebo 31/78, tobi neb 78/153 Eradication of the organism negative culture, at 4 weeks (n/N): 49/159 vs 12/84* negative culture, at 8 weeks (n/N): 23/159 vs 10/83* negative culture, at 20 weeks (n/N): 52/156 vs 13/79* negative culture, at 24 weeks (n/N): 38/159 vs 17/84* Nutritional status	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria See inclusion criteria			Patients treated with Tobramycin had greater mean weight gain at all visits ($p<0.01$)* bodyweight change from baseline to 24 weeks: significant increase in Tobramycin (95%CI 1.5 to 2.1) and placebo (95%CI 0.6 to 1.5) groups* BMI change from baseline to 20 weeks: significant increase in Tobramycin group (95%CI 0.3 to 0.6); no significant increase in placebo group*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				BMI at 20 weeks: significantly higher in the Tobramycin group (p<0.01)* Quality of life Not reported Adverse events patients with treatment-related AE during the 24 weeks study period (n/N): 25/161 vs 13/85* patients with serious AE during the 24 weeks study period (n/N): 17/161 vs 22/85* Deaths over during the 24 weeks study period	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(n/N): 1/61 vs 2/86 Emergence of resistant organisms/ AB resistance frequency of Tobramycin-resistant P. Aeruginosa at 24 weeks (end of the study) (n/N): 35/153 vs 14/78 Lenoir 2007 FEV1 mean (SD) % change in FEV1 (% predicted), at 1 to 3 months from baseline (4 weeks): placebo 2.53 (18.50); tobi neb 16.11 (13.50) mean FEV1 (%	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				predicted) at the end of treatment: placebo 62.3 (20.9); tobi neb 73.8 (19.5) Time to next exacerbation not reported Eradication of the organism negative culture at 4 weeks (end of treatment) (n/N): 10/29 vs 5/30* negative culture at 6 weeks follow-up (n/N): 3/29 vs 3/30* Nutritional status weight-change (kg) at 4 weeks (end of treatment) (mean, SD):	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				0.39 (0.9) vs 0.16 (0.9) Quality of life not reported Adverse events treatment-related AE during the 4-week treatment phase (n/N): 3/29 vs 7/30* serious AE during the 4-week treatment phase (n/N): 1/29 vs 3/30* deaths during the 4-week treatment phase (n/N):0/29 vs 1/30* Emergence of resistant organisms/ AB resistance not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Ramsey 1999 FEV1 change in FEV1 from baseline to week 20: placebo -2.0%; tobi neb 10.0%; p<0.001 Time to next exacerbation proxy outcome: frequency of one or more hospital admissions over 3 months and up to 12 months (20 weeks): placebo 117/232; tobi neb 95/232 Eradication of the organism proxy: density of P.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Aeruginosa in sputum samples at week 20 (log10 CFU per gram): -0.8 vs +0.3 * Nutritional status not reported Quality of life not reported Adverse events minor AE - auditory impairment, at 24 weeks (end of the study) (n/N): 0/152 vs 0/148 minor AE - tinnitus, at 24 weeks (end of the study) (n/N): 8/258 vs 0/262 minor AE - voice alteration, at 24 weeks	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(end of the study) (n/N): 33/258 vs 17/262 major AE - Haemotypsis, at 24 weeks (end of the study) (n/N): 69/258 vs 81/262 major AE - pneumothorax, at 24 weeks (end of the study) (n/N): 1/258 vs 4/262 Deaths at 24 weeks (end of the study) (n/N): 0/258 vs 4/262 Emergence of resistant organisms/ AB resistance frequency of Tobramycin-resistant P. Aeruginosa at 24 weeks (end of the	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				study) (n/N): 51/223 vs 17/218 frequency of new isolates of drug resistant B. Cepacia (n/N): 0/258 vs 0/262 frequency of new isolates of drug resistant S. Maltophilia (n/N): 3/258 vs 1/262 frequency of new isolates of drug resistant A. xylosidans (n/N): 1/258 vs 1/262 frequency of new isolates of drug resistant Aspergillus (n/N): 4/196 vs 20/193 Ramsey 1993 FEV1	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				mean % change in FEV1 (% predicted), at 1 to 3 months (28 days adjusted for baselin): tobi neb vs. placebo: 4.32 (95% CI: 1.6, 7.04) Time to next exacerbation proxy: pulmonary exacerbations at 4 weeks: placebo 2/35; tobi neb 5/36 Eradication of the organism proxy: density of P. Aeruginosa at 4 weeks (CFU/g, log10) (mean±SE; 95%CI): -	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				1.87±0.30 (2.47 to -1.27) (n=58)* Nutritional status not reported Quality of life not reported Adverse events minor AE - auditory impairment, during the 42-week observation period (n/N): 0/36 vs 0/35 Emergence of resistant organisms/ AB resistance emergence of P. Cepacia: 3 infected during the 4-week study period, no significant differences	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				between Tobramycine and placebo periods (p>0.7)* emergence of P. Maltophilia: 10 infected during the 4-week study period, no significant differences between Tobramycine and placebo periods (p>0.7)* emergence of resistant P. Aeruginosa strains (n/N): 10/71 during the4-week study period, no significant differences between Tobramycine and	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				placebo periods (p>0.5)* Murphy 2004 FEV1 not reported Time to next exacerbation proxy: number of subjects hospitalised for respiratory reasons (52 weeks); control 23/90 vs tobi neb 10/91; p=0.011* Eradication of the organism not reported Nutritional status not reported Quality of life not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Adverse events not repoted Emergence of resistant organisms/ AB resistance not reported COMPARISON: INHALED TOBRAMYCIN VS COLISTIN Hudson 2002 FEV1 mean % change in FEV1 (% predicted), at 4 weeks of AB therapy (mean, SD): see NMA data extraction table Time to next exacerbation not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Eradication of the organism proxy: change in sputum P. Aeruginosa density Log10 cfu mL-1, at 4 weeks of AB therapy (mean, SD) (ITT population): -0.86±1.43 (n=50) vs -0.60±1.651 (n=50)* proxy: change in sputum P. Aeruginosa density Log10 cfu mL-1, at 4 weeks of AB therapy (mean, SD) (microbiologically evaluable population): -0.79±1.35 (n=42) vs -	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				0.47±1.53 (n=37)* Nutritional status not reported Quality of life not reported Adverse events minor AE - increased cough, by the end of the 4-week study period (n/N): 5/53 vs 11/62 minor AE - increased sputum, by the end of the 4-week study period (n/N): 6/53 vs 8/62 minor AE - dyspnea, by the end of the 4-week study period (n/N): 5/53 vs 7/62 minor AE - pharyngitis,	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				by the end of the 4-week study period (n/N): 7/53 vs 3/62 major AE - patients with ≥1 serious AE by the end of the 4-week study period (n/N): 8/53 vs 7/62* Emergence of resistant organisms/ AB resistance no evidence of development of highly tobramycin-resistant P. Aeruginosa in either group at 8 weeks follow-up*	
Full citation Schuster, A., Haliburn, C., Doring, G., Goldman, M. H., Freedom Study, Group, Safety, efficacy and convenience of	Sample size N=380 (Safety population: patients who	Interventions Intervention Treatment: inhaled	Details Randomization No detail given	Results Lung function	Limitations Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: unclear risk (the process is not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
colistimethate sodium dry powder for inhalation (Colobreathe DPI) in patients with cystic fibrosis: a randomised study, Thorax, 68, 344-50, 2013 Ref Id 331950 Country/ies where the study was carried out Europe (Countries not specified) Study type Open-label RCT Aim of the study To investigate whether colistimethate formulated as a dry powder inhaler can be as effective as inhaled antibiotics given via a nebuliser in controlling chronic P aeruginosa infection in cystic fibrosis patients. Study dates March 2003 - October 2007 Source of funding Funding for the study was provided by Forest Laboratories UK, Dartford	received at least one dose of medication) Treatment (CDPI) n=187 [One patient dropped out immediately following randomisation and did not receive treatment] Comparison (TIS) n=193 N=374 (ITT population) Treatment (CDPI) n=183 Comparison (TIS) n=191 Characteristics (Treatment vs. comparison) Age (mean±SD): 21.3±9.72 vs. 20.9±9.30 -	colistimethate sodium (CDPI) Formulation: capsules Duration: 24-weeks Dosing: 1.6625 MU twice daily Comparison tobramycin inhaler solution (TIS) Formulation: solution for inhalation Duration: three 28-day cycles Dosing: twice-daily 300 mg/5 ml	Allocation concealment Described as “centrally randomized”, but no details given Blinding Described as open-lable Data collection Patients underwent study assessments at baseline and at 24 weeks.	CDPI - TIS: -0.98 (95% CI: -2.74, 0.86) Time to next pulmonary exacerbation Not reported Eradication of the specified organism from sputum/airway cultures Not reported Nutritional status Not reported Quality of life Not reported Adverse events Safety population reported. CDPI	Allocation concealment: unclear risk (the process is not reported) Blinding: low risk (This study is described as open-label RCT) Incomplete data: Low risk (ITT performed) Selective reporting: low risk (All the outcomes stated in the methods and the study protocol are appropriately reported) Other: low risk (None detected) OVERALL QUALITY: moderate risk of bias Other information (+) multicentre prospective RCT and large sample size (+) outcome assessor were blinded to the treatment being given (+) ITT performed (-) unclear randomization (-) no blinded Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Total: 21.1 ±9.49 Male (%): 56.3 vs 52.9 - Total:54.5 FEV1 % predicted (mean±SD): 49.14±14.895vs. 50.80 ±6.336 - Total: 49.78±11.980 Inclusion criteria 66 European CF centres Confirmed CF diagnoses ≥ 6 years of age Chronically colonised with P aeruginosa infection, defined as at least 2 positive sputum cultures within the last 12			(n=186) vs. TIS (n=193) n(%) Withdrawals due to an AE 22 (11.8) vs. 5 (2.6) Mild AE 159 (85.0) vs. 165 (85.5) Moderate AE 123 (65.8) vs. 97 (50.3) Severe AE 48 (25.7) vs. 13 (6.7) Cough 193 (15.7) vs. 123 (10.3) Dyspnoea 81 (6.6) vs. 98 (8.2) Productive cough 62 (5.0) vs. 76 (6.4)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	months prior to the first day of trial medication Stable clinical condition: no evidence of a current acute respiratory exacerbation at the pre-run visit Exclusion criteria Patients were excluded if they had: presence of Burkholderia cepacia complex infection in the airways, ongoing pulmonary exacerbation (based on a modified Fuchs definition) sensitivity to any study medication				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Sheldon, C. D., Assoufi, B. K., Hodson, M. E., Regular three monthly oral ciprofloxacin in adult cystic fibrosis patients infected with Pseudomonas aeruginosa, Respiratory Medicine, 87, 587-93, 1993 Ref Id 331984 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Remmington 2016 Characteristics See Cochrane SR Remmington 2016 Inclusion criteria See Cochrane SR Remmington 2016 Exclusion criteria See Cochrane SR Remmington 2016	Interventions See Cochrane SR Remmington 2016	Details See Cochrane SR Remmington 2016	Results See Cochrane SR Remmington 2016	Limitations See Cochrane SR Remmington 2016 Other information
Full citation Tappenden,P., Harnan,S., Uttley,L., Mildred,M., Carroll,C., Cantrell,A., Colistimethate sodium powder and tobramycin	Sample size EAGER trial N randomised: 553	Interventions EAGER trial Intervention Tobramycin DPI	Details EAGER trial Design: RCT, open label	Results EAGER trial Note: Data is presented as	Limitations QUALITY OF THE TA AMSTAR: 11/11 QUALITY OF THE INDIVIDUAL STUDIES

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
powder for inhalation for the treatment of chronic Pseudomonas aeruginosa lung infection in cystic fibrosis: systematic review and economic model, Health Technology Assessment (Winchester, England), 17, v-xvii, 2013 Ref Id 322218 Country/ies where the study was carried out UK Study type Health Technology Assessment Aim of the study To evaluate the clinical effectiveness and cost-effectiveness of Colismethate sodium dry powder of inhalation (DPI) and Tobramycin DPI for the treatment of chronic P. Aeruginosa lung infection in CF. Study dates Searches up to March 2011 Source of funding The National Institute for Health Research Health Technology Assessment programme. Individual study funding: EAGER trial: Novartis Pharmaceuticals COLO/DPI/02/06: Forest Laboratories	Intervention: 329 Control: 224 Number withdrawn before medication: 36 Intervention: 21 Control: 15 Number withdrawn after medication or lost to follow-up: 121 Intervention: 83 Control: 38 COLO/DPI/02/06 N randomised: 380 Intervention: 187 Control: 193 Number withdrawn before	Device: T-326 Inhaler Dose:112 mg twice daily Schedule: 28 days on treatment followed by 28 days off treatment Comparison Tobramycin inhalation solution Device: PARI LC Plus jet nebuliser Dose: 300 mg/5 ml twice daily Schedule: 28 days on treatment followed by 28 days off treatment COLO/DPI/02/06 Intervention Colistimethate sodium DPI	Duration: 24 weeks 127 centres, 15 countries COLO/DPI/02/06 Design: RCT, open label Duration: 24 weeks 66 centres in EU countries, Russia and the Ukraine COLO/DPI/02/05 Design: RCT, open label with cross-over Duration: 8 weeks Three centres in the UK	Tobramycin inhalation powder vs Tobramycin inhalation solution Lung function see NMA table Number of people experiencing 1 or more exacerbations see NMA table Time to next pulmonary exacerbation not reported Eradication of the specified organism from sputum/airway cultures mean change in P. Aeruginosa sputum density	The quality was assessed using 3 tools. Data was extracted for the CRD criteria only. EAGER trial Random allocation: yes Adequate concealment: yes Similar groups at the outset: yes Blinding: no Unexpected imbalance in drop-outs? were they explained or adjusted for? yes/ no All outcomes reported?: no ITT analysis? was this appropriate? appropriate methods used? yes/ yes/ no COLO/DPI/02/06 Random allocation: unclear Adequate concealment: yes Similar groups at the outset: yes Blinding: no Unexpected imbalance in drop-outs? were they explained or adjusted for? yes/yes All outcomes reported?: no ITT analysis? was this appropriate? appropriate methods used? yes/ yes/ yes COLO/DPI/02/05 Random allocation: yes Adequate concealment: unclear Similar groups at the outset: unclear Blinding: no Unexpected imbalance in drop-outs? were they explained or adjusted for? no/ na

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
COLO/DPI/02/05: Forest Laboratories	medication: 7 Intervention: not reported Control: not reported Number withdrawn after medication or lost to follow-up: 53 Intervention: 32 Control: 21 COLO/DPI/02/05 N randomised: 16 Number withdrawn before medication: 0 Number withdrawn after medication or lost to follow-up: 3	Device: Turbospin device Dose: 125 mg twice daily Schedule: continuous treatment Comparison Tobramycin inhalation solution Device: LC Plus jet nebuliser Dose: 300 mg/5 ml twice daily Schedule: 28 days on treatment followed by 28 days off treatment COLO/DPI/02/05 Intervention Colistimethate sodium DPI Device: Turbospin device		log10 CFU, at 4 weeks: -1.76 (SD 1.96) (n=308) vs −1.32 (SD 2.03) (n=209) mean change in P. Aeruginosa sputum density log10 CFU, at 20 weeks: -1.61 (SD 2.03) (n=308) vs −0.77 (SD 1.78) (n=209) negative P. Aeruginosa culture: 11.6% vs 9.9% Nutritional status Not reported Quality of life Not reported Adverse events	All outcomes reported?: yes ITT analysis? was this appropriate? appropriate methods used? yes Other information Full report: http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0011/94295/FullReport-hta17560.pdf

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Characteristics EAGER trial Age (mean, SD): 26 (11.4) vs 25 (10.2) Gender, male (%): 55.5% vs 55.0% FV1% predicted: 53 (SD 14.2; SE 0.81) vs 53 (SD 15.9; SE 1.11) Chronic macrolide use: 60.7% vs 59.8% No differences in chronic macrolide use, or use of anti-pseudomonal txt before trial COLO/DPI/02/06	Dose: 125 mg twice daily Schedule: continuous treatment Comparison Colistimethate sodium solution Device: NR Dose: 2 MU twice daily Schedule: continuous treatment		mild or moderate AE (%/N): 73.4%/308 vs 68,5%/209 serious AE (%/N): 27,4%/308 vs 29,2%/209 productive cough (n/N): 56/308 vs 41/209 dyspnea (n/N): 48/308 vs 26/209 vomiting (n/N): 19/308 vs 12/209 headache (n/N): 35/308 vs 25/209 haemoptysis (n/N): 40/308 vs 26/209 Emergence of resistant organisms/	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Age (mean, SD): 21.3(9.72) vs 20.9 (9.30) Gender, male (%): 56.3% vs 53.2% FV1% predicted: 51.76 (SE 1.02) vs 50.82 (SE 0.99) Mucolytics: 74.3% vs 79.1% Macrolides: 49.7% vs 51.3% COLO/DPI/02/05 Age (mean, SD): 37.5% were ≥8 and <13 years; 62.5% were ≥13 Gender, male (%): NR FV1% predicted:			antibiotic resistance P. aeruginosa isolates (all phenotypes) with MIC > 8 µg/ml (resistant) at baseline 68/308 (22.1%) P. aeruginosa isolates (all phenotypes) with MIC ≤ 8µg/ml (susceptible) at baseline 240/308 (77.9%) MIC > 8 µg/ml at the end of cycle 3 19.1% Increased MIC of tobramycin against P. aeruginosa from baseline to day 28 of cycle 3: Fourfold or	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	75.92 (SE 11.86) vs 79.51 (SE 7.707) All patients were on nebulised colistimethate sodium Patients were permitted to continue with pre-existing non-antipseudomonal CF medications Inclusion criteria INCLUSION CRITERIA FOR THE TA Study design: RCTs. Population: people aged ≥ 6 years with CF and chronic P. aeruginosa pulmonary infection. (Children of			greater increase: 67/199 (33.7%); Twofold or greater increase: 97/199 (48.7%); (unclear which numbers relate to which group) COLO/DPI/02/06 Note: Data is presented as Colistimethate sodium dry powder vs Tobramyin nebulised solution Lung function see NMA table Number of people experiencing 1 or more	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	< 6 years of age were excluded from the assessment, as they are subject to different treatment regimens, methods of assessment of lung function differ, and licensing has not been sought for this age group). Interventions: Studies assessing the effectiveness of colistimethate sodium DPI or tobramycin DPI Comparators: the comparator intervention or other			exacerbations see NMA table Time to next pulmonary exacerbation Time to next acute exacerbation (mean): 63.70 vs 59.30 days proxy: time to first additional anti-pseudomonal treatment (mean number of days): 55.28 (43.2) (n=183) vs 51.79 (41.9) (n=191) days Eradication of the specified organism from sputum/airway cultures Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	antipseudomonal antibiotics for nebulised inhalation, including, as a minimum, colistimethate sodium for nebulised inhalation or tobramycin for nebulised inhalation. Outcomes: rate and extent of microbial response; lung function; respiratory symptoms; frequency and severity of acute exacerbations; HRQoL; and AEs of treatment; complianc INCLUSION CRITERIA FOR THE INDIVIDUAL STUDIES			Nutritional status BMI change from baseline to week 24 (mean, SD): 0.08 (0.78) (n=183) vs 0.17 (0.89) (=191) kg Quality of life Physical (adj mean change from baseline to week 24): 0.26 vs −1.56; p=0,353 Vitality (adj mean change from baseline to week 24): 0.86 vs −1.40; p=0.293 Emotion (adj mean change from baseline to week 24): 2.23 vs	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	EAGER trial Age: ≥ 6 years old FEV1: > 25% to < 75% predicted Patients with chronic P. aeruginosa infection (sputum or throat cultures positive for P. aeruginosa within 6 months of screening and at baseline) COLO/DPI/02/0666 Age: ≥ 6 years old FEV1 > 25 to < 75% predicted Patients with chronic P. aeruginosa infection (≥2 sputum or			0.47; p=0.244 Eating (adj mean change from baseline to week 24): 0.48 vs 0.66; p=0.925 Treatment burden (adj mean change from baseline to week 24): 5.62 vs 2.75; p=0,091 Health perceptions (adj mean change from baseline to week 24): 0.25 vs −2.71; p=0.159 Social (adj mean change from baseline to week 24): 3.10 vs 0.92; p=0.153	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	throat cultures positive for P. aeruginosa within 6 months of screening) Run-in inclusion criteria: patients to receive ≥2 nebulised tobramycin on/off cycles immediately prior to randomisation Non-smokers or a past smoker who had not smoked within the past 12 months Patients who, on first day of trial medication administration (Visit 1), had ≥ 28			Body image (adj mean change from baseline to week 24): 7.83 vs 5.98; p=0.385 Role (adj mean change from baseline to week 24): 0.65 vs 1.87; p=0.607 Weight (adj mean change from baseline to week 24): 0.88 vs −1.93; p=0.461 Respiratory (adj mean change from baseline to week 24): 2.99 vs 3.51; p=0.756 Digestion (adj mean change from baseline to	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	days but ≤ 35 days off tobramycin COLO/DPI/02/0566 Age: ≥ 8 years old FEV1 > 25% prediction Non-smokers or a past smoker who had not smoked within the past Exclusion criteria EXCLUSION CRITERIA FOR THE TA studies based on animal models; preclinical and biological studieS non-RCTs editorials, opinion pieces;			week 24): 5.06 vs 2.89; p=0.077 Adverse events study drug-related AE at 24 weeks (n/N): 153/187 vs 90/193 patients withdrawn due to serious AE at 24 weeks (n/N): 22/187 vs 5/193 productive cough at 24 weeks (n/N): 38/187 vs 44/193 chest discomfort at 24 weeks (n/N): 26/187 vs 34/193 dyspnea at 24 weeks (n/N):	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	reports published as meeting abstracts only where insufficient details were reported studies published only in languages other than English studies in which the population was not restricted to CF, unless data for just this population was presenteD			49/187 vs 52/193 vomiting at 24 weeks (n/N): 6/187 vs 8/193 haemoptysis at 24 weeks (n/N): 20/187 vs 13/193 Emergence of resistant organisms/ antibiotic resistance not reported COLO/DPI/ 02/05 Note: Data is presented as Colistin inhalation powder vs Colistin inhalation solution Lung function see NMA table Number of people	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				experiencing 1 or more exacerbations see NMA table Time to next pulmonary exacerbations not reported Eradication of the specified organism from sputum/airway cultures not reported Nutritional status not reported Quality of life not reported Adverse events dyspnea at 8 weeeks follow-up (n/N): 3/16 vs 4/15 vomiting at 8 weeeks follow-up	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(n/N): 2/16 vs 0/15 productive cough at 8 weeeks follow-up (n/N: 2/16 vs 1/15 chest discomfort a t 8 weeeks follow-up (n/N): 4/16 vs 2/15 Emergence of resistant organisms/ antibiotic resistance not reported	
Full citation Trapnell, B. C., McColley, S. A., Kissner, D. G., Rolfe, M. W., Rosen, J. M., McKevitt, M., Moorehead, L., Montgomery, A. B., Geller, D. E., Phase, F. T. I. Study Group, Fosfomycin/tobramycin for inhalation in patients with cystic fibrosis with pseudomonas airway infection, American Journal of Respiratory & Critical Care Medicine, 185, 171-8, 2012 Ref Id	Sample size N=119 GROUP A (placebo) n=40 [Completing study: 32– for safety or tolerability: 6] GROUP B (FTI 80/20 mg) n=38 [Completing	Interventions Intervention Treatment: Fosfomycin/to bramycin for inhalation (FTI) A) 160/40 mg or B) 80/20 mg Formulation: solution for inhalation Duration: 4-weeks	Details Randomizati on Randomizati on used an interactive voice recognition system (code generated by Gilead Sciences) (p 2 additional	Results Lung function (see NMA abstraction tables) Time to next pulmonary exacerbatio n Not reported Eradication of the specified	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: low risk Allocation concealment: unclear risk (the process is not reported) Blinding: low risk Incomplete data: unclear risk (On one hand missing outcome data are balanced in numbers between groups, on the other hand there is insufficient information about attrition/exclusions to permit judgement of yes or not)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
332159 Country/ies where the study was carried out US Study type Double-blind, placebo-controlled, multicentre RCT - (NMA only) Aim of the study To evaluate the safety and efficacy of a 28-day course of Fosfomycin/tobramycin for inhalation (FTI) versus placebo, following a 28-day, open-label, run-in course of aztreonam for inhalation solution (AZLI). Study dates June 2008 to January 2010: patient enrolment 2012: results publication Source of funding Funding from Food and Drug Administration grant 1R01FD003016-01 and National Institutes of Health General Clinical Research Center grants M01 RR00188 and M01 RR10733	study: 35– for safety or tolerability: 1] GROUP C (FTI 160/40 mg) n=41 [Completing study: 34 – for safety or tolerability: 8] Characteristics (A vs B vs C) Age (mean±SD): 31±8.8 vs. 35±10.9 vs. 31±10.1 - Total: 32 ±10.1 Male (%): 68% vs 55% vs 49% - Total: 57% FEV1 % predicted (mean±SD): 48±13.6 vs. 50±13.4 vs. 48±14.6 - Total: 49 ±13.8	Dosing: twice daily Comparison Placebo: 5/10 mg lactose monohydrate powder 7.3/14.6 mg NaCl; 2/4 mL 0.17% NaCl diluent Formulation: solution for inhalation Duration: 4-weeks All patients were treated with AZLI (75 mg aztreonam; 52.5 mg lysine monohydrate; reconstituted in 1 mL 0.17% NaCl diluent) during the 28-day, open-label, run-in period.	file) and it was stratified by disease severity at screening (FEV1 ≤ 50% and FEV1 > 50% predicted). Allocation concealment No details given Blinding Described as double-blinded Data collection Patients underwent study assessments at baseline and at 4 weeks.	organism from sputum/airway cultures Not reported Nutritional status Not reported Quality of life Not reported Adverse events Not reported	Selective reporting: low risk (All the outcomes stated in the methods and the study protocol are appropriately reported) Other: low risk (None detected) OVERALL QUALITY: moderate risk of bias Other information (+) multicentre prospective RCT and large sample size (+) double blinded (-) unclear allocation concealment (-) relatively short timeframe Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria 33 US CF centres Confirmed CF diagnoses ≥18 yr of age FEV1 ≥ 25%, and FEV1 ≤ 75% predicted at screening colonised with P aeruginosa infection able to perform reproducible pulmonary function tests Exclusion criteria Patients were excluded if they had: administration of intravenous, oral, or inhaled				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	antipseudomonal antibiotics or changes in azithromycin regimen within 14 days prior to screening, or changes in antimicrobial, bronchodilator, corticosteroid, hypertonic saline, or dornase alfa medications, or physiotherapy technique or schedule within 7 days				
Full citation Wainwright,C.E., Quittner,A.L., Geller,D.E., Nakamura,C., Wooldridge,J.L., Gibson,R.L., Lewis,S., Montgomery,A.B., Aztreonam for inhalation solution (AZLI) in patients with cystic fibrosis, mild lung impairment, and P. aeruginosa, Journal of	Sample size Placebo vs. aztreonam Treated: 81 vs. 76 Completed study: 81 vs. 76	Interventions Aztreonam: 75mg aztreonam, 52.5mg lysine monohydrate Placebo: 5mg lactulose, 7.3mg NaCl	Details Randomization Stratified by age (6–13, 14–17, ≥18 years) and geographic region (North	Results Aztreonam vs. placebo Lung function - % change in FEV1 predicted	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: described Allocation concealment: method not reported Blinding: double blind, but method not reported Incomplete data: low risk Selective reporting: low risk, but sponsored by Gildead Sciences

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cystic Fibrosis, 10, 234-242, 2011 Ref Id 310385 Country/ies where the study was carried out Australia, USA Study type Double-blind, multicentre, placebo-controlled RCT Aim of the study To evaluate Aztreonam for inhalation solution as antipseudomonal treatment in people with CF with P. Aeruginosa. Study dates June 2008 to June 2009 Source of funding Sponsored by Gilead Sciences, Inc and by NIH General Clinical Research Center grants M01 RR00400, M01 RR10733, and M01 RR00188	Completed treatment: 79 vs. 71 Characteristics Demographic characteristics were well balanced between treatment arms The majority of patients were 6–17 years of age (56.7%) Most patients were receiving dornase alfa (81.5%) and pancreatic enzymes (88.5%) at baseline Patients had received a mean of 2.9 courses of TIS in the previous year; 65.0% of patients	Both diluted in 0.17% saline and self-administered with the investigtional eFlow PARI electronic nebuliser Patients self-administered a short acting bronchodilator before each study drug dose	America, Australia; randomization code generated by Gilead Sciences) Allocation concealment Nnot reported Blinding Double-blind, details not reported Data collection Not reported Data analysis For the primary efficacy analysis (CFQ-R) treatment effect was assessed by a parametric analysis of covariance (ANCOVA), treatment and age group were	from baseline Relative change (SE) in FEV1% predicted from baseline to day 28: 0.29 (0.85) (n=76) vs. -2.5 (0.82) (n=81), p=0.021 Mean change from baseline (0.27 vs. -2.37) calculated from relative change from baseline (therefore SD not calculable) Number of people with ≥1 exacerbations Not reported Time to next pulmonary exacerbation	Other: none Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	had received≥1 course. Inclusion criteria ≥ 6 years old documented CF FEV1 > 75% P. Aeruginosa present in expectorated sputum or throat swab culture samples at screening or documented in two samples within the previous 12 months (1 of them 3 months before screening) ≥ 2 of the following chronic and/or intermittent CF symptoms for ≥ 28		fixed effects and baseline CFQ-R RSS score was a covariate Analysis of other continuous variables used similar ANCOVA models, with respective baseline values as covariates Analyses included all randomly assigned patients receiving at least 1 dose of study drug Sample size of 140 would provide >89% power to detect a 10-point difference between groups in mean change from baseline at	Not reported Eradication of the specified organism from sputum/airway cultures Log10 PA CFUs in sputum, adj mean change (SE) at 28 days: -1.4 (0.36) (n=76) vs -0.14 (0.36) (n=81), p=0.016 Nutritional status Not reported Quality of life (CFQ-R) (better represented by higher outcomes) CFQ-R RSS, adj mean change (SE) at 28 days: 3.22 (1.7) (n=75) vs	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	days before baseline with no worsening of symptoms within 7 days before baseline no need for for inmediate antipseudomonal AB treatment of an impending recommendation able to perform reproductible pulmonary function test Exclusion criteria known hypersensitivity to monobactam AB inability to tolerate short-acting bronchodilators		day 28 on the CFQ-R RSS using a 2 sided 0.05 level test assuming a standard deviation of 17.5	1.41 (1.6) (n=81) CFQ-R PF, adj mean change (SE) at 28 days: 1.8 (1.6) (n=76) vs -0.69 (1.5) (n=80) CFQ-R RSS, adj mean change (SE) at 42 days: 3.0 (1.7) (n=75) vs 2.9 (1.7) (n=81) Adverse events Patients experiencing 1 or more AE: 59/76 vs 62/81 Mild to serious AE (in pt experiencing AE): 54/59 vs 59/62 txt related cough (n/%): 31 (38.3) vs. 35	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	lung transplantation history previous enrollment in an Aztreonam trial			(46.1); p=0.337 txt related productive cough (n/%): 13 (16.0) vs 18 (23.7); p=0.316 txt related respiratory tract congestion (n/%): 6 (7.4) vs 11 (14.5); p=0.201 Serious AE (n/N): 9/76 vs 3/81 Emergence of resistant organisms/ antibiotic resistance There was no evidence for persistent increases in the isolation of Burkholderia spp., Stenotrophomonas	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				maltophilia, Achromobacter xylosoxidans, Aspergillus spp., or S. aureus.	
Full citation Flume, P. A., Clancy, J. P., Retsch-Bogart, G. Z., Tullis, D. E., Bresnik, M., Derchak, P. A., Lewis, S. A., Ramsey, B. W., Continuous alternating inhaled antibiotics for chronic pseudomonal infection in cystic fibrosis, Journal of Cystic Fibrosis, 15, 809-815, 2016 Ref Id 566978 Country/ies where the study was carried out US Study type Double-blind, randomised trial, phase 3 Aim of the study To evaluate the safety and efficacy of a continuous alternating therapy (CAT) regimen with aztreonam for inhalation solution (AZLI; Cayston®; Gilead Sciences, Inc.) and nebulised tobramycin (TIS;	Sample size Randomised: CAT 43, tobi neb 47 Treated in comparative phase: CAT 42, tobi neb 46 Characteristics Mean (SD) age, years 28.4 (11.4); p=0.96 Female 51/88 (58%); p=1.00 Mean FEV1% predicted (SD) 50.0 (16.4); p=0.96 CFQ-R RSS score at Day	Interventions Enrolled subjects received TIS 300 mg twice daily (BID) during a 28-day run-in phase (Fig. supplement). This was followed by randomization to a 24-week comparative phase Subjects received 3 cycles of 28-days of double-blind AZLI or placebo (1:1 randomization) alternating with 28-days	Details Randomisation Eligible subjects were stratified by disease severity (forced expiratory volume at 1 s [FEV1] ≤50% or N50% predicted at Day 1) and number of acute respiratory exacerbations (1, 2, or ≥3; determined by the investigator) that required hospitalizatio	Results Lung function (% change in FEV1 predicted from baseline) Values at Weeks 4, 12, and 20 were averaged, adjusted mean (SE) change from baseline: CAT 1.37 (0.67); tobi neb 0.04 (0.66) Mean difference (95% CI) 1.33 (−0.55, 3.20)	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: low risk - subjects stratified Allocation concealment: not reported Blinding: insufficient detail Incomplete data: unclear Selective reporting: sponsored by Gildead Sciences and not all final results available for continuous outcomes - reported as the mean of weeks 4, 12 and 20 Other: recruitment finished early leading to an under powered study Other information PDEs were defined as a change or worsening from baseline of 1 or more documented signs or symptoms (decreased exercise tolerance or appetite; increased cough, sputum, or chest congestion; or other signs/symptoms) associated with use of IV or non-study inhaled antibiotics and were verified by a blinded independent adjudication committee review of the data.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
TOBI; Novartis) in adult and pediatric subjects with CF and chronic pulmonary PA infections Study dates December 2012 to January 2015 Source of funding Sponsored by Gilead Sciences who was involved in the study design, in the collection, analysis, and interpretation of the data	1, mean (SD): CAT 60.2 (18.3); tobi neb 64.2 (15.2); p=0.16 Azithromycin use at Day 1 and/or during comparative phase, yes, n (%): CAT 34 (81.0); tobi neb 36 (78.3); p=0.80 Inclusion criteria ≥6 years of age with documented evidence of PA lung infection, FEV1 25–75% predicted received ≥1 course of IV antibiotic treatment for a pulmonary exacerbation within the	of open-label TIS TIS was delivered using an LC Plus nebulizer (PARI Respiratory Equipment) and Pulmo-Aide compressor (DeVilbiss Healthcare) AZLI was delivered using the eFlow Nebulizer System (PARI) Placebo was lactose monohydrate and sodium chloride, reconstituted with the same diluent used for AZLI (0.17% w/v sodium chloride solution) A short acting bronchodilator	n or IV antibiotic use during the previous year. Allocation concealment Method not reported Blinding The blinded adjudication committee identified respiratory-related hospitalisations. No further details reported Data collection Secondary endpoints were collected after each course. The blinded adjudication committee identified respiratory-related hospitalizatio	p=0.16 Time to next pulmonary exacerbation Median (95% CI) time to first PDE: CAT 175.0 days (76.0, NE) tobi neb 140.0 days (90.0, NE) hazard ratio [95% CI]: 0.89 [0.50, 1.59] p = 0.71 Proxy outcome: number of patients that experienced pulmonary exacerbations requiring oral or IV AB CAT 21/42, tobi neb 26/46	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	previous 12 months stable regimen for any chronic use of azithromycin, bronchodilators, dornase alfa, hypertonic saline, and/or corticosteroid medications, or physiotherapy techniques/ regimen for ≥28 days before enrollment subjects receiving any antibiotic treatment, including AZLI or TIS, were eligible for screening, including	was administered before every AZLI/ placebo dose	ns. No further details reported. Data analysis Planned enrollment was 250 subjects; 125 subjects per arm would provide ≥85% power to declare superiority of alternating AZLI/TIS to placebo/TIS in the PDE rate, assuming an approximately 40% difference in exacerbation rate (2-sided, 0.05 level) Efficacy analyses included all randomized subjects (intention-to-treat), safety analyses	Eradication of the specified organism from sputum/airway cultures Adjusted mean changes from baseline sputum PA density after each course during the comparative treatment phase were small (0.36 to −0.55 log10 CFU/g). Differences between treatment groups were not statistically significant. Nutritional status Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	subjects receiving intermittent, continuous, or continuous alternating aerosolized antibiotic treatment, but subjects could not be receiving any antibiotics (except azithromycin) when starting the TIS run-in phase Exclusion criteria subjects who used b50% of expected vials during any course of antibiotics were discontinued from study treatment complete inclusion/exc		included treated subjects. A family alpha-spending rule controlled the Type 1 error rate of 0.05, with the primary endpoint analysis serving as the gatekeeper and secondary endpoints tested sequentially (α = 0.05) based on the closed testing procedure The primary endpoint (rate of PDEs) was analyzed by negative binomial regression with an offset	Quality of life Adjusted mean (SE) CFQ-R RSS scores averaged from Weeks 4, 12, and 20 from baseline: CAT +1.00 (1.74); tobi neb −2.06 (1.63); p = 0.21 Adverse events CAT vs. tobi neb cough 32/42 (76.2%) vs. 20/42 (71.7%) dyspnea 13/42 (31.0%) vs. 24/46 (52.2%) grade 2 or 4 severity 13/42 (31.0%) vs.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	lusion criteria are listed in the online supplement		parameter accounting for follow-up time (2-sided, 0.05 level) Average changes from baseline FEV1% predicted and CFQ-R RSS scores were analyzed using an MMRM method, with terms for baseline value, previous exacerbations (1, 2, ≥3), treatment, visit, and treatment-by-visit interaction	14/46 (30.4%) grade 1 or 2 severity 21/42 (50.0%) vs. 24/46 (52.2%) Emergence of resistant organisms/ antibiotic resistance Methicillin-resistant S. aureus (MRSA) present at ≥1 visit: tobi neb 18/45 (40.0%); CAT 11/42 (26.2%)	
Full citation Ahmed, Treatment for chronic Staphylococcus aureus chest infection in people with cystic	Sample size Characteristics	Interventions Intervention Any combinations	Details No trials were identified for	Results	Limitations Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
fibrosis. http://www.cochrane.org/CD011581/CF_treatment-chronic-staphylococcus-aureus-chest-infection-people-cystic-fibrosis, 2016 Ref Id 590834 Country/ies where the study was carried out Study type Cochrane systematic review Aim of the study To assess the evidence regarding the effectiveness of long-term antibiotic treatment regimens for chronic infection with methicillin-sensitive Staphylococcus aureus (MSSA) infection in people with cystic fibrosis and to determine whether this leads to improved clinical and microbiological outcomes. Study dates Date of the last search of the Group's Cystic Fibrosis Trials Register: 03 March 2016. Source of funding	Inclusion criteria Exclusion criteria	of topical, inhaled, oral or intravenous (IV) antimicrobials used with the objective of suppressive therapy for chronic infection with S. aureus Comparison Placebo No treatment.	inclusion in this review.		
Full citation Forest Laboratories UK. , A randomised, open label study to compare the efficacy and safety of a dry powder formulation of	Sample size See Tappenden 2013	Interventions See Tappenden 2013	Details See Tappenden 2013	Results See Tappenden 2013	Limitations See Tappenden 2013 Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
inhaled colistimethate sodium and nebulised TNSFI (tobramycin nebuliser solution for inhalation, TOBI®) in cystic fibrosis patients with Pseudomonas aeruginosa lung infection. Final protocol no: COLO/DPI/02/06. , 2011 Ref Id 590835 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Characteristics See Tappenden 2013 Inclusion criteria See Tappenden 2013 Exclusion criteria See Tappenden 2013				
Full citation Forest Laboratories UK. , Colistimethate sodium powder for inhalation for the treatment of Pseudomonas lung infection in cystic fibrosis – Forest submission to NICE. COLO/DPI/02/05. , 2011 Ref Id 590836 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Tappenden 2013 Characteristics See Tappenden 2013 Inclusion criteria See Tappenden 2013 Exclusion criteria	Interventions See Tappenden 2013	Details See Tappenden 2013	Results See Tappenden 2013	Limitations See Tappenden 2013 Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	See Tappenden 2013				

G.12 Immunomodulatory agents

Review question: What is the effectiveness of immunomodulatory agents in the management of lung disease, for example corticosteroids, azithromycin?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Auerbach, H. S., Williams, M., Kirkpatrick, J. A., Colten, H. R., Alternate-day prednisone reduces morbidity and improves pulmonary function in cystic fibrosis, Lancet, 2, 686-8, 1985 Ref Id 365436 Country/ies where the study was carried out USA Study type	Sample size See Cochrane SR Cheng 2015 Characteristics See Cochrane SR Cheng 2015 Inclusion criteria See Cochrane SR Cheng 2015 Exclusion criteria See Cochrane SR Cheng 2015	Interventions See Cochrane SR Cheng 2015	Details See Cochrane SR Cheng 2015	Results See Cochrane SR Cheng 2015	Limitations See Cochrane SR Cheng 2015 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT Aim of the study Study dates Source of funding					
Full citation Balfour-Lynn, I. M., Klein, N. J., Dinwiddie, R., Randomised controlled trial of inhaled corticosteroids (fluticasone propionate) in cystic fibrosis, Archives of Disease in Childhood, 77, 124-30, 1997 Ref Id 361047 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Balfour-Lynn 2012 Characteristics See Cochrane SR Balfour-Lynn 2012 Inclusion criteria See Cochrane SR Balfour-Lynn 2012 Exclusion criteria See Cochrane SR Balfour-Lynn 2012	Interventions See Cochrane SR Balfour-Lynn 2012	Details See Cochrane SR Balfour-Lynn 2012	Results See Cochrane SR Balfour-Lynn 2012	Limitations See Cochrane SR Balfour-Lynn 2012 Other information None.
Full citation Balfour-Lynn, I. M., Lees, B., Hall, P., Phillips, G., Khan, M., Flather, M., Elborn, J. S., Cf Wise Investigators,	Sample size See Cochrane SR Balfour-Lynn 2012 Characteristics See Cochrane SR Balfour-Lynn 2012	Interventions See Cochrane SR Balfour-Lynn 2012	Details See Cochrane SR Balfour-Lynn 2012	Results See Cochrane SR Balfour-Lynn 2012	Limitations See Cochrane SR Balfour-Lynn 2012 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Multicenter randomized controlled trial of withdrawal of inhaled corticosteroids in cystic fibrosis, American Journal of Respiratory & Critical Care Medicine, 173, 1356-62, 2006 Ref Id 330332 Country/ies where the study was carried out UK Study type RCT Aim of the study Study dates Source of funding	Inclusion criteria See Cochrane SR Balfour-Lynn 2012 Exclusion criteria See Cochrane SR Balfour-Lynn 2012				
Full citation Clement, A., Tamalet, A., Leroux, E., Ravilly, S., Fauroux, B., Jais, J. P., Long term effects of azithromycin in patients with cystic fibrosis: A double blind, placebo controlled trial,	Sample size See Cochrane SR Southern 2012 Characteristics See Cochrane SR Southern 2012 Inclusion criteria See Cochrane SR Southern 2012 Exclusion criteria	Interventions See Cochrane SR Southern 2012	Details See Cochrane SR Southern 2012	Results See Cochrane SR Southern 2012	Limitations See Cochrane SR Southern 2012 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Thorax, 61, 895-902, 2006 Ref Id 330590 Country/ies where the study was carried out France Study type RCT Aim of the study Study dates Source of funding	See Cochrane SR Southern 2012				
Full citation De Boeck, K., De Baets, F., Malfroot, A., Desager, K., Mouchet, F., Proesmans, M., Do inhaled corticosteroids impair long-term growth in prepubertal cystic fibrosis patients?, European Journal of Pediatrics, 166, 23-8, 2007 Ref Id 365519 Country/ies where the study was carried out Belgium Study type	Sample size See Cochrane SR Balfour-Lynn 2012 Characteristics See Cochrane SR Balfour-Lynn 2012 Inclusion criteria See Cochrane SR Balfour-Lynn 2012 Exclusion criteria See Cochrane SR Balfour-Lynn 2012	Interventions See Cochrane SR Balfour-Lynn 2012	Details See Cochrane SR Balfour-Lynn 2012	Results See Cochrane SR Balfour-Lynn 2012	Limitations See Cochrane SR Balfour-Lynn 2012 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT Aim of the study Study dates Source of funding					
Full citation Eigen, H., Rosenstein, B. J., FitzSimmons, S., Schidlow, D. V., A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis. Cystic Fibrosis Foundation Prednisone Trial Group, Journal of Pediatrics, 126, 515-23, 1995 Ref Id 365535 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Cheng 2015 Characteristics See Cochrane SR Cheng 2015 Inclusion criteria See Cochrane SR Cheng 2015 Exclusion criteria See Cochrane SR Cheng 2015	Interventions See Cochrane SR Cheng 2015	Details See Cochrane SR Cheng 2015	Results See Cochrane SR Cheng 2015	Limitations See Cochrane SR Cheng 2015 Other information None.
Full citation Equi,A., Balfour-Lynn,I.M., Bush,A., Rosenthal,M., Long term azithromycin in	Sample size See Cochrane SR Southern 2012 Characteristics	Interventions See Cochrane SR Southern 2012	Details See Cochrane SR Southern 2012	Results See Cochrane SR Southern 2012	Limitations See Cochrane SR Southern 2012 Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
children with cystic fibrosis: A randomised, placebo-controlled crossover trial, Lancet, 360, 978-984, 2002 Ref Id 310518 Country/ies where the study was carried out UK Study type RCT Aim of the study Study dates Source of funding	See Cochrane SR Southern 2012 Inclusion criteria See Cochrane SR Southern 2012 Exclusion criteria See Cochrane SR Southern 2012				Included in NMA only.
Full citation Greally, P., Hussain, M. J., Vergani, D., Price, J. F., Interleukin-1 alpha, soluble interleukin-2 receptor, and IgG concentrations in cystic fibrosis treated with prednisolone, Archives of Disease in Childhood, 71, 35-9, 1994 Ref Id 365566	Sample size See Cochrane SR Cheng 2015 Characteristics See Cochrane SR Cheng 2015 Inclusion criteria See Cochrane SR Cheng 2015 Exclusion criteria See Cochrane SR Cheng 2015	Interventions See Cochrane SR Cheng 2015	Details See Cochrane SR Cheng 2015	Results See Cochrane SR Cheng 2015	Limitations See Cochrane SR Cheng 2015 Other information See Cochrane SR Cheng 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Ireland Study type RCT Aim of the study Study dates Source of funding					
Full citation Konstan,M.W., Byard,P.J., Hoppel,C.L., Davis,P.B., Effect of high-dose ibuprofen in patients with cystic fibrosis, New England Journal of Medicine, 332, 848-854, 1995 Ref Id 233726 Country/ies where the study was carried out USA Study type RCT Aim of the study Study dates Source of funding	Sample size See Cochrane SR Lands 2016 Characteristics See Cochrane SR Lands 2016 Inclusion criteria See Cochrane SR Lands 2016 Exclusion criteria See Cochrane SR Lands 2016	Interventions See Cochrane SR Lands 2016	Details See Cochrane SR Lands 2016	Results See Cochrane SR Lands 2016	Limitations See Cochrane SR Lands 2016 Other information None.
Full citation	Sample size N: 224	Interventions GROUP 1: placebo	Details	Results	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Lai, H. C., FitzSimmons, S. C., Allen, D. B., Kosorok, M. R., Rosenstein, B. J., Campbell, P. W., Farrell, P. M., Risk of persistent growth impairment after alternate-day prednisone treatment in children with cystic fibrosis, New England Journal of Medicine, 342, 851-9, 2000 Ref Id 329828 Country/ies where the study was carried out USA Study type Retrospective cohort study Aim of the study To evaluate the long-term growth of children with cystic fibrosis who had participated in a multicenter clinical trial (Eigen 1995) of treatment with	Characteristics Age range: 6 to 14 years GROUP 1: placebo: N: 73, Gender split: M: 35/ F: 3 GROUP 2: 1 mg Prednisone/kg: N: 75, Gender split: M: 46/ F: 29 GROUP 3: 2 mg Prednisone/kg: N: 76, Gender split: M: 29/ F: 31 Inclusion criteria Children who participated in the prednisone trial (Eigen 1995) Exclusion criteria Not reported	GROUP 2: 1 mg Prednisone/kg GROUP 3: 2 mg Prednisone/kg	Retrospective cohort study (10 years follow up of a Double-blind multicentre RCT - Eigen 1995)	Absolute height at 18 Years of Age - mean (SD); cm Male GROUP 1: placebo - N:21, 174.6 (6.8) GROUP 2: 1 mg Prednisone/kg -N:34, 170.7(7.6) GROUP 3: 2 mg Prednisone/kg -N:31, 170.5(6.6) Female GROUP 1: placebo - N:23, 160.3(6.9) GROUP 2: 1 mg Prednisone/kg - N:23, 159.3 (4.9) GROUP 3: 2 mg Prednisone/kg - N:20, 159.8(6.7) Absolute weight at 18 Years of Age - mean (SD); kg Male GROUP 1: placebo - N:21, 63.7(9.3) GROUP 2: 1 mg Prednisone/kg - N:34, 59.1(7.9) GROUP 3: 2 mg Prednisone/kg - N:31, 57.0(9.4) Female GROUP 1: placebo - N:23, 51.9(7.2)	The quality assessment was conducted using the NOS scale for observational studies: Selection: unclear risk (the participants were selected from a previous RCT. Although it can be argued randomisation was kept, it is not possible to determine whether participants received other treatments after the original trial was finished) Comparability: low risk of bias (The study does control for important factors such as lung disease) Outcome: high risk of bias (loss to follow-up in > 20%) Other information The study showed that growth slowed down to such an extent that it reduced the final height of 4 cm in prepubertal males, but not in females. This was a retrospective cohort study (10 years follow up of a RCT). There is some likelihood for attrition bias. The Authors identifi ed children who participated in the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
steroids (alternate day treatment with oral prednisone) from 1986 through 1991. Study dates 2000 Source of funding Supported by a postdoctoral research fellowship from the Cystic Fibrosis Foundation (to Dr. Lai) and a grant from the National Institutes of Health (2R01 DK34108).				GROUP 2: 1 mg Prednisone/kg - N:23, 49.6(7.6) GROUP 3: 2 mg Prednisone/kg - N:20, 53.6(10.1) Growth throughout the 10-Year Study Period (height and weight Z scores - p-value only) Height male: P=0.03 ("the z scores for height remained significantly lower in the two prednisone groups than in the placebo group after 10 years of follow-up" - P854). female: P=0.26 ("The z scores for height in girls treated with prednisone [...] were no significantly lower than those of girls who received placebo p855) Weight male: P=0.04 ("z scores for weight in boys treated with high-dose prednisone were significantly lower than those in boys who received placebo P855) female: P=0.84("no significant differences among the three groups	prednisone trial (Eigen 1995) and obtained data on their growth from the U.S. Cystic Fibrosis Foundation Patient Registry in Bethesda. Of the 285 children enrolled, 42 were Canadian; data on these patients therefore were not reported to the U.S. registry. Of the remaining 243 children, 19 could not be correctly identified from the registry.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				were found with regard to z scores for weight for the period after prednisone therapy was discontinued P855)	
Full citation Lands,L.C., Milner,R., Cantin,A.M., Manson,D., Corey,M., High-Dose Ibuprofen in Cystic Fibrosis: Canadian Safety and Effectiveness Trial, Journal of Pediatrics, 151, 249-254, 2007 Ref Id 237873 Country/ies where the study was carried out Canada Study type RCT Aim of the study Study dates Source of funding	Sample size See Cochrane SR Lands 2016 Characteristics See Cochrane SR Lands 2016 Inclusion criteria Exclusion criteria	Interventions See Cochrane SR Lands 2016	Details See Cochrane SR Lands 2016	Results See Cochrane SR Lands 2016	Limitations See Cochrane SR Lands 2016 Other information None.
Full citation Robinson, P., Schechter, M. S., Sly, P. D., Winfield, K., Smith, J.,	Sample size N: 63 Mean age (SD): 16 (10.5) years	Interventions 500 mg oral clarithromycin twice daily for 5 months (with a 1-month	Details Double blind crossover RCT.	Results Robinson 2012 Lung function (FEV1)	Limitations The quality assessment was conducted using the Cochrane risk of bias tool.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Brennan, S., Shinkai, M., Henke, M. O., Rubin, B. K., Clarithromycin therapy for patients with Cystic Fibrosis: A randomized controlled trial, Pediatric Pulmonology, 47, 551-557, 2012 Ref Id 361614 Country/ies where the study was carried out Australia Study type RCT Aim of the study The objective of this study was to evaluate the effect of clarithromycin on pulmonary function in adults and children with CF. Study dates 2012 (date of online publication) Source of funding This study was funded by research grants to BKR from the United States Cystic Fibrosis Foundation, Abbott	Characteristics Mean age (SD): 16 (10.5) years Gender split: 40 M/ 23 F Inclusion criteria proven diagnosis of CF defined as clinical symptoms presence of two recognized CF gene mutations and/or a positive sweat test as evidenced by sweat chloride level above 60 mmol/L by pilocarpine iontophoresis Exclusion criteria Subjects were excluded if they had: FEV1 < 30% predicted at enrollment, Mycobacterium in a sputum culture, a respiratory exacerbation requiring IV antibiotics in the 60 days before entering the protocol, or had used any investigational drug or device in the 60 days before entering the protocol. any significant (>30 ml) hemoptysis in the preceding year, requirement for oxygen therapy, or the presence of	wash-out) VERSUS placebo		Short-term FEV1 % predicted clarithromycin VERSUS placebo: N: 29; Mean (SD): 0.9 (9.8) VERSUS N: 23; Mean (SD): 1.4 (8.4) Short-term exacerbations per patient clarithromycin VERSUS placebo: n/N: 54/29 VERSUS n/N: 44/23 Quality of life measures Not reported Nutritional status Not reported Time to next pulmonary exacerbation Not reported Adverse effects (abdominal pain) Not reported Mortality Not reported	Random sequence generation: unclear risk of bias (Randomization table was generated by the Wake Forest University General Clinical Research Center Pharmacy) Allocation concealment: unclear risk of bias (No details given) Blinding: low risk of bias (Reported as double blinded) Incomplete outcome data: unclear risk of bias (ITT analysis performed, but relatively high number of withdrawal -10 out of 62 dropped out) Selective reporting: unclear risk of bias (All listed outcomes reported, but reporting was confined to those considered to be most important and findings which were not statistically significant were not reported) Other bias: low risk of bias (None identified) Other information 10 subjects withdrew from the study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Laboratories, and the NIH (GCRC Grant to Wake Forest University).	any significant liver or renal disease Subjects allergic to or intolerant of macrolides, or who were taking medications that adversely interact with macrolide antibiotics (moxifloxacin, sildenafil, or pimozide) were not enrolled.				
Full citation Saiman, L., Anstead, M., Mayer-Hamblett, N., Lands, L. C., Kloster, M., Hocevar-Trnka, J., Goss, C. H., Rose, L. M., Burns, J. L., Marshall, B. C., Ratjen, F., A. Z. Azithromycin Study Group, Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa: a randomized controlled trial, JAMA, 303, 1707-15, 2010 Ref Id 331904	Sample size See Cochrane SR Southern 2012 Characteristics See Cochrane SR Southern 2012 Inclusion criteria See Cochrane SR Southern 2012 Exclusion criteria See Cochrane SR Southern 2012	Interventions See Cochrane SR Southern 2012	Details See Cochrane SR Southern 2012	Results See Cochrane SR Southern 2012	Limitations See Cochrane SR Southern 2012 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA Study type RCT Aim of the study Study dates Source of funding					
Full citation Saiman, L., Marshall, B. C., Mayer-Hamblett, N., Burns, J. L., Quittner, A. L., Cibene, D. A., Coquillette, S., Fieberg, A. Y., Accurso, F. J., Campbell, P. W., 3rd, Macrolide Study, Group, Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial, JAMA, 290, 1749-56, 2003 Ref Id 331908	Sample size See Cochrane SR Southern 2012 Characteristics See Cochrane SR Southern 2012 Inclusion criteria See Cochrane SR Southern 2012 Exclusion criteria See Cochrane SR Southern 2012	Interventions See Cochrane SR Southern 2012	Details See Cochrane SR Southern 2012	Results See Cochrane SR Southern 2012	Limitations See Cochrane SR Southern 2012 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA Study type RCT Aim of the study Study dates Source of funding					
Full citation Sordelli,D.O., Macri,C.N., Maillie,A.J., Cerquetti,M.C., A preliminary study on the effect of anti-inflammatory treatment in cystic fibrosis patients with Pseudomonas aeruginosa lung infection, International Journal of Immunopathology and Pharmacology, 7, 109-117, 1994 Ref Id 172282 Country/ies where the study was carried out Argentina Study type RCT	Sample size See Cochrane SR Lands 2016 Characteristics See Cochrane SR Lands 2016 Inclusion criteria See Cochrane SR Lands 2016 Exclusion criteria See Cochrane SR Lands 2016	Interventions See Cochrane SR Lands 2016	Details See Cochrane SR Lands 2016	Results See Cochrane SR Lands 2016	Limitations See Cochrane SR Lands 2016 Other information Included in NMA only.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Study dates Source of funding					
Full citation Southern,Kevin W., Barker,Pierre M., SolisMoya,Arturo, Patel,Latifa, Macrolide antibiotics for cystic fibrosis, Cochrane Database of Systematic Reviews, -, 2012 Ref Id 239262 Country/ies where the study was carried out Study type Cochrane SR Aim of the study The SR aims to assess the optimal type, dose and duration of macrolide therapy by 1) testing the hypothesis that, in people with CF, macrolide antibiotics improve clinical status compared to placebo or another	Sample size 5 randomised control trials (RCTs) SR were included from this Cochrane: Clement 2006 Equi 2002 Saiman 2003 Saiman 2010 Wolter 2002 Characteristics Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Clement 2006 N:82 young people with CF (40 in azithromycin group, 42 in placebo group. 35 in treatment group and 37 in placebo group completed trial) Age: 6-21 years, mean age 11.0 years, SD 3.3 years FEV1 >40% predicted Equi 2002 N: 41 children Age range: 8 - 18 years Saiman 2003	Interventions Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Clement 2006 Azithromycin 250 mg tablet 3 times per week (>40 kg, 500 mg) versus placebo. Equi 2002 Azithromycin, 250 mg (500 mg if weight > 40 kg) once a day for 6 months versus placebo Saiman 2003 Azithromycin, 500 mg (250 mg if weight <40 kg) 3 days a week versus placebo Saiman 2010 Azithromycin (250 mg 3 times a week, increased to 500, if weight >36 kg) versus placebo; for 6 months Wolter 2002	Details Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Clement 2006 Multicentre, double-blind, placebo-RCT Equi 2002 Randomised placebo controlled cross-over trial Saiman 2003 Multicentre placebo-RCT Saiman 2010 Multi-centre placebo-controlled parallel design Wolter 2002 Randomised placebo-controlled trial	Results Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Additional data extracted is marked with a * Equi 2002 Lung function (% predicted FEV1 at 2 – 4 - 6 months) at 2 monthsN: 20; Mean (SD): 4.05 (7.45) VERSUS N: 21; Mean (SD): 0.76 (15.43) at 6 monthsN: 20; Mean (SD): 4.85 (9.71) VERSUS N: 21; Mean (SD): 2.35 (13.58) Quality of life measures Not reported Nutritional status Not reported Time to next pulmonary exacerbation (Free of pulmonary exacerbation) Hazard ratio azithromycin v placebo: not reported Adverse effects	Limitations Quality of the SR AMSTAR score: 10/11 Quality of the individual primary studies The risk of bias assessment has been taken from the SR. Clement 2006 Random sequence generation: low risk of bias ("Centralised secure randomisation department") Allocation concealment: low risk of bias (Centralised, study number assigned by interactive voice response system, study kits distributed by chief pharmacist in each centre) Blinding: low risk of bias (Identically packaged, all participants and investigators blinded) Incomplete outcome data: low risk of bias (A complete ITT analysis undertaken on primary outcome and pulmonary

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
antibiotic and 2) do not have unacceptable adverse effects. Study dates Searches up to 29 February 2012. Source of funding Not reported	N: 185 participants: Age, mean (SD) - years*: 20.2(7.9) in the Azithromycin group (n:87); 20.6(8.6) in the Placebo group (n:98) Eligibility: adults and children with CF (> 6 years) with chronic P. aeruginosa chest infection (> 1 year) and an FEV1 >30% predicted. Saiman 2010 N*: 263 Age, mean (SD) - years*: 10.7(3.25) in the Azithromycin group (n:131); 10.6(3.10) in the Placebo group (n:129) Eligibility: Young CF patients (6-18 years) without chronic P. aeruginosa airway infection (clear (2 or more cultures) for > 12 months) Wolter 2002 N:60 adult participants. Mean age 27.9 (SD, 6.5). The placebo group contained more men (20/30 versus 9/30), was taller, heavier and had better lung function (FEV1 mean (SD), 62.3 (24.8) versus 50.9 (18.)	Azithromycin, 250 mg once a day for 3 months versus placebo		Not reported Mortality Not reported Clement 2006 Lung function (% predicted FEV1 at 2 – 4 - 6 – 8 -10 -12 months) at 2 months N: 40; Mean (SD): 0.8 (16.6) VERSUS N: 42; Mean (SD): -1.3 (14.3) at 6 months N: 40; Mean (SD): 2.8 (18.3) VERSUS N: 42; Mean (SD): -3 (17.6) at 12 months N: 40; Mean (SD): -4.3 (17.9) VERSUS N: 42; Mean (SD): -1.5 (15.4) Quality of life measures actual data in each group were not reported Nutritional status (change in BMI z score at 12 months follow-up) N: 40; Mean (SD): 0.03 (0.40) VERSUS N: 42; Mean (SD): -0.12(0.44) Time to next pulmonary exacerbation (Free of pulmonary exacerbation at 6 and 12 months) Hazard ratio azithromycin v placebo 0.37 (95% CI 0.22 - 0.63).	exacerbation data. Some per protocol analysis on other outcomes) Selective reporting: unclear risk of bias (Some data at intermediate time points not reported -requested from authors, who kindly provided some IPD, although intermediate time points not available) Other bias: low risk of bias (None identified) Equi 2002 Random sequence generation: low risk of bias (Provided by Statistics Dept. at Pfizer, USA) Allocation concealment: low risk of bias (Hospital Pharmacy department, described in detail) Blinding: low risk of bias (All parties involved, identical packaging for intervention and placebo) Incomplete outcome data: low risk of bias (Complete ITT analysis undertaken on primary outcome. Not clear from paper whether primary outcome was a post hoc protocol change, but subsequent

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria Exclusion criteria			Adverse effects Not reported Mortality Not reported Saiman 2003 Lung function (% predicted FEV1 at 1 – 3 - 6 months) at 1 months N: 87; Mean (SD): 4.01 (13.03) VERSUS N: 97; Mean (SD): 0.2 (9.1) at 3 months N: 87; Mean (SD): 2.33 (12.47) VERSUS N: 95; Mean (SD): 0.32 (11.99) at 6 months N: 84; Mean (SD): 4.44 (13.6) VERSUS N: 93; Mean (SD): -1.77 (10.66) Quality of life measures (Change in total quality of life score - CFQ-R)* physical factor N: 85; Mean (SD): 0.8 (9.9) VERSUS N: 92; Mean (SD): -1.9 (8.8) psychological factor N: 85; Mean (SD): 1.6 (12.1) VERSUS N: 92; Mean (SD): 1.2 (10.9) body image factor N: 85; Mean (SD): 3.1 (14.5) VERSUS N: 92; Mean (SD): 1.7 (14.8)	correspondence has confirmed that this was determined a priori) Selective reporting: low risk of bias (Not clear if primary outcome calculation (months 4 and 6 averaged for relative change) was an a priori decision) Other bias: low risk of bias (Adequate washout, authors have provided IPD) Saiman 2003 Random sequence generation: low risk of bias (By CF TDN Co-ordinating Centre. Randomisation included a valid allocation strategy to ensure equivalence between placebo and intervention with respect to weight, respiratory function and site of study) Allocation concealment: low risk of bias (Centralised secure randomisation system at the co-ordinating centre) Blinding: low risk of bias (All study personnel and participants) Incomplete outcome data: low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Total N: 85; Mean (SD): 1.7 (7.5) VERSUS N: 92; Mean (SD): -0.1 (7.5) Nutritional (change in weight) Mean difference (SE): 0.7 (0.33) Time to next pulmonary exacerbation (Free of pulmonary exacerbation) Hazard ratio azithromycin v placebo 0.65 (95% CI 0.44 - 0.0.95) Adverse effects Not reported Mortality Not reported Saiman 2010 Lung function (% predicted FEV1 at 6 months) N: 125; Mean (SD): 5.4 (13.3) VERSUS N: 124; Mean (SD): 3.4 (12.4) Quality of life measures Not reported Nutritional status (change in weight, height, BMI)* actual data in each group were not reported Time to next pulmonary exacerbation (Free of pulmonary exacerbation)* Hazard ratio azithromycin v placebo 0.50 (95% CI 0.31- 0.79).	(Clear ITT analysis of primary outcome) Selective reporting: low risk of bias (Outcomes clearly reported. Subsequent subgroup analysis published separately) Other bias: low risk of bias (None identified) Saiman 2010 Random sequence generation: low risk of bias (University of South Florida generated assignments via secure centralized randomisation system) Allocation concealment: low risk of bias (Data co-ordinating centre distributed blinded study drug kits) Blinding: low risk of bias (Identically packaged tablets) Incomplete outcome data: low risk of bias (Modified ITT analysis (3 patients in placebo arm did not receive study drug and were removed) of primary outcome and most others) Selective reporting: low risk of bias (All outcomes reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Adverse effects Not reported Mortality Not reported Wolter 2002 Lung function (% predicted FEV1 at 3 months) N: 22; Mean (SD): 2.95 (9.22) VERSUS N: 21; Mean (SD): -0.91(5.99) Quality of life measures (CRDQ) Not reported (Chronic Respiratory Disease Questionnaire, which is not validated in CF) Nutritional status Not reported Time to next pulmonary exacerbation Not reported Adverse effects Not reported Mortality Not reported	Other bias: low risk of bias (Very clearly reported study) Wolter 2002 Random sequence generation: unclear risk of bias (Hospital pharmacy staff, exact method not stated - "randomised prior to commencement of study"). Allocation concealment: low risk of bias (By hospital pharmacy) Blinding: low risk of bias (Identical capsules and number, all parties blind) Incomplete outcome data: low risk of bias (ITT analysis performed on primary outcome, others reported per protocol) Selective reporting: low risk of bias (All outcomes reported) Other bias: unclear risk of bias (Baseline characteristics significantly different between interventions, see above "Participants") Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Wolter, J., Seeney, S., Bell, S., Bowler, S., Masel, P., McCormack, J., Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial, Thorax, 57, 212-6, 2002 Ref Id 332316 Country/ies where the study was carried out Australia Study type RCT Aim of the study Study dates Source of funding	Sample size See Cochrane SR Southern 2012 Characteristics See Cochrane SR Southern 2012 Inclusion criteria See Cochrane SR Southern 2012 Exclusion criteria See Cochrane SR Southern 2012	Interventions See Cochrane SR Southern 2012	Details See Cochrane SR Southern 2012	Results See Cochrane SR Southern 2012	Limitations See Cochrane SR Southern 2012 Other information Included in NMA only.
Full citation BalfourLynn, Ian M., Welch, Karen, Inhaled corticosteroids for cystic fibrosis, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, 2016	Sample size 2 randomised control trials (RCTs) SR were included from this Cochrane: Balfour-Lynn 1997 (referred to as the UK trial in the Cochrane SR) Balfour-Lynn 2006 (referred to as the CF WISE 2006 trial in the Cochrane SR)	Interventions Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Balfour-Lynn 1997 Fluticasone propionate 500 mcg	Details Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Balfour-Lynn 1997 Randomised, double-blind, placebo-	Results Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. Additional data extracted is marked with a * Balfour-Lynn 1997 See NMA data extraction	Limitations Quality of the SR AMSTAR score: 10/11 Quality of the individual primary studies The risk of bias assessment has been taken from the SR. Balfour-Lynn 1997

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 537371 Country/ies where the study was carried out Study type Cochrane SR Aim of the study The SR aims to assess the effectiveness of regular use of inhaled corticosteroids (ICS) when compared to not receiving ICS, in the management of people with CF. in terms of: 1) lung function (including tests of lung function, bronchial hyperreactivity, exercise tolerance); 2) need for hospital admission or antibiotic treatment for respiratory exacerbations; 3) well-being of people with CF (in relation to nutritional status and quality of life); 4) survival rate;	Boeck 2007 (referred to a Belgian trial 2007 in the Cochrane SR) Characteristics Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Additional data extracted is marked with a * Balfour-Lynn 1997 36 participants, aged 16 years to 41 years, with established CF pulmonary disease Balfour-Lynn 2006 N: 171 (86 male) Participants aged over 6 years, diagnosed with CF and attending 18 paediatric and adult UK CF centers. Age range 6 - 53 years. Mean age 14 years in fluticasone group and 15.8 years in placebo group. Eligibility - age over 6 years, FEV1 ≥40% predicted. Participants excluded if had used oral corticosteroids within the previous 3 months or very high dose of ICS.	twice daily via a metered dose inhaler and spacer or matching placebo given for 2 years Balfour-Lynn 2006 Fluticasone propionate given at equivalent dose to ICS participant taking before trial entry or placebo via a volumatic spacer. de Boeck 2007 Fluticasone 500 mcg dry powder inhaler twice daily or lactose placebo dispensed in identical canister.	controlled, parallel trial. Balfour-Lynn 2006 Randomised, double-blind, placebo-controlled withdrawal trial of 8 months duration. de Boeck 2007 Randomised, double-blind, muticentre trial	Balfour-Lynn 2006 Lung function (%predicted FEV1 at 6 months) N: 84; Mean (SD): 76 (19) VERSUS N: 87; Mean (SD): 73 (18) Quality of life measures Not reported Nutritional status Not reported Time to next pulmonary exacerbation Inhaled corticosteroid VERSUS placebo - at 1 monthsn/N: 69/84 VERSUS n/N: 77/87 Inhaled corticosteroid VERSUS placebo - at 3 monthsn/N: 48/84 VERSUS n/N: 47/87 Inhaled corticosteroid VERSUS placebo - at 6 monthsn/N: 36/84 VERSUS n/N: 38/87 Adverse effects (changes in growth velocity - change in height (cm) at 8 months) N: 42; Mean (SD): 41 (2.2) VERSUS N: 38; Mean (SD): 35 (2.6) Mortality Not reported de Boeck 2007 Lung function	Random sequence generation (selection bias): Unclear risk (Described as randomised, but no further details given) Allocation concealment (selection bias) Unclear risk (Not reported) Blinding (performance bias and detection bias) - All outcomes: Low risk (Described as double-blind) Incomplete outcome data (attrition bias) - All outcomes: Low risk (More than 15% of participants were excluded, but reasons given and numbers equal across groups. At 24 months data on FEV1 were only available on 8 participants in the fluticasone group and 9 in the placebo group) Selective reporting (reporting bias) - Low risk (All outcomes reported) Balfour-Lynn 2006 Random sequence generation: low risk of bias (Randomisation by permuted blocks of 4) Allocation concealment: low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and 5) harmful effects. Study dates Searches up to 03 September 2012. Source of funding Not Reported	de Boeck 2007 N: 29 Mean age: 8.2 years in the fluticasone group; 9.0 years in the placebo group* Eligibility: pre-pubertal children (20 from 1 centre and 9 from another centre) who were clinically stable (defined as at least 2 months after any hospital admission and 2 weeks after a respiratory exacerbation) with FEV1at least 60% predicted. Excluded if had intake of oral or inhaled steroids for more than 2 weeks within past 6 months or any intake of these drugs including intranasal steroids within last 4 weeks or a clinical diagnosis of aspergillosis or participating in another clinical trial Inclusion criteria See characteristics of included studies. Exclusion criteria See characteristics of included studies.			a) % predicted FEV1 at 6 months- N: 12; Mean (SD): 95 (13.84) VERSUS N: 15; Mean (SD): 91 (15.48) b) % predicted FEV1 at 6 months- N: 12; Mean (SD): 95 (13.84) VERSUS N: 15; Mean (SD): 97 (11.61) c) % predicted FEV1 at 12 months- N: 12; Mean (SD): 90 (20.76) VERSUS N: 15; Mean (SD): 88 (15.48) d) % predicted FEV1 at 12 months- N: 12; Mean (SD): 91 (17.3) VERSUS N: 15; Mean (SD): 92 (11.61) Quality of life measures Not reported Nutritional status Not reported Time to next pulmonary exacerbation Not reported Adverse effects (changes in growth velocity - change in height (cm) at 12 months) N: 12; Mean (SD): 3.96 (0.69) VERSUS N: 15; Mean (SD): 5.49 (1.47) Mortality Not reported	(Randomisation was carried out independently at the Clinical Trials & Evaluation Unit of Royal Brompton Hospital and allocation of individuals was carried out over the telephone to the trial centres) Blinding: low risk of bias (All trial personnel and participants were blinded to treatment -placebo). Incomplete outcome data: low risk of bias (Intention-to-treat analysis was based on all participants) Selective reporting: low risk of bias (All stated outcomes reported) Other bias: low risk of bias (No other potential source of bias identified) de Boeck 2007 Random sequence generation: low risk of bias (Stated that used random number sequence) Allocation concealment: unclear risk of bias (Not mentioned in text) Blinding: low risk of bias (Described as double-blind, but no details of who exactly was blinded.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Placebo dispensed in identical canister, so probably participant and clinician blinded) Incomplete outcome data: low risk of bias (Less than 15% of participants were excluded. Of the 20 initially included participants, 2 were excluded -1 discontinued treatment after 3 months and 1 did not keep follow-up appointments) Selective reporting: low risk of bias (All outcomes reported) Other bias: low risk of bias (No other potential source of bias identified) Other information Balfour-Lynn 2006 This study is a "withdrawal trial" in which participants who were already taking inhaled fluticasone were randomised to continue fluticasone or start placebo
Full citation Cheng, K., Ashby, D., Smyth, R. L., Oral steroids for long-term use in	Sample size 3 randomised control trials (RCTs) SR were included from this Cochrane: Auberch 1985	Interventions Where possible data were extracted from the Cochrane SR. The full text of the	Details Where possible data were extracted from the Cochrane SR. The full text of the	Results Where possible data were extracted from the Cochrane SR. The full text of the primary study	Limitations Quality of the SR AMSTAR score: 11/11 Quality of the individual primary studies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
cystic fibrosis, Cochrane Database of Systematic Reviews, 12, CD000407, 2015 Ref Id 424435 Country/ies where the study was carried out Study type Cochrane SR Aim of the study This review aims to determine whether there is clear evidence that one anti-inflammatory treatment, oral corticosteroids, is beneficial in the treatment of lung disease in people with CF by assessing the following hypotheses for long-term anti-inflammatory use: reduce the number of days of intravenous antibiotics for respiratory exacerbations; reduce the need for hospital admission	Eigen 1995 Greally 1994 Characteristics Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Auberch 1985 N:45 (participants recruited) Age range: 1 - 12 years. Eligibility: CF diagnosed on clinical features and raised sweat electrolytes. Mild to moderate pulmonary disease. 24 assigned to placebo group and 21 to prednisone group. 11 participants did not complete study (7 placebo, 4 prednisone) - 2 moved cities, 5 excluded for non-compliance and steroids prescribed to 4 for clinical indications. Eigen 1995 N: 285 (participants recruited) Age range 6 - 14 years Eligibility: CF diagnosed on clinical features and 2 raised sweat chloride (or sweat sodium) values; clinical stability	primary study was checked for accuracy and completeness. Additional data extracted is marked with a * Auberch 1985 Prednisone 2 mg/kg (maximum 60 mg) on alternate days placebo Eigen 1995 Prednisone 2 mg/kg or prednisone 1 mg/kg on alternate days (maximum dose 60 mg) Placebo Participants who missed 30% or more of total prescribed study medication were labelled as non-compliant but still included in analysis. Greally 1994 Soluble prednisolone 2 mg/kg/ daily for 14 days and then 1 mg/kg/ day on alternate days for 10 weeks (maximum dose 40 mg) Identical inert placebo tablets	primary study was checked for accuracy and completeness. Auberch 1985 Double-blinded RCT Eigen 1995 Double-blinded multicentre (15 centres) RCT Greally 1994 Randomised. Double-blinded.	was checked for accuracy and completeness. Eigen 1995 Lung function (FEV1) actual data in each group were not reported Quality of life measures Not reported Nutritional status (weight) Not reported Time to next pulmonary exacerbation Not reported Adverse effects (a-cataracts; b-diabetes; c-grow retardation) a-cataracts Oral corticosteroids (1 mg prednisone) VERSUS placebon/N: 3/95 VERSUS n/N: 7/95 Oral corticosteroids (2 mg prednisone) VERSUS placebon/N: 11/95 VERSUS n/N: 7/95 b-diabetes Oral corticosteroids (1 mg prednisone) VERSUS placebon/N: 3/95 VERSUS n/N: 1/95 Oral corticosteroids (2 mg prednisone) VERSUS placebon/N: 6/95 VERSUS n/N: 1/95 c- grow retardation	The risk of bias assessment has been taken from the SR. Auberch 1985 Random sequence generation: unclear risk of bias (Described as randomised, but method not stated) Allocation concealment: unclear risk of bias (Unclear) Blinding: unclear risk of bias (Described as double-blind, but this might not have been possible since at the doses used, it would have been obvious which participants were in the treatment group) Incomplete outcome data: low risk of bias (11 participants did not complete study:7 placebo, 4 prednisone;- 2 moved cities, 5 excluded for non-compliance and steroids prescribed to 4 for clinical indications) Eigen 1995 Random sequence generation: low risk of bias (Randomised within each centre by computer-generated random

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
for respiratory exacerbations; improve or prevent the decline in objective tests of lung function (forced expiratory volume in one second (FEV1); forced vital capacity (FVC); and forced expiratory flow 25-75% (FEF25-75)); improve exercise tolerance; improve nutritional status; are associated with adverse effects including changes in appearance including Cushingoid appearance, growth suppression, diabetes mellitus, cataracts, osteoporosis and opportunistic infection; improve quality of life; improve survival. Study dates Searches up to 15 May 2013. Source of funding	without hospitalisation for CF-related problems within 2 months of entry; serum IgG within 2 standard deviations of normal for centre or hypogammaglobulinaemia; reliable performance of lung function tests for at least 6 months prior to enrolling in trial; FEV1 > 60% predicted and FEV1/FVC ratio > 60% predicted. Exclusion criteria included previous treatment with oral, inhaled or nasal corticosteroids for more than 2 weeks within 6 months of entry or any form of corticosteroids in previous month, evidence of liver disease, treatment with non-steroidal anti-inflammatory treatment Greally 1994 N: 45 (participants recruited) -24 assigned to placebo group and 21 to prednisone group. Age range: 1 - 12 years. Eligibility: CF diagnosed on clinical features and raised sweat electrolytes. Mild to moderate pulmonary disease. Inclusion criteria			Oral corticosteroids (1 mg prednisone) VERSUS placebon/N: 24/95 VERSUS n/N: 11/95 Oral corticosteroids (2 mg prednisone) VERSUS placebon/N: 31/95 VERSUS n/N: 11/95 Mortality Not reported Auberch 1985 Lung function (%predicted FEV1 at 4 years)* N: 21; Mean (SD): 103 (not reported) VERSUS N: 24; Mean (SD): 83 (not reported) Quality of life measures Not reported Nutritional status (height and weight)* actual data in each group were not reported Time to next pulmonary exacerbation Not reported Adverse effects Not reported Mortality (6 months follow up) n/N: 0/21 VERSUS n/N: 1/24 Greally 1994	number sequence in blocks of 6) Allocation concealment: unclear risk of bias (Unclear) Blinding: unclear risk of bias (Described as double-blind and same number of tablets given for each regimen, but true blinding might not have been possible since at the doses used, it would have been obvious from treatment effects which participants were in the treatment group) Incomplete outcome data: unclear risk of bias (Participants who missed 30% or more of total prescribed study medication were labelled as non-compliant but still included in analysis) Greally 1994 Random sequence generation: Unclear risk (Described as randomised, but method not stated) Allocation concealment: Unclear risk (Unclear) Blinding (performance bias and detection bias): All outcomes - Unclear risk (Described as

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
NHS North West Region R & D Programme, UK.	See characteristics of included studies. Exclusion criteria See characteristics of included studies.			Lung function (%predicted FEV1) (UP TO 2 WEEKS)N: 12; Mean (SD): 7.7 (7.97) VERSUS N: 12; Mean (SD): -1 (7.97) (UP TO 12 WEEKS)N: 12; Mean (SD): 6.3 (9.56) VERSUS N: 12; Mean (SD): -1.8 (9.56) Quality of life measures Not reported Nutritional status (absolute change in weight –kg) N: 13; Mean (SD): 0.35 (4.27) VERSUS N: 12; Mean (SD): 0.01 (2.31) Time to next pulmonary exacerbation Not reported Adverse effects Not reported Mortality Not reported	double-blind and placebo and prednisolone tablets were identical, but true blinding might not have been possible since at the doses used, it would have been obvious which participants were in the treatment group) Incomplete outcome data (attrition bias): All outcomes - Low risk (No withdrawals) Other information Greally 1994 11 participants did not complete study (7 placebo, 4 prednisone) - 2 moved cities, 5 excluded for non-compliance and steroids prescribed to 4 for clinical indications.
Full citation Lands, L. C., Stanojevic, S., Oral non-steroidal anti-inflammatory drug therapy for lung disease in cystic fibrosis, Cochrane Database of Systematic	Sample size 4 randomised control trials (RCTs) SR were included from this Cochrane: Konstan 1991 Konstan 1995 Lands 2007 Sordelli 1994 Characteristics	Interventions Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Konstan 1991	Details Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Konstan 1991	Results Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Additional data extracted is marked with a * Konstan 1991	Limitations Quality of the SR AMSTAR score: 11/11 Quality of the individual primary studies The risk of bias assessment has been taken from the SR. Konstan 1991

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Reviews, 4, CD001505, 2016 Ref Id 469625 Country/ies where the study was carried out Study type Cochrane SR Aim of the study The SR aims to determine the effectiveness of treatment with non-steroidal anti-inflammatory drugs (NSAIDs) in preventing pulmonary deterioration and maintaining an optimal level of pulmonary function among those with CF. Study dates Searches up to 15 May 2013. Source of funding Internal sources (Institute of Child Health, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK	Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Konstan 1991 N: 19 children with CF Age range: 6-12 years. Eligibility: diagnosed clinically and by sweat test, aged 6-12 years. Eligible if FEV1 > 30% predicted for age, height and gender; judged to be clinically stable; no history of adverse effects with aspirin, ibuprofen or other NSAID; not taking 'interfering medication' (not defined). 13 (7 male) in treatment group and 6 (3 male) in placebo group. 1 female in placebo group dropped out on day 1 because of difficulty with venous access. Konstan 1995 N: 85 people with CF Age range: 5-39 years. Eligibility: people with CF, diagnosed clinically and by sweat test, not treated with intravenous antibiotics in preceding 2 months and with FEV1 at least 60%	3-month dose escalation study. Participants received 300 mg of drug orally and twice daily during the first month, and, depending on pharmacokinetic studies, 400 mg in the second month, and 600 mg in the third month. Control - placebo. Konstan 1995 Participants randomly assigned to receive high-dose oral ibuprofen twice daily for 4 years or placebo twice daily for 4 years. Dose 20-30 mg per kg of body weight, to a maximum of 1600 mg, determined by pharmacokinetic analyses. Lands 2007 All participants underwent a baseline pharmoacokinetic study (baseline every hour for 3 hours), employing 200 mg tablets (Upjohn-Pharmacia) at a	Double-blinded RCT, 3-month dose escalation study in children with CF. Konstan 1995 Double-blinded RCT Lands 2007 Multicentre double-blind RCT Sordelli 1994 RCT (no blinded)	Lung function (FEV1) actual data in each group were not reported Quality of life measures Not reported Nutritional status (absolute change in weight) Not reported Time to next pulmonary exacerbation Not reported Adverse effects (abdominal pain decrease)* n/N: 8/13 VERSUS n/N: 4/6 Mortality Not reported Konstan 1995 Lung function (% predicted FEV1) all ages N: 41; Mean (SD): -2.17 (3.65) VERSUS N: 43; Mean (SD): -3.6 (3.61) Under 13 years at randomisation N: 24; Mean (SD): -1.49 (3.77) VERSUS N: 25; Mean (SD): -4.2 (3.75) 13 years or over at randomisation N: 17; Mean (SD): -3.13 (3.22) VERSUS N: 18; Mean (SD): -2.77 (3.22)	Random sequence generation: low risk of bias (Adequate, randomisation was based upon a computer-generated randomisation sequence) Allocation concealment: low risk of bias (Adequate, the randomisation sequence was provided by the pharmaceutical company -Upjohn) Blinding: low risk of bias (Described as double blinded. The pharmaceutical company provided the clinics with identical-appearing placebo tablets) Incomplete outcome data: low risk of bias (Less than 15% of participants excluded (three participants) due to poor venous access, behavioural problems and difficulty in transport to follow up trial visits) Selective reporting: high risk of bias (Outcomes listed were reported, but the trial investigators monitored a large number of potential adverse effects of ibuprofen: reporting was confined to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
External sources (Tenovus, Scotland, UK)	predicted. 42 (26 male) were in the treatment group and 43 (15 male) in placebo group; age range 5-39 years. Exclusion criteria: systemic or inhaled corticosteroids used within two years of recruitment or inhaled sodium cromoglycate used within 6 months of recruitment. Lands 2007 N:142 children with CF Age range: 6-18 years. Eligibility: Inclusion criteria: FEV1 >60% predicted at time of entry into the trial, with no hospitalizations in the previous 2 months. Exclusion criteria: people who had taken systemic corticosteroids or non-steroidal anti-inflammatory agents for more than 1 month in the past year, had abnormal hepatic, renal, hematoologic disorders or coagulopathy, documented evidence of peptic ulcer disease(endoscopy) or allergic bronchopulmonary aspergillosis, or a history of hypersensitivity reactions to non-steroidal anti-inflammatory agents.	dose of 20 to 30 mg/kg to a maximum of 1600 mg. The number of assigned pills were then adjusted by the coordinating pharmacologist to provide a peak plasma concentration of 50 to 100 microg/ml for each participant in the study. Participants then were asked to take the prescribed number of pills (ibuprofen or placebo) twice daily Sordelli 1994 Participants were randomized to active treatment with piroxicam and 21 (11 male) to treatment with placebo. Piroxicam and placebo were taken by the participants in a single morning dose. Treatment was suspended during periods of hospitalization and reinstated after discharge.		Quality of life measures Not reported Nutritional status as (annual rate of change in % ideal body weight overall and by age) all ages N: 41; Mean (SD): 0.05 (1.97) VERSUS N: 43; Mean (SD): 0.94 (1.86) Under 13 years at randomisation N: 24; Mean (SD): -0.05 (2.01) VERSUS N: 25; Mean (SD): -1.5(2) 13 years or over at randomisation N: 17; Mean (SD): 0.19 (1.44) VERSUS N: 18; Mean (SD): -0.15 (1.44) Time to next pulmonary exacerbation Not reported Adverse effects (a- Increase in abdominal pain; b- Decrease in abdominal pain) a- Increase in abdominal pain n/N: 5/41 VERSUS n/N: 7/43 b- Decrease in abdominal pain N/N: 1/70 VERSUS n/N: 4/72 Mortality Not reported Lands 2007	those considered to be most important and findings which were not statistically significant were not reported) Other bias: unclear risk of bias (Reported adverse events) Konstan 1995 Random sequence generation: low risk of bias (Adequate, randomisation was carried out with permuted blocks of four participants each stratified by age (under 13 years, 13 to 18 years and 19 years or over) Allocation concealment: low risk of bias (Adequate, paper states that only the pharmacologist and pharmacist were privy to the allocation) Blinding: low risk of bias (Described as double blinded. The placebo tablets were identical in appearance to the ibuprofen tablets) Incomplete outcome data: low risk of bias (Analysis was based on intention-to-treat. A total of 28 participants withdrew from study, with

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Sordelli 1994 N: 41 people with CF Age range: 5 - 37 years Eligibility: people with CF, diagnosed by sweat test and clinically, and regularly attending the CF clinic at the Children's Hospital in Buenos Aires. Inclusion criteria See characteristics of included studies. Exclusion criteria See characteristics of included studies.	Participants for whom treatment was suspended for more than 30 days were removed from the trial		Lung function (FEV1) all ages N: 70; Mean (SD): -1.49 (4.77) VERSUS N: 72; Mean (SD): -2.69 (4.84) Under 13 years at randomisation N: 45; Mean (SD): -2.02 (4.63) VERSUS N: 53; Mean (SD): -2.44 (4.66) 13 years or over at randomisation N: 25; Mean (SD): -0.39 (5.05) VERSUS N: 19; Mean (SD): -3.59 (5.49) Quality of life measures Not reported Nutritional status (body mass index) Not reported Time to next pulmonary exacerbation Not reported Adverse effects (Increase in abdominal pain) n/N: 1/70 VERSUS n/N: 4/72 Mortality Not reported Sordelli 1994 Lung function (FEV1) See NMA data extraction Quality of life measures Not reported Nutritional status	similar numbers in both groups (15 in treatment group, 13 in placebo group). Selective reporting: high risk of bias (Outcomes listed were reported, but the trial investigators monitored a large number of potential adverse effects of ibuprofen: reporting was confined to those considered to be most important and findings which were not statistically significant were not reported) Other bias: unclear risk of bias (Intention-to-treat and completed treatment analysis are presented, intention-to-treat analysis was only used in the meta-analysis. Reported adverse events. Funded by the Cystic Fibrosis Foundation and the National Institutes of Health) Lands 2007 Random sequence generation: low risk of bias (Adequate, participants were allocated using a predefined block-randomisation schedule)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Not reported Time to next pulmonary exacerbation Not reported Adverse effects Not reported Mortality Not reported	Allocation concealment: low risk of bias (Adequate, a central pharmacy coded and shipped the tablets to the participating centers; the code was broken by the central pharmacy only on request from the Safety and Monitoring Committee) Blinding: low risk of bias (Described as double blinded. Paper states that participants, care-givers and study personnel were all blinded to treatment assignment) Incomplete outcome data: low risk of bias (Analysis was based on intention-to-treat. 18 participants -9 in each group- did not complete full 2 years of follow up, 11 due to adverse events -4 in treatment group, 7 in placebo group; details of these events in paper. Selective reporting: low risk of bias (Outcomes listed were reported) Other bias: unclear risk of bias (Reported adverse events. Funders did not have a role in the analysis or publication of results)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Sordelli 1994 Random sequence generation: unclear risk of bias (Authors confirmed randomised, but no details available regarding method yet) Allocation concealment: unclear risk of bias (No details given) Blinding: high risk of bias (Authors confirmed not blinded) Incomplete outcome data: unclear risk of bias (Insufficient information available to make judgement) Selective reporting: unclear risk of bias (Insufficient information available to make judgement) Other bias: unclear risk of bias (Insufficient information available to make judgement) Other information Konstan 1995 A total of 28 participants withdrew from study, with similar numbers in both groups (15 in treatment group, 13 in placebo group). Lands 2007

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					18 participants (9 in each group) did not complete full 2 years of follow up, 11 due to adverse events (4 in treatment group, 7 in placebo group).

G.13 Nurtitional interventions

Review question: What is the clinical and cost effectiveness of nutritional interventions in people with cystic fibrosis?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Powers, S. W., Stark, L. J., Chamberlin, L. A., Filigno, S. S., Sullivan, S. M., Lemanek, K. L., Butcher, J. L., Driscoll, K. A., Daines, C. L., Brody, A. S., Schindler, T., Konstan, M. W., McCoy, K. S., Nasr, S. Z., Castile, R. G., Acton, J. D., Wooldridge, J. L., Ksenich, R. A., Szczesniak,	Sample size N=78 intervention: N=36 control: N=42 Characteristics Children with CF and pancreatic insufficiency Age: 2-6 years. Mean age: 3.8 years Inclusion criteria Confirmed CF diagnosis and confirmed	Interventions Behavioural intervention Individualized nutritional counselling targeting increased energy and fat intake and training in behavioural child management skills. Calorie and fat intake goals were set to meet the minimum 140% of the average estimated energy requirement, with 40% of calories derived from fat. Control: educational intervention Education on general nutrition information Education and attention control treatment	Details Study setting. Multicentre clinical trial from 7 accredited CF centres. Recruitment and randomization. Childr en were identified from a clinical database and reviewing medical records at each CF center. Eligible participants were randomized using a permuted block design for assignment using 2 strata (WAZ score ≤ −1.0 or −1.0 < WAZ score ≤ 1.0).	Results Indices of nutrition and growth Mean (SD) change in weight z score at 6 months (post-treatment): Behavioural intervention (N=36): 0.12 (0.40) vs educational intervention (N=42): 0.06 (0.32) Mean (SD) change in weight z score at 18 months: Behavioural intervention (N=36): 0.15 (0.48) vs educational intervention (N=42): 0.11 (0.62) Mean (SD) change in height z score at 18 months: Behavioural	Limitations The quality of the study was assessed using the Cochrane tool for risk of bias: Random sequence generation: Low risk (Eligible participants were randomized using a permuted block design. Randomization was based on a computer-generated predetermined schedule produced by a biostatistician) Allocation concealment: Unclear risk (No details given)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
R. D., Rausch, J. R., Stallings, V. A., Zemel, B. S., Clancy, J. P., Behavioral and nutritional treatment for preschool-aged children with cystic fibrosis: a randomized clinical trial, JAMA Pediatrics, 169, e150636, 2015 Ref Id 406428 Country/ies where the study was carried out USA Study type RCT Aim of the study To test whether behavioural and nutritional treatment (intervention) was superior to an education and attention control treatment in increasing energy intake, weight z score	pancreatic insufficiency; at least 6 months post-CF diagnosis; no restrictions in consuming a high-fat diet. Exclusion criteria Weight z score greater than 1.0 (age and sex adjusted); current use of supplemental nutrition through enteral or parenteral feeding; diagnosis of other conditions or use of current medication known to affect growth; diagnosis of developmental delay; genetic potential for height as acceptable according to the 2002 consensus conference	Both groups Both treatments were delivered in person or telehealth (via telephone). Sessions occurred weekly for 8 weeks then monthly for 4 months (6 months). Participants then returned to standard care for 1 year.	Randomization was based on a computer-generated predetermined schedule produced by a biostatistician and concealed from study personnel until baseline assessment measures were complete. Randomization assignment was supplied via secure email to the study therapist when the participant had met eligibility criteria. Families were aware that there were 2 different behavioral/educational treatments but were unaware of the differences of the specific components of each treatment. Data collection. Weight and height were assessed by staff trained by an expert in anthropometry in children using standardized procedures and blinded to the child's	intervention (N=36): 0.09 (0.26) vs educational intervention (N=42): -0.02 (0.32) Frequency of participants reporting any adverse events related to the digestive system (typically abdominal pain or stool issue) at 6 months: behavioural intervention (N=36): 29 (81%) vs educational intervention (N=42): 21 (50%), p value 0.005 FEV1 Not reported Quality of life Not reported Pulmonary exacerbations Not reported Adverse effects Not reported Patient and parent or carer satisfaction Not reported	Blinding: Unclear risk (Blinding for staff implementing the interventions was not possible; Randomization was concealed from study personnel until baseline assessment measures were complete; Randomization assignment was supplied via secure email to the study therapist when the participant had met eligibility criteria. Families were aware that there were 2 different behavioral/educational treatments but were unaware of the differences of the specific components of each treatment) Incomplete outcome data: Low risk (No drop-outs) Selective reporting: Low risk (Height z score is not reported at 6 months, only at 18 months, however this is consistent with the study objectives) Other bias: Low risk (None identified)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and height z score. Study dates The study was conducted at 7 CF centers between January 2006 and November 2012. Source of funding Funding for the Families Understanding Nutrition Study was provided by the National Institute of Diabetes and Digestive and Kidney Diseases (grants R01 DK054915-06A1; principal investigator [PI]: Dr Powers and NOT-OD-09-056; PI: Dr Powers), the Cystic Fibrosis Foundation Therapeutics Inc (05A0; PI: Dr Powers). The Families Understanding Nutrition Study was supported	guidelines; and dietary intake exceeding 140%of the average estimated energy requirement (based on sex, age, and active physical activity level; and intake assessed using 3-day diet recall)		treatment group assignment. Children were measured in minimal clothing and without shoes to obtain height andweight. The child'sweight in kilograms,measured to the nearest 100g, was obtained using a digital scale (Scaletronix Inc). The child's height was obtained using a stadiometer (Holtain) and measured to the nearest millimeter. Height was obtained standing unless the child was unwilling to stand, then a supine measurement was obtained (n = 1 at baseline; 2 at posttreatment; and 0 at followup). All measurements were obtained in triplicate and the mean used for analyses. The WAZ and HAZ scores were calculated using the mean measurement and the Centers for Disease Control and Prevention Anthropometric Software Program. For		Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
by the National Institutes of Health Cystic Fibrosis Core Center (grant P30 DK 27651; PI: Dr Konstan), National Center for Advancing Translational Sciences of the National Institutes of Health (grant UL1TR000077; PIs: James Heubi, MD, and Joel Tsevat,MD, MPH), and, for some of the postdoctoral fellows who contributed to the trial, the National Institute of Diabetes and Digestive and Kidney Diseases (grant T32DK063929; program director: Dr Powers).			adverse events, symptoms were assessed using questionnaires at each treatment session. Data analysis. Analyses of WAZ and HAZ change scores were carried out within the PROC GLM procedure (SAS Institute Inc) using an analysis of covariance model with sex, P aeruginosa status at baseline, treatment modality, and baseline value of the corresponding outcome variable as covariates. Frequency of adverse events was disaggregated by body system. Only adverse events related to body systems with 5 or more adverse events were reported.		
Full citation Morton, A., Wolfe, S., Enteral tube feeding for cystic	Sample size People with CF of any age. Characteristics -	Interventions Supplemental enteral tube feeding for one month or longer vs no specific intervention.	Details -	Results No studies were identified for inclusion in this review.	Limitations AMSTAR score: 10/11 (Publication bias was not mentioned) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
fibrosis, Cochrane Database of Systematic Reviews, 4, CD001198, 2015 Ref Id 451664 Country/ies where the study was carried out Study type Cochrane SR Aim of the study To assess if supplemental enteral tube feeding improves clinical outcomes and quality of life in people with CF. Study dates Date of last seach: February 2015 Source of funding -	Inclusion criteria - Exclusion criteria -				-
Full citation Smyth, R. L., Rayner, O., Oral calorie supplements for cystic fibrosis,	Sample size Hanning 1993 N= 20 20 randomised 16 studied	Interventions Hanning 1993 Intervention: oral calorie supplements Dietary supplements, drink powders, milk shakes, tinned	Details Hanning 1993 Random allocation using sealed envelopes	Results Hanning 1993 Indices of nutrition or growth Mean (SD) change in weight (kg) at 6 months:	Limitations Smyth 2014 AMSTAR score: 9/11 (Publication bias was not mentioned; declarations of interest

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cochrane Database of Systematic Reviews, 11, CD000406, 2014 Ref Id 358331 Country/ies where the study was carried out Hanning 1993: Canada Kalnins 2005: Canada Poustie 2006: UK Study type Smyth 2014 Cochrane systematic review Hanning 1993 Randomised controlled trial, parallel design Kalnins 2005 Quasi-randomised controlled trial, parallel design Poustie 2006 Multicentre randomised	Kalnins 2005 N= 15 participants were enrolled but 2 dropped out. 2 out of 7 in the supplement group did not continue taking supplements but they were analysed as ITT Poustie 2006 N= 102 Characteristics Hanning 1993 Children and young people with CF Age: 7-15 Kalnins 2005 Participants with CF Age: >10 years. Mean (SD) age on entry to trial: advice group:16.4 years (6.7); supplement	puddings to achieve 25% of normal energy recommendations in addition to normal diet for 6 months Control: usual care Kalnins 2005 Intervention: Oral calorie supplementation High calorie drink to increase energy intake by 20% of predicted energy needs for 3 months Control: Nutritional counselling Nutritional counselling to increase energy intake by 20% of predicted energy needs by eating high calorie foods for 3 months Poustie 2006 Intervention 1: Oral calorie supplements for 12 months Intervention 2: Routine dietary advice (usual care) for 12 months	Parallel design, no intention-to-treat analysis Kalnins 2005 Quasi-randomised controlled trial Parallel design ITT was used Study period: 3 months, follow-up: 3 months Poustie 2006 Multicentre randomised controlled trial Parallel design	Supplements (N=9): 2.52 (1.33) vs Control (N=7): 1.33 (1.35) Mean (SD) change in weight as % expected for age and height at 6 months: Supplements (N=9): 0.6 (9.77) vs Control (N=7): -2.7 (9.62)** Mean (SD) change in height as % of expected for age at 6 months: Supplements (N=9): 0.1 (24.22) vs Control (N=7): 1.7 (16.38)** FEV1 Mean (SD) change in FEV1 % predicted at 6 months: Supplements (N=9): -9.7 (14.3) vs control (N=7): -4.3 (10.54)** Quality of life Not reported* Pulmonary exacerbations Not reported* Adverse effects Not reported* Patient and parent or carer satisfaction Not reported* Kalnins 2005 Indices of nutrition and growth Mean (SD) change in weight (kg) at 3 months:	were only mentioned in relation to the authors of the systematic review but not in relation to the included studies). Hanning 1 Random sequence generation (selection bias): Low risk (Random allocation based on a table of random numbers) Allocation concealment (selection bias): Low risk (Used sealed envelopes) Blinding (performance bias and detection bias) (all outcomes): Unclear risk (Investigators performing lung muscle-function tests and athropometry were unaware of the participant's study group) Incomplete outcome data (attrition bias) (all outcomes): Low risk (No intention-to-treat analysis. 20 randomised, 16 studied. Four participants did not complete the trial because they found the time demand for testing or the travelling distance to be excessive)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
controlled trial, parallel design Aim of the study Smyth 2014 To establish whether in people with CF, oral calorie supplements: increase daily calorie intake; and improve overall nutritional intake, nutritional indices, lung function, survival and quality of life. To assess adverse effects associated with using these supplements. Hanning 1993 To assess the relationships between nutritional status on the one hand and skeletal muscle strength, power and endurance; and respiratory strength and respiratory endurance on the other in	group: 19.5 years (11.3). Poustie 2006 Children and young people with CF Age: 2 - 15 years Inclusion criteria Hanning 1993 > 7 years of age, mild to moderate lung disease. * Kalnins 2005 < 90% ideal weight for height or 5% reduction in ideal weight for height over 3 months. Poustie 2006 Children with at least one of following criteria: BMI <25th centile but > 0.4th centile; or no increase in weight over the			Supplements (N=7): 1.46 (2.15) vs Control (N=6): 2.15 (2.59) Mean (SD) change in height (cm) at 3 months: Supplements (N=7): 2.17 (2.54) vs Control (N=6): 2.55 (2.36) Mean (SD) change in weight for height (%) at 3 months: Supplements (N=7): 0.71 (4.5) vs Control (N=6): 1.67 (3.33) Mean (SD) change in weight z score at 3 months: Supplements (N=7): 0.1 (0.50) vs Control (N=6): 0.1 (0.57)** Mean (SD) change in weight z score at 6 months: Supplements (N=7): -0.1 (0.57) vs Control (N=6): 0.2 (0.66) ** Mean (SD) change in height z score at 3 months: Supplements (N=7): 0.1 (0.70) vs Control (N=6): 0.1 (1.01)** Mean (SD) change in height z score at 6 months: Supplements (N=7): 0.1 (0.66) vs Control (N=6): 0.2 (1.05)** Mean (SD) change in % ideal body weight at 3 months: Supplements	Other bias: High risk (The treated group appeared to be in better clinical condition at baseline) Kalnins 2005 Random sequence generation (selection bias): Unclear risk (Quasi-randomised controlled trial: participants were segregated by age and sex, initial participants from each group randomly allocated to intervention or control (paper does not state how initial randomisation occurred), then each subsequent participant was allocated a different group from the previous one) Allocation concealment (selection bias): High risk (Inadequate, used alternate allocation) Blinding (performance bias and detection bias) (all outcomes): Unclear risk (Not possible to blind dietitian or participant - it was stated that apart from the "study monitors" (nurse and dietitian), all

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children and young people with CF. To determine the effects of noninvasive nutritional intervention on these indexes early in the course of lung disease. * Kalnins 2005 To compare the effects of oral dietary supplements with dietary counseling on energy intake and nutritional status in malnourished young people and adults with CF. * Poustie 2006 To determine whether oral protein energy supplements, used long term in children with cystic fibrosis who are moderately	previous 3 months; or 5% decrease in weight from baseline over a period of < 6 months. Exclusion criteria Hanning 1993 Receiving supplemental tube feeding or total parenteral nutrition. * Kalnins 2005 Patients with CF-related diabetes, a gastrostomy tube, CF-associated liver disease, FEV1 < 30%, O2 dependence, and those already receiving routine supplements. * Poustie 2006 Children were excluded if they had cystic fibrosis related			(N=7): -1 (5.72) vs Control (N=6): 1 (9.33) ** Mean (SD) change in % ideal body weight at 6 months (3 months after the end of the intervention): Supplements (N=7): -3 (5.73) vs Control (N=6): 0 (9.33) ** FEV1 Mean (SD) change in FEV1 (% predicted) at 3 months: Supplements (N=7): -6.6 (14.6) vs Control (N=6): 1.6 (13.3) Mean (SD) change in FEV1 (% predicted) at 6 months: Supplements (N=7): -4 (16.12) vs Control (N=6): 4 (18.41)** Quality of life Not reported* Pulmonary exacerbations Not reported* Adverse effects Not reported* Patient and parent or carer satisfaction Not reported* Poustie 2006 Indices of nutrition and growth Mean (SD) change in weight (kg) at 3 months: Supplements (N=48): 1.11	other investigators were blinded, but it was not clear whether all investigators who assessed the outcome measures were blinded. Incomplete outcome data (attrition bias) (all outcomes): Low risk (2 participants dropped out, one in each group after completing baseline (reasons included feeling unwell and change of mind) and were not followed up; 2 out of 7 participants allocated to the supplement group were not taking supplements at 3 months, but were included in the analysis, which was judged to be ITT. Other bias: Unclear risk (Unable to make clear judgement) Poustie 2006 Random sequence generation (selection bias): Low risk (Generation of the randomisation sequence used random number tables) Allocation concealment (selection bias): Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
malnourished, improve nutritional and other outcomes. * Study dates Smyth 2014 Last search: 03 July 2014 Hanning 1993 Not reported * Kalnins 2005 Not reported * Poustie 2006 Not reported * Source of funding Smyth 2014 Not reported Hanning 1993 Dietary supplements for the study were donated by Nestlé enterprises Ltd, Kraft General Foods, Canada Inc; The Quaker Oats Company, Fortino's Supermarket	diabetes or liver disease or FEV1 < 30% or if, during the previous three months, they had been diagnosed as having cystic fibrosis or had received enteral nutrition. Children who were excluded were considered eligible later if these criteria no longer applied. *			(1.25) vs Control (N=51): 0.77 (0.73) Mean (SD) change in weight (kg) at 6 months: Supplements (N=50): 2.05 (1.8) vs Control (N=51): 1.72 (1.18) Mean (SD) change in weight (kg) at 12 months: Supplements (N=50): 3.13 (2.35) vs Control (N=52): 2.97 (1.97) Mean (SD) change in weight centile (percentile) at 3 months: Supplements (N=48): 2.12 (6.58) vs Control (N=51): 0.4 (4.98) Mean (SD) change in weight centile (percentile) at 6 months: Supplements (N=50): 2.75 (9.56) vs Control (N=51): 0.63 (5.6) Mean (SD) change in weight centile (percentile) at 12 months: Supplements (N=50): 0.83 (10.96) vs Control (N=52): -1 (7.14) Mean (SD) change in height (cm) at 3 months: Supplements (N=48): 1.65 (0.86) vs Control (N=51): 1.68 (0.8) Mean (SD) change in height (cm) at 6 months: Supplements (N=50): 3.09 (1.03) vs Control (N=51): 3.56 (2.92)	(Used sealed opaque envelopes) Blinding (performance bias and detection bias) (all outcomes): Low risk (Not possible to blind clinicians and participants, but the researcher undertaking the analysis of outcomes was masked as to the allocation groups) Incomplete outcome data (attrition bias) (all outcomes): Low risk (Analysis was by intention to treat. All 102 randomised children completed the trial. However, unable to collect interim data on 2 children from the supplement group (owing to parental choice or illness) and 1 child from the standard care group (illness). Spirometry data available for 70 of the 72 participants aged 5 and above). Other bias: Low risk (No other potential source of bias identified). Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ltd; and A & P Supermarkets. Motivational prizes and coupons were donated by local outlets of A and A Records and Tapes, Burger King, Swiss Chalet,and Harvey's. * Kalnins 2005 Supported by Mead Johnson, Canada. * Poustie 2006 The trial was funded by a grant from the UK Cystic Fibrosis Trust, which, after initial peer review of the protocol and receipt of regular interim reports, had no further role in the design of the trial, analysis of the results, or reporting of the findings. *				Mean (SD) change in height (cm) at 12 months: Supplements (N=50): 5.91 (0.85) vs Control (N=52): 5.85 (1.85) Mean (SD) change in height centile (percentile points) at 3 months: Supplements (N=48): 0.57 (3.69) vs Control (N=51): 1.13 (3.81) Mean (SD) change in height centile (percentile points) at 6 months: Supplements (N=50): 0.24 (0.27) vs Control (N=51): 1.98 (9.7) Mean (SD) change in height centile (percentile points) at 12 months: Supplements (N=50): 0.53 (6.94) vs Control (N=52): 1.18 (5.62) Mean (SD) change in BMI (kg/m2) at 3 months: Supplements (N=48): 0.19 (0.65) vs Control (N=51): 0.05 (0.41) Mean (SD) change in BMI (kg/m2) at 6 months: Supplements (N=50): 0.39 (0.87) vs Control (N=51): 0.15 (0.67) Mean (SD) change in BMI (kg/m2) at 12 months: Supplements (N=50): 0.32	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(1.03) vs Control (N=52): 0.24 (0.78) Mean (SD) change in BMI centile (percentile points) at 3 months: Supplements (N=48): 2.72 (11.42) vs Control (N=51): -0.56 (8.47) Mean (SD) change in BMI centile (percentile points) at 6 months: Supplements (N=50): 4.46 (15.5) vs Control (N=51): -1.29 (12.66) Mean (SD) change in BMI centile (percentile points) at 12 months: Supplements (N=50): 0.67 (18.2) vs Control (N=52): -2.32 (9.63) FEV1 Mean (SD) change in FEV1 (% predicted) at 3 months: Supplements (N=31): -2.55 (12.28) vs Control (N=38): 5.37 (12.97) Mean (SD) change in FEV1 (% predicted) at 6 months: Supplements (N=32): -1.78 (11.51) vs Control (N=38): 1.61 (16.45) Mean (SD) change in FEV1 (% predicted) at 12 months: Supplements (N=32): -3.41 (13.5) vs Control (N=38): -1.5 (14.89) Quality of life	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Not reported* Pulmonary exacerbations Not reported* Adverse effects Not reported* Patient and parent or carer satisfaction Not reported* * Extracted from individual paper. **Calculated by the NGA team using a correlation of 0.7	
Full citation Savage, E., Beirne, P. V., Ni Chroinin, M., Duff, A., Fitzgerald, T., Farrell, D., Self-management education for cystic fibrosis, Cochrane Database of Systematic Reviews, 9, CD007641, 2014 Ref Id 451702 Country/ies where the study was carried out	Sample size Watson 2008 N= 74 adults were enrolled and stratified by disease severity into low or high risk disease. Intervention: N= 37 Control: N = 37 48 adults completed the study through to 12-month follow-up assessment	Interventions Intervention: Nutrition education General and disease-specific nutrition education (’Eat Well with CF’) Content: knowledge on general and disease-specific nutrition topics (energy intake, digestion, pancreatic enzyme replacement, managing appetite, exercise, dietary fibre, reading food labels, body image); self-management skills on goal setting in small incremental steps to establish new behaviours Mode of delivery: written material focusing on weekly activities, taking approximately 30 minutes each week; supplementary workshops (introductory, weeks 5	Details Watson 2008. RCT, parallel design. The study was conducted with adults from the CF clinic of Papworth Hospital, Cambridge, UK. For quality of life, CFQOL - Questionnaire from Gee paper, specific to CF 9 domains, 52 items, was used. Only U test statistic and P values were reported for each QoL domain. * * Information extracted from primary study	Results Watson 2008. Indices of nutrition and growth Mean (SD) change in weight (kg) at 6 months: Intervention (N=23): 0.4 (7.63) vs control (N=25): 0.8 (8.09) ** Mean (SD) change in weight (kg) at 12 months: Intervention (N=23): 0.8 (7.51) vs control (N=25): 1.2 (8.28) ** FEV1 Mean (SD) change in FEV1 % predicted at 6 months: Intervention (N=23): 2.3	Limitations Savage 2014 AMSTAR score: 10/11 (Declarations of interest and sources of support were reported for the systematic review but not for the included studies). Watson 2008 Random sequence generation (selection bias): Low risk (The trial authors state that a “minimisation method of randomisation was used to ensure that the same number of patients were allocated to each group”

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Watson 2008: UK Study type Savage 2014 Cochrane systematic review Watson 2008 RCT, parallel design Aim of the study Savage 2014 To assess the effects of self-management education interventions on improving health outcomes for people with CF and their caregivers. Watson 2008 To test the hypothesis that adults with CF completing "Eat Well with CF" would have an improved nutritional status, improvement in specific nutrition knowledge, and an improvement in self-efficacy regarding their	23 in intervention group 25 in control group Characteristics Watson 2008 Individuals with CF older than 16 years of age Mean (range) age: intervention group 26.4 (17.2 - 43.2) years; control group 24.2 (16.9 - 38.1) years Gender: intervention group (12 males, 11 females); control group (14 males, 11 females) Disease status: intervention group - mean BMI (kg/m2) = 21.3; pancreatic insufficiency (n	and 10) and weekly telephone calls delivered by a dietitian Duration: 10 weeks. Setting: home (weekly written activities) and hospital (workshops) Control: Standard treatment		(19.52) vs control (N=25): 0.81 (16.75) ** Mean (SD) change in FEV1 % predicted at 12 months: Intervention (N=23): 0.2 (19.16) vs control (N=25): -0.79 (16.98)** Quality of life physical functioning at 6 months: P= 0.05 physical functioning at 12 months: P= 0.61 social functioning at 6 months: P= 0.85 social functioning at 12 months: P= 0.54 treatment issues at 6 months: P= 0.74 treatment issues at 12 months: P= 0.68 chest symptoms at 6 months: P= 0.59 chest symptoms at 12 months: P= 0.62 emotional response at 6 months: P= 0.45 emotional response at 12 months: P= 0.07 concerns for the future at 6 months: P= 0.46 concerns for the future at 12 months: P= 0.03 interpersonal relationships at 6 months: P= 0.75 interpersonal relationships at 12 months: P= 0.64	(Watson 2008: page 848) Allocation concealment (selection bias): Low risk (No details are provided by the trial authors in the published records.Information provided by the principal author on request states that “an independent randomiser was used who was part of the R and D [Research and Development] department of the hospital”. and which was “supervised by the project statistician...independently of the investigator” Blinding (performance bias and detection bias): Unclear risk (The trial authors state that “The study could not be blinded to either the subjects or the investigators because of the nature of the intervention” (Watson 2008: 848). Information provided by the principal author on request states that “no blinding” of outcome assessors took place. It is unclear if providers of care or data

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ability to cope with a special diet, compared to those receiving standard care. * Study dates Savage 2014 Date of the last search of the Cochrane Cystic Fibrosis and Genetic Disorders Groups Trials Register: 22 August 2013 Data of the last searches of databases through EBSCO (CINAHL; Psychological and Behavioural Sciences Collection; PsychInfo; SocINDEX) and Elsevier (Embase) and handsearch of relevant journals and conference proceedings: 01 February 2014. Watson 2008 The duration of the study was	= 21); Psuedomonas aeruginosa in sputum (n = 18); non-Psuedomonas (n = 5); homozygous DF508 (n = 13); heterozygous DF508 (n = 7); other (n = 3); control group - mean BMI (kg/m2) = 21.1; pancreatic insufficiency (n = 22); Pseudomonas aeruginosa in sputum (n = 21); non-Psuedomonas (n = 4); homozygous DF508 (n = 16); heterozygous DF508 (n = 8); Other (n = 1) Inclusion criteria Watson 2008 For inclusion, participants had to be older			body image at 6 months: P= 0.24 body image at 12 months: P= 0.59 career issues at 6 months: P= 0.15 career issues at 12 months: P= 0.28 Pulmonary exacerbations Not reported* Adverse effects Not reported* Patient and parent or carer satisfaction Not reported* * Data extracted from individual paper ** Change calculated by the NGA team assuming a correlation of 0.7	analysts were blinded from knowing which group participants were randomised to) Incomplete outcome data (attrition bias) (all outcomes): Low risk (Of the 74 adults enrolled with equal numbers in the intervention (n = 37) and control (n = 37) groups, 48 were included in the “completer analysis” at 12 months follow-up (23 in intervention group, and 25 in control group). Incomplete outcome data are reported for each assessment point for intervention and control groups as follows: Intervention group: baseline data are reported as missing from 3 of the 37 allocated to group due to relocation (n = 1) and non-return of questionnaires (n = 2). At 6 months follow-up, data from a further 6 participants are reported as missing due to withdrawal from the study (n = 3), defaulting from follow-up (n=2) or death (n=1). At 12 months follow-up, data from a further 5

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
from January 2003 to August 2005 Source of funding Savage 2014 Internal sources: University College Cork, Ireland. External sources: Health Research Board, Ireland. Watson 2008 The research was funded by the NHS Regional Research and Development grant. Helen Watson was supported by the Papworth Hospital Respiratory Research Fund. Additional funding was provided by Solvay Healthcare (Southampton, UK) *	than 16 years, able to understand written English, not partaking in other research. Exclusion criteria Watson 2008 Participants were excluded if they were on heart/lung transplant list or were pregnant or lactating				participants are reported as missing due to defaulting from follow-up (n = 4) or death (n = 1). The number of participants in the intervention group included in the "completer analysis" is reported as 23. Control group: baseline data are reported as missing from 3 of the 37 allocated to group due to relocation (n = 1) and non-return of questionnaires (n = 2). At 6 months follow-up, data from a further 2 participants are reported as missing due to relocation (n = 1) or death (n = 1). At 12 months follow-up, data from a further 7 participants are reported as missing due to defaulting from follow-up (n = 6) or death (n = 1). The number of participants in the control group included in the "completer analysis" is reported as 23. Missing outcome data are balanced in numbers across both groups with similar reasons for missing data across both groups.)

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					Selective reporting (reporting bias): Unclear risk (All outcomes mentioned in the published record are reported. It is unclear if additional outcomes were pre-specified in the study protocol but not reported) Other bias: Low risk (No other potential source of bias identified) Other information Watson 2008 The primary outcome measure of an increase in weight after 12 months was used to calculate the required sample size. For this, data on weight gain in patients attending the CF clinic of the study centre from 1998 to 2000 were reviewed. The trial authors stated that: “By using the ’Eat Well with CF’ programme it was anticipated that subjects mean (SD) weight would increase by 3 (3) kg after 12 months. With

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					80% power and two-sided significance of 5% and allowing for 15% dropout or loss to follow-up, the recruitment target was 46 participants per group" (Watson 2008: page 848). Microbiological segregation was introduced during the course of the study which prohibited the use of group workshops. Consequently the study could not continue and therefore target levels of recruitment could not be achieved. The trial authors define high disease risk as participants with < 30% predicted FEV1, on enteral feeding, or with diabetes.
Full citation Goldbeck,Lutz, Fidika,Astrid, Herle,Marion, Quittner,Alexandra L., Psychological interventions for individuals with cystic fibrosis and their families,	Sample size Powers 2003 N=12 Behavioural and nutrition intervention: N=7 Nutrition intervention only: N=5 Stark 1996	Interventions Powers 2003 Intervention 1: Behavioural management training plus nutritional intervention Nutrition intervention with strategies for enhancing calorie intake - behavioral management training for parents designed to encourage children to eat food	Details Cochrane Systematic Review Powers 2003 Parallel RCT Stark 1996 Parallel RCT with half participants receiving intervention first then other half 3 months later - not reported. 4	Results Powers 2003 Indices of nutrition and growth Mean (SD) change in weight (kg) at 1 year (post-treatment): Nutritional intervention plus behavioural management training (n=4): 1.32 (0.64)	Limitations Goldbeck 2014 AMSTAR score: 9/11 (Publication bias was not mentioned; declarations of interest and sources of support were provided in relation to the systematic review but not in relation to the included studies).

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Cochrane Database of Systematic Reviews, -, 2014 Ref Id 320813 Country/ies where the study was carried out Powers 2003: USA Stark 1996: USA Stark 2009: USA Study type Cochrane Systematic Review Powers 2003 Parallel RCT Stark 1996 Parallel RCT with half participants receiving intervention first then other half 3 months later - not reported. 4 families changed group after randomisation due to conflicting vacation scheduling, thus not truly randomized Goldbeck 2014	N=10. 1 withdrew from control group after randomisation. Total sample=9 Behavioural intervention: N=5 Wait list control: N=4) Stark 2009 Population of interest N= 177 (met eligibility). Randomised N= 79. There were 6 dropouts in both arms prior to treatment, 67 participants were included in the analysis. Behavioural intervention plus nutrition education: N=33 Nutrition education: N=34 Characteristics Powers 2003 Infants and children with CF aged less	consistent with CF dietary recommendations. Intervention 2: Nutritional intervention only Both groups received 8 sessions (45 to 60 minutes) over 1 year: Sessions 1 to 4 (3 months) intensive education Stark 1996 Intervention: Group behavioural intervention. 7 weekly sessions - baseline assessment plus snack, breakfast, relaxation skills training, lunch, dinner and maintenance strategies targeted over following 7 sessions. Duration of treatment: 6 weeks.* Control: Wait list control. Parent meeting and 7-day food diaries at times corresponding to baseline and last week of intervention. Stark 2009 Intervention 1: Behavioural intervention Behavioral intervention in group setting for change around nutrition and energy (Be-In-CHARGE!; n = 33) (available online at www.oup.com/us/pediatricpsych) f or 9 weeks. Intervention 2: Nutrition education	families changed group after randomisation due to conflicting vacation scheduling, thus not truly randomized Stark 2009 RCT. The parent satisfaction questionnaire used a 7-point scale (higher numbers indicated greater satisfaction)	vs nutritional intervention alone (n=4): 1.75 (0.57) Mean (SD) change in height (cm) at 1 year (post-treatment): Nutritional intervention plus behavioural management training (n=4): 5.1 (2.36) vs nutritional intervention alone (n=4): 7.13 (0.99) Mean (SD) change in % ideal body weight at 1 year (post-treatment): Nutritional intervention plus behavioural management training (N=4): 8.49 (20.07) vs nutritional intervention alone (N=3): 9.4 (27.29) *** Mean (SD) change in weight % for age at 1 year (post-treatment): Nutritional intervention plus behavioural management training (N=4): 4.2 (10.04) vs nutritional intervention alone (N=4): 4.8 (13.70)*** FEV1 Not reported* Quality of life Not reported* Pulmonary exacerbations Not reported* Adverse effects Not reported* Patient and parent or carer satisfaction	Powers 2003 Random sequence generation (selection bias): Unclear risk (not reported) Allocation concealment (selection bias): Unclear risk (not reported) Blinding (performance bias and detection bias): High risk (Unclear) Incomplete outcome data (attrition bias) (all outcomes): Unclear risk (The authors recorded the drop-outs (33%) and presented the reasons. However, reasons for drop-outs are not reported separately for both conditions. They additionally reported that a comparison of children who withdrew from the study and those who completed the study protocol yielded no significant differences on demographic and anthropometric data Stark 1996 Random sequence generation (selection bias): Unclear risk (The authors did not describe details of random generation process. It is

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Cochrane systematic review Stark 2003 Parallel RCT Stark 2009 RCT Aim of the study Goldbeck 2014 To determine whether psychological interventions for people with cystic fibrosis provide significant psychosocial and physical benefits in addition to standard medical care. Powers 2003 To examine the feasibility and potential effectiveness of a behavioural intervention targeting improvements in calorie consumption and weight gain in a sample of 12- to 36-month-old	than 3 years old. Pancreatic insufficiency. Stark 1996 Children with CF Age range: 5.3 years to 10.1 years. Mean age: 7.3 years (SD = 1.7). Stark 2009 Children and young people with CF aged from 4 to 12 years Pancreatic insufficiency; and weight for age and height ≤40th percentile. Inclusion criteria Powers 2003 Children were < 3 years old, had a confirmed diagnosis of CF with pancreatic insufficiency, were prescribed an	Nutrition education in group setting for 9 weeks. * Information extracted from individual paper		Not reported* Stark 1996 Indices of nutrition and growth Mean (SD) change in weight (kg) at 6 weeks (posttreatment)*: Behavioural group treatment (n=5): 1.7 (3.83) vs wait list control (n=4): 0 (4.73) ** Cochrane reports N=3 Mean (SD) change in height (cm) at 6 weeks (posttreatment)*: Behavioural group treatment (n=5): 1.2 (8.06) vs wait list control (n=4): 1.3 (15.38) ** Mean (SD) change in weight (z score) at 6 weeks (posttreatment)*: Behavioural group treatment (n=5): 1.93 (0.62) vs wait list control (n=4): 0.05 (0.44)** FEV1 Mean (SD) change in FEV1% at posttreatment: Behavioural group treatment (n=5): -6 (9,51) vs wait list control (n=4): 0,5 (20,32) ** Quality of life Not reported* Pulmonary exacerbations	just stated that 'the nine subjects were randomly assigned to either a behavioral intervention or a wait list control group' (Stark 1996). Allocation concealment (selection bias): Unclear risk (The authors did not provide information about adequate concealment of allocation) Blinding (performance bias and detection bias): High risk (Participants and personnel providing the intervention were not able to be blinded due to the nature of the intervention and the study design (wait-list-control design). However all objective measures (e.g. weight) are not likely to be influenced by the lack of blinding) Incomplete outcome data (attrition bias) (all outcomes): Low risk (The authors reported that there was no attrition) Selective reporting (reporting bias): Unclear risk (The authors

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
toddlers with CF and their families* Stark 1996 To replicate a behavioural treatment protocol developed by Stark and colleagues using a wait list control group of children with CF as a comparison to the children receiving treatment.* Stark 2009 To evaluate the efficacy of a behavioural plus nutrition education intervention, Be-In-CHARGE!, compared to nutrition education alone, on calorie intake and weight gain in children with CF and pancreatic insufficiency. * * Information extracted from individual paper	unrestricted fat diet * Stark 1996 Not reported.* Stark 2009 Age 4-12 years, confirmed diagnosis of CF, pancreatic insufficiency, weight for age or for height ≤ 40th percentile. Participants were recruited from 5 CF centres located in the Eastern, Midwestern, and Southern USA. Exclusion criteria Powers 2003 Other disease or condition known to affect growth. Stark 1996 Not reported* Stark 2009 Medical condition that would affect growth or appetite (e.g.			Not reported* Adverse effects Not reported* Patient and parent or carer satisfaction Not reported* Stark 2009 Indices of nutrition and growth Mean (SD) change in weight (kg) at 9 weeks (post-treatment): Nutritional intervention plus behavioural management training (n=33): 1.47 (1.27) vs nutritional intervention alone (n=34): 0.92 (1.03) Mean (SD) change in weight (kg) at two years follow-up: Nutritional intervention plus behavioural management training (n=28): 6.97 (3.6) vs nutritional intervention alone (n=31): 6.45 (3.67) Mean (SD) change in height (cm) at two years follow-up: Nutritional intervention plus behavioural management training (n=28): 13.34 (1.93) vs nutritional intervention alone (n=31): 13.54 (2.93) Mean (SD) BMIz change at 9 weeks (post-treatment):	reported all pre-specified outcomes. It is unclear if additional outcomes were pre-specified in the study protocol but not reported) Stark 2009 Random sequence generation (selection bias): Low risk (Participants were 'randomised to the treatment arms by coin flip by research assistant and postdoctoral fellow together' (Stark 2009, p.916)) Allocation concealment (selection bias): Low risk (Assignment could not be foreseen by participants and investigators enrolling participants because of coin flipping by research assistant and postdoctoral fellow together) Blinding (performance bias and detection bias): Unclear risk (The authors of the study state that 'families were never explicitly told which treatment they had been assigned'

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Goldbeck 2014 Most recent search of the Cystic Fibrosis and Genetic Disorders Group's register: 19 December 2013 Most recent search of the Depression, Anxiety and Neurosis Group's register: 12 November 2013 Powers 2003 Toddlers and their parents were approached for participation in the study from July 1997 to July 1998* Stark 1996 Not reported* Stark 2009 Not reported * * Information extracted from individual paper	steroids), significant developmental delay or mental health diagnosis of depression or psychosis (parent or child); positive sputum culture for Burkholderia cepacia; FEV1 < 40% of predicted; or receiving enteral or parenteral nutrition. *			Nutritional intervention plus behavioural management training (n=33): 0.38 (0.46) vs nutritional intervention alone (n=34): 0.18 (0.47) Mean (SD) change in BMI z score at two years follow-up: Nutritional intervention plus behavioural management training (n=28): 0.13 (0.81) vs nutritional intervention alone (n=31): -0.22 (0.5) Mean (SD) change height z score at two years follow-up: Nutritional intervention plus behavioural management training (n=28): 0.03 (0.3) vs nutritional intervention alone (n=31): 0.04 (0.32) FEV1 FEV1 change at two years follow-up: Nutritional intervention plus behavioural management training (n=13): 0.16 (22) vs nutritional intervention alone (n=15): -5 (13) Quality of life Not reported* Pulmonary exacerbations Not reported* Adverse effects Not reported* Patient and parent or carer satisfaction	(Stark et al 2009, p.916). But, 'as with any behavioral intervention, it is not possible to keep subjects unaware of the treatment they are receiving or therapists the treatment they are providing' (Stark 2009, p.921). No details are provided about blinding of outcome assessors. Incomplete outcome data (attrition bias) (all outcomes): Low risk (Of the 79 enrolled children 40 were assigned to the nutrition education group (NE) and 39 to the behaviour plus nutrition education group. There have been 6 drop outs in both arms prior to treatment. Data of 67 children was available for analysis post-treatment (NE n = 33 and behavioural plus nutrition education intervention n = 34). 24 month follow-up data of 28 children in the behaviour plus nutrition education intervention group and of 31 children in the NE group was available for analysis. The authors provided a flow diagram

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Goldbeck 2014 Internal sources: Royal Liverpool Children's NHS Trust, UK; National Institute of Health, USA. External sources: No sources of support supplied Powers 2003 This research was supported in part by Grants R01 DK54915 and K24 DK59973 from the National Institutes of Health (NIH)/National Institute of Diabetes and Digestive and Kidney Diseases (to Scott W. Powers) and Grants 96-81 and 97-76R from the Genentech Foundation for Growth and Development (to Scott W. Powers).				Parent satisfaction at post-treatment: Parents in both groups reported high ratings of satisfaction with treatment (>6 in a 7 point scale) with no statistically significant difference on eight of nine dimensions (p>0.05) (which related to the parents' satisfaction with the child progress, the impact of the program on child caloric intake and mealtime behaviour, the group leader's teaching skills, and whether they would recommend the program to a friend). For "approach used to increase child's calorie intake" the behavioural plus nutrition education intervention was rated superiod (p=0.005). However, ratings of both groups were above 6. * * Extracted from primary paper ** Calculated by the NGA technical team using data from primary paper and using a correlation of 0.7 *** Calculated by the NGA team using data from Cochrane and using a correlation of 0.7	of participants randomised to both study arms and assessed at each point in time from baseline to 24-month follow up (see Stark 2009, p.916 Figure 1). Selective reporting (reporting bias): Low risk (The study protocol is available and all of the study's pre-specified outcomes have been reported) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Additional support was provided by United States Public Health Service Grant M01 RR 08084 from the National Center for Research Resources of the NIH. * Stark 1996 The research was supported by a grant from the National Cystic Fibrosis Foundation (no. 2117) to Lori J. Stark* Stark 2009 This study was supported by grants R01 DK50092 and D24 DK 059492 from the National Institutes of Health (L.J.S.. Additional support was provided by grant M01 RR 0808 from the National Center for Research					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Resources of the NIH. * *Information extracted from individual paper					
Full citation Chinuck, R., Dewar, J., Baldwin, D. R., Hendron, E., Appetite stimulants for people with cystic fibrosis, Cochrane Database of Systematic Reviews, 7, CD008190, 2014 Ref Id 365496 Country/ies where the study was carried out Eubanks 2002: USA Homnick 2004: USA Marchand 2000: USA Study type Chinuck 2014 Cochrane Systematic Review	Sample size Eubanks 2002 N=17 participants Intervention: N=10 Placebo: N=7 Homnick 2004 18 patients enrolled, 16 completed study Intervention: N=8 Placebo: N=8 Marchand 2000 12 participants Characteristics Eubanks 2002 Age: > 6 years Sex: 8 females, 9 males Inclusion criteria: pancreatic insufficiency FEV1>40% growth failure	Interventions Eubanks 2002 Intervention: appetite stimulant Megasterol acetate 10 mg/kg/day (adjusted at subsequent visits) Duration: 6 months * Control Placebo Homnick 2004 Intervention: appetite stimulant Cyproheptadine hydrochloride 4mg 4 x daily. 2 mg daily for 1 week, then 4mg daily for 11 weeks. (Total duration intervention: 12 weeks)* Control Placebo Marchand 2000 Intervention: appetite stimulant Megasterol acetate 10 mg/kg/day Intervention implemented for 12 weeks * Control Placebo	Details Eubanks 2002 Double-blinded, placebo-controlled RCT. Parallel design. Homnick 2004 Double-blinded, placebo-controlled RCT. Parallel design. Marchand 2000 Double-blinded, placebo-controlled RCT. Cross-over design.	Results Eubanks 2002 Indices of nutrition and growth Change in weight (kg) at 3 months, mean (SD): Appetite stimulants (N=10): 4.3 (2.9) vs placebo (N=7): 1.3 (1.4) Change in weight (kg) at 6 months, mean (SD): Appetite stimulants (N=10): 5.3 (3.6) vs placebo (N=7): 1.5 (1.6) Change in weight z score at 3 months, mean (SD): Appetite stimulants (N=10): 0.72 (0.77) vs placebo (N=7): 0.07 (0.22) Change in weight z score at 6 months, mean (SD): Appetite stimulants (N=10): 0.76 (0.73) vs placebo (N=7): 0.02 (0.2) FEV1 Change in FEV1 % at 3 months, mean (SD): Appetite stimulants (N=10):	Limitations Chinuck 2014 AMSTAR score: 10/11 (Declarations of interest by the authors of the systematic review are provided, however the review did not mention the declarations of interest related to the included studies) Eubanks 2002 Random sequence generation (selection bias): Low risk (Quote: "Participants allocated by computer-generated randomisation schedule") Allocation concealment (selection bias): Unclear risk (Method of concealment not described) Blinding (performance bias and detection bias) (Participants): Low risk (Double-blind) Blinding (performance bias and detection bias)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Eubanks 2002 RCT, parallel design Homnick 2004 RCT, parallel design Marchand 2000 RCT, cross-over design Aim of the study Chinuck 2014 To systematically search for and evaluate evidence on the beneficial effects of appetite stimulants in the management of CF-related anorexia and synthetize reports of any side-effects Eubanks 2002 To test whether megestrol acetate would have beneficial effects on growth in patients with CF and pancreatic insufficiency * Homnick 2004	defined as no weight gain in the preceding 6 months Homnick 2004 Age: adults and children Sex: 10 females, 6 males Marchand 2000 Age: mean age 7.4 years. Age range: 21 months to 10.4 years* Sex: 9 females, 3 males * Information extracted from individual paper Inclusion criteria Eubanks 2002 Inclusion criteria: pancreatic insufficiency; FEV1> 40%; growth failure defined as no weight gain in the preceding 6 months; percent ideal body weight of			9.85 (13.85) vs placebo (N=7): -3.7 (17.3) Change in FEV1 % at 6 months, mean (SD): Appetite stimulants (N=10): 6.47 (6.64) vs placebo (N=7): 0.83 (12.4) Quality of life Not reported* Pulmonary exacerbations The number of pulmonary exacerbations requiring intravenous antibiotics was similar with 6 courses of intravenous antibiotics administered to each group of patients.* Adverse effects Frequency of adverse effects (constipation) at 6 months: Appetite stimulants (N=10): 1 vs placebo (N=7): 0 Patient and parent or carer satisfaction Not reported* Homnick 2004 Indices of nutrition and growth Mean (SD) change in weight z score at 3 months: intervention (N=5) 0.572 (0.457) vs control (N=7) 0.04 (0.305) Mean (SD) change in weight (kg) at 3 months (12	(Clinicians): Low risk (Double-blind) Blinding (performance bias and detection bias) (Outcome assessors): Low risk (Participants, treating physician and ancillary staff blinded) Incomplete outcome data (attrition bias) (all outcomes): High risk (3 patients in the placebo group withdrew when they failed to observe a treatment effect, which is a potential source of bias) Selective reporting (reporting bias): High risk (Unexpected measures used to report outcomes i.e. weight for age z-score only, instead of being additional to weight as a mean (SD). Other bias: Low risk (No other evident risk of additional bias) Homnick 2004 Random sequence generation (selection bias): Low risk (SAS small block randomisation)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To determine the effects of cyproheptadine hydrochloride on appetite, weight, and other clinical indicators in children and adults with mild to moderate CF.* Marchand 2000 To determine whether the administration of megestrol acetate induces weight gain in malnourished patients with CF, and to assess the composition of weight gain. * Study dates Chinuck 2014 Last search of online database: 01 April 2014. Last search of the Cystic Fibrosis Trial Register: 08 April 2014 Eubanks 2002 Not reported *. Duration: 6 months Homnick 2004	<85%*, weight <5th percentile for age*, or weight for height <5th percentile*. Homnick 2004 Age ≥ 5 years, ability to perform spirometry, and ideal body weight for height < 100%. * Marchand 2000 Loss of weight or plateau in weight gain for more than 3 months; weight-for-height less than 85%, and a negative change in weght z score. * Exclusion criteria Eubanks 2002 Diabetes; pregnancy or lactation; history of deep vein thrombosis;			weeks): intervention (N=8): 3.45 (9.01) vs control (N=8): 1.1 (9.68)** Mean (SD) change in height (cm) at 3 months (12 weeks): intervention (N=8): 1.2 (12.88) vs control (N=8): 1.0 (11.74)** Mean (SD) change in BMI (weight/height2) at 3 months (12 weeks): intervention (N=8): 1.17 (1.28) vs control (N=8): 0.29 (1.99) ** Mean (SD) change in BMI (percentile) at 3 months (12 weeks): intervention (N=8): 12.88 (12.93) vs control: (N=8) 1.78 (9.08) ** Mean (SD) change in % ideal body weight at 3 months (12 weeks): intervention (N=8): 6.29 (4.79) vs control (N=8): 1.15 (5.28)** FEV1 Not reported* Quality of life Not reported* Pulmonary exacerbations Not reported* Adverse effects Not reported* Patient and parent or carer satisfaction Not reported*	Allocation concealment (selection bias): Unclear risk (Not discussed) Blinding (performance bias and detection bias) (Participants): Low risk (Only the pharmacist and study coordinator remained unblinded, participants were blinded) Blinding (performance bias and detection bias) (Clinicians): Low risk (Only the pharmacist investigator and study coordinator remained unblinded, clinicians were blinded) Blinding (performance bias and detection bias) (Outcome assessors): Low risk (Only the pharmacist investigator and study coordinator remained unblinded, outcome assessors were blinded) Incomplete outcome data (attrition bias) (all outcomes): Low risk (No outcome related drop-out) Selective reporting (reporting bias): High risk (Outcome stated in the 'Methods' section (pulmonary

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported*. Duration: 12 weeks. Marchand 2000 Not reported*. Duration: 12 weeks treatment followed by 12 week washout period and then 12 weeks alternate treatment Source of funding Chinuck 2014 Internal sources: Nottingham University Hospital, City Campus, UK. External sources: Nottingham University, UK. Eubanks 2002 Supported by the National Institutes of Health (grant Nos. P30-DK54781, P50-DK53090, GCR-MOI-RR0032, and Maternal Child Health Pediatric	awaiting lung transplantation; aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >100 U/L or other evidence of liver dysfunction. * Homnick 2004 Any previous intolerance to antihistamines including CH; current use of narcotic or sedative medications; use of any appetite stimulant or systemic corticosteroids within 30 days prior to study start; pregnancy; inability to perform spirometry; inability to withhold other antihistamines for 1 week prior to study start;			Marchand 2000 Indices of nutrition and growth Change in weight z score at 3 months, mean (SD): intervention (N=5) 0.742 (0.783) vs control (N=6) -0.05 (0.783) FEV1 Not reported. Quality of life Not reported* Pulmonary exacerbations Frequency of pulmonary exacerbations at 3 months: intervention (N=6): 5 vs control (N=6): 3 Adverse effects See pulmonary exacerbations Patient and parent or carer satisfaction Not reported* * Data extracted from individual paper **Change calculated by the NGA team assuming correlation of 0.7. In relation to the Homnick paper, N for each outcome was unclear so N of people who completed the study was used.	function) was not reported. Other bias: Low risk (Significant differences reported in FEV1 % predicted between the placebo and CH groups at baseline; mean (SD) 42.3 (17.6) in the placebo group and 68.9 (28.1) in the CH group (P = 0.0392), but allowing for an adjustment of the P value for testing multiple outcomes the difference is not significant and is not evidence for a risk of bias) Marchand 2000 Random sequence generation (selection bias): Unclear risk (Quote: "... patients were randomized.", no detailed information) Allocation concealment (selection bias): Unclear risk (Not discussed) Blinding (performance bias and detection bias) (Participants): Low risk (Double-blind) Blinding (performance bias and detection bias)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pulmonary Care Center grant No. MCJ-019161), the Cystic Fibrosis Foundation, and Bristol Myers-Squibb. * Homnick 2004 Grant sponsor: MSU/KCMS CF Center Grant; Grant sponsor: Bronson Community Research Fund. * Marchand 2000 The study was supported by a grant from Bristol-Myer-Squibb and the General Clinical Research Center at the Medical University of South Carolina. *	and operation of equipment that may be dangerously affected by drowsiness such as farm equipment or public transportation. * Marchand 2000 Diabetes; documented glucose intolerance; history of thrombosis; previous transplant (liver or lung); use of corticosteroids, birth-control pills, or appetite stimulants; other ongoing causes of growth failure; and pregnancy. *				(Clinicians): Low risk (Double-blind) Blinding (performance bias and detection bias) (Outcome assessors): Low risk (No specific information, but weight measurement unlikely to be affected by not blinding assessor) Incomplete outcome data (attrition bias) (all outcomes): High risk (6 out of 12 patients dropped out. No reason given for 3 patients, 2 for developed diabetes following MA, 1 for glucose intolerance on placebo. Not clear if these drop-outs were on first or second period of cross-over trial. No data used from dropouts) Selective reporting (reporting bias): High risk (Outcome stated in the 'Methods' section (pulmonary function) was not reported. Plus QoL not stated in the 'Methods' section, but reported in the 'Results' Other bias: Low risk (No other evident risk of additional bias) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation White, H., Morton, A. M., Conway, S. P., Peckham, D. G., Enteral tube feeding in adults with cystic fibrosis; patient choice and impact on long term outcomes, Journal of Cystic Fibrosis, 12, 616-22, 2013 Ref Id 366595 Country/ies where the study was carried out UK Study type Cohort study Aim of the study To examine adherence to the guidelines for initiation of enteral tube feeding and to determine the nutritional and clinical impact of up to three year of enteral tube feeding.	Sample size N= 21 15 in the intervention group 6 in the control group Initially, 23 people were randomized. However, two patients in the intervention group died within the study, and subsequent analysis was undertaken on those who accepted ETF and survived (N=15) and those who declined (N=6). Characteristics Adults with CF All patients had pancreatic insufficiency and were treated with pancreatic enzyme replacement therapy	Interventions Intervention: Enteral tube feeding Supplemental enteral tube feeding administered over 3 years. All patients consumed a polymeric 2 kcal/ml enteral tube feed, providing 20-60% of daily energy intake as an overnight enteral tube feed, allowing free dietary intake during the day. Control: Usual care	Details Setting. Adult CF Unit, Leeds, UK Data collection. Anthropometric and respiratory parameters were noted at one year time intervals from 1 year prior to starting ETF, at baseline, and during the following 3 years. In those patients who declined ETF the same measures were recorded at the point where the standard criteria for starting ETF were met and at annual intervals for 3 years. Data analysis. Weight change was calculated by comparing weight at each time point to baseline weight and then calculating the percentage weight change achieved. Data were analysed for normal distribution. Descriptive statistics were used to evaluate the demographic characteristics of all patients. Unpaired t-tests (2-tailed) were	Results Indices of nutrition and growth Mean (SD) change in weight (kg) at 1 year: ETF (n=15): 7.3 (3.8) vs non-ETF (n=6): -0.3 (2.64) Mean (SD) change in weight (kg) at 2 years: ETF (n=15): 8.3 (6.01) vs non-ETF (n=6): -0.8 (2.57) Mean (SD) change in weight (kg) at 3 years: ETF (n=15): 8.9 (6.26) vs non-ETF (n=6): -0.1 (2.59) Mean (SD) change in BMI (kg/m2) at 1 year: ETF (n=15): 2.7 (1.18) vs non-ETF (n=6):-0.2 (0.46) Mean (SD) change in BMI (kg/m2) at 2 years: ETF (n=15): 2.9 (1.58) vs non-ETF (n=6): -0.3 (0.44) Mean (SD) change in BMI (kg/m2) at 3 years: ETF (n=15): 3.3 (1.74) vs non-ETF (n=6): 0.8 (0.43) FEV1 Mean (SD) change in FEV1 (% predicted) at 1 year: ETF (n=15): 5.3 (14.41) vs non-ETF (n=6): -5.3 (14.24) Mean (SD) change in FEV1 (% predicted) at 2 years: ETF (n=15): 4.2	Limitations The quality of this study was assessed with the Newcastle-Ottawa scale assessment tool: Selection: High risk (Those who accepted ETF had lower BMI, lower FEV1% predicted and more days on intravenous antibiotic treatment at baseline, although the difference was not statistically significant) Comparability: High risk (The study does not control for any factor) Outcome: Low risk (Length of follow-up was adequate; 2 out of 17 died in intervention group and were excluded from the analysis; cause of death for each one of these patients was unrelated to enteral tube feeding. No deaths amongst the 6 participants in the control group). Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported Source of funding Not reported	Mean (SD) age at baseline: ETF: 21.8 (3.6) vs non-ETF: 23.0 (5.7), p=0.6 Sex, males/females ratio at baseline: ETF: 8/17 vs non-ETF: 3/6, p=1.0 Mean (SD) BMI (kg/m2) at baseline: ETF: 16.8 (1.6) vs non-ETF: 18.05 (1.7), p=0.08 Mean (SD) FEV1 (% predicted) at baseline: ETF: 39.5 (18.9) vs non-ETF: 56.3 (21.0), p=0.08 Inclusion criteria All patients attending the Adult CF Unit, Leeds UK, who fulfilled the criteria for commencement of ETF (CF Trust 2002) between		used to compare anthropometric data and lung function between those who opted to undertake or decline ETF. Pearson's Chi2 test was used to compare proportions betwee the two groups. Any participant not surviving to 3 years was then excluded from the analysis and analysed separately. In participants surviving to 3 years, longitudinal effects of enteral tube feeding upon weight gain, BMI, pulmonary function were evaluated using ANOVA (repeat measures) to explore the differences over time between the two groups over the 3 year time period and paired t-tests (1 tailed) for comparison between successive years. Data were analysed using SPSS version 19.0 (Chicago, Illinois).	(14.65) vs non-ETF (n=6): -8 (15.96) Mean (SD) change in FEV1 (% predicted) at 3 years: ETF (n=15): 1.2 (13.95) vs non-ETF (n=6): -11 (15.16) Quality of life Not reported Pulmonary exacerbations Mean (SD) change in days on IV treatment at 1 year: ETF (n=15): 20.7 (31.96) vs non-ETF (n=6):2.8 (21.92) Mean (SD) change in days on IV treatment at 2 years: ETF (n=15): 28 (54.64) vs non-ETF (n=6): -8 (17.36) Mean (SD) change in days on IV treatment at 3 years: ETF (n=15): 43.2 (73.45) vs non-ETF (n=6): 7 (25.72) Adverse effects Not reported Patient and parent or carer satisfaction Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	January 2004 and May 2008. The criteria were BMI<19 kg/m2 and/or 5% acute weight loss over a 2 month period with a failure or oral nutritional supplements to adequately improve nutritional status. Exclusion criteria Presence of pancreatic sufficiency, pregnancy or lung transplantation during the 3 year follow-up period.				
Full citation Bradley, G. M., Carson, K. A., Leonard, A. R., Mogayzel, P. J., Jr., Oliva-Hemker, M., Nutritional outcomes	Sample size N=40 Patients with gastrostomy: N=20 Patients without gastrostomy	Interventions Intervention: Gastrostomy for enteral tube feeding Control: No gastrostomy	Details Setting. Cystic fibrosis Center in Baltimore, Maryland, US Data collection. This is a retrospective study, CF Foundation Patient Registry	Results Indices of nutrition and growth Mean (SD) change in height z-score at 6 months: Cases (N=20): 0.5 (0.41) vs controls (N=20): 0.3 (0.80)*	Limitations The quality of this study was assessed with the Newcastle-Ottawa scale assessment tool: Selection: Low risk of bias. The non-exposed group were also patients

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
following gastrostomy in children with cystic fibrosis, Pediatric Pulmonology, 47, 743-8, 2012 Ref Id 366345 Country/ies where the study was carried out US Study type Retrospective cohort study Aim of the study To evaluate if children with cystic fibrosis who have a BMI <50th percentile and receive supplemental feeds via a gastrostomy are more likely to achieve BMI ≥50th percentile than matched children who are managed according to standardised nutrition protocol but do not	(control arm): N=20 Characteristics Males, n/N: patients with gastrostomy: 8/20 vs patients without gastrostomy: 8/20 Caucasian ethnicity, n/N: patients with gastrostomy: 17/20 vs patients without gastrostomy: 19/20 Median age (range) in years at CF diagnosis: patients with gastrostomy (n=20): 0.74 (0-6.58) vs patients without gastrostomy (n=20): 1.74 (0-9.41) One mutation F508del, n/N: patients with gastrostomy: 12/20 vs patients without gastrostomy: 11/20		database and hospital medical records were used for data collection. Nutritional (weight, height, BMI) and lung function (percent predicted FEV1) data were obtained at the index visit, at 6-month follow up (±3 months) and at 1 year follow up (±3 months). Height, weight and BMI z-scores were calculated using CDC reference equations. For the controls, in addition to the standard nutritional evaluation and counseling, it was specified if they received oral nutritional supplementation, an appetite stimulant or gastroenterology referral for gastrostomy placement at any time during a 1-year follow-up period. For the cases, following data on gastrostomy was collected: technique used for gastrostomy placement, length of stay at hospital	Mean (SD) change height z-score at 1 year: Cases (N=20): 0.1 (0.40) vs controls (N=20): 0 (0.80)* Mean (SD) change in weight z-score at 6 months: Cases (N=20): 0.67 (0.56) vs controls (N=20): 0.05 (0.58)* Mean (SD) change in weight z-score at 1 year: Cases (N=20): 0.64 (0.52) vs controls 0.2 (0.56)* Mean (SD) change in BMI z-score at 6 months: Cases (N=20): 0.9 (0.6) vs controls (N=20): 0.08 (0.48)* Mean (SD) change in BMI z-score at 1 year: Cases (N=20): 0.78 (0.55) vs controls (N=20): 0.39 (0.39)* FEV1 percent predicted Mean (SD) change in FEV1 percent predicted at 6 months: Cases (N=14): -1.3 (16.24) vs controls (N=13): 3.2 (14.72)* Mean (SD) change in FEV1 percent predicted at 1 year: Cases (N=14): -1.6 (15.94) vs controls (N=13): 6.6 (16.62)* Quality of life Not reported	in the same CF centre and both groups received the same nutrition protocol and in addition, the exposed group received a gastrostomy. The characteristics of the exposed group and the control group were largely similar, although their baseline height and weight z-scores were somewhat different, although neither difference reached statistical significance. Comparability: High risk of bias. The study does not control for any factor. Outcome: Low risk of bias. Not described who and how outcome measurements were done and if blinding was used. Blinding was likely not used since this is a retrospective study (i.e. not a study at the time of the measurements) using medical records and registry data. However, the outcomes of interest are weight, height, BMI and FEV, therefore, the measurements can be

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
receive gastrostomy. Study dates January 2005 to April 2010 Source of funding NIH grant 5 T32 HD 44355-8; National Center for Research Resources grant UL1 RR 025005	Two mutations F508del, n/N: patients with gastrostomy: 4/20 vs patients without gastrostomy: 6/20 Pancreatic insufficiency, n/N: patients with gastrostomy: 20/20 vs patients without gastrostomy: 20/20 History of airway infection with P. aeruginosa, n/N: patients with gastrostomy: 18/20 vs patients without gastrostomy: 13/20 History of airway infection with Burkholderia cepacia, n/N: patients with gastrostomy: 2/20 vs patients without		following the procedure with reasons for prolonged stay if appropriate, type of supplemental formula given via gastrostomy, primary schedule for administration, and complications encountered at the time of the procedure and during the first year of follow up. Data analysis. Cases were compared to controls using McNemar's test for categorical measures and paired t-test or Wilcoxon signed rank test for continuous measures. The proportion of cases and controls reaching the outcome BMI ≥50th percentile at the 6-month and 1-year follow ups was compared using Fisher's exact test abnd exact logistic regression analysis was used to estimate the odds ratio and confidence interval. Analysis was	Pulmonary exacerbations Not reported Adverse effects Not reported Patient and parent or carer satisfaction Not reported *Calculated by the NGA technical team	considered reliable. The follow up was done at 6 months and 1 year. Even longer follow up would useful as well in order to know the long term effect of gastrostomy, as the authors themselves note as well. As this is a retrospective study using medical records and registry data, there were no losses to follow up. However, data on FEV1 at baseline was only available for 14 exposed cases and 13 un-exposed controls (out of 20 patients in each group). Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	gastrostomy: 0/20 History of airway infection with Methicillin-resistant Staph. aureus, n/N: patients with gastrostomy: 4/20 vs patients without gastrostomy: 7/20 CF-related diabetes, n/N: patients with gastrostomy: 2/20 vs patients without gastrostomy: 2/20 CF-related liver disease, n/N: patients with gastrostomy: 3/20 vs patients without gastrostomy: 1/20 Mean (SD) age in years at index visit: patients with gastrostomy (n=20): 9.0 (4.4) vs patients without gastrostomy		performed using SAS version 9.22. A		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(n=20): 9.1 (4.7) Mean (SD) height z score at index visit: patients with gastrostomy (n=20): -0.94 (0.50) vs patients without gastrostomy (n=20): -0.51 (1.06) Mean (SD) weight z score at index visit: patients with gastrostomy (n=20): -1.40 (0.55) vs patients without gastrostomy (n=20): -1.06 (0.74) Mean (SD) BMI z-score at index visit: patients with gastrostomy (n=20): -1.19 (0.60) vs patients without gastrostomy (n=20): -1.10 (0.50) Mean (SD) FEV1 % predicted in				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	years at index visit: patients with gastrostomy (n=20): 76.0(19.5) vs patients without gastrostomy (n=20): 75.7 (19.0) Inclusion criteria Patients with cyctic fibrosis who -were 2-20 years of age -received health care at a cystic fibrosis center in Baltimore, US -had gastrostomy placed between January 2005 and April 2010 -had at least one year of post-gastrostomy data Control group consisted of pair-matched children or				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	young people who were also followed at the same CF Center but who did not have a gastrostomy. The "cases" and "controls" were matched at the time the case received a gastrostomy based on the following criteria: age ±2.5 years, sex, pancreatc status, BMI percentile ±10% and, if available, percent predicted FEV1 ±20%. Exclusion criteria Patients who had gastrostomy placed for reasons other than nutritional supplementatio n.				
Full citation	Sample size	Interventions See Cochrane SR Goldbeck 2014	Details	Results	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Stark, L. J., Quittner, A. L., Powers, S. W., Opipari-Arrigan, L., Bean, J. A., Duggan, C., Stallings, V. A., Randomized clinical trial of behavioral intervention and nutrition education to improve caloric intake and weight in children with cystic fibrosis, Archives of Pediatrics & Adolescent Medicine, 163, 915-21, 2009 Ref Id 366969 Country/ies where the study was carried out USA Study type RCT Aim of the study Study dates Source of funding	See Cochrane SR Goldbeck 2014 Characteristics See Cochrane SR Goldbeck 2014 Inclusion criteria See Cochrane SR Goldbeck 2014 Exclusion criteria See Cochrane SR Goldbeck 2014		See Cochrane SR Goldbeck 2014	See Cochrane SR Goldbeck 2014	See Cochrane SR Goldbeck 2014 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Watson, H., Bilton, D., Truby, H., A randomized controlled trial of a new behavioral home-based nutrition education program, "Eat Well with CF," in adults with cystic fibrosis, Journal of the American Dietetic Association, 108, 847-52, 2008 Ref Id 346635 Country/ies where the study was carried out UK Study type RCT Aim of the study Study dates Source of funding	Sample size See Cochrane SR Savage 2014 Characteristics See Cochrane SR Savage 2014 Inclusion criteria See Cochrane SR Savage 2014 Exclusion criteria See Cochrane SR Savage 2014	Interventions See Cochrane SR Savage 2014	Details See Cochrane SR Savage 2014	Results See Cochrane SR Savage 2014	Limitations See Cochrane SR Savage 2014 Other information None.
Full citation Poustie, V. J., Russell, J. E., Watling, R. M., Ashby, D.,	Sample size See Cochrane SR Smyth 2014 Characteristics	Interventions See Cochrane SR Smyth 2014	Details See Cochrane SR Smyth 2014	Results See Cochrane SR Smyth 2014	Limitations See Cochrane SR Smyth 2014 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Smyth, R. L., Calico Trial Collaborative Group, Oral protein energy supplements for children with cystic fibrosis: CALICO multicentre randomised controlled trial, BMJ, 332, 632-6, 2006 Ref Id 366523 Country/ies where the study was carried out UK Study type RCT Aim of the study Study dates Source of funding	See Cochrane SR Smyth 2014 Inclusion criteria See Cochrane SR Smyth 2014 Exclusion criteria See Cochrane SR Smyth 2014				
Full citation Kalnins, D., Corey, M., Ellis, L., Pencharz, P. B., Tullis, E., Durie, P. R., Failure of conventional strategies to	Sample size See Cochrane SR Smyth 2014 Characteristics See Cochrane SR Smyth 2014 Inclusion criteria	Interventions See Cochrane SR Smyth 2014	Details See Cochrane SR Smyth 2014	Results See Cochrane SR Smyth 2014	Limitations See Cochrane SR Smyth 2014 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
improve nutritional status in malnourished adolescents and adults with cystic fibrosis, Journal of Pediatrics, 147, 399-401, 2005 Ref Id 366437 Country/ies where the study was carried out Canada Study type Quasi-randomised controlled trial Aim of the study Study dates Source of funding	See Cochrane SR Smyth 2014 Exclusion criteria See Cochrane SR Smyth 2014				
Full citation Homnick, D. N., Homnick, B. D., Reeves, A. J., Marks, J. H., Pimentel, R. S., Bonnema, S. K., Cyproheptadine is an effective appetite stimulant in cystic fibrosis,	Sample size See Cochrane SR Chinuck 2014 Characteristics See Cochrane SR Chinuck 2014 Inclusion criteria	Interventions See Cochrane SR Chinuck 2014	Details See Cochrane SR Chinuck 2014	Results See Cochrane SR Chinuck 2014	Limitations See Cochrane SR Chinuck 2014 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pediatric Pulmonology, 38, 129-34, 2004 Ref Id 331091 Country/ies where the study was carried out USA Study type RCT Aim of the study Study dates Source of funding	See Cochrane SR Chinuck 2014 Exclusion criteria See Cochrane SR Chinuck 2014				
Full citation Powers, S. W., Byars, K. C., Mitchell, M. J., Patton, S. R., Schindler, T., Zeller, M. H., A randomized pilot study of behavioural treatment to increase calorie intake in toddlers with cystic fibrosis, Children's Health Care, 32, 297-311, 2003 Ref Id 451892	Sample size See Cochrane SR Goldbeck 2014 Characteristics See Cochrane SR Goldbeck 2014 Inclusion criteria See Cochrane SR Goldbeck 2014 Exclusion criteria See Cochrane SR Goldbeck 2014	Interventions See Cochrane SR Goldbeck 2014	Details See Cochrane SR Goldbeck 2014	Results See Cochrane SR Goldbeck 2014	Limitations See Cochrane SR Goldbeck 2014 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA Study type RCT Aim of the study Study dates Source of funding					
Full citation Eubanks, V., Koppersmith, N., Wooldridge, N., Clancy, J. P., Lyrene, R., Arani, R. B., Lee, J., Moldawer, L., Atchison, J., Sorscher, E. J., Makris, C. M., Effects of megestrol acetate on weight gain, body composition, and pulmonary function in patients with cystic fibrosis, Journal of Pediatrics, 140, 439-44, 2002 Ref Id	Sample size See Cochrane SR Chinuck 2014 Characteristics See Cochrane SR Chinuck 2014 Inclusion criteria See Cochrane SR Chinuck 2014 Exclusion criteria See Cochrane SR Chinuck 2014	Interventions See Cochrane SR Chinuck 2014	Details See Cochrane SR Chinuck 2014	Results See Cochrane SR Chinuck 2014	Limitations See Cochrane SR Chinuck 2014 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
329665 Country/ies where the study was carried out USA Study type RCT Aim of the study Study dates Source of funding					
Full citation Marchand, V., Baker, S. S., Stark, T. J., Baker, R. D., Randomized, double-blind, placebo-controlled pilot trial of megestrol acetate in malnourished children with cystic fibrosis, Journal of Pediatric Gastroenterology & Nutrition, 31, 264-9, 2000 Ref Id 365658 Country/ies where the study was carried out	Sample size See Cochrane SR Chinuck 2014 Characteristics See Cochrane SR Chinuck 2014 Inclusion criteria See Cochrane SR Chinuck 2014 Exclusion criteria See Cochrane SR Chinuck 2014	Interventions See Cochrane SR Chinuck 2014	Details See Cochrane SR Chinuck 2014	Results See Cochrane SR Chinuck 2014	Limitations See Cochrane SR Chinuck 2014 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
USA Study type RCT Aim of the study Study dates Source of funding					
Full citation Hanning, R. M., Blimkie, C. J., Bar-Or, O., Lands, L. C., Moss, L. A., Wilson, W. M., Relationships among nutritional status and skeletal and respiratory muscle function in cystic fibrosis: does early dietary supplementation make a difference?, American Journal of Clinical Nutrition, 57, 580-7, 1993 Ref Id 366418 Country/ies where the study was carried out	Sample size See Cochrane SR Smyth 2014 Characteristics See Cochrane SR Smyth 2014 Inclusion criteria See Cochrane SR Smyth 2014 Exclusion criteria See Cochrane SR Smyth 2014	Interventions See Cochrane SR Smyth 2014	Details See Cochrane SR Smyth 2014	Results See Cochrane SR Smyth 2014	Limitations See Cochrane SR Smyth 2014 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Canada Study type RCT Aim of the study Study dates Source of funding					
Full citation Stark, L. J., Mulvihill, M. M., Powers, S. W., Jelalian, E., Keating, K., Creveling, S., Byrnes-Collins, B., Harwood, I., Passero, M. A., Light, M., Miller, D. L., Hovell, M. F., Behavioral intervention to improve calorie intake of children with cystic fibrosis: treatment versus wait list control, Journal of Pediatric Gastroenterology & Nutrition, 22, 240-53, 1996 Ref Id 363074	Sample size See Cochrane SR Goldbeck 2014 Characteristics See Cochrane SR Goldbeck 2014 Inclusion criteria See Cochrane SR Goldbeck 2014 Exclusion criteria See Cochrane SR Goldbeck 2014	Interventions See Cochrane SR Goldbeck 2014	Details See Cochrane SR Goldbeck 2014	Results See Cochrane SR Goldbeck 2014	Limitations See Cochrane SR Goldbeck 2014 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA Study type RCT Aim of the study Study dates Source of funding					

G.14 Exocrine pancreatic insufficiency

Review question: In people with cystic fibrosis, what is the effectiveness of enzyme replacement therapy in the treatment of exocrine pancreatic insufficiency?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Mitchell, E. A., Quested, C., Marks, R. E., Pinnock, R. E., Elliott, R. B., Comparative trial of viokase, pancreatin and Pancrease pancrelipase (enteric coated beads) in the treatment of malabsorption in cystic fibrosis, Australian Paediatric Journal, 18, 114-7, 1982 Ref Id 346478	Sample size n=12 Characteristics Group: children Age (mean±SD): 9.6±2.1 Gender (M/F): 4/ 8 Inclusion criteria Patients with CF (diagnosis established by abnormally high sweat and sodium and chloride levels and increased faecal fat excretion). Chest disease fairly stable. Antibiotics given when medically indicated.	Interventions Intervention 1: Non-EC low-dose (Viokase® 16 capsules)* Intervention 2: Non-EC high-dose (Viokase® 32 capsules)* Intervention 3: EC low-dose (Pancrease® 11 capsules)	Details Procedure: carried out in 4 sequential 4-week periods. A 3-day stool collection was taken out at the end of each 4-week treatment period. No attempt was made to modify the diet. Outcome measure: Dietary fat intake was estimated from a 3-day food record kept by the parents during each of the stool collection periods, and stool fat measure by previously described methods (Van	Results Faecal fat (g/kg/day) 3.2±0.8 vs. 3.2±0.9 Faecal fat (g/day) 8.7±4.1 vs. 11.5±6.9 Fat absorption (%) 89.5±4.2 vs. 85.4±11.2 Stool frequency (bowel actions/ day) 1.7±0.7 vs. 1.8±0.8 Abdominal pain	Limitations Assessed with Cochrane risk of bias tool: Random sequence generation (selection bias): Unclear risk of bias (Not reported) Allocation concealment (selection bias): Unclear risk of bias (Not reported) Blinding (performance bias and detection bias): Unclear risk of bias (Not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out New Zealand Study type Cross-over trial Aim of the study To examine the effectiveness of Pancrease® with that of a widely prescribed conventional product (Viokase® pancreatin capsules) COMPARISON 2. HIGH DOSE VS LOW DOSE Study dates Not reported. Source of funding Not reported, but Pancrease® pancrealipase capsules were supplied by Ethnor Pty. Ltd.	Exclusion criteria Not reported.	Pancreatin or pancrealipase: pancrealipase Product name: Pancrease® Constituent enzymes: each capsule contains 4,000 USNF lipase units; 25,000 USNF protease units; 20,000 USNF amylase units Type of PERT: EC Formulation: beads Timing of administration: not reported Number of tablets and doses taken: 11 capsules/ day Diet/ meal supplementation: not reported With or w/out gastric acid suppression: no AA given Intervention 4: EC high-dose (Pancrease® 22 capsules) Pancreatin or pancrealipase: pancrealipase Product name: Pancrease®	der Kamer 1958). At the end of the study parents rated the treatments in order of preference. Setting: outpatient paediatrics clinic Randomisation method: not reported Allocation concealment: not reported Blinding: not reported Statistics: a William's ballanced cell design was employed to compensate for possible residual effects. For the stool frequency and side effects data, the scores of each 4-week period were combined into a single score and ranked for each child. Rank scores were analysed by Wilcoxon-Man-Whitney U-statistics. For weight change data a two-tailed paired test was performed	No difference. Data not reported. Treatment preferences High dose (Pancrease® 22) was considered better.	Incomplete outcome data (attrition bias): Low risk (All participants completed the treatments of interest) Selective reporting (reporting bias): Low risk (there were no important or systematic differences between groups in terms of those for whom outcome data were not available) Other bias: Low risk (the comparison groups received the same care apart from the intervention(s) studied; there was no difference in fat intake between the groups; the study used a precise definition of outcome; a valid and reliable method was used to measure stool fat, although the method used to diagnose side effects was unclear; the study had an appropriate time of follow-up; all groups were followed

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		Constituent enzymes: each capsule contains 4,000 USNF lipase units; 25,000 USNF protease units; 20,000 USNF amylase units Type of PERT: EC Formulation: beads Timing of administration: not reported Number of tablets and doses taken: 22 capsules/ day Diet/ meal supplementation: not reported With or w/out gastric acid suppression: no AA given *Interventions with non-EC PERT (Viokase) are not relevant to the protocol			up for an equal length of time) Other information Potential conflict of interest? Measure of fat intake self-reported. Patients on their own diet. Study does report weight change results, but follow-up is <28 days Results for tables 2 and 4 cannot be reported, blurred copy of the paper
Full citation Beker, L. T., Fink, R. J., Shamsa, F. H., Chaney, H. R., Kluft, J., Evans, E., Schidlow, D. V., Comparison of weight-	Sample size n=21 Characteristics Group: children Gender (M/F): 13/ 8 Age (mean±SD): 11.5±3.2 (5 to 28)	Interventions High dose: Pancreatin or pancrealipase: not reported Product name: not reported	Details Procedure: Patients were hospitalized for 9 days, with a 48-h wash out period between regimes. The enzyme dosage was given in combination to	Results Fecal fat excretion (g/24 h) mean±SEM: 10.3±2.4 vs. 15.3±3.7 Fat absorption (%)	Limitations Assessed with Cochrane risk of bias tool: Random sequence generation (selection bias): Low risk (An

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
based dosages of enteric-coated microtablet enzyme preparations in patients with cystic fibrosis, Journal of Pediatric Gastroenterology & Nutrition, 19, 191-7, 1994 Ref Id 346496 Country/ies where the study was carried out USA Study type Open-label cross over clinical trial Aim of the study To evaluate the effectiveness of large doses of lipase in improving the absorption of dietary fat by using and EC microtablet enzyme preparation. Study dates Not reported. Source of funding Funded in part by a grant from the R.W. Johnson Pharmaceutical Research Institute.	Inclusion criteria Diagnosis of CF based on abnormal sweat chloride levels of >60 mEq/L. (Gibson & Cooke). Pancreatic insufficiency for >6 months. >2 years old Exclusion criteria Patients in other study protocols. Patients taking other drugs that could augment the effect of enzymes (antacid, H2, antidiarrheal drugs...).	Constituent enzymes: lipase Type of PERT: EC Formulation: microtablets Timing of administration: not reported Number of tablets and doses taken: 1500U lipase per kg/body weight for meal & 750U lipase per kg/body weight for snack in appropriate combination Diet/ meal supplementation: if necessary high-fat foods given to achieve 100g diet With or w/out gastric acid suppression: no AA given Low dose: Pancreatin or pancrealipase: not reported Product name: not reported Constituent enzymes: lipase Type of PERT: EC	achieve ≥4,000; 12,000 & 16,000 U of lipase to provide the lowest number of capsules possible. Subjects were instructed about the fat content of hospital menu and were supplemented with high-fat foods to achieve an estimated 100g fat diet. A 72-h stool collection was obtained at the end of each dosage regimen. Outcome measures: Stool collections were assessed for fecal fat using the van de Kamer method. Setting: hospital Randomization: simple randomization scheme generated from random digit tables Concealment: not reported Blinding: open-label Statistics: an equivalent to the ANOVA for cross-over trials, the two-sample t test was used. A t test compared the sum of both treatment periods was used to determine if there was treatment effect.	Mean±SEM: 91.2±1.6 vs. 86.2±3.2 Side effects Episodes of constipation or elevations in serum uric acid levels on either enzyme dose were not observed.	appropriate method of randomization was used; the groups were comparable at baseline). Allocation concealment (selection bias): Unclear risk (Unclear if there was appropriate allocation concealment) Blinding (performance bias and detection bias): Unclear risk (Participants were not "blind" to treatment allocation; those administering care and investigators were not "blind" either; however fecal fat is an objective measure) Incomplete outcome data (attrition bias): Low risk (There were no important or systematic differences between groups in terms of those who did not complete treatment). Selective reporting (reporting bias): Low risk (there were no

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		Formulation: microtablets Timing of administration: not reported Number of tablets and doses taken: 500U lipase per kg/body weight for meal & 250U lipase per kg/body weight for snack in appropriate combination Diet/ meal supplementation: if necessary high-fat foods given to achieve 100g diet With or w/out gastric acid suppression: no AA given			important or systematic differences between groups in terms of those for whom outcome data were not available). Other bias: Low risk (the comparison groups received the same care apart from the intervention(s) studied; although fat intake was not standardized there were no significant differences in fat intake between the groups; the study used a precise definition of outcome and a valid and reliable method was used to determine the outcome; the study had an appropriate time of follow-up; all groups were followed up for an equal length of time) Other information Potential conflict of interest. No carry-over effect ($p<0.05$)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Durie, P. R., Bell, L., Linton, W., Corey, M. L., Forstner, G. G., Effect of cimetidine and sodium bicarbonate on pancreatic replacement therapy in cystic fibrosis, Gut, 21, 778-86, 1980 Ref Id 333989 Country/ies where the study was carried out Canada Study type Cross-over Aim of the study To compare the use of cimetidine as adjunt to PERT in a restricted population of adolescent patients with CF and steatorrhoea. Study dates Not reported Source of funding Not reported.	Sample size n=21 Characteristics Age: 10 to 21 years old Gender: not reported Inclusion criteria Patients with CF (diagnosed confirmed by a raised sweat chloride determination >60 mmol) All patients had malabsorption by history Patients on receiving PERT treatment Exclusion criteria Individuals with normal pancreatic function, cardiac disorders, hepatobiliary disease, diabetes or severe pulmonary symptoms.	Interventions Group 1: Pancrealipase alone Pancreatin or pancrealipase: pancrealipase Product name: Cotazym® (not authorized in the UK, but same active principle) Constituent enzymes: not reported Type of PERT: EC Formulation: capsules Timing of administration: not reported Number of tablets and doses taken: 26 capsules/ day (6 capsules per meal & 3 capsules per snack) Diet/ meal supplementation: not modifications made to diet, but food was recorded. Mean intake during study 116±39.9 fat With or w/out gastric acid suppression: no AA given	Details Procedure: Each treatment period consisted of 3 days of equilibration followed by 4 days of stool collection. A registered nurse coordinated the study and provided instructions for the completion of food records, administration of drugs and stool collection. Outcome measure: Stool was analyzed for fat using the Van der Kamer method. A stool sheet was used to record the nature and frequency of bowel movements. Setting: CF clinic at the Hospital for Sick Children, Toronto Randomization method:not reported Allocation method: not reported Blinding: not reported Statistical analysis: Stool fat was analyzed using the ANOVA for cross-classifications (randomized blocks) with subsampling. Faecal outputs of fat were compared by ANOVA for	Results Faecal fat (g/24h) Pancrealipase + cimetidine: 20.3±12.6 Pancrealipase alone: 31.3±15.5 (p=0.01) Faecal fat (% of intake) Pancrealipase + cimetidine: 17.8±9.7 Pancrealipase alone: 27.6±13.3 (p=0.01)	Limitations Assessed with Cochrane risk of bias tool: Random sequence generation (selection bias): Unclear risk (Not reported. Unclear if the groups were comparable at baseline). Allocation concealment (selection bias): Unclear risk (Not reported) Blinding (performance bias and detection bias): Unclear risk (Not reported; however fecal fat is an objective measure, thus blinding may not be very important) Incomplete outcome data (attrition bias): Unclear risk (Of the 21 patients that entered the study, 3 withdrew voluntarily after 3 days (no explanation). Three patients were withdrawn on evidence of poor

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		Group 2: pancrealipase + cimetidine Pancreatin or pancrealipase: pancrealipase Product name: Cotazym® (not authorized in the UK, but same active principle) Constituent enzymes: not reported Type of PERT: EC Formulation: capsules Timing of administration: not reported Number of tablets and doses taken: 26 capsules/ day (6 capsules per meal & 3 capsules per snack) Diet/ meal supplementation: not modifications made to diet, but food was recorded. Mean intake during study 116±39.9 fat. With or w/out gastric acid suppression: cimetadine, supplied as 200g & 300g tablets, give in 4 equal doses (1h after food and at bedtime)	randomized blocks and paired t-test.		drug and diet compliance and inadequate stool collection. One patient withdrew because of a possible complication with cimetidine; unclear if there were important or systematic differences between groups in terms of those who did not complete treatment) Selective reporting (reporting bias): Unclear risk (see withdrawals described above) Other bias: Low risk (the comparison groups received the same care apart from the intervention(s) studied; the study had an appropriate time of follow-up; all groups were followed up for an equal length of time) Other information Important lost to follow-up (15 of 21 completed the study)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		in a total dose of 20 mg/kg/day			One patient withdraw because of a possible complication with cimetidine.
Full citation Brady, M. S., Rickard, K., Yu, P. L., Eigen, H., Effectiveness and safety of small vs. large doses of enteric coated pancreatic enzymes in reducing steatorrhea in children with cystic fibrosis: a prospective randomized study, Pediatric Pulmonology, 10, 79-85, 1991 Ref Id 346528 Country/ies where the study was carried out USA Study type A prospective randomized cross-over study Aim of the study To evaluate the effectiveness and safety of a relatively large dose (patient's usual dose) vs a small dose (1/4 usual dose)	Sample size n=9 Characteristics Group: children Gender (M/F): 5/ 4 Age (median/ range): 9yr 5mo (6yr 10mo to 10yr 2mo) Inclusion criteria Children with CF (diagnosis established by duplicate sweat chloride measurements of greater than 60 mEq/L, according to Gibson and Cooke). Patients who experienced malabsortion by history and consumed relatively large doses of EC enzymes (eg. >25 capsules/day) Nourished subjects (weight for height > 5th percentile) Serum albumin concentration ≥3.2 g/dl No patient received antibiotics or any drugs known to interfere with	Interventions High-dose: the usual clinically established dose of EC enzyme capsules Pancreatin or pancrealipase: not reported Product name: not reported Constituent enzymes: Type of PERT: EC Formulation: capsules Timing of administration: immediately before meals Number of tablets and doses taken: mean±SE 12±1.2: range 8 to 18 capsules per meal Diet/ meal supplementation: all participants received same amount of daily fat (94±6) With or w/out gastric acid suppression: no AA given	Details Procedure: carried out in 2 consecutive 7-day treatment periods. Each treatment period consisted of 3 days at home (wash-out and recovery period) followed by 4 days of weighted food intake and 72h stool collection in the hospital Outcome measure: all stools were analyzed for fat using the method of van de Kamer Setting: inpatients at the Indiana University Hospital Randomisation method: was done balancing by gender, but details are not reported Allocation concealment: not reported Statistics: mean & SEM calculated for all outcomes, including fat excretion. An ANOVA for cross-over designs was performed to compare large vs low dose. A one-tailed paired t-test was	Results Fecal fat excretion (as % of fat intake) - as % of intake (mean±SEM): 8.7±2.2 vs. 13±3.0; p=0.037 - g/kg/24h (mean±SEM): 0.296±0.093 vs. 0.497±0.126; p=0.039 - g/24h. (mean±SEM): 7.89±1.77 vs. 11.92±2.42; p=0.051	Limitations Limitations assessed with the Cochrane risk of bias tool: Random sequence generation (selection bias): Unclear risk (Not reported. Unclear if the groups were comparable at baseline) Allocation concealment (selection bias): Unclear risk (Not reported) Blinding (performance bias and detection bias): Unclear risk of bias (Not reported, however given the nature of the outcomes it may not have an impact) Incomplete outcome data (attrition bias): Low risk (The groups were comparable for treatment completion)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of EC pancreatic enzymes. (COMPARISON 2. HIGH DOSE VS LOW DOSE) Study dates Not reported Source of funding Partly funded by Indiana University research grant MO1 RR 00750-15	uric acid metabolism or excretion. Exclusion criteria None reported.	Low-dose: one-fourth of the usual dose of EC enzyme capsules Pancreatin or pancrealipase: not reported Product name: not reported Constituent enzymes: Type of PERT: EC Formulation: capsules Timing of administration: immediately before meals Number of tablets and doses taken: mean±SE 3±0.4: range 2 to 5 capsules per meal Diet/ meal supplementation: all participants received same amount of daily fat (94±6) With or w/out gastric acid suppression: no AA given Treatment details: 7,020 units of lipase	used to determine the significance of the differences between doses within each subject.		Selective reporting (reporting bias): Low risk (The groups were comparable with respect to the availability of outcome data) Other bias: Low risk (the comparison groups received the same care apart from the intervention(s) studied; the study used a precise definition of outcome; a valid and reliable method was used to measure the outcomes; the study had an appropriate time of follow-up; all groups were followed up for an equal length of time) Other information Conflict of interest: not reported Possible indirectness: inpatients only? Only includes patients who experienced malabsorption by history

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Doses non-standardized
Full citation Heijerman, H. G., Lamers, C. B., Bakker, W., Dijkman, J. H., Improvement of fecal fat excretion after addition of omeprazole to pancrease in cystic fibrosis is related to residual exocrine function of the pancreas, Digestive Diseases & Sciences, 38, 1-6, 1993 Ref Id 346581 Country/ies where the study was carried out Netherlands Study type Double-blind, randomised cross-over fashion using single dummy technique Aim of the study To investigate the effect of omeprozole-induced gastric acid inhibition on fecal fat excretion during treatment with a standard dose of	Sample size N = 11 Characteristics Male/Female: 5/6 Age: 20 - 42 All patients had pulmonary involvements and used pancreatic enzyme supplements because of pancreatic insufficiency. 1 patient had insulin-dependent diabetes mellitus. No patient had previous gastrointestinal surgery or renal failure. Inclusion criteria - Patients with a faecal fat excretion of more than 10% during treatment wit pancrease 2 capsules three times a day Exclusion criteria Not reported.	Interventions 2 different modalities for 14 days cross-over (28 days in total). 1) Pancrease 2 caps, 3 per day and omeprozole placebo 2) Pancrease 2 caps, 3 per day and omeprozole 20 mg once in the morning Pancrease: 5000 units lipase, 2900 units amylase, 330 units protease per capsule	Details Pancreatic function tests were performed after an overnight fast. Two basal blood samples with an interval of 10 minutes were taken, followed by a test meal consisting of 200 ml Noridrink (Nutricia, Zoertermeer, The Netherlans) and 200 g yoghurt to which 50 g glucose (to all apart from participant with diabetes) and 2 mmol of synthetic peptide NBT-PAPA, bentitomide has been added. The meal consisted of 16.6 g protein, 20 g fat and 93.8 g carbohydrate (around 622 cal / 2611 J). Omeprozole or matching placebo was given 30 minutes before breakfast while pancrease was taken 3 times a day, one capsule before and one capsule directly after each meal. During last 5 days of each treatment period, all subjects were on their usual diet with a fixed daily fat intake, identical during both	Results Faecal fat excretion (% of daily fat intake): Treat A: Pancreas alone: mean: 22.9, median: 20, range: 12 to 44; vs Treat B: Pancrease + Omeprazole: mean: 18.1, median: 17, range: 4 to 45. Change of faecal fat excretion (%): Mean: 18.8; median: 19; range: -42 to 75. Change in faecal fat excretion = [(B - A)/A]	Limitations Assessed with Cochrane risk of bias tool: Random sequence generation (selection bias): Unclear risk (Method of randomisation unclear; groups were not comparable at baseline because daily intake of fat differed, it was low for 3/11 participants) Allocation concealment (selection bias): Unclear risk (Not reported) Blinding (performance bias and detection bias): Low risk (Double blind) Incomplete outcome data (attrition bias): Low risk (All participants completed treatment) Selective reporting (reporting bias): Low risk (The groups were comparable

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
pancrease and its relation with residual exocrine pancreatic function as determined by noninvasive tests. Study dates Not reported. Source of funding Not reported.			treatment periods. On the last 3 days of each treatment period, fat excretion was measured on the last day of each treatment period according to Van de Kamer et al, 1949 method. Randomisation method Unclear Allocation concealment Unclear Statistical analysis Differences in faecal fat excretion were calculated using Wilcoxon's rank-sum test for paired differences.		with respect to the availability of outcome data) Other bias: Low risk (The comparison groups received the same care apart from the intervention(s) studied. The study used a precise definition of outcome. A valid and reliable method was used to determine the outcome. The study had an appropriate length of follow-up. All groups were followed up for an equal length of time). Other information
Full citation Heijerman, H. G., Lamers, C. B., Bakker, W., Omeprazole enhances the efficacy of pancreatin (pancrease) in cystic fibrosis, Annals of Internal Medicine, 114, 200-1, 1991 Ref Id 346607	Sample size n=9 Characteristics Mean age in years: 29 (23-42) Adult patients who had CF with pulmonary and pancreatic involvement. Diagnostic of CF by a positive quantitative sweat test: choride concetration › 60 mmol/l.	Interventions I1. Pancrease low dose Pancreatin or pancrealipase: pancreatin Product name: Pancrease (Cilag, Herentals) Constituent enzymes (per capsule): 5000u lipase, 2900u	Details Procedure: During the last 5 days of each treatment period, all patients were on their usual diet with a fixed daily fat intake, which was identical during each treatment period. On the last 3 days of the fixed daily fat intake a 72h stool collectin was done	Results Fetal fat excretion (% of intake) Comparison 2. High dose vs low dose: I2 vs I1. median: 18 (10-34) vs. 20 (12-44) Comparison 3: PERT vs PERT+AA I3 vs I1:	Limitations Assessed with Cochrane risk of bias tool: Random sequence generation (selection bias): Unclear risk (Method of randomisation unclear; unclear if the groups were comparable at baseline)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Holland Study type Double-blind, placebo-controlled, randomized crossover study Aim of the study The effect of Omeprazole therapy as adjunt to two different doses of Pancrease on fecal fat excretion in adult patients with CF. (COMPARISON 1. AA VS NON-AC) (COMPARISON 2. HIGH DOSE VS LOW DOSE) Study dates Not reported Source of funding Not reported. However Pancrease and matching placebos were provided by Cylag Limited Herentals (Belgium) and Omeprazole and matching placebos by Hässle Mölndal (Sweeden)	Inclusion criteria Patients with a fecal fat excretion of more than 10% during treatment with Pancrease, 2 capsules/ 3 times per day. Exclusion criteria None reported.	amylase, 330u amylase Type of PERT: EC Formulation: microspheres Timing of administration: 3 times per day, divided in aliquots of half the dose just before and after the meals Number of tablets and doses taken: 6 capsules (2 capsules/ 3 times day) Diet/ meal supplementation: not given With or w/out gastric acid suppression: without I2. Pancrease high dose only 4 capsules/ 3 times day Pancreatin or pancrealipase: pancreatin Product name: Pancrease (Cilag, Herentals) Constituent enzymes (per capsule): 5000u lipase, 2900u amylase, 330u amylase Type of PERT: EC	Outcome measure: fat content determined by the method of Van de Kamer Setting: not reported Randomisation method: not reported Allocation concealment: not reported Statistics: Wilcoxon rank-sum test for paired differences	median: 14 (6-32) vs. 20 (12-44) I4 vs I2: median: 9 (4-25) vs. 18 (10-34)	Allocation concealment (selection bias): Unclear risk (Unclear if there was appropriate allocation concealment) Blinding (performance bias and detection bias): Low risk (Participants and those administering care were blinded to treatment allocation, although the authors do not explain how this was done; Unclear if investigators were kept blinded to participants' exposure to the intervention and to other confounding and prognostic factors). Incomplete outcome data (attrition bias): Low risk (All participants completed treatment) Selective reporting (reporting bias): Low risk (Outcome data available for all participants)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		Formulation: microspheres Timing of administration: 3 times per day, divided in aliquots of half the dose just before and after the meals Number of tablets and doses taken: 12 capsules (4 capsules/ 3 times day) Diet/ meal supplementation: not given With or w/out gastric acid suppression: without I3. Pancrease low dose + AA Pancreatin or pancrealipase: pancreatin Product name: Pancrease (Cilag, Herentals) Constituent enzymes (per capsule): 5000u lipase, 2900u amylase, 330u amylase Type of PERT: EC Formulation: microspheres Timing of administration: 3 times per day, divided			Other bias: Low risk (The comparison groups received the same care apart from the intervention(s) studied. The study used a precise definition of outcome. A valid and reliable method was used to determine the outcome. The study had an appropriate length of follow-up. All groups were followed up for an equal length of time). Other information Conflict of interest: not reported Wash out period

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		in aliquots of half the dose just before and after the meals Number of tablets and doses taken: 6 capsules (2 capsules/ 3 times day) Diet/ meal supplementation: not given With or w/out gastric acid suppression: Omeprazole 20 mg/day 30' before breakfast I4. Pancrease high dose + AA Pancreatin or pancrealipase: pancreatin Product name: Pancrease (Cilag, Herentals) Constituent enzymes (per capsule): 5000u lipase, 2900u amylase, 330u amylase Type of PERT: EC Formulation: microspheres Timing of administration: 3 times per day, divided in aliquots of half the dose just before and after the meals			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		Number of tablets and doses taken: 12 capsules (4 capsules/ 3 times day) Diet/ meal supplementation: not given With or w/out gastric acid suppression: Omeprazole 20 mg/day 30' before breakfast			
Full citation Francisco, M. P., Wagner, M. H., Sherman, J. M., Theriaque, D., Bowser, E., Novak, D. A., Ranitidine and omeprazole as adjuvant therapy to pancrelipase to improve fat absorption in patients with cystic fibrosis, Journal of Pediatric Gastroenterology & Nutrition, 35, 79-83, 2002 Ref Id 333998 Country/ies where the study was carried out	Sample size 10 adults and 12 children Characteristics 15 males Adults age: 18 to 36 yo Children age: 6 to 17 yo Inclusion criteria Patients with CF confirmed by a sweat test and pancreatic insufficiency Patients were not receiving other agents to modify intestinal Exclusion criteria Pregnant patients Patients with cholestasis (bilitrrubin concentration pH> 1.5 mg/dl)	Interventions PERT treatment was the same for all patients in the trial: Pancreatin or pancrealipase: pancrealipase Product name: Pancrease® MT10 or MT16 Constituent enzymes: not reported Type of PERT: EC Formulation: microtablet Timing of administration: not reported Number of tablets and doses taken: not reported	Details Procedure:patients were studied at baseline whilst receiving their usual dose of PERT and where needed the dosages were adjusted before adding adjuvant therapy. All patients were changed to Pancrease M10 or M16, equivalent to their usual home dosage and received enzymes from the same lot. Adjuvant therapy was started 3 days before admission. Patients received a controlled diet based on an analysis conducted during 3 days of eating their usual home diets. The diet for	Results Fat absorption* Adults Low dose ranitidine: 84.45, 91.42, 94.7, 97.45, 97.45, 95.52, 72.28, 96.3, 96.55, 86.24 High dose ranitidine: 87.56, 91.87, 88.62, ND, 81.89, 79.88, 81, 97.02, 93.48, 91.11 Omeprazole: 84.72, 90.88, 94.27, ND, 84.45, 88.26, 65.48, 85.13, 92.39, 87.4 Placebo: 75.47, 90.86, 88.59, 89.8, 79.01, 93.76, 60.22, 94.73, 96.21, 80.48 Children	Limitations Assessed with Cochrane risk of bias tool: Random sequence generation (selection bias): Unclear risk (details not reported) Allocation concealment (selection bias): Unclear risk (Unclear if there was adequate concealment allocation) Blinding (performance bias and detection bias): Low risk (Participants and those administering care were kept blinded to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
USA Study type Double-blind placebo controlled crossover study Aim of the study To measure the effect of acid suppressant therapy of fat absorption in patients with CF who received a pH-sensitve, ECM enzyme product Study dates Not reported Source of funding Glaxo-Wellcome, Merck and Ortho-McNeil provided the drugs	Patients with hepatosplenomegaly	Diet/ meal supplementation: diet fat was kept constant, no exact data reported With or w/out gastric acid suppression: there are four intervention conditions Low-dose or high-dose ranitidine: children weighting ≤40 kg were given ranitidine 5 mg/kg or 10 mg/kg daily, divided into 2 equal doses 30 minutes before breakfast and dinner. Children weighting >40 kg and adults received 150 mg or 300 mg twice daily. Omeprazole (adults only): 20 mg daily, 30 minutes before breakfast Placebo	each fat-balance study period was kept constant for fat content and the number of meals and snacks per day. Carmine red. 1,000 mg was administered at the time the controlled diet started, and a second dose of carmine red was administered 72h later. Stool collection started after the first red stool had passed and continued until the second red marker was passed. Outcome measure: Fat absorption was calculated as 72-hour dietary fat intake (g). Quantitative fat analysis was performed according to Van de Kamer method. Setting: inpatients Randomization method: the order of treatment was randomly assigned, although the details were not reported Allocation concealment: not reported Blinding: double-blind, details not reported Statistics: paired t-test.	Low dose ranitide: 87.65, 95.69, 72.38, 75.74, 86.34, 80.85, 89.38, 74.67, 68.15, 63.81, 90.55, 94.69 High dose ranitide: 93.27, 80.5, 86.25, 78.19, 88.02, 61.78, 88.77, 69.84, 69.01, 75.59, 81.31, 94.33 Placebo: 92.24, 72.58, 72.53, 88.5, 88.35, 72.12, 92.51, 85.11, 72.12, 60.85, 75.62, 93.25 *The paper provided raw data. Medians and p values were calculated by the technical team.	treatment allocation, although details on how this was done were not reported; unclear if investigators were kept blinded to participants' exposure to intervention and important confounding and prognostic factors) Incomplete outcome data (attrition bias): Low risk (There were no important or systematic differences between groups in terms of those who did not complete treatment. Data is missing only for 1 adult for the high dose and Omeprazole comparisons). Selective reporting (reporting bias): Low risk (The groups were comparable with respect to the availability of outcome data) Other bias: Low risk (The comparison groups received the same care apart from

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					the intervention(s) studied. The study used a precise definition of outcome. A valid and reliable method was used to determine the outcome. The study had an appropriate length of follow-up. All groups were followed up for an equal length of time). Other information Small population for adult interventions with high-dose ranitidine and omeprazole

G.15 Distal ileal obstruction syndrome

Review question: What are the effective strategies for treatment and secondary prevention of distal ileal obstruction syndrome?

No clinical evidence was identified for this review.

G.16 Liver disease

Review question: What is the effectiveness of ultrasound scanning to detect clinically important cystic fibrosis related liver disease?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Fagundes, E. D. T., Silva, R. A. P., Roquete, M. L. V., Penna, F. J., Reis, F. J. C., Goulart, E. M. A., Duque, C. G., Validation of the Williams ultrasound scoring system for the diagnosis of liver disease in cystic fibrosis, Jornal de Pediatria, 80, 380-386, 2004 Ref Id 354000 Country/ies where the study was carried out Brazil Study type Prospective cohort study Aim of the study To describe the hepatic abnormalities viewed in the ultrasound scans of CF patients at the Cystic Fibrosis	Sample size n=70 CF patients Characteristics Mean age, years (SD): 10.9 (6.4) 60% male 14.3% met the clinical and/or biochemical criteria for liver disease Inclusion Criteria -Confirmed CF diagnoses Exclusion Criteria Other causes of liver disease, such as Wilson's disease, hepatitis B and C, deficiency of alpha-1-antitrypsin and auto-immune hepatitis	Tests Reference test Clinical and biochemical criteria. The clinical examination was considered abnormal when the presence of a palpable spleen and/or hepatomegaly, defined as the presence of a palpable liver more than 2.5 cm below the right costal margin (RCM), of firm consistency. Abnormal biochemistry was defined as a significant and persistent increase, of at least 1.5 times the upper limit of the reference range, of at least two of the enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP) or gamma-glutamyltranspeptidase (GGT), for a period	Methods Setting: CF outpatient clinic at a Brazilian university Seventy cystic fibrosis patients were followed prospectively and underwent clinical, biochemical and ultrasound examinations. The ultrasound findings were compared to the results of the clinical and biochemical examinations. Clinical and biochemical criteria were used as the gold standard for the validation of the Williams ultrasound score. We calculated the sensitivity, specificity, and positive and negative predictive values for the Williams score. The patients were divided into two groups: normal (score = 3) or abnormal (score > 3) ultrasound examination.	Results Williams US score versus clinical and/or biochemical criteria for detection of CFLD n=70 True positive=5* False positive=5* False negative=5* True negative=55* Sensitivity=50 (95% CI: 22.0-75.1)* Specificity=91.7 (95% CI: 87.0-95.8)* Positive LR= 6.0 (95% CI: 1.70-18.07)* Negative LR= 0.55 (95% CI: 0.26-0.90)* AUROC=NR *Calculated by the NGA technical team from data reported in the article NR=not reported LR = likelihood ratio	Limitations QUADAS 2 checklist Patient selection Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes 1.A Could the selection of patients have introduced bias? LOW RISK OF BIAS 1.B Is there concern that the included patients do not match the review question? LOW CONCERN Index Test Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? N/A 2.A Could the conduct or interpretation of the index test have introduced bias? LOW RISK

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Outpatients Clinic at the Hospital das Clínicas of UFMG, to compare these ultrasound findings with biochemical and clinical criteria and validate the Williams score for the diagnosis of CF-associated liver disease. Study dates 1999-2000 Source of funding Not reported		of more than 6 months. Index tests Williams ultrasound score: normal ultrasound results (score = 3) or abnormal (score > 3). Patients underwent the hepatobiliary ultrasound examination at the Radiology Service of the Hospital das Clínicas at UFMG. All examinations were performed by the same ultrasound operator with no regard to the clinical and biochemical situation of the patients. The apparatus employed was from the Siemens Prima line, a multi-frequency (2.6 to 5.0 MHz) Sonoline Prima, with convex probe.Abnormalities in the echogenicity of the hepatic parenchyma and edge were noted as was periportal fibrosis, in accordance with the scoring			2.B Is there concern that the index test, its conduct, or interpretation differ from the review question? LOW CONCERN Reference Standard Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes 3.A Could the reference standard, its conduct, or its interpretation have introduced bias? LOW RISK 3.B Is there concern that the target condition as defined by the reference standard does not match the review question? LOW RISK Flow and Timing Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
		devised by Williams et al. Signs suggestive of steatosis, the presence of ascites and collateral portal system damage were noted in addition to measurements for the liver, spleen and gallbladder taken with the electronic pachymeter. The right lobe of the liver was measured from the phrenic cupola to its lower edge, at the level of the right hemiclavicular line, to the right of the gallbladder bed and the left lobe, in turn, from the phrenic cupola to the lower edge, at the level of the sagittal line. The longitudinal axis of the spleen was measure at the level of the medial axillary line and the anterior-posterior along the left flank. Reference values for liver and spleen measurements for the different age groups were taken from a study by Konus et al.			4.A Could the patient flow have introduced bias? LOW RISK Other information None.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Karlas, T., Neuschulz, M., Oltmanns, A., Guttler, A., Petroff, D., Wirtz, H., Mainz, J. G., Mossner, J., Berg, T., Troltzsch, M., Keim, V., Wiegand, J., Non-invasive evaluation of cystic fibrosis related liver disease in adults with ARFI, transient elastography and different fibrosis scores, PLoS ONE [Electronic Resource], 7, e42139, 2012 Ref Id 354030 Country/ies where the study was carried out Germany Study type Case-control study Aim of the study Evaluate transient elastography (TE), acoustic radiation force impulse imaging (ARFI),	Sample size 55 adults with CF 14 with CFLD Characteristics Total study cohort/without CFLD/with CFLD/CFLD without cirrhosis/CFLD with cirrhosis Male, n: 31/24/7/4/3 Age, year, mean (SD): 31.9(8.8)/32.9(9.0)/29.0(8.0)/29.6(7.8)/28.3(8.9) Inclusion Criteria Adult CF patients Exclusion Criteria Patients with pregnancy, age < 18 years, and liver transplantation	Tests Reference test Cystic fibrosis-related liver disease was defined if at least 2 of the following conditions were present on at least 2 consecutive examinations spanning a 1-year period [6,7]: (1) Ultrasound confirmed hepatomegaly; (2) elevated serum liver enzyme levels of ALT, AST, AP, or GGT; (3) ultrasound abnormalities other than hepatomegaly (i.e., increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly). An ultrasonographic pattern of simple liver steatosis did not represent a diagnostic criterion. In case of distinct ultrasonographic signs of liver cirrhosis (i.e. coarse nodularity, presence of portal	Methods Adult CF patients were prospectively investigated at presentation to the pulmonary outpatient clinic for clinical routine examinations. Patients with pregnancy, age 18 years, and liver transplantation were not included. Patients underwent conventional upper abdomen ultrasound evaluation, elastography and blood tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), bilirubin, gammaglutamyltransferase (GGT), blood count, INR, albumin, creatinine, and cholesterol) at the same day. Fasting for at least three hours was required prior to examination, however exceptions were permitted when clinically required. Previous ultrasound reports, recent pulmonary	Results TE versus published criteria for detection of CFLD n=49 True positive=6* False positive=1* False negative=8* True negative=34* Sensitivity=42.9 (95% CI: 22.6-49.6)* Specificity=97.1 (95% CI: 89.0-99.8)* Positive LR= 15.0 (95% CI: 2.06-328.3)* Negative LR= 0.59 (95% CI: 0.51-0.87)* AUROC=0.68 (95% CI: 0.53-0.80) APRI versus published criteria for detection of CFLD n=55 True positive=12* False positive=12* False negative=2* True negative=29* Sensitivity=85.7 (95% CI: 60-97.4)* Specificity=70.7 (95% CI: 62.0-74.7)*	Limitations QUADAS 2 checklist Patient selection Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Yes 1.A Could the selection of patients have introduced bias? LOW RISK OF BIAS 1.B Is there concern that the included patients do not match the review question? LOW CONCERN Index Test Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? N/A 2.A Could the conduct or interpretation of the index test have introduced bias? UNCLEAR 2.B Is there concern that the index test, its conduct, or interpretation differ from the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
and fibrosis indices for CFLD detection. Study dates April-Dec 2010 Source of funding None		hypertension and rarefication of peripheral portal veins) and clinical signs (e.g. esophageal varices, splenomegaly) of liver cirrhosis CFLD patients were classified as cirrhotics. Index tests -Transient elastography (TE): all subjects were examined in a supine position immediately after ARFI measurement. TE was performed in a right intercostal space in resting respiratory position. 10 valid measurements were taken according to the manufacturer's recommendation (M probe). Measurements were performed by experienced operators (TK, VK, MN, MT). Patients with an interquartile range (IQR).median value/3 or a success rate below 60% were considered as invalid	function tests (time span < 6 months), and results of previous routine blood tests were collected from clinical records. TE and ARFI were performed in 55 adult CF patients. In addition, AST/Platelets-Ratio-Index (APRI), and Forns' score were calculated. Healthy probands and patients with alcoholic liver cirrhosis served as controls	Positive LR= 2.93 (95% CI: 1.58-3.86)* Negative LR= 0.20 (95% CI: 0.04-0.65)* AUROC=0.82 (95% CI: 0.69-0.91) FORNS versus published criteria for detection of CFLD n=55 True positive=13* False positive=16* False negative=1* True negative=25* Sensitivity=92.9 (95% CI: 67.8-99.6)* Specificity=61.0 (95% CI: 52.4-63.3)* Positive LR= 2.38 (95% CI: 1.43-2.71)* Negative LR= 0.12 (95% CI: 0.006-0.61)* AUROC=0.79 (95% CI: 0.65-0.89) TE versus published criteria for detection of CFLD cirrhosis n=14 True positive=6* False positive=2* False negative=0.5** True negative=6*	review question? LOW CONCERN Reference Standard Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear 3.A Could the reference standard, its conduct, or its interpretation have introduced bias? LOW RISK 3.B Is there concern that the target condition as defined by the reference standard does not match the review question? LOW RISK Flow and Timing Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? No 4.A Could the patient flow have introduced bias? LOW RISK

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
		and excluded from further analysis. -AST/Platelets-Ratio-Index (APRI) -Forns' score was calculated according to the formula: score=7.811-3:131 x platelet count (109 /l)+ 0.781 x ln GGT (UI/l) + 3.467 x ln age (years)- 0.014xcholesterol (mg/dl)		Sensitivity=92.3 (95% CI: 56.2-100)* Specificity=75 (95% CI: 45.7-81.2)* Positive LR= 3.69 (95% CI: 1.04-5.33)* Negative LR= 0.10 (95% CI: 0-0.96)* AUROC=0.88 (95% CI: 0.59-0.99) APRI versus published criteria for detection of CFLD cirrhosis n=14 True positive=5* False positive=1* False negative=1* True negative=7* Sensitivity=83.3 (95% CI: 45.0-98.5)* Specificity=87.5 (95% CI: 58.8-98.9)* Positive LR= 6.67 (95% CI: 1.09-88.5)* Negative LR= 0.19 (95% CI: 0.02-0.94)* AUROC=0.88 (95% CI: 0.59-0.99) FORNS versus published criteria for detection of CFLD cirrhosis n=14	Other information None.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				True positive=4* False positive=0.5** False negative=2* True negative=8* Sensitivity=66.7 (95% CI: 30.1-75.0)* Specificity=94.1 (95% CI: 68.3-100)* Positive LR= 11.3 (95% CI: 0.95-6684670)* Negative LR= 0.35 (95% CI: 0.25-1.02)* AUROC=0.85 (95% CI: 0.57-0.98) *Calculated by the NGA technical team from data reported in the article **0.5 person was added by the NGA technical team to calculate likelihood ratios and 95% confidence intervals. LR = likelihood ratio	
Full citation Kitson, M. T., Kemp, W. W., Iser, D. M., Paul, E., Wilson, J. W., Roberts, S. K., Utility of transient elastography in the non-invasive evaluation of cystic	Sample size n=50 adults Characteristics All (n=50)/CFLD (n=25)/No CFLD (n=25) Age, years, mean (SD): 23.3	Tests Reference test Diagnosis of CFLD was established according to established criteria if least two of the following conditions on consecutive examinations	Methods Setting: large CF referral centre in Australia Fifty adult patients with CF were prospectively studied: 25 with CFLD and 25 without CFLD. The presence of CFLD	Results LSM ≥6.8kPa using TE versus recent guidelines for detection of CFLD n=50 True positive=19* False positive=2* False negative=6* True negative=23*	Limitations QUADAS 2 checklist Patient selection Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
fibrosis liver disease, Liver International, 33, 698-705, 2013 Ref Id 354034 Country/ies where the study was carried out Australia Study type Case-control study Aim of the study To evaluate LSM as a diagnostic tool in adults with CFLD. Study dates 2009-2010 Source of funding Not reported	(9.6)/30.5 (9.3)/34.1 (9.8) Male, %: 46/44/48 Diabetes, %: 40/52/28 UDCA, %: 58/88/28 Inclusion Criteria Adult patients with CF and CFLD. Exclusion Criteria Other causes of abnormal liver enzyme levels	spanning a one-year period were present: (i) Hepatomegaly and/or splenomegaly confirmed by ultrasound, (ii) abnormal serum liver enzyme levels, consisting of elevation above the upper limit of normal of 2 of the following: ALT, AST, GGT, (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins; splenomegaly; presence of porto-systemic collatoeral veins; ascites). Index tests -Transient elastography (TE): Liver stiffness by TE was evaluated usingFibroScan® apparatus and mediam (M) probe by 3 experienced operators. All readings were taken from the right lobe of the liver	and portal hypertension (PHT) was assessed according to strict established criteria based on serial biochemistry and imaging. All patients underwent LSM; APRI, Hepascore(®) and Forns score were calculated. This is a prospective case-control study of 50 adults with CF. Control subjects were unmatched patients with CF, but without evidence of liver disease. Cases were patients with CFLD. Optimal LSM values for the prediction of CFLD, PHT and varices were identified by estimating sensitivity and specificity for various cut offs.	Sensitivity=76 (95% CI: 61.6-82.5)* Specificity=92 (95% CI: 77.6-98.5)* Positive LR= 9.5 (95% CI: 2.75-55.6)* Negative LR= 0.26 (95% CI: 0.18-0.50)* AUROC=0.87 (95% CI: 0.77-0.98) LSM ≥ 8.9 kPa using TE versus recent guidelines for detection of portal hypertension for all patients n=50 True positive=7* False positive=4* False negative=1* True negative=38* Sensitivity=87.5 (95% CI: 51.4-99.3)* Specificity=90.5 (95% CI: 83.6-92.7)* Positive LR= 9.19 (95% CI: 3.14-13.66)* Negative LR= 0.14 (95% CI: 0.01-0.58)* AUROC=0.96 (95% CI: 0.92-1.00) LSM ≥ 8.9 kPa using TE versus recent guidelines	Did the study avoid inappropriate exclusions? Yes 1.A Could the selection of patients have introduced bias? LOW RISK OF BIAS 1.B Is there concern that the included patients do not match the review question? LOW CONCERN Index Test Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? N/A 2.A Could the conduct or interpretation of the index test have introduced bias? UNCLEAR 2.B Is there concern that the index test, its conduct, or interpretation differ from the review question? LOW CONCERN Reference Standard Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
		with an appropriate site for LSM readings identified in the mid-axillary line using conventional US. The median value of 10 successful acquisitions, expressed in kPA, was taken as representative of LSM. TE was considered valid if 10 successful measurements with a success rate ≥ 60% and an interquartile range (IQR)/median ratio ≤ 30% of the median were obtained. -AST/Platelets-Ratio-Index (APRI) performed at baseline		for detection of portal hypertension for CFLD patients n=25 True positive=7* False positive=4* False negative=1* True negative=13* Sensitivity=87.5 (95% CI: 52.9-99.3)* Specificity=76.5 (95% CI: 60.2-82.0)* Positive LR= 3.7 (95% CI: 1.33-5.53)* Negative LR= 0.16 (95% CI: 0.01-0.78)* AUROC=0.91 (95% CI: 0.79-1.00) APRI ≥ 0.49 versus recent guidelines for detection of portal hypertension for all patients n=50 True positive=7* False positive=3* False negative=1* True negative=39* Sensitivity=87.5 (95% CI: 52.0-99.3)* Specificity=92.9 (95% CI: 86.1-95.1)*	3.A Could the reference standard, its conduct, or its interpretation have introduced bias? LOW RISK 3.B Is there concern that the target condition as defined by the reference standard does not match the review question? LOW RISK Flow and Timing Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? No 4.A Could the patient flow have introduced bias? LOW RISK Other information

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Positive LR= 12.3 (95% CI: 3.74-20.3)* Negative LR= 0.14 (95% CI: 0.01-0.56)* AUROC=0.97 (95% CI: 0.93-1.00) APRI ≥ 0.49 versus recent guidelines for detection of portal hypertension for CFLD patients n=25 True positive=7* False positive=1* False negative=1* True negative=16* Sensitivity=87.5 (95% CI: 54.8-98.9)* Specificity=94.1 (95% CI: 78.7-99.5)* Positive LR= 14.9 (95% CI: 2.6-189.4)* Negative LR= 0.13 (95% CI: 0.01-0.58)* AUROC=0.98 (95% CI: 0.93-1.00) Forns ≥ 6.8 versus recent guidelines for detection of portal hypertension for all patients n=50 True positive=7*	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				False positive=6* False negative=1* True negative=36* Sensitivity=87.5 (95% CI: 50.7-99.3)* Specificity=85.7 (95% CI: 78.7-88.0)* Positive LR= 6.13 (95% CI: 2.38-8.26)* Negative LR= 0.15 (95% CI: 0.01-0.63)* AUROC=0.93 (95% CI: 0.85-1.00) Forns ≥ 6.8 versus recent guidelines for detection of portal hypertension for CFLD patients n=25 True positive=7* False positive=3* False negative=1* True negative=14* Sensitivity=87.5 (95% CI: 53.2-99.3)* Specificity=82.4 (95% CI: 66.2-87.9)* Positive LR= 5.0 (95% CI: 1.6-8.2)* Negative LR= 0.15 (95% CI: 0.01-0.71)* AUROC=0.93 (95% CI: 0.82-1.00)	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				LSM ≥ 8.9 kPa using TE versus recent guidelines for detection of oesophageal varices for all patients n=23 True positive=6* False positive=4* False negative=0* True negative=13* Sensitivity=100 (95% CI: 57.8-100)* Specificity=76.5 (95% CI: 61.6-76.5)* Positive LR= 4.25 (95% CI: 1.51-4.25)* Negative LR= 0 (95% CI: 0-0.69)* AUROC=0.91 (95% CI: 0.78-1.00) APRI ≥ 0.49 versus recent guidelines for detection of oesophageal varices for all patients n=23 True positive=6* False positive=1* False negative=0* True negative=16* Sensitivity=100 (95% CI: 60.0-100)*	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Specificity=94.1(95% CI: 80.0-94.1)* Positive LR= 17.0 (95% CI: 3.0-17.0)* Negative LR= 0 (95% CI: 0-0.50)* AUROC=0.99 (95% CI: 0.96-1.00) APRI ≥ 0.49 versus recent guidelines for detection of oesophageal varices for CFLD patients n=13 True positive=6* False positive=0.5** False negative=0* True negative=7* Sensitivity=100 (95% CI: 62.9-100)* Specificity=93.3(95% CI: 63.7-93.3)* Positive LR= 15.0 (95% CI: 1.73-15.0)* Negative LR= 0 (95% CI: 0-0.58)* AUROC=1.00 (95% CI: 1.00-1.00) Forns ≥ 6.8 versus recent guidelines for detection of oesophageal varices for all patients	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				n=23 True positive=6* False positive=2* False negative=0* True negative=15* Sensitivity=100 (95% CI: 58.9-100)* Specificity=88.2 (95% CI: 73.7-88.2)* Positive LR= 8.5 (95% CI: 2.2-8.5)* Negative LR= 0 (95% CI: 0-0.56)* AUROC=0.98 (95% CI: 0.93-1.00) Forns ≥ 6.8 versus recent guidelines for detection of oesophageal varices for CFLD patients n=13 True positive=6* False positive=1* False negative=0* True negative=6* Sensitivity=100 (95% CI: 62.9-100)* Specificity=85.7 (95% CI: 53.9-85.7)* Positive LR= 7.0 (95% CI: 1.37-7.0)* Negative LR= 0 (95% CI: 0-0.69)*	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				AUROC=0.98 (95% CI: 0.91-1.00) *Calculated by the NGA technical team from data reported in the article **0.5 person was added by the NGA technical team to calculate likelihood ratios and 95% confidence intervals LR = likelihood ratio	
Full citation Lewindon, P. J., Shepherd, R. W., Walsh, M. J., Greer, R. M., Williamson, R., Pereira, T. N., Frawley, K., Bell, S. C., Smith, J. L., Ramm, G. A., Importance of hepatic fibrosis in cystic fibrosis and the predictive value of liver biopsy, Hepatology, 53, 193-201, 2011 Ref Id 332925 Country/ies where the study was carried out Australia	Sample size 40 children with suspected cystic fibrosis liver disease Characteristics 24 females 16 males Age: 2.38-18.73 years at enrollment Median age=10.64 years 96% Caucasian 20% had cystic fibrosis related diabetes 68% f508 homozygotes Median FEV1 value=83.5%	Tests Reference standard -Dual pass percutaneous liver biopsy with US guidance under general anesthesia (14-Fr Tru-Cut, throw length =20 mm) from the right lobe via the same skin incision with different angles of insertion. The tissue was immediately fixed in 10% buffered formalin and embedded in paraffin. Liver sections were evaluated by a hepatopathologist (Richard Williamson) blinded to the clinical data; more than 10	Methods Setting: major cystic fibrosis referral clinic of the Royal Children's Hospital (Brisbane, Australia) At enrollment, the following were performed or determined for all patients: history, physical examination, Df508 genotype, lung function, serum amino-transferases, liver synthetic function (international normalized ratio and albumin), and liver US as well as upper gastrointestinal endoscopy, serum draw	Results n=40 patients Ultrasound versus biopsy True positive=25* False positive=5* False negative=6* True negative=4* Sensitivity=0.81 (95% CI: 0.73-0.89)* Specificity=0.44 (95% CI: 0.17-0.73)* Positive LR= 1.45 (95% CI: 0.87-3.3)* Negative LR= 0.44 (95% CI: 0.15-1.64)* AUROC=0.63 (95% CI: NR)	Limitations QUADAS 2 checklist Patient selection Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes 1.A Could the selection of patients have introduced bias? LOW RISK OF BIAS 1.B Is there concern that the included patients do not match the review question? LOW CONCERN Index Test Were the index test results interpreted without knowledge

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study type Prospective cohort study Aim of the study To evaluate dual-pass liver biopsy and the commonly used clinical tools available to clinicians when they are confronted with a patient with suspected CFLD. To look at the ability of the latter to predict hepatobiliary fibrosis on biopsy, and compare the value of biopsy to the value of clinical modalities currently used to predict adverse outcomes (i.e.,PHT and/or liver failure) and mortality over prolonged clinical follow-up (up to 12 years). Study dates Between 1999 and 2009 Source of funding National Health and Medical Research	9/40 had portal hypertension (PHT) Inclusion Criteria Patients with suspected cystic fibrosis defined as the following: -hepatomegaly (HM) with or without splenomegaly -a persistent (>6-month) elevation of serum alanine aminotransferase (ALT; level > 1.5 x upper limit of normal) -abnormal liver US findings (abnormal echogenicity or a nodular edge) Exclusion Criteria Patients with liver synthetic dysfunction or a history of hepatobiliary surgery	levels of tissue sections stained with hematoxylin and eosin or hematoxylin and Van Gieson's stain were used. For fibrosis scoring, the Scheuer F0-F4 staging system was used (F0 =no fibrosis, F4 = cirrhosis). Only sections with at least five portal tracts were deemed adequate for assessment. Index tests -Clinical examinations: Hepatomegaly with or without splenomegaly -Serum ALT levels performed at enrollment -Ultrasound images were obtained after fasting to induce gallbladder distension, using real-time scanners: Acuson Sequoia (Siemens Medical, Erlangen, Germany) with 2.5- to 4-MHz or 5.5- to 8.5-MHz probes or ATL HDI 5000 (Philips Medical Systems,	for research, and dual-pass liver biopsy under general anesthesia. Follow-up were up to 12 years, until death, transplantation, or survival as of March 2009. All patients received standard CF pulmonary and nutritional care, all patients with biopsy-confirmed fibrosis were prescribed ursodeoxycholic acid (15 mg/kg/day), all patients were reviewed at least on a 6-month basis. For the purposes of this study, prospectively recorded follow-up data included clinical progress, occurrence of cystic fibrosis–related diabetes mellitus (CFRD; defined as insulin-dependent diabetes mellitus), survival, solid organ transplantation, forced expiratory volume in 1 second (FEV1), liver	Clinical exam-Hepatomegaly (HM) versus biopsy True positive=21* False positive=6* False negative=10* True negative=3* Sensitivity= 0.68 (95% CI: 0.61-0.77)* Specificity= 0.33 (95% CI: 0.10-0.65)* Positive LR=1.02 (95% CI: 0.67-2.23)* Negative LR=0.97 (95% CI: 0.35-4.11)* AUROC=0.51 (95% CI: NR) ALT versus biopsy True positive=0.5** False positive=0.5** False negative=17* True negative=23* Sensitivity=0.03 (95% CI: 0-0.06)* Specificity=0.98 (95% CI: 0.96-1.0)* Positive LR=1.34 (95% CI: 0-1408086.43)* Negative LR=0.99 (95% CI: 0.94-1.04)* AUROC=0.59 (95% CI: NR)	of the results of the reference standard? Yes If a threshold was used, was it pre-specified? N/A 2.A Could the conduct or interpretation of the index test have introduced bias? LOW RISK OF BIAS 2.B Is there concern that the index test, its conduct, or interpretation differ from the review question? LOW CONCERN Reference Standard Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes 3.A Could the reference standard, its conduct, or its interpretation have introduced bias? LOW RISK 3.B Is there concern that the target condition as defined by the reference standard does not match the review question? LOW RISK Flow and Timing Was there an appropriate interval between index test(s) and reference standard? No,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Council of Australia and Royal Children's Hospital Foundation of Brisbane		Best, the Netherlands) with 2- to 5-MHz or 5- to 7- MHz probes. Sonographic images were reviewed by a pediatric radiologist (Kieran Frawley) blinded to clinical and biopsy findings and previous interpretations. Briefly, liver images were recorded as nodular edge, nodular, heterogeneous, or normal echogenicity with or without splenomegaly. Normal US was defined as normal echogenicity with no splenomegaly. US evidence of PHT included a nodular liver with splenomegaly.	aminotransferases, liver synthetic function, and occurrence of PHT.	US+HSM+LFT versus biopsy for F1-F4 fibrosis HSM=hepatosplenomegaly True positive=17* False positive=20* False negative=0.5** True negative=3* Sensitivity=0.97 (95% CI: 0.85-1.0)* Specificity=0.13 (95% CI: 0.04-0.15)* Positive LR=1.12 (95% CI: 0.89-1.18)* Negative LR=0.22 (95% CI: 0-3.6)* AUROC=0.69 (95% CI: NR) US+HSM+LFT versus biopsy for F2-F4 significant fibrosis True positive=14* False positive=12* False negative=3* True negative=11* Sensitivity=0.82 (95% CI: 0.62-0.95)* Specificity=0.48 (95% CI: 0.33-0.57)* Positive LR=1.58 (95% CI: 0.93-2.22)* Negative LR=0.37 (95% CI: 0.09-1.15)*	both tests conducted at enrollment Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes 4.A Could the patient flow have introduced bias? LOW RISK Other information

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				AUROC=0.68 (95% CI: NR) LR = likelihood ratio NC=not calculable NR=not reported *Calculated by the NGA technical team from data reported in the article **0.5 person was added by the NGA technical team to calculate likelihood ratios and 95% confidence intervals.	
Full citation Lindblad, A., Glaumann, H., Strandvik, B., Natural history of liver disease in cystic fibrosis, Hepatology, 30, 1151-8, 1999 Ref Id 329857 Country/ies where the study was carried out Sweden Study type Prospective cohort study Aim of the study	Sample size n=124 followed up during 1976-1993 n=27 received biopsy in 1976-1979 n=41 received biopsy in 1989-1993 Characteristics 41 patients who received biopsy in 1989-1993 Median age 19 years, range 5 to 43 years Further characteristics details on 41 patients not	Tests Reference standard Liver biopsy performed under general anesthesia in patients younger than 16 years and under local anesthesia in older patients. The biopsy specimen was prepared according to routine methods and stained with hematoxylineosin, periodic acid-Schiff diastase treatment, reticulin, and iron stains. The biopsies were evaluated regarding fibrosis (normal;	Methods Setting: Stockholm Cystic Fibrosis Center All patients had pathological sweat tests (chloride .60 mmol/L). Patients with pancreatic insufficiency were treated with pancreatic enzymes (enteric-coated microspheres after 1982) and multivitamins including vitamin A. During the entire study, additional vitamin E in water-soluble form was prescribed to all patients, as was the oral mucolytic bromhexine	Results Results are only for 1989-1993 n=41 AUROC not reported for all tests For moderate or severe fibrosis and cirrhosis outcome LFT versus biopsy True positive=14* False positive=15* False negative=0* True negative=12* Sensitivity=1.0 (95% CI: 0.78-1.0)* Specificity=0.44 (95% CI: 0.33-0.44)*	Limitations QUADAS 2 checklist Patient selection Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes 1.A Could the selection of patients have introduced bias? LOW RISK OF BIAS 1.B Is there concern that the included patients do not match the review question? LOW CONCERN

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
To evaluate the natural history of CF-associated liver disease over a 15-year period in a well-controlled population of patients with CF by biochemical markers, liver biopsies, and, during the latest years, also ultrasonography (US). Study dates 1976-1993 Source of funding Swedish Medical Research Council	reported in the study Clinical Data on All Patients With CF Attending the CF Center During the Year 1993 n=140 Women/men: 75/65 Age, year-mean (median): 16.5 (15) BMI mean (median): 21 (21) 45 homozygous for F508 genotype 40 heterozygous for F508 genotype Mean FEV 1.0, %: 70 Number of patients with late diagnosis (older than 10 years of age), n (%): 13 (9) Inclusion Criteria All patients with Cystic Fibrosis cared for at the Stockholm CF center and attended the center 2 or more times	slight, enlarged portal zones; moderate, tendency towards septa formation; severe, bridging fibrosis; and cirrhosis, complete septa with regenerative noduli). Steatosis, bile duct proliferation, and inflammation were classified as absent, slight, moderate, or severe. A minimum of 4 portal zones were evaluated in each biopsy. Index tests - Ultrasonography characterized as normal or pathological (increased and/or irregular echogenicity) -Liver function test included serum activities of alanine transaminase (ALT), aspartate transaminase (AST), and g-glutamyltransferase (gGT) (with an upper reference level of ,0.8,	and inhalation of salbutamol and saline and/or N-acetyl cysteine. Patients chronically colonized with Pseudomonas aeruginosa, Stenotrophomonas maltophilia, and Burkholderia cepacia were treated with intravenous antibiotics (an aminoglycoside and a b-lactam) for minor signs of exacerbations, whereas patients not colonized with these organisms were treated with oral antibiotics covering Staphylococcus aureus and/or Haemophilus influenzae, generally flucloxacillin or trimethoprim-sulpha. After 1985, most intravenous antibiotic courses were given at home. Intralipid 10% (Kabi, Stockholm, Sweden) at a dose of 10 mL/kg body weight was given regularly to most patients in connection with intravenous courses of antibiotics or at signs of failure to thrive.	Positive LR= 1.8 (95% CI: 1.17-1.8)* Negative LR= 0 (95% CI: 0-0.67)* Ultrasound versus biopsy True positive=12* False positive=8* False negative=2* True negative=19* Sensitivity=0.86 (95% CI: 0.61-0.97)* Specificity=0.70 (95% CI: 0.58-0.76)* Positive LR= 2.9 (95% CI: 1.45-4.13)* Negative LR= 0.2 (95% CI: 0.03-0.67)* US+LFT versus biopsy True positive=12* False positive=7* False negative=2* True negative=20* Sensitivity=0.86 (95% CI: 0.62-0.97)* Specificity=0.74 (95% CI: 0.62-0.80)* Positive LR= 3.31 (95% CI: 1.6-4.9)* Negative LR= 0.19 (95% CI: 0.03-0.63)*	Index Test Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? N/A 2.A Could the conduct or interpretation of the index test have introduced bias? UNCLEAR 2.B Is there concern that the index test, its conduct, or interpretation differ from the review question? LOW CONCERN Reference Standard Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear 3.A Could the reference standard, its conduct, or its interpretation have introduced bias? LOW RISK-there were 10 people who had no biopsy but were identified to have biochemical liver disease 3.B Is there concern that the target condition as defined by the reference standard does

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	between 1976 and 1993 Exclusion Criteria -Patients who were seen only once during the period at the CF center -Chronic hepatitis B infection and late diagnosis of CF at the age over 60 -Less than 4 years of age	,0.8, and ,0.5 µkata/l, respectively). -Combined US and LFT	All patients were investigated annually for inflammatory status and lung function tests including forced vital capacity (FVC), forced expiratory volume in one second (FEV 1.0), chest radiograph, serum levels of retinol and a-tocopherol, liver function tests (LFTs), and the fatty acid pattern of serum phospholipids. After 1989, ultrasonography (US) of the liver was also performed annually. Antipyrine and galactose elimination capacity tests were performed in connection with liver biopsies. During the period 1976 to 1979, percutaneous liver biopsy was performed in 27 patients (median age 11 years, range 2 to 27 years), in most patients it was performed at least twice with a 1- to 3-	For moderate or severe fibrosis and cirrhosis and/or moderate to severe steatosis outcome LFT versus biopsy True positive=19* False positive=10* False negative=4* True negative=8* Sensitivity=0.83 (95% CI: 0.68-0.94)* Specificity=0.44 (95% CI: 0.26-0.58)* Positive LR= 1.49 (95% CI: 0.92-2.25)* Negative LR= 0.39 (95% CI: 0.11-1.22)* Ultrasound versus biopsy True positive=16* False positive=4* False negative=7* True negative=14* Sensitivity=0.70 (95% CI: 0.54-0.80)* Specificity=0.78 (95% CI: 0.58-0.92)* Positive LR= 3.13 (95% CI: 1.3-9.5)* Negative LR= 0.39 (95% CI: 0.22-0.8)* US+LFT versus biopsy True positive=15*	not match the review question? LOW RISK Flow and Timing Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? No, 10 out of 41 patients did not receive biopsy Did patients receive the same reference standard? Yes Were all patients included in the analysis? No-only 41 out of 124 were analysed 4.A Could the patient flow have introduced bias? HIGH RISK Other information

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			year interval. During the years 1980 to 1988 very few biopsies were performed. From 1989 to 1993, liver biopsies were performed in 41 patients, aged 5 years or older (median age 19 years, range 5 to 43 years). During the last part of the study 13 patients were prescribed ursodeoxycholic acid (UDCA) and 12 of them were followed up for 2 years with biopsies. Only the first biopsy before treatment with UDCA was evaluated in the present study. Definitions: Biochemical liver disease (BLD) was defined as elevation above the upper reference level of any serum liver enzyme included in the LFT for at least 2 consecutive years in patients 4 years of age or older. A patient was thereafter classified as BLD even if LFT results	False positive=4* False negative=8* True negative=14* Sensitivity=0.65 (95% CI: 0.5-0.76)* Specificity=0.78 (95% CI: 0.58-0.92)* Positive LR= 2.94 (95% CI: 1.18-9.1)* Negative LR= 0.45 (95% CI: 0.26-0.87)* LR = likelihood ratio *Calculated by the NGA technical team from data reported in the article	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			were later normalized. Clinical liver disease was defined as multilobular cirrhosis (MLC) and always included clinical (hepato) splenomegaly with esophageal varices or signs of hypersplenism and biopsy-proven cirrhosis. All other patients were classified as having no liver disease (NLD). Statistical Analysis: An analysis of variance test, the Mann-Whitney U test, the x2 test with Yates'correction, Fisher's exact test, and the Kruskal-Wallis test were used when appropriate. The level of significance was set to 0.05.		
Full citation Mueller-Abt, P. R., Frawley, K. J., Greer, R. M., Lewindon, P. J., Comparison of ultrasound and biopsy findings in children with cystic fibrosis related liver	Sample size n=30 children with CF Characteristics 13 girls/17 boys Mean age, years: 10	Tests Reference standard Percutaneous liver biopsy using ultrasound guidance. The ultrasound was used for biopsy guidance only and a detailed ultrasound assessment of the	Methods Setting: CF clinic A retrospective analysis of ultrasound findings was per- formed in 30 CF-patients (13 girls, 17 boys) who underwent a liver biopsy and	Results n=30 Ultrasound versus biopsy for liver disease or cirrhosis outcome True positive=15* False positive=3* False negative=8* True negative=4*	Limitations QUADAS 2 checklist Patient selection Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
disease, Journal of Cystic Fibrosis, 7, 215-21, 2008 Ref Id 354053 Country/ies where the study was carried out Australia Study type Retrospective cohort study Aim of the study To determine if hepatic ultrasound findings in paediatric patients with cystic fibrosis and suspected liver disease are related to histopathological results derived from liver biopsies. Study dates 1997-2003 Source of funding Not reported	Age range: 11 months to 17 years Inclusion Criteria -All patients attending the CF clinic with positive sweat tests confirming CF. -Evidence of biochemical liver disease (persistent elevation of ALT above upper limit of normal over a period of at least 6 months) -Clinical hepatomegaly or hepatosplenomegaly -Sonographic evidence of liver disease Exclusion Criteria Not reported	liver was not performed at the time of the biopsy. Two samples, to limit sampling error, were obtained from the right lobe using a triggered trucut to obtain 20 mm cores. In all specimens, at least 6 portal tracts were available for analysis and a Scheuer grading for fibrosis was allocated to each patient by a histopathologist blinded to US findings. Scheuer-Score of 0 was regarded as normal, a score of 1–2 as mild to moderate reversible periportal changes and 3–4 was assessed as definite fibrosis/cirrhosis. Index standard US scans were obtained after a 4-hour fast in children under 2 years and a 6- hour fast in children over 2 years for gallbladder distension. Sonographic images were independently	ultrasound between April 1997 and September 2003. The CF-patients undergoing liver biopsy were identified from the cystic fibrosis clinic database. Ethical approval of this study was granted by the institutional ethics committee as part of a wide study into liver fibrosis in cystic fibrosis. All patients were attending the CF clinic with positive sweat tests confirming CF. Patients underwent liver biopsy if two out of three of the following criteria were fulfilled: 1. evidence of biochemical liver disease (persistent elevation of ALT above upper limit of normal over a period of at least 6 months), 2. clinical hepatomegaly or hepatosplenomegaly, 3. sonographic evidence of liver disease. Informed consent was obtained from the parents for the biopsy. The time interval between biopsy and ultrasound was between	Sensitivity=0.65 (95% CI: 0.55-0.74)* Specificity=0.57 (95% CI: 0.22-0.87)* Positive LR= 1.52 (95% CI: 0.7-5.78)* Negative LR= 0.61 (95% CI: 0.29-2.06)* AUROC NR Ultrasound versus biopsy for cirrhosis outcome only True positive=8* False positive=1* False negative=6* True negative=15* Sensitivity=0.57 (95% CI: 0.36-0.64)* Specificity=0.94 (95% CI: 0.75-1.00)* Positive LR= 9.14 (95% CI: 1.47-192.8)* Negative LR= 0.46 (95% CI: 0.36-0.85)* AUROC NR NR= not reported LR = likelihood ratio *Calculated by the NGA technical team from data reported in the article	Did the study avoid inappropriate exclusions? Yes 1.A Could the selection of patients have introduced bias? LOW RISK OF BIAS 1.B Is there concern that the included patients do not match the review question? LOW CONCERN Index Test Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? N/A 2.A Could the conduct or interpretation of the index test have introduced bias? LOW RISK OF BIAS 2.B Is there concern that the index test, its conduct, or interpretation differ from the review question? LOW CONCERN Reference Standard Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
		reviewed two times on hardcopies by a pediatric radiology fellow (investigator 1) and an experienced paediatric radiologist (investigator 2). The reviewers were unaware of the clinical findings and previous interpretation and were blinded to the histology. After independent review a consensus result was reached in cases with differing interpretations for each of the ultrasound criteria evaluated. A summary interpretation of the findings was performed by each reviewer. There were three categories: normal, indeterminate (suggestion of liver disease but no definite signs of cirrhosis) and cirrhosis. Cases without liver abnormality were graded as normal. Increased hepatic echogenicity, heterogeneity and/or increased attenuation in the absence of	0 and 183 days (mean 42 days).		3.A Could the reference standard, its conduct, or its interpretation have introduced bias? LOW RISK 3.B Is there concern that the target condition as defined by the reference standard does not match the review question? LOW CONCERN Flow and Timing Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes 4.A Could the patient flow have introduced bias? LOW RISK Other information

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
		nodularity of the liver surface were classified as indeterminate. Splenomegaly as an isolated finding was also regarded as indeterminate. All patients with nodularity of the liver surface were classified as cirrhosis.			
Full citation Patriquin, H., Lenaerts, C., Smith, L., Perreault, G., Grignon, A., Filiatrault, D., Boisvert, J., Roy, C. C., Rasquin-Weber, A., Liver disease in children with cystic fibrosis: US-biochemical comparison in 195 patients, Radiology, 211, 229-32, 1999 Ref Id 333103 Country/ies where the study was carried out Canada Study type Prospective cohort study	Sample size n=195 children Characteristics 112 boys, 83 girls; mean age, 8.5 years, age range 1-23 years Inclusion Criteria Children with CF Exclusion Criteria Not reported	Tests Reference test US: US scans were obtained without sedation after a 4-hour fast in children aged 2–6 years and after an 8-hour fast in patients older than 6 years. One of the following commercially available machines was used: Ultramark 5, 8, or 9 (Advanced Technology Laboratories, Seattle, Wash) or Quantum II (Siemens Medical Systems, Erlangen, Germany) with a 3.5-, 5.0-, or 7.0-MHz transducer. The sonograms were obtained by one of five pediatric radiologists	Methods Setting: CF clinic For 1 year, all 195 children (112 boys, 83 girls; mean age, 8.5 years) attending a CF clinic underwent abdominal US and a standard set of liver function tests. Aspartate aminotransferase, alanine aminotransferase, and □-glutamyltransferase levels were analyzed. US signs were interpreted as follows: hypoechogenicity with prominent portal tracks as edema, hyperechogenicity as steatosis, and increased attenuation and nodules within or at the edge of the liver as cirrhosis.	Results LFT: ALT versus US n=195 True positive=24* False positive=33* False negative=14* True negative=124* Sensitivity=63.2 (95% CI: 48.0-76.3)* Specificity=79.0 (95% CI: 75.3-82.2)* Positive LR= 3.0 (95% CI: 1.95-4.28)* Negative LR= 0.47 (95% CI: 0.29-0.69)* AUROC=NR GGT versus US n=195 True positive=19* False positive=15* False negative=19*	Limitations QUADAS 2 checklist Patient selection Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes 1.A Could the selection of patients have introduced bias? LOW RISK OF BIAS 1.B Is there concern that the included patients do not match the review question? LOW CONCERN Index Test Were the index test results interpreted without knowledge

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study To determine if abnormal liver architecture at ultrasonography (US) is related to abnormal function in children with cystic fibrosis (CF). Study dates 1999 Source of funding Not reported		(H.P., G.P., A.G., D.F., J.B.) and were later reviewed by one of the five. No radiologist was aware of the biochemical results at the time of examination or review. US included a survey of the entire abdomen as well as a detailed examination of liver architecture. This included liver echogenicity, which was compared with that of the renal cortex. The liver was called hyperechoic if it was brighter than the cortex of the right kidney and if the walls of portal veins were difficult to distinguish from the adjacent liver parenchyma. Sound attenuation by the liver was assessed and was considered to be increased if the posterior surface of the liver was not visible with a transducer frequency that allowed sound penetration and depiction of the kidney	Signs of portal hypertension also were sought. US signs were compared with liver function test results.	True negative=142* Sensitivity=50.0 (95% CI: 36.2-62.4)* Specificity=90.4 (95% CI: 87.1-93.4)* Positive LR= 5.23 (95% CI: 2.80-9.53)* Negative LR= 0.55 (95% CI: 0.40-0.73)* AUROC=NR AST versus US n=195 True positive=18* False positive=19* False negative=20* True negative=138* Sensitivity=47.4 (95% CI: 33.4-60.6)* Specificity=87.9 (95% CI: 84.5-91.1)* Positive LR= 3.91 (95% CI: 2.16-6.80)* Negative LR= 0.60 (95% CI: 0.43-0.79)* AUROC=NR *Calculated by the NGA technical team from data reported in the article NR=not reported LR = likelihood ratio	of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? N/A 2.A Could the conduct or interpretation of the index test have introduced bias? LOW RISK 2.B Is there concern that the index test, its conduct, or interpretation differ from the review question? LOW CONCERN Reference Standard Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes 3.A Could the reference standard, its conduct, or its interpretation have introduced bias? LOW RISK 3.B Is there concern that the target condition as defined by the reference standard does not match the review question? LOW RISK Flow and Timing Was there an appropriate interval between index test(s) and reference standard? No,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
		through the liver. Evidence of nodules within and at the surface of the liver was sought. The caliber of the intrahepatic bile ducts was noted, and they were termed dilated if they exceeded 2 mm in diameter. Evidence of portal hypertension was sought (spleno-megaly, collateral veins, lesser omental thick- ening); when found, Doppler US was performed. The presence and direction of blood flow in the splanchnic and intrahepatic portal veins was assessed, and portosystemic collateral vessels, especially esophageal varices, were sought. US abnormalities of liver architecture were interpreted as follows: hyperechogenicity as steatosis and heteroechogenicity of liver architecture accompanied by increased sound attenuation as cirrhosis. Nodules			US and LFTs performed on same day Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes 4.A Could the patient flow have introduced bias? LOW RISK Other information

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
		within or at the edge of the liver were also interpreted as cirrhosis. Hypoechoic liver parenchyma and bright periportal echoes of normal thickness also were noted, but no pathologic interpretation was attributed to these findings. Index tests Liver function tests included total and direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), □glutamyltransferase (GGT), albumin, pre-albumin, prothrombin time, and fasting and postprandial endogenous bile acid (cholylglycine) tests.			
Full citation Rath, T., Hage, L., Kugler, M., Menendez Menendez, K., Zachoval, R.,	Sample size n=45 Characteristics CFLD n=17/ 53% male	Tests Reference test Diagnosis of CFLD was established according to recent	Methods 45 CF patients were included in the study and received transient elastography. Differential regulation of	Results n=45	Limitations QUADAS 2 checklist Patient selection

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Naehrlich, L., Schulz, R., Roderfeld, M., Roeb, E., Serum Proteome Profiling Identifies Novel and Powerful Markers of Cystic Fibrosis Liver Disease, PLoS ONE, 8, 2013 Ref Id 340488 Country/ies where the study was carried out Germany Study type Prospective cohort study Aim of the study To identify new experimental biomarkers for the detection of CFLD. Study dates 2008-2010 Source of funding Deutsche Forschungsgemeinschaft (RO 957/7-1 and RO 957/8-1), a research Grant of the University Medical Center Giessen and Marburg (UKGM	No CFLD n=28/ 61% male Mean age, y (SD): no CFLD- 21.4 (11.8); CFLD-29 (10.8) Inclusion Criteria -Diagnosis of CF was established by sweat test and later confirmed by genetic tests in all subjects Exclusion Criteria -Other causes for chronic liver disease	guidelines if least two of the following conditions on at least two consecutive examinations spanning a one-year period were present: (i) Hepatomegaly (liver span >2 cm below the costal margin on the medioclavicular line) confirmed by ultrasound, (ii) two abnormal serum liver enzyme levels (ALT, AST, γGT > ULN), (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins). Index tests -Transient elastography (TE): Liver stiffness by TE was evaluated using the same FibroScan® (Echosens, Paris, France) device in all patients. Non-invasive measurements were performed by a single	220 different serum proteins was assessed in a subgroup of patients with and without CFLD. Most interesting candidate proteins were further quantified and validated by ELISA in the whole patient cohort. To assess a potential relation of biomarker expression to the degree of hepatic fibrosis, serum biomarkers were further determined in 18 HCV patients where liver histology was available.	APRI versus recent guidelines for detection of CFLD True positive=8* False positive=2* False negative=9* True negative=27* Sensitivity=47.1 (95% CI: 28.2-56.7)* Specificity=93.1 (95% CI: 82.0-98.7)* Positive LR= 6.82 (95% CI: 1.57-44.7)* Negative LR= 0.57 (95% CI: 0.44-0.88)* AUROC=0.75 (95% CI: 0.58-0.91) NCC estimates based upon information in the paper--n adds up to 46 due to rounding errors (i.e. they haven't given sensitivities to a great enough degree of accuracy). ALP versus recent guidelines for detection of CFLD True positive=12* False positive=5* False negative=5* True negative=23* Sensitivity=70.6 (95% CI: 49.5-85.5)*	Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes 1.A Could the selection of patients have introduced bias? LOW RISK OF BIAS 1.B Is there concern that the included patients do not match the review question? LOW CONCERN Index Test Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? N/A 2.A Could the conduct or interpretation of the index test have introduced bias? LOW RISK OF BIAS 2.B Is there concern that the index test, its conduct, or interpretation differ from the review question? LOW CONCERN Reference Standard

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
10/2010 GI), and from ZooMAP (01KI1003E, Bundesministerium fÃ¼r Bildung und Forschung, BMBF)		experienced investigator blinded to the clinical status of the patients on the right lobe of the liver through the intercostal space at a depth of 25 and 65 mm from skin surface. In children below 15 kg of weight the FibroScan® S probe, developed for liver stiffness measurements in children, was used. For each patient, the stiffness value was calculated as the median of ten successful measurements. TE was considered valid if 10 successful measurements with a success rate ≥ 60% and an interquartile range ≤ 30% of the median were obtained. Results are expressed in kilopascal (kPa). Total examination time was approximately 5 minutes per patient. -Alkaline phosphatase (ALP) -AST/Platelets-Ratio-Index (APRI)		Specificity=82.1 (95% CI: 69.3-91.2)* Positive LR= 3.95 (95% CI: 1.61-9.74)* Negative LR= 0.36 (95% CI: 0.16-0.73)* AUROC=0.61 (95% CI: 0.44-0.79) TE versus recent guidelines for detection of CFLD True positive=14* False positive=0.5** False negative=3* True negative=28* Sensitivity=82.4 (95% CI: 64.2-85.3)* Specificity=98.2 (95% CI: 87.4-100)* Positive LR= 46.9 (95% CI: 5.1-25489647)* Negative LR= 0.18 (95% CI: 0.15-0.41)* AUROC=0.91 (95% CI: 0.78-1.00) LR = likelihood ratio NC=not calculable NR=not reported *Calculated by the NGA technical team from data reported in the article	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes 3.A Could the reference standard, its conduct, or its interpretation have introduced bias? LOW RISK 3.B Is there concern that the target condition as defined by the reference standard does not match the review question? LOW RISK Flow and Timing Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes 4.A Could the patient flow have introduced bias? LOW RISK Other information

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				**0.5 person was added by the NGA technical team to calculate likelihood ratios and 95% confidence intervals.	
Full citation Rath, T., Menendez, K. M., Kugler, M., Hage, L., Wenzel, C., Schulz, R., Graf, J., Nahrlich, L., Roeb, E., Roderfeld, M., TIMP-1/-2 and transient elastography allow non invasive diagnosis of cystic fibrosis associated liver disease, Digestive & Liver Disease, 44, 780-7, 2012 Ref Id 354071 Country/ies where the study was carried out Germany Study type Prospective cohort study Aim of the study Compare the value of transient	Sample size 145 CF patients (75 children, 70 adults) Characteristics Paediatric CF patients No CFLD (n=45)/CFLD (n=30) Male, %: 60/30 Age, years, mean (SD): 10.9 (4.9)/10.6 (4.3) Adult CF patients No CFLD (n=32)/CFLD (n=29)/CFLD + PHT Male, %: 53/48/66 Age, years, mean (SD): 32.3 (9.3)/30.6 (8.6)/32.2 (5.8) Inclusion Criteria Diagnosis of CF was established	Tests Reference test Diagnosis of CFLD was established according to recent guidelines if least two of the following conditions on at least two consecutive examinations spanning a one-year period were present: (i) Hepatomegaly (liver span >2 cm below the costal margin on the medioclavicular line) confirmed by ultrasound, (ii) two abnormal serum liver enzyme levels (ALT, AST, γGT > ULN), (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins). Diagnosis of PHT was based on clinical and	Methods 145 CF patients (75 children, 70 adults) were prospectively studied and received transient elastography. CF liver disease was diagnosed according to recent guidelines. Serum concentrations of YKL-40, HA, PIIIP, MMP-9, TIMP-1 and TIMP-2 were determined by ELISA.	Results TE at 5.5 kPA cut-off versus recent guidelines for detection of CFLD only-all CF patients n=136 True positive=39* False positive=11* False negative=35* True negative=51* Sensitivity=52.7 (95% CI: 44.9-58.9)* Specificity=82.3 (95% CI: 72.9-89.7)* Positive LR= 2.97 (95% CI: 1.65-5.70)* Negative LR= 0.58 (95% CI: 0.46-0.76)* AUROC=0.68 (95% CI: 0.59-0.77) TE at 5.5 kPA cut-off versus recent guidelines for detection of CFLD only-adult CF patients n=61 True positive=16* False positive=7*	Limitations QUADAS 2 checklist Patient selection Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes 1.A Could the selection of patients have introduced bias? LOW RISK OF BIAS 1.B Is there concern that the included patients do not match the review question? LOW CONCERN Index Test Were the index test results interpreted without knowledge of the results of the reference standard? Yes If a threshold was used, was it pre-specified? N/A 2.A Could the conduct or interpretation of the index test

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
elastography and experimental fibrosis markers for the detection of liver disease in CF patients Study dates 2008-2010 Source of funding Deutsche Forschungsgemeinschaft, ZooMAP, University Medical Ctr Giessen and Marburg	by sweat test and later confirmed by genetic tests in all subjects Exclusion Criteria Other causes for chronic LD	lab data combined with sonographic or endoscopic signs of PHT. Index tests -Transient elastography (TE): Liver stiffness by TE was evaluated using the same FibroScan® (Echosens, Paris, France) device in all patients. Non-invasive measurements were performed by a single experienced investigator blinded to the clinical status of the patients on the right lobe of the liver through the intercostal space at a depth of 25 and 65 mm from skin surface. In children below 15 kg of weight the FibroScan® S probe, developed for liver stiffness measurements in children, was used. For each patient, the stiffness value was calculated as the median of ten successful		False negative=13* True negative=25* Sensitivity=55.2 (95% CI: 40.7-66.8)* Specificity=78.1 (95% CI: 65.0-88.7)* Positive LR= 2.52 (95% CI: 1.16-5.89)* Negative LR= 0.57 (95% CI: 0.38-0.91)* AUROC=0.69 (95% CI: 0.56-0.81) TE at 5.5 kPA cut-off versus recent guidelines for detection of CFLD only-paediatric CF patients n=75 True positive=24* False positive=7* False negative=21* True negative=23* Sensitivity=53.3 (95% CI: 43.2-61.2)* Specificity=76.7 (95% CI: 61.4-88.4)* Positive LR= 2.29 (95% CI: 1.12-5.28)* Negative LR= 0.61 (95% CI: 0.44-0.93)* AUROC=0.68 (95% CI: 0.56-0.81)	have introduced bias? LOW RISK OF BIAS 2.B Is there concern that the index test, its conduct, or interpretation differ from the review question? LOW CONCERN Reference Standard Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes 3.A Could the reference standard, its conduct, or its interpretation have introduced bias? LOW RISK 3.B Is there concern that the target condition as defined by the reference standard does not match the review question? LOW RISK Flow and Timing Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
		measurements. TE was considered valid if 10 successful measurements with a success rate ≥ 60% and an interquartile range ≤ 30% of the median were obtained. Results are expressed in kilopascal (kPa). Total examination time was approximately 5 minutes per patient.		TE at 11.5 kPA cut-off versus recent guidelines for detection of CFLD and PHT-adult CF patients n=70 True positive=6* False positive=1* False negative=3* True negative=60* Sensitivity=66.7 (95% CI: 36.2-77.2)* Specificity=98.4 (95% CI: 93.9-99.9)* Positive LR= 40.67 (95% CI: 5.91-877.4)* Negative LR= 0.34 (95% CI: 0.23-0.68)* AUROC=0.86 (95% CI: 0.66-1.00) A cut-off of 5.5 kPa was optimal for TE for the diagnosis of CFLD in every patient cohort, whereas a cut-off of 11.5 kPa was optimal for TE for the diagnosis of PHT in adult CF patients with PHT LR = likelihood ratio *Calculated by the NGA technical team from data reported in the article	Were all patients included in the analysis? Yes 4.A Could the patient flow have introduced bias? LOW RISK Other information
Full citation	Sample size	Tests	Methods	Results	Limitations

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Sadler, M. D., Crotty, P., Fatovich, L., Wilson, S., Rabin, H. R., Myers, R. P., Noninvasive methods, including transient elastography, for the detection of liver disease in adults with cystic fibrosis, Canadian Journal of Gastroenterology & Hepatology, 29, 139-44, 2015 Ref Id 354082 Country/ies where the study was carried out Canada Study type Prospective cohort study Aim of the study To evaluate the diagnostic performance of noninvasive methods for the detection of CFLD with a focus on transient elastography (TE)	n=127 Characteristics All patients n=127 Age, median years (interquartile range): 27 (22-37) Male (%): 60 (47) 25% were prescribed UDCA With CFLD n=18 Age, median years (interquartile range): 28 (18-32) Male (%): 10 (56) 83% were prescribed UDCA Without CFLD n=109 Age, median years (interquartile range): 27 (22-37) Male (%): 50 (42) 14% were prescribed UDCA Inclusion Criteria ≥18 years of age with CF Exclusion Criteria	Reference test Diagnosis of CFLD was established according to previously published criteria if least two of the following conditions were present: (i) Hepatomegaly and/or splenomegaly confirmed by ultrasonography, (ii) abnormal liver biochemistry consisting of elevated levels of any two of ALT, AST, or GGT, (iii) ultrasound abnormalities other than hepatomegaly (increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly presence). Index tests -Liver stiffness measurement by transient elastography (TE) using FibroScan® probe.	Setting: Adult CF clinic of Calgary and Southern Alberta At enrollment, patient demographics, anthropometric measurements, CF transmembrane regulator genetic mutations, UDCA use and history of CF-related complications, diabetes mellitus and lung transplantation were recorded. All patients underwent a physical exam and routine lab investigations. Individuals with examination findings suggestive of liver disease or abnormal liver biochemistry underwent ab ultrasonography (n=78). Spirometry values from pulmonary function testing on the day of enrollment were also recorded. Patients at the Adult CF Clinic of Calgary and Southern Alberta (n=127) underwent liver stiffness measurement (LSM) by TE using the	LSM using TE versus published criteria for CFLD diagnosis n=127 ≥3.7 kPa True positive=16* False positive=69* False negative=2* True negative=40* Sensitivity=89 (95% CI: 66-98)* Specificity=37 (95% CI: 33-38)* Positive LR= 1.40 (95% CI: 0.98-1.59)* Negative LR= 0.30 (95% CI: 0.05-1.04)* AUROC NR ≥5.3 kPa** True positive=12* False positive=19* False negative=6* True negative=90* Sensitivity=67 (95% CI: 43-85)* Specificity=83 (95% CI: 79-86)* Positive LR= 3.83 (95% CI: 2.04-5.87)* Negative LR= 0.40 (95% CI: 0.18-0.72)* AUROC=0.78 (95% CI: 0.65-0.92)	QUADAS 2 checklist Patient selection Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes 1.A Could the selection of patients have introduced bias? LOW RISK OF BIAS 1.B Is there concern that the included patients do not match the review question? LOW CONCERN Index Test Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? N/A 2.A Could the conduct or interpretation of the index test have introduced bias? UNCLEAR 2.B Is there concern that the index test, its conduct, or interpretation differ from the review question? LOW CONCERN

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates 2010-2011 Source of funding AI-HS, CIHR, and Canadian Liver Foundation	Hepatitis B or C	-Aspartate aminotransferase to Platelets-Ratio-Index (APRI) was calculated as (AST/upper limit of normal for AST) x (100/platelets (x109/L)). -FibroTest (FT) was calculated based on age, sex, GGT, total bili-alpha-2macroglobulin, apolipoproten A1 and haptoglobin.	FibroScan (FS, Ecosens, France) M probe; aspartate aminotransferase to platelet ratio index (APRI) and FibroTest (FT) scores were also calculated. The diagnostic performance of these tools for the detection of CFLD (defined as two or more the following criteria: abnormal liver biochemistry, hepatomegaly or sonographic abnormalities other than steatosis) were compared using the area under ROC curves.	>6.0 kPa True positive=10* False positive=10* False negative=8* True negative=99* Sensitivity=56 (95% CI: 34-75)* Specificity=91 (95% CI: 87-94)* Positive LR= 6.06 (95% CI: 2.65-12.32)* Negative LR= 0.49 (95% CI: 0.27-0.76)* AUROC NR APRI versus published criteria for CFLD diagnosis n=122 Sample size reported do not match with the reported number of patients with and without CFLD. >0.4 True positive=9* False positive=9* False negative=9* True negative=100* Sensitivity=50 (95% CI: 29-69)*	Reference Standard Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear 3.A Could the reference standard, its conduct, or its interpretation have introduced bias? LOW RISK 3.B Is there concern that the target condition as defined by the reference standard does not match the review question? LOW RISK Flow and Timing Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? No Were all patients included in the analysis? No 4.A Could the patient flow have introduced bias? HIGH RISK Other information

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Specificity=92 (95% CI: 88-95)* Positive LR= 6.06 (95% CI: 2.48-13.50)* Negative LR= 0.55 (95% CI: 0.33-0.80)* AUROC=0.70 (95% CI: 0.54-0.86) >0.5** True positive=9* False positive=7* False negative=9* True negative=102* Sensitivity=50 (95% CI: 29-68)* Specificity=94 (95% CI: 90-97)* Positive LR= 7.79 (95% CI: 2.99-19.44)* Negative LR= 0.53 (95% CI: 0.33-0.78)* AUROC NR FibroTest versus published criteria for CFLD diagnosis n=106 >0.10** True positive=14* False positive=38* False negative=3* True negative=51*	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Sensitivity=82 (95% CI: 58-95)* Specificity=57 (95% CI: 53-60)* Positive LR= 1.93 (95% CI: 1.22-2.37)* Negative LR= 0.31 (95% CI: 0.08-0.80)* AUROC=0.76 (95% CI: 0.62-0.90) >0.20 True positive=6* False positive=10* False negative=11* True negative=79* Sensitivity=35 (95% CI: 16-53)* Specificity=89 (95% CI: 85-93)* Positive LR= 3.14 (95% CI: 1.10-7.80)* Negative LR= 0.73 (95% CI: 0.47-0.98)* AUROC NR *Calculated by the NGA technical team from data reported in the article **Optimal cut-offs of tests defined by the maximal sum of sensitivity and specificity LR = likelihood ratio	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				NR= not reported	
Full citation Witters, P., De Boeck, K., Dupont, L., Proesmans, M., Vermeulen, F., Servaes, R., Verslype, C., Laleman, W., Nevens, F., Hoffman, I., Cassiman, D., Non-invasive liver elastography (Fibroscan) for detection of cystic fibrosis-associated liver disease, Journal of Cystic Fibrosis, 8, 392-9, 2009 Ref Id 330202 Country/ies where the study was carried out Belgium Study type Prospective cohort study Aim of the study To evaluate the diagnostic accuracy compared to other diagnostic tools as	Sample size n=66 Characteristics The CF group (n = 66) consisted of 36 male and 30 female patients with a mean age of 13.6 ± 7.8 yr (32 patients < 12 yr, 24 patients between 12 and 18 yr and 10 patients > 18 yr. Six patients (9%) had evidence of clinical CFLD (hepatomegaly or splenomegaly) and 7 (11%) had evidence of biochemical CFLD. Ultrasonography revealed hepatomegaly in 15 (23%) patients and splenomegaly in 16 patients (24%). 26 patients (39%) had clinical, biochemical or ultrasonographic CFLD.	Tests Reference standard The North-American cystic fibrosis foundation (CFF) consensus workgroup defines CFLD as the presence of either clinical or biochemical liver disease. -Clinical liver disease was defined as the presence of hepatomegaly or splenomegaly -Biochemical liver disease was defined as the elevation of 2 of these tests: Liver tests (AST, ALT, alkaline phosphatase, bilirubin and gamma-GT) from all CF patients from January 1996 to July 2007 were studied and patients with persistently elevated liver tests were identified (3–6 months, 1.5 times age-dependent upper limit of normal). Index tests	Methods Setting: CF clinic at the university hospital Fibroscan measurements were performed in 66 CF patients. Age-specific cutoff values were determined in a control population (n = 59) and was set at 5.63kPa for <12 years and 6.50kPa for ≥12 years. The measurements were compared to clinical data, biyearly biochemistry and ultrasound.	Results Ultrasound versus clinical CFLD definition in detection of CFLD n=66 patients True positive=4* False positive=20* False negative=2* True negative=40* Sensitivity=66.7 (95% CI: 25.0-93.9)* Specificity=66.7 (95% CI: 62.5-69.4)* Positive LR= 2.0 (95% CI: 0.67-3.07)* Negative LR= 0.50 (95% CI: 0.09-1.2)* AUROC=0.77 (95% CI: 0.51-1.02) Ultrasound versus biochemical CFLD definition in detection of CFLD n=66 patients True positive=3* False positive=20* False negative=3* True negative=40* Sensitivity=50.0 (95% CI: 14.3-85.6)*	Limitations QUADAS 2 checklist Patient selection Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear 1.A Could the selection of patients have introduced bias? LOW RISK OF BIAS 1.B Is there concern that the included patients do not match the review question? LOW CONCERN Index Test Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes for Clinical,biochemical and ultrasound index tests and was determined for Fibroscan using a control population 2.A Could the conduct or interpretation of the index test

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
well as the relation of the liver stiffness to risk factors for CFLD Study dates 1996-2007 Source of funding Not reported	A control group with no liver disease (n = 59) consisted of 26 male and 33 female subjects with a mean age of 10.2 ± 3.7 yr (41 patients < 12 yr, 18 patients 12–18 yr) and were investigated to define normal values of liver stiffness only. Inclusion Criteria -CF patients followed up in CF clinic at a university hospital: Clinical liver disease was defined as the presence of hepatomegaly or splenomegaly Exclusion Criteria Not reported	-FibroScan: Liver stiffness was assessed by transient elastography (Fibroscan, Echosens, Paris). At least 10 measurements per patient are obtained, using the standard probe. Median values and interquartile range (IQR, kPa) are reported. A success-rate of at least 60% was considered necessary. In the paediatric population special care was taken in order to make sure there was no A-shaped wave on the elastogram which indicates an incorrectly accepted (non-automatically rejected) measurement leading to an overestimation of the stiffness produced by influence of the surrounding rib bone and soft tissue. Fibroscan liver disease was defined as a result above the age-related upper limit of normal liver stiffness.		Specificity=66.7 (95% CI: 63.1-70.2)* Positive LR= 1.5 (95% CI: 0.39-2.88)* Negative LR= 0.75 (95% CI: 0.21-1.36)* AUROC=0.62 (95% CI: 0.40-0.84) Ultrasound versus CFF consensus definition in detection of CFLD n=66 patients True positive=7* False positive=16* False negative=4* True negative=39* Sensitivity=63.6 (95% CI: 33.6-87.0)* Specificity=70.9 (95% CI: 64.9-75.6)* Positive LR= 2.19 (95% CI: 0.96-3.56)* Negative LR= 0.51 (95% CI: 0.17-1.02)* AUROC=0.70 (95% CI: 0.51-0.89) Fibroscan versus clinical CFLD definition in detection of CFLD n=66 patients True positive=5*	have introduced bias? LOW RISK 2.B Is there concern that the index test, its conduct, or interpretation differ from the review question? LOW CONCERN Reference Standard Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear 3.A Could the reference standard, its conduct, or its interpretation have introduced bias? LOW RISK 3.B Is there concern that the target condition as defined by the reference standard does not match the review question? LOW CONCERN Flow and Timing Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
		- Ultrasound: Ultrasonographic liver disease was defined as a Williams score of at least 4/9 (i.e. intermediate coarse to irregular liver parenchyma, liver edge nodularity and/or moderate to severe periportal fibrosis).		False positive=9* False negative=1* True negative=51* Sensitivity=83.3 (95% CI: 38.7-99.1)* Specificity=85.0 (95% CI: 80.5-86.6)* Positive LR= 5.6 (95% CI: 2.0-7.4)* Negative LR= 0.20 (95% CI: 0.01-0.76)* AUROC=0.93 (95% CI: 0.85-1.01) Fibroscan versus biochemical CFLD definition in detection of CFLD n=66 patients True positive=3* False positive=10* False negative=3* True negative=50* Sensitivity=50.0 (95% CI: 14.5-85.3)* Specificity=83.3 (95% CI: 79.8-86.9)* Positive LR= 3.0 (95% CI: 0.72-6.5)* Negative LR= 0.60 (95% CI: 0.17-1.07)* AUROC=0.78 (95% CI: 0.61-0.95)	Were all patients included in the analysis? Yes 4.A Could the patient flow have introduced bias? LOW RISK Other information

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Fibroscan versus CFF consensus definition in detection of CFLD n=66 patients True positive=7* False positive=7* False negative=4* True negative=48* Sensitivity=63.6 (95% CI: 34.4-86.0)* Specificity=87.3 (95% CI: 81.4-91.8)* Positive LR= 5.0 (95% CI: 1.86-10.43)* Negative LR= 0.42 (95% CI: 0.15-0.81)* AUROC=0.86 (95% CI: 0.74-0.98) *Calculated by the NGA technical team from data reported in the article LR = likelihood ratio	
Full citation Lemaitre, C., Dominique, S., Billoud, E., Eliezer, M., Montialoux, H., Quillard, M., Riachi, G., Koning, E., Morisse-Pradier, H., Savoye, G., Savoye-Collet, C., Goria, O.,	Sample size N=25 (out of cohort of 64) Characteristics of studied patients were not statistically different compared to the	Tests Index test: Transient Elastography LSM by transient elastography was measured by Fibroscan(Echosens, Paris, France, size M) Ten measurements were taken in 3	Methods Design: retrospective one-year cross-sectional cohort study Setting: cystic fibrosis reference centre at Rouen University Hospital Procedure:	Results Transient elastography versus liver function test or ultrasound for detection of CFLD n=23 True positive=3* False positive=3* False negative=1* True negative=16*	Limitations QUADAS 2 checklist Patient selection Was a consecutive or random sample of patients enrolled? No Was a case-control design avoided? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Relevance of 3D Cholangiography and Transient Elastography to Assess Cystic Fibrosis-Associated Liver Disease?, Canadian Respiratory JournalCan Respir J, 2016, 4592702, 2016 Ref Id 537183 Country/ies where the study was carried out France Study type Retrospective cohort study Aim of the study To describe the usefulness of magnetic resonance imaging (MRI) and liver stiffness measurement (LSM) for the assessment of CFLD. Study dates Between July 2009 and July 2010. Source of funding	whole CF population. Characteristics Median age, years (range): 25 (18 to 43) Gender (M/F): 0.46 MI: 16% (n=4) Pancreatic insufficiency: 88% (n=22) UDCA treatment: 40% (n+10) FEV1%> 67.6% (50.4 to 84.8) Inclusion Criteria All adult patients with CF, investigated by hepatobiliary MRI and by transient elastography for liver stiffness measurement (LSM) between July 2009 and July 2010 Exclusion Criteria Patients in whom CFTR-related disorder was limited to one-organ dysfunction (i.e., congenital	different sites, and results are expressed as a mean of 10 valid measurements Results were expressed in kilopascal (kPa) using the Metavir scoring system based on previous study of transient elastography in chronic biliary disease (Corpechot 2006): Metavir F0-F1 score corresponded to LSM of ¡Ý7.2 kPa, and F2, F3, and F4 corresponded to ¡Ý7.3 kPa, 9.8 kPa, and 17.3 kPa, respectively Index test: Biliary and Hepatic Magnetic Resonance Imaging Performed with 1.5 Tesla (Philips Achieva, Philips Medical Systems, Best, Netherlands) The following sequences were performed: (1) T1-weighted sequence, axial image (TR 183ms, TE 2.3ms, FOV 70 mm, slice thickness 7 mm, angle	clinical and genetic characteristics were retrospectively collected from patient charts biochemical analysis (LFT, platelet counts, prothrombin time, albumin, and renal function) and routine abdominal US results including hepatic dysmorphia or PHT signs were also collected In all patients with abnormal LFT (any test > twice the normal values), additional workup was available including search for hepatitis B, hepatitis C, ferritin, transferrin saturation, and fasting lipid profile. Pulmonary function was collected, including forced expiratory volume. Statistical analysis Statistical analysis was conducted using SAS software version 9.3 SI units were used for all laboratory values with data summarized using mean ± standard	Sensitivity=75 (95% CI: 24.2-98.6)* Specificity=84.2 (95% CI: 73.5-69.2)* Positive LR= 4.75 (95% CI: 0.91-9.12)* Negative LR= 0.30 (95% CI: 0.02-1.03)* AUROC=NR MRI versus liver function test or ultrasound for detection of CFLD n=23 True positive=4* False positive=2* False negative=7* True negative=10* Sensitivity=36.4 (95% CI: 14.7-51.1)* Specificity=83.3 (95% CI: 63.5-96.8)* Positive LR= 2.18 (95% CI: 0.40-16.06)* Negative LR= 0.76 (95% CI: 0.50-1.34)* AUROC=NR *Calculated by the NGA technical team from data reported in the article NR=not reported LR = likelihood ratio	Did the study avoid inappropriate exclusions? Unclear 1.A Could the selection of patients have introduced bias? LOW RISK OF BIAS 1.B Is there concern that the included patients do not match the review question? LOW CONCERN Index Test Were the index test results interpreted without knowledge of the results of the reference standard? Yes (the radiologist were blinded) If a threshold was used, was it pre-specified? Yes 2.A Could the conduct or interpretation of the index test have introduced bias? LOW RISK 2.B Is there concern that the index test, its conduct, or interpretation differ from the review question? LOW CONCERN Reference Standard Is the reference standard likely to correctly classify the target condition? Unclear Were the reference standard results interpreted without

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Not reported.	bilateral absence of vas deferens).	55¡ã, 152 ¡Á 432); (2) T2-weighted sequence, axial SPAIR (TR 4459ms, TE 70ms, FOV 76 mm, slice thickness 6 mm, angle 90¡ã, 218 ¡Á 320); (3) T2-weighted sequence, axial HR (TR 1573ms, TE 100ms, FOV 79 mm, slice thickness 7 mm, angle 90¡ã, 341 ¡Á 560); (4) T2-weighted sequence diffusion 2b (TR 1489ms, TE 59ms, FOV 90 mm, slice thickness 6 mm, 92 ¡Á 67); (5) 3D MR cholangiogram (TR 1341ms, TE 574ms, FOV 100 mm, slice thickness 2.4 mm, angle 90¡ã, 221 ¡Á 560); (6) in and out phase sequence (TR 175ms, TE 2.3ms (in), 4.8ms (out), FOV 40¡ã, slice thickness 4 mm, angle 80¡ã, 224 ¡Á 192). Radiologists (CSC and EK) reviewed all MRI results blinded to clinical or biochemical parameters and	deviation (SD) for continuous variables Number (%) for all recorded categorical variables describing the study population LSM are expressed in kPa as median (IQR) Student's t-test was used to compare continuous variables Chi square test was used when comparing categorical variables To assess the diagnostic performance of LSM for prediction of PHT, the area under the receiver operating curve (AUROC) was calculated. Optimal LSM for prediction of PHTwas identified by estimating sensitivity and specificity for various cut-offs. Prevalence of abnormalities in MRI and LSM was compared regarding the presence or not of LFT and/or US abnormalities using chi-square test and Fisher's exact test.		knowledge of the results of the index test? Unclear 3.A Could the reference standard, its conduct, or its interpretation have introduced bias? UNCLEAR 3.B Is there concern that the target condition as defined by the reference standard does not match the review question? UNCLEAR Flow and Timing Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? 2 participants missing 4.A Could the patient flow have introduced bias? UNCLEAR Other information Conflict of interest: none.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
		reached decisions by consensus. The following items were studied for each patient using a standardized scale: atrophy of either right or left hepatic lobe and/or hypertrophy of the caudate lobe, marked lobulations of liver surface, first-segment hypertrophy, splenomegaly (long axis superior to 12 cm), portal vein dilatation (diameter superior to 12 mm), splenic vein dilatation, intrahepatic or extrahepatic biliary duct irregularity (segmental strictures and dilatations), ascites, and steatosis. Reference standard: liver function test or ultrasound Details not reported			
Full citation Woodruff, S. A., Sontag, M. K., Accurso, F. J., Sokol, R. J., Narkewicz, M. R., Prevalence of	Sample size N=298 children with CF identified by newborn screening. Characteristics	Tests Monitoring strategy based on the assessment of liver function tests.	Methods Procedure: Clinical and laboratory data were collected prospectively. AST, ALT and GGT was obtained.	Results Prognostic value of AST - Hazards ratio (95% CI): ≥1.5× ULN: 6.53 (2.02–21.1)	Limitations The quality of this study was assessed using the tool proposed by Hayden et al. (2006), as suggested by NICE methods manual (2014)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
elevated liver enzymes in children with cystic fibrosis diagnosed by newborn screen, Journal of Cystic Fibrosis, no pagination, 2016 Ref Id 566881 Country/ies where the study was carried out USA Study type Prospective cohort study Aim of the study To determine the prognostic value to elevated liver enzymes in children with CF diagnoses by newborn screening. Study dates 1982 to 2005 Source of funding Not reported.	Method of diagnosis Newborn screening 240 (80.5%) Meconium ileus 42 (14.1%) Missed on newborn screen 16 (5.4%) Age at diagnosis, weeks (median, IQR) 3.8 (2.4–5.7) Male gender (N, %) 147 (49.3) Hispanic ethnicity 35 (11.7%) CFTR mutation severity Severe (2 classes 1–3) 209 (76.3%) Milder (at least 1 class 4 or 5) 24 (8.8%) Unknown 15 (14.9%) Inclusion Criteria All children with CF born in Colorado from 1982 to 2005, diagnosed by newborn screening, the presence of meconium ileus,		Children were seen twice per year for the first 2 years of life and then annually. UDA data was not available in the database before 2005, so authors developed a standardized evaluation and management pathway, that included starting ursodeoxycholic acid therapy at 10–20 mg/kg/day only if AST, ALT or GGT were ≥2× the upper limit of normal for age (ULN) for ≥6 months or if there was clinical evidence of advanced liver disease (e.g., splenomegaly, firm hepatomegaly or complications of portal hypertension) from 1990 forward. Pancreatic enzyme replacement therapy was initiated on all infants at diagnosis and continued unless there was verification of pancreatic sufficiency. The authors followed CF Foundation guidelines for nutritional and pulmonary therapies.	≥2.0× ULN: 6.52 (0.72–138.5) Prognostic value of ALT Hazards ratio (95% CI): ≥1.5× ULN: 1.95 (0.81–4.27) ≥2.0× ULN: 1.88 (0.82–3.91) Prognostic value of GGTP - Hazards ratio (95% CI): ≥1.5× ULN: 4.03 (1.15–13.45) ≥2.0× ULN: 2.44 (0.86-6.13) Hazards Ratios for the presence of clinically diagnosed liver disease, adjusted for sex, CFTR mutation severity, and the presence of meconium ileus.	(full citation: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37) 1. The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. YES 2. Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. YES 3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias. YES 4. The outcome of interest is adequately measured in study participants, sufficient to limit potential bias. YES 5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. YES 6. The statistical analysis is appropriate for the design of

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	or who were missed by newborn screening. A sweat chloride N60 mmol/L or two pathologic CFTR mutations consistent with CF were considered positive evidence of CF. Exclusion Criteria Not reported.		ALT was determined at annual well CF visits starting in 1982 with subsequent inclusion of AST and GGT in 1990. Values were classified as normal, elevated (any elevation above the ULN), ≥1.5× ULN, ≥2× ULN and ≥3× ULN based on normal values for age and sex at the time of their determination. Statistical analysis: Product-Limit Survival Estimates were used to assess the age at first abnormality for AST, ALT and GGT. Early liver enzyme elevation (defined as present before 5 years of age) and persistent elevation defined as 2 or more abnormal values obtained at least 6 months apart at the annual visits. Univariate relative risks were calculated for persistent elevation (for ≥1.5× and 2×ULN) with the presence of meconium ileus, sex, CFTR mutation severity and Hispanic ethnicity.		the study, limiting potential for the presentation of invalid results. YES OVERALL QUALITY: HIGH Other information Conflict of interest: 1 author was a consultant at Vertex. No other interest to declare.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			Due to missing values in children who did not have an 'annual visit' recorded, data from all visits were used, and the mean clinical outcome for each year of age (rounded to the nearest year of age) was calculated. Clinical advanced liver disease was defined as the presence of cirrhosis (by imaging or liver histology), portal hypertension (by the presence of ascites, splenomegaly or thrombocytopenia, esophageal or gastric varices, or portal hypertensive gastropathy) or stage 3/4 fibrosis on liver biopsy obtained for clinical indications.Statistical significance was assessed by using an $\alpha = 0.05$. SAS 9.2 (Carey, NC) was used for all analyses.		

G.17 Ursodeoxycholic acid

Review question: What is the effectiveness of ursodeoxycholic acid for preventing liver disease progression in people with cystic fibrosis?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation O'Brien, S., Fitzgerald, M. X., Hegarty, J. E., A controlled trial of ursodeoxycholic acid treatment in cystic fibrosis-related liver disease, European Journal of Gastroenterology and Hepatology, 4, 857-863, 1992 Ref Id 340385 Country/ies where the study was carried out Ireland Study type Randomised controlled trial Aim of the study To assess the effect of UDCA on liver function, biliary excretion and nutrition. Study dates	Sample size N = 12 Characteristics All participants had CF related liver disease. Evidence of advanced liver disease was present in 11/12 participants (91.7%) as determined by the presence of portal hypertension and or histological features of CFRLD. None of the participants had experienced any deterioration in liver function or complications of their liver disease during the 6 month trial. Median age in yrs (range): UDCA (n = 6): 17 (12 - 20) Control (n = 6): 17.5 (14 - 25) Gender (M/F): UDCA: 2/4 Control: 4/2	Interventions Intervention UDCA, 20 mg/kg per day Control No additional treatment	Details Patients were evaluated at 3 month intervals with clinical examination, pulmonary function tests, liver biochemistry, serum albumin and prothrombin tim and at 6 months with biliary scintigraphy. Setting Adult Cystic Fibrosis Centre Randomisation method 6 patients were randomised to receive UDCA and 6 were randomised to receive no additional treatment. Allocation concealment Sealed envelopes Statistics All data expressed as mean ± SEM. Values before and after treatment compared with Wilcoxon signed ranks tests.	Results Baseline enzyme values (IU/L) AST UDCA: 79.3 ± 11.3 Control: 75.2 ± 23.0 ALT UDCA: 81.2 ± 12.4 Control: 73.5 ± 23.6 GGT UDCA: 129.0 ± 36.2 Control: 133 ± 62.9 After 6 months: AST UDCA: 49.5 ± 7.8; n=6 Control: 50.8 ± 9.2; n=6 ALT UDCA: 49.0 ± 7.3; n=6 Control: 49.2 ± 8.9; n=6 GGT UDCA: 40.0 ± 10.4; n=6 Control: 136.0 ± 83.3; n=6 Mean change of enzymes from baseline (IU/L): AST UDCA: -29.8 Control: -24.4 ALT	The quality of this trial was assessed using the Cochrane risk of bias assessment tool. Random sequence generation: unclear (specific method of randomisation was not reported) Allocation concealment: low risk Blinding of participants and personnel: low risk (both participants and individuals administering the intervention were kept blind to treatment allocation) Blinding of outcome assessment: low risk (outcome assessors were blinded) Incomplete outcome data: low risk (All groups were followed up for an equal length of time, all participants completed the trial) Selective reporting: low risk (The groups were comparable with respect to the availability of outcome data). Other bias: low risk (The groups were comparable at baseline, including all major confounding and prognostic factors. The comparison

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
June 1988 - December 1989 Source of funding None reported.	Splenomegaly/varices UDCA: 5/6 Control: 5/6 Inclusion criteria CF and presence of liver disease defined on the basis of hepatomegaly and/or splenomegaly, confirmed by abdominal ultrasound and/or liver biochemistry (GGT > 50 IU/L, 5'nucleotidase > 15 IU/L) for at least 6 months. No evidence of recent viral infection (confirmed by viral screen tests) No hepatotoxic drug within the previous 3 months No alcohol ingestion Exclusion criteria Questionable drug compliance Presence of normal liver function tests			UDCA: -32.2 Control: -24.3 GGT UDCA: -89 Control: 3 Baseline Bilirubin value (umol/l) UDCA: 14.2 ± 5.9 Control: 11.8 ± 1.8 Bilirubin, after 6 months: UDCA: 13.2 ± 3.6 Control: 9.2 ± 1.6 Mean change in bilirubin (umol/l): UDCA: -1 Control: -2.6	groups received the same care apart from the intervention(s) studied. The study had an appropriate length of follow-up. The study used a precise definition of outcome. A valid and reliable method was used to determine the outcome. OVERALL QUALITY: LOW RISK OF BIAS Other information None
Full citation Merli, M., Bertasi, S.,	Sample size N = 51 Characteristics	Interventions UDCA	Details The patients were randomised to receive	Results (Results from UDC-Tau group not presented).	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Servi, R., Diamanti, S., Martino, F., De Santis, A., Goffredo, F., Quattrucci, S., Antonelli, M., Angelico, M., Effect of a medium dose of ursodeoxycholic acid with or without taurine supplementation on the nutritional status of patients with cystic fibrosis: a randomized, placebo-controlled, crossover trial, Journal of Pediatric Gastroenterology & Nutrition, 19, 198-203, 1994 Ref Id 340405 Country/ies where the study was carried out Italy Study type Randomised, cross-over Aim of the study	Sex: Male: n = 27; Female: n = 24 Age, median (range): 14 yrs (8 - 32) Liver disease: 10/51 participants had persistent abnormality in liver function tests (AST, ALT and cholestatic enzymes). Of these, 2 had liver cirrhosis. Inclusion criteria Diagnosis of CF, documented by raised sweat chloride vales and pulmonary and digestive symptoms Evidence of malnutrition, determined by body mass percentile (BMP) ≤ 90% age > 6 yrs good compliance with previous monitored treatments no previous UDCA treatment Exclusion criteria None reported.	12 mg/kg/day orally in 2 doses alone or with taurine (TAU, 18 - 22 mg/kg/day) for 6 months. Placebo Glucose tablets	either UDCA alone or with taurine for 6 months. For each group, the treatment period was compared with a 6 month placebo period. A 1 month washout period was instituted for patients who had received UDCA before they went on to placebo. Setting Patients were selected from a larger cohort followed at the Cystic Fibrosis Centre and the Department of Paediatrics at the University of Rome. Randomisation method The treatment-placebo or placebo-treatment sequence was randomised within each group. Allocation concealment Not reported. Statistics Data expressed as mean ± SD. Student t test for paired data was used to compare values before and after 6 months.	After 6 months (mU/ml): Placebo: AST: 34 ± 13; n=19 ALT: 27 ± 13; n=19 GGT: 25 ± 16; n=19 UDCA: AST: 38 ± 16 ALT: 25 ± 15 GGT: 20 ± 9.0 Mean change from baseline (mU/ml): Placebo: AST: 2 ALT: 0 GGT: 5 UDCA: AST: 5 ALT: -3 GGT: -2 In 8 participants who had biochemical evidence of liver disease, liver function tests improved. All participants who did not have CF related liver disease (11/19) did not develop liver disease.	The quality of this trial was assessed using the Cochrane risk of bias assessment tool. Random sequence generation: high risk (randomisation was done, however the groups were not comparable at baseline, as more participants (n = 8) had liver damage in UDCA-TAU group than UDCA (n = 2). Allocation concealment: unclear Blinding of participants and personnel: unclear (blinding for participants and personnel not reported) Blinding of outcome assessment: unclear (not reported) Incomplete outcome data: low risk (there were no important or systematic differences between groups in terms of those who did not complete treatment, however 5 participants in UDCA and 4 in UDCA-TAU group did not complete treatment). Selective reporting: low risk (the groups were comparable with respect to the availability of outcome data) Other bias: low risk (The comparison groups received the same care apart from the intervention(s) studied. All groups were followed up for an equal length of time. The

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To investigate whether the administration of a medium dose of UDCA ameliorates the nutritional status of malnourished young adult CF patients with chronic liver disease. Study dates April 1990 - February 1991 Source of funding None reported.					study had an appropriate length of follow-up. The study used a precise definition of outcome. A valid and reliable method was used to determine the outcome. Overall quality: Unclear/unknown risk Other information Only 8 had biochemical evidence of liver disease at baseline, 11/19 had no biochemical evidence of liver disease.
Full citation Cheng, Katharine, Ashby, Deborah, Smyth, Rosalind L., Ursodeoxycholic acid for cystic fibrosis-related liver disease, Cochrane Database of Systematic Reviews, 2014 Ref Id 340505	Sample size N = 118 participants 3 studies (Colombo 1996, Merli 1994, O'Brien 1992). Results from Merli 1994 and O'Brien 1992 are presented here as authors could not obtain individual participant data (raw data) from 1 study included (Colombo 1996). Characteristics Included studies: Colombo 1996,	Interventions UDCA 1 study (O'Brien 1992) UDCA + Taurine 2 studies (Merli 1994, Colombo 1996).	Details Merli 1994: cross-over trial of UDCA (12 mg/kg/day) alone or with taurine (18 - 22 mg/kg/day) for 6 months and then each treatment group was compared with placebo (glucose) for 6 months. O'Brien 1992: UDCA 20 mg/kg/day for 6 months, control: no additional therapy. Randomisation method	Results Data from 2 studies (Merli 1994 and O'Brien 1992) was presented in this Cochrane review. Data from Colombo 1996 was extracted separately. Lack of normalisation of AST Merli 1994 UDCA: 1/1 Control: 2/2 O'Brien 1992 UDCA: 5/5 Control: 3/6	Limitations In a well-conducted, relevant systematic review: The review addresses an appropriate and clearly focused question that is relevant to the guideline review question: Yes The review collects the type of studies you consider relevant to the guideline review question: Yes The literature search is sufficiently rigorous to identify all the relevant studies: Full paper (Bittner 1991) not identified in sys review, only abstract paper.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out UK Study type Cochrane systematic review Aim of the study To analyse evidence that UDCA improved indices of liver function, reduces the risk of developing chronic liver disease and improves outcomes in general cystic fibrosis. Study dates Evidence last searched on 29 May 2014. Source of funding NHS North West Region R&D Programme, UK.	Merli 1994, O'Brien 1992 In 2 trials, the comparison was placebo (Colombo 1996, Merli 1992). In the third, the comparison was existing conventional therapy (O'Brien 1992). Length of follow-up was generally short and ranged from 6 months (Merli 1994, O'Brien 1992) and 12 months (Colombo 1996). Important long term outcomes such as death was not reported. Participants O'Brien 1992: participants with CF (diagnosed by sweat test and clinically) with liver disease. N = 12, age: 12 - 42 yrs. Merli 1994: participants with CF (raised sweat chloride values and clinical symptoms). N = 51, only 10 had liver disease (8 with		Merli 1994 and O'Brien 1992: Randomisation stated, with no details on randomisation method provided. Blinding Merli 1994: no description of blinding method provided.	Lack of normalisation of ALT Merli 1994 UDCA: 0/2 Control: 1/1 O'Brien 1992 UDCA: 4/6 Control: 2/3 Lack of normalisation of GGT Merli 1994 UDCA: 0/1 Control: 0/1 O'Brien 1992 UDCA: 2/5 Control: 2/3 Need for liver transplant Merli 1994 UDCA: 0/6 Control: 0/12 O'Brien 1992 UDCA: 0/6 Control: 0/6	Study quality is assessed and reported: Yes An adequate description of the methodology used is included, and the methods used are appropriate to the question: Yes Indirectness: Not all participants from 1 study included (Merli 1994) have liver disease. Attrition bias: Merli 1994 - 9 participants (5 UDCA, 4 UDCA + taurine) withdrew, were not followed up and analysed. Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	enlarged liver and fibrosis and 2 with cirrhosis). Inclusion criteria Included in this Cochrane review are RCTs (published or unpublished). Trials where pseudo-randomisation methods are used such as alternation. Exclusion criteria Non RCTs.				
Full citation Colombo, C., Battezzati, P. M., Podda, M., Bettinardi, N., Giunta, A., Ursodeoxycholic acid for liver disease associated with cystic fibrosis: a double-blind multicenter trial. The Italian Group for the Study of Ursodeoxycholic Acid in Cystic Fibrosis, Hepatology, 23, 1484-90, 1996 Ref Id	Sample size N = 55 UDCA With Taurine: n=15 Without Taurine: n=15 Placebo With taurine: n=12 Without Taurine: n=13 Characteristics CF had been diagnosed at a median age of 1 year (range: 1 month - 13 years) Liver disease had been diagnosed at a median age of 9 years (range: 2 months - 18 years).	Interventions Participants to receive, on a weight basis: UDCA or placebo at the daily dose of 1 to 3 300 mg capsules for 1 year. Patients in the 2 groups who received UDCA assumed an average daily dose of 12 ± 3 mg/kg body weight (range: 10 - 20 mg). Taurine or a second placebo at the dose of 1 to 3 500 mg	Details Clinical and standard laboratory evaluations were performed at the time of enrolment and every 3 months thereafter. Blood samples were obtained for determination of serum liver enzyme levels (alanine and aspartate aminotransferase, GGT and alkaline phosphatase), total and conjucated bilirubin, cholinesterase, total and high density lipoprotein cholesterol, triglycerides, glucose, albumin, gamma globulins,	Results In patients receiving UCDA + taurine and Placebo + Taurine, there is a difference in participants at baseline in terms of number of oesophageal varices. Therefore, only results for UDCA without Taurine and Placebo without Taurine are presented. Change / normalisation of hepatocellular enzymes (baseline and follow-up after 12 months) GGT Baseline UDCA without Taurine: 2.4 ± 1.6; n=15 Placebo without Taurine: 2.8 ± 2.6; n=12	Limitations The quality of this trial was assessed using the Cochrane risk of bias assessment tool. Random sequence generation: unclear (randomization was conducted, but patients in UDCA group had more oesophageal varices than placebo) Allocation concealment: unclear (not reported) Blinding of participants and personnel: low risk (both were blinded) Blinding of outcome assessment: low risk (blinded) Incomplete outcome data: low risk (2 participant from UDCA with Placebo/without Taurine

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
340507 Country/ies where the study was carried out Italy Study type Double-blind, multicenter trial Aim of the study To evaluate efficacy and safety of treatment with UDCA on an extended spectrum of outcome measures. In addition, the effects of taurine supplements, which was administered randomly to patients taking UDCA or placebo. Objective The primary objective was to compare treatment groups with respect to changes in clinically relevant and nutritional parameters	Gender (Male/Female): 33/22 Age, mean (SD) UDCA + Taurine: 14.2 ± 4.2 UDA without Taurine: 11.3 ± 3.6 Placebo + Taurine: 14.8 ± 3.7 Placebo without Taurine: 12.8 ± 3.8 With multilobular cirrhosis UDCA + Taurine: 8 UDCA without Taurine: 8 Placebo + Taurine: 6 Placebo without Taurine: 6 With oesophageal varices (at study entry) UDCA + Taurine: 4 UDA without Taurine: 1 Placebo + Taurine: 0 Placebo without Taurine: 0 Inclusion criteria Patients with a diagnosis of CF and chronic liver disease with persistent alterations of serum liver enzymes.	capsules daily were randomly added double-blind to patients in either group.	immunoglobulins, prothrombin time, complete blood counts, urea and creatine. Bloos samples for determination of fasting serum bile acid levels Setting 12 Italian centers. The tests were performed in the clinical laboratory of each participating center by routine automated techniques. Randomisation method A centrally computer-generated list Allocation concealment Does not state method of concealment, only states "double-blind". Statistical analysis Serum liver enzymes were standardised according to reference values for each laboratory and expressed as upper limit of reference values. ANOVA for factorial designs was used for estimation of the effects of UDCA, of taurine and of their interaction.	% Change UDCA without Taurine: -26 ± 35; n=15 Placebo without Taurine: -15 ± 33; n=12 AST Baseline UDCA without Taurine: 2.1 ± 1.3; n=15 Placebo without Taurine: 2.1 ± 1.8; n=12 % Change UDCA without Taurine: -24 ±25; n=15 Placebo without Taurine: -10 ± 40; n=12 ALT Baseline UDCA without Taurine: 2.2 ± 1.0; n=15 Placebo without Taurine: 3.6 ± 4.3; n=12 % Change UDCA without Taurine: -30 ± 32; n=15 Placebo without Taurine: -17 ± 41; n=12 Withdrawal Two patients, both in the UDCA + placebo (UDCA without taurine) group were withdrawn for deterioration of clinical conditions involving pulmonary disease in one	group did not complete treatment) Selective reporting: low risk (the groups were comparable in terms of availability of data reported) Other bias: low risk (The comparison groups received the same care apart from the intervention(s) studied. All groups were followed up for an equal length of time. The study had an appropriate length of follow-up. The study used a precise definition of outcome). Overall quality: low risk Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
(Shwackman-Kulczycki score (SKS)), faecal fat excretion, serum prealbumin and lipid levels, prothrombin time and urinary creatine besides improvement in serum liver enzymes (serum transaminases, GGTP, and 5'-nucleotidase). Study dates June - December 1990 Source of funding Not reported.	Diagnosis of Cf previously established on the basis of: increased sweat chloride concentrations, typical symptoms of pulmonary and pancreatic involvement Chronic liver disease was defined on the basis of: presence of hepatomegaly, confirmed by abnormal ultrasonographic findings (increased liver size, nonhomogeneous echogenic pattern and irrecgular surface), the presence of abnormal liver biochemistries (serum transaminases, GGT) of at least 1 year duration. Presence of serum transaminase and GGT levels exceeding 1.5 times the upper limit of normal reference values on at least 3 determinations over		Bartlett's test was used for testing of homogeneity of variances. When nonhomogeneity of variances or departure from normality were detected, data were analysed using a logarithmic transformation or the rank transformation approach. The associations between changes in serum liver enzyme levels and UDCA dosage, expressed on a weight basis, was studies by multiple regression analysis. In this analysis, the final values of serum liver enzymes were included as the independent variable, the logarithm of the dose and baseline serum liver enzyme values as independent variables. Intention to treat analysis Yes	case and liver disease in another. Liver transplantation The one patient who deteriorated due to liver disease had jaundice (liver failure) and became a candidate for liver transplantation, which was performed successfully.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	the year before entry into the study was required for admission into study. Exclusion criteria Less than 3 years old Serum bilirubin > 3 mg/dL Ascites Chronic viral hepatitis concominent severe pulmonary disease previous episodes of variceal bleeding or encephalopaty Portosystemic shunting Patients previously treated with corticosteroids or other immunosuppressant agents in previous 6 months patients previously included in other clinical studies on UDCA				
Full citation Lepage, G., Paradis, K., Lacaille, F., Senechal, L.,	Sample size N = 19 Characteristics All patients had CF and liver dysfunction.	Interventions UDCA administered at a dosage of 15 mg/kg per day.	Details 19 participants were randomly assigned to receive either placebo or UDCA. Participants	Results Normal range enzyme values (IU/L) - obtained from normal, aged matched controls AST: <43	Limitations The quality of this trial was assessed using the Cochrane risk of bias assessment tool.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ronco, N., Champagne, J., Lenaerts, C., Roy, C. C., Rasquin-Weber, A., Ursodeoxycholic acid improves the hepatic metabolism of essential fatty acids and retinol in children with cystic fibrosis, Journal of Pediatrics, 130, 52-8, 1997 Ref Id 340509 Country/ies where the study was carried out Canada Study type Double-blind, crossover study of 1 year duration. Aim of the study To examine changes in the lipid profile and in the status of fat-soluble vitamins in response to UDCA.	Cirrhosis was suspected in 12 patients because of the presence of a nodular or hard liver, splenomegaly, the presence of indicators of portal hypertension on Doppler ultrasonography or a combination of these. Sex (M/F): 13 male and 6 females Age: 7 - 17 years (11.9 ± 0.6 years) Inclusion criteria Entry criteria for liver dysfunction: abnormal findings in at least 2 liver function tests (AST, ALT, GGT) and an abnormal findings in an abdominal ultrasound examination or liver biopsy or both. Exclusion criteria None stated.	In absence of 50% decrease of alanine transaminase (ALT) or aspartate transaminase (AST) or both within 2 months, the dose was increased to 30 mg/kg. Placebo	completed 6 months of placebo and then treated with 6 months of UDCA - participants acted as their own controls. After crossover study completed, patients taking UDCA were allowed to continue to to take it for a mean period of 25 ± 2 months. 13 participants continued to take UDCA as: 1 patient died, 4 moved away and 1 discontinued medication. Only data for the 1 year trial will be presented here. Randomisation Method unclear, only "randomly assigned" stated. Allocation concealment Not reported Statistics All results were expressed as mean ± SEM. Differences between placebo and UDCA at 6 months were assessed by repeated measures analysis of variance (ANOVA) and by paired t test.	ALT: <25 GGT: <30 Baseline enzyme values in participants (IU/L), median (range) AST: 67 (46 - 348) ALT: 52 (27 - 186) GGT: 58 (35 - 194) Enzyme values, mean ± SEM AST After 6 mo Placebo: 95.6 ± 17.4; n=19 After 6 mo UDCA: 61.0 ± 8.8; n=19 ALT After 6 mo Placebo: 70.8 ± 10.7; n=19 After 6 mo UDCA: 40.3 ± 8.8*; n=19 *p < 0.05 when compared to placebo GGT After 6 mo Placebo After 6 mo Placebo: 70.7 ± 9.1; n=19 After 6 mo UDCA: 21.3 ± 2.6**; n=19 **p < 0.001 when compared to placebo	Random sequence generation: unclear Allocation concealment: unclear (not reported) Blinding of participants and personnel: unclear Blinding of outcome assessment: unclear Incomplete outcome data: low risk (all participants completed the trial) Selective reporting; low risk (The groups were comparable with respect to the availability of outcome data) Other bias: low risk (The comparison groups received the same care apart from the intervention(s) studied. All groups were followed up for an equal length of time. The study had an appropriate length of follow-up. The study used a precise definition of outcome) Overall quality: Unclear/unknown risk Other information Poor outcome reporting. Dose of UDCA increased by double within 2 months if a 50% decrease of ALT, AST or both was absent.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported. Source of funding Medical Research Council of Canada and Canadian Cystic Fibrosis Foundation.					

G.18 Cystic fibrosis related diabetes

Review question: What is the most effective strategy to monitor for the onset of CF-related diabetes (CFRD)?

No clinical evidence was identified for this review.

G.19 Bone mineral density

Review question: What is the most effective strategy to monitor for the identification of reduced bone mineral density in people with Cystic Fibrosis?

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
Full citation Baker, J. F., Putman, M. S., Herlyn, K., Tillotson, A. P., Finkelstein, J. S., Merkel, P. A., Body composition, lung	Sample size n=63 adults with CF Mean age (SD): 31.7 (8.0) years (18 to 57) 50.9% male	Prognostic test/ tool/ factor Low baseline BMD, defined as z-score ≤ -1 Very low baseline BMD, defined as z-score ≤ -2 Standard dual-energy X-ray absorptiometry (DXA)	Sample selection Subjects underwent scanning to measure BMD and a medical interview to obtain history information Data collection	Results Change in posterior-anterior spine BMD at 2 years z-score ≤1 at baseline not significantly and	Limitations The methodological limitations were assessed using a critical appraisal tool for the evaluation of the quality of prognosis studies in systematic

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
function, and prevalent and progressive bone deficits among adults with cystic fibrosis, Joint, Bone, Spine: Revue du RhumatismeJoint Bone Spine, 83, 207-11, 2016 Ref Id 457420 Country/ies where the study was carried out United States of America Study type Retrospective case series Aim of the study To assess independent predictors of baseline and 2-year changes in bone mineral density in adults with CF. Study dates Unclear. Source of funding Veterans Affairs Clinical Science Research & Development	Characteristics Adults with CF from Massachusetts General Hospital Cystic Fibrosis Care Center Inclusion criteria Elevated sweat chloride level or mutational analysis diagnostic for cystic fibrosis Exclusion criteria Organ transplant recipients	on a QDR4500A model (Hologic Inc, Bedford, MA)	DXA scanning at the PA spine to measure BMD using QDR4500A model (Hologic Inc, Bedford, MA) Physical examination Medical interview: medical history, physical activity, menstrual/pubertal development, fracture history Laboratory assessments Lung spirometry Activity level: interview Scans performed using a QDR4500A model (Hologic Inc, Bedford, MA) Data analysis Multivariate model adjusting for: age, gender, fat-free max index and height Group comparisons: Chi2 tests and t-tests or non-parametric equivalents for non-normally distributed data Body composition variables: multiple variable models to adjust for height and gender. Correlations and univariate linear regression: to evaluate factors associated with BMD Z-core Hypothesis driver linear regression models: to identify predictors of change in PA spine BMD Z-score	independently associated with greater BMD loss (p-value = 0.81) z-score ≤2 at baseline not significantly and independently associated with greater BMD loss (p-value = 0.47)	reviews (Hayden et al. 2006): Study participation The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. PARTLY (date of recruitment unclear, random sample from CF care centre) Study attrition Loss to follow-up (from sample to study population) is not associated with key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. UNSURE (60% followed up at 2 years, no explicit reasons for loss provided other than subjects without follow up scan at 2 years were significantly younger with lower baseline Z-scores) Prognostic factor measurement

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
National Center for Research Resources National Institute of Arthritis and Musculoskeletal and Skin Diseases CF foundation			GEE marginal models with correlation structures: to evaluate longitudinal change in PA spine BMD Z-score Follow-up repeat scan performed at 2 years (data available for n=39)		The prognostic factor of interest is adequately measured in study participants to sufficient to limit potential bias. YES (every image reviewed by bone densitometrist) Outcome measurement The outcome of interest is adequately measured in study participants to sufficiently limit potential bias. PARTLY (outcomes clearly defined. No detail on blind measurements) Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. YES (multivariable and longitudinal models adjusted for age, gender, FFMI, height) Analysis The statistical analysis is appropriate for the design

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
					of the study, limiting potential for the presentation of invalid results. YES Other information Subjects that did not have a repeat PA spine DXA were significantly younger and tended to have lower baseline PA spine z-scores.
Full citation Bhudhikanok, G. S., Wang, M. C., Marcus, R., Harkins, A., Moss, R. B., Bachrach, L. K., Bone acquisition and loss in children and adults with cystic fibrosis: a longitudinal study, Journal of Pediatrics, 133, 18-27, 1998 Ref Id 366725 Country/ies where the study was carried out United States of America Study type	Sample size n=47 children and young people with CF (26 females and 15 males) Characteristics Mean age, range: 20.6 years (8.4 to 48.5 years)30 female, 19 male Boy and young males n=9 Adult males n=6 Girls and young females n=11 Adult females n=15 Inclusion criteria A diagnosis of CF based on elevated sweat chloride	Prognostic test/ tool/ factor Baseline lumbar spine BMD (z-score for age and sex) • Males o Children and young people < 18 years: -1.0±0.9 o Adults ≥ 18 years: -2.5±1.4 • Females o Children and young people < 18 years: -1.5±1.5 o Adults ≥ 18 years: -1.9±1.6 Baseline femoral neck BMD (z-score for age and sex) • Males o Children and young people < 18 years: -0.8±0.6 o Adults ≥ 18 years: -	Sample selection Data collection Anthropometric and clinical data: assessed by protocols and questionnaires Disease severity: Shwachman-Kulczycki score Laboratory assessment BMD: DXA (QDR 1000W, Hologic Corporation, Waltham) for lumbar spine, left proximal femur and whole body, BMAD was calculated to estimate volumetric bone density for the spine and hip. Percentage change in BMD and absolute change in BMD Z-score were calculated. Data analysis Wilcoxon rank-sum test: to compare changes in BMD and BMD Z-score	Results Change in lumbar spine BMD (z-score for age and sex) at mean 17 months follow-up Males Children and young people < 18 years: -0.2±0.5; ns Adults ≥ 18 years: 0.1±0.2; ns Females Children and young people < 18 years: -0.6±0.8; p<0.05 Adults ≥ 18 years: 0.1±0.3; ns Change in femoral neck BMD (z-score for age and sex) at	Limitations The methodological limitations were assessed using a critical appraisal tool for the evaluation of the quality of prognosis studies in systematic reviews (Hayden et al. 2006): Study participation The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. PARTLY (explicit inclusion/exclusion criteria not listed) Study attrition

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
Prospective case series Aim of the study To determine patterns of bone mineral acquisition in children and young adults with cystic fibrosis and to identify clinical and laboratory correlates of change in bone mineral density. Study dates July 1992 - July 1993 Source of funding None listed.	concentrations after pilocarpine iontophoresis. Exclusion criteria Not reported	2.5±0.8 • Females o Children and young people < 18 years: -2.0±1.6 o Adults ≥ 18 years: -2.2±1.6 Baseline femoral neck BMD (z-score for age and sex) Males Children and young people < 18 years: -0.8±0.6 Adults ≥ 18 years: -2.5±0.8 Females Children and young people < 18 years: -2.0±1.6 Adults ≥ 18 years: -2.2±1.6 Baseline whole body BMD (z-score for age and sex) Males Children and young people < 18 years: -0.3±0.5 Adults ≥ 18 years: -2.0±1.2 Females	One sample t-test: to test for changes in clinical and bone measure at baseline and follow-up Scatterplots and nonparametric Spearman's rank correlations: to examine associations between outcome variables and anthropometric and clinical factors Multiple regression: to evaluate association of predictor variables with outcome variables, to compare BMAD and biochemical markers of bone turnover SAS v6.09 and 6.11 for Unix. Follow-up Mean 17 months (11 to 25 months) (data available for n=41) after initial evaluation	mean 17 months follow-up Males Children and young people < 18 years: -0.2±0.4; ns Adults ≥ 18 years: -0.2±0.4; ns Females Children and young people < 18 years: -0.3±0.8; ns Adults ≥ 18 years: 0.1±0.4; ns Change in femoral neck BMD (z-score for age and sex) at mean 17 months follow-up Males Children and young people < 18 years: -0.6±0.4; p<0.005 Adults ≥ 18 years: 0.1±0.3; ns Females Children and young people < 18 years: -0.4±0.3; p<0.005 Adults ≥ 18 years: -0.0±0.2; ns	Loss to follow-up (from sample to study population) is not associated with key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. YES (reasons for loss to follow-up given) Prognostic factor measurement The prognostic factor of interest is adequately measured in study participants to sufficient to limit potential bias. YES Outcome measurement The outcome of interest is adequately measured in study participants to sufficient to limit potential bias. PARTLY (wide range of follow-up time: 11 to 25 months) Confounding measurement and account Important potential confounders are appropriately accounted

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
		Children and young people < 18 years: -1.3±1.2 Adults ≥ 18 years: -1.3±1.2			for, limiting potential bias with respect to the prognostic factor of interest. UNSURE (treatment not documented over the course of longitudinal study) Analysis The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. YES Overall quality: Other information
Full citation Brenckmann, C., Papaioannou, A., Freitag, A., Hennessey, R., Hansen, S., Ioannidis, G., Webber, C., Adachi, J., Osteoporosis in Canadian adult cystic fibrosis patients: a descriptive study, BMC Musculoskeletal	Sample size n=40 adult CF patients attending a tertiary care hospital Characteristics Mean age (SD): 28.7 (8.4) Range: 19-52 Inclusion criteria Symptomatic and genetic diagnosis of CF Exclusion criteria	Prognostic test/ tool/ factor Baseline mean (SD) z-scores: Left hip BMD: -0.9 (1.1) Right hip BMD:-1.0 (1.1) Lumbar spine BMD: -1.1 (1.3) Baseline mean (SD) gm/cm2: Total BMD: 1.2 (0.1)	Sample selection Data collection Clinical and laboratory data was obtained from a clinic database and pharmaceutical data from in-patient pharmacy DXA scanning of the lumbar spine, femoral neck and total hip to measure BMD using Hologic QDR4500A machine T and Z-scores were calculated. WHO criteria for T-score was used: -1.0 to -2.5 indicates osteopenia and < -2.5 indicates osteoporosis	Results BMD annual change: Change in hip BMD: Left hip: -3.01% (95% CI -4.76 to -1.26) Right hip: -3.06% (95% CI -4.69 to -1.43) Change in lumbar spine BMD: -0.86% (95% CI -2.46 to 0.75)	Limitations The methodological limitations were assessed using a critical appraisal tool for the evaluation of the quality of prognosis studies in systematic reviews (Hayden et al. 2006): Study participation The study sample represents the population of interest with regard to key characteristics,

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
Disorders, 4, 13, 2003 Ref Id 329545 Country/ies where the study was carried out Canada Study type Observational study Aim of the study To evaluate the prevalence of osteoporosis, the prevalence of non-vertebral fractures, and the change in bone mineral density in adult cystic fibrosis patients receiving care at a tertiary hospital Study dates 1999 Source of funding None listed	Not reported		Scans were performed in two consecutive years for 21 patients Data analysis Paired two-tailed one-sample t-tests and 95% CI: to determine if mean changes in BMD were significantly different from baseline Follow-up Scans were performed in two consecutive years for 27 patients	Change in total body BMD (n=21): 0.0% (SD 1.4%)	sufficient to limit potential bias to the results. UNCLEAR (all CF patients attending a tertiary hospital, inclusion/exclusion criteria details sparse) Study attrition Loss to follow-up (from sample to study population) is not associated with key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. YES (prevalence study limited loss to follow-up) Prognostic factor measurement The prognostic factor of interest is adequately measured in study participants to sufficient to limit potential bias. YES Outcome measurement The outcome of interest is adequately measured in study participants to sufficient to limit potential bias. PARTLY (no

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
					mention of review methodology) Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. NO (The majority of patients measured for annual change in BMD had the second scan for clinical reasons and were receiving additional treatment and therefore the sample for this measurement is skewed) Analysis The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. (UNSURE) Overall quality: Other information Subgroup analysis was not possible as sample size was too small. N=21 participants were

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
					receiving oral or IV corticosteroids
Full citation Haworth, C. S., Selby, P. L., Horrocks, A. W., Mawer, E. B., Adams, J. E., Webb, A. K., A prospective study of change in bone mineral density over one year in adults with cystic fibrosis, Thorax, 57, 719-23, 2002 Ref Id 366737 Country/ies where the study was carried out United Kingdom Study type Prospective case series Aim of the study To identify appropriate therapeutic strategies and the optimal time for intervention Study dates	Sample size n=114 adults with cystic fibrosis Characteristics Mean (SD) age: 25.1 (6.9) years (15 to 49) Young cohort ≤ 24 years n=55 Adult cohort ≥ 25 years n=59 Inclusion criteria Confirmed diagnosis of CF by raised sweat chloride test, gene analysis or an appropriate cystic fibrosis phenotype. Exclusion criteria Not reported	Prognostic test/ tool/ factor Details reported in a previous study: Lumbar spine BMD Femoral neck BMD Total hip BMD QCT and DXA DXA scans performed using: Hologic QDR 4500A densitometer (Hologic Inc., Bedford, MA, USA) Baseline lumbar spine BMD (mg/ml by CQT): Young cohort ≤ 24 years: 176.1 (166.9 to 185.2) Adult cohort ≥ 25 years: 170.8 (161.3 to 180.3) Baseline lumbar spine BMD (g/cm2 by DXA): Young cohort ≤ 24 years: 0.918 (0.8882 to 0.953) Adult cohort ≥ 25 years: 0.942 (0.909 to 0.975) Baseline femoral neck BMD (g/cm2 by DXA): Young cohort ≤ 24 years: 0.839 (0.801 to 0.877) Adult cohort ≥ 25 years: 0.781 (0.756 to	Sample selection All patients attending Manchester Adult Cystic Fibrosis Unit Data collection BMD assessed on recruitment and follow up by DXA, SXA, QCT Biochemical measurements Clinical assessment: FEV and anthropomorphic measurements, questionnaire to assess physical activity Data analysis Analysis using SPSS v7.0 One sample t-test or Wilcoxon signed rank test: to determine significance of annual change in BMD Independent sample t-tests: to identify whether differences in BMD annual change between specific patient groups Spearman's rank correlations: to identify clinical and biochemical correlates of BMD annual change at skeletal site Follow-up 114 patients re-attended for BD a median of 12 (12-13)	Results Annual change in lumbar spine BMD (mg/ml by CQT): Young cohort ≤ 24 years: -1.7% (-4.4 to 1.1) Adult cohort ≥ 25 years: 0.7% (-1.5 to 2.8) Annual change in lumbar spine BMD (g/cm2 by DXA): Young cohort ≤ 24 years: -0.9% (-2.0 to 0.2) Adult cohort ≥ 25 years: -0.0% (-1.3 to 1.2) Annual change in femoral neck BMD (g/cm2 by DXA): Young cohort ≤ 24 years: -2.5% (-3.8 to -1.2); p-value <0.001 Adult cohort ≥ 25 years: -1.9% (-2.9 to -0.8); p-value <0.001 Annual change in total hip BMD (g/cm2 by DXA): Young cohort ≤ 24 years: -2.2% (-3.3 to -1.0); p-value <0.001	Limitations The methodological limitations were assessed using a critical appraisal tool for the evaluation of the quality of prognosis studies in systematic reviews (Hayden et al. 2006): Study participation The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. YES Study attrition Loss to follow-up (from sample to study population) is not associated with key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. UNSURE (reasons stated for study withdrawal but BMD Z scores at each site were lower in patients who dropped out)

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
April - December 1997 Source of funding Cystic Fibrosis Research Trust, UK		0.819) Baseline total hip BMD (g/cm2 by DXA): Young cohort ≤ 24 years: 0.917 (0.880 to 0.953 Adult cohort ≥ 25 years: 0.881 (0.844 to 0.918)	months after their initial BMD assessment	Adult cohort ≥ 25 years: -1.5% (-2.4 to -0.6); p=0.001	Prognostic factor measurement The prognostic factor of interest is adequately measured in study participants to sufficient to limit potential bias. YES Outcome measurement The outcome of interest is adequately measured in study participants to sufficient to limit potential bias. YES Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. UNSURE Analysis The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. PARTLY (multiple

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
					correlations used at p<0.05) Overall quality: Other information
Full citation Papaioannou, A., Kennedy, C. C., Freitag, A., O'Neill, J., Pui, M., Ioannidis, G., Webber, C., Pathak, A., Hansen, S., Hennessey, R., Adachi, J. D., Longitudinal analysis of vertebral fracture and BMD in a Canadian cohort of adult cystic fibrosis patients, BMC Musculoskeletal Disorders, 9, 125, 2008 Ref Id 329956 Country/ies where the study was carried out Canada Study type	Sample size N=49 adults with CF Characteristics Mean age (SD): 25.2 (9.4) years 42.9% male Inclusion criteria Moderate to severe respiratory impairment At least one chest radiograph or DXA scan in previous year CF confirmed by positive sweat test and DNA analysis Exclusion criteria Patients accepted on lung-transplant list or received prior organ transplant	Prognostic test/ tool/ factor DXA Baseline mean (SD) T-score/ Z-score: Lumbar spine BMD: -0.80 (1.10) Proximal femur BMD: -0.57 (0.97) Whole body BMD: -0.71 (1.11)	Sample selection All patients who attended Adult Cystic Fibrosis Clinic at McMaster University Medical Centre during 2002 Data collection Radiology review: first and last chest radiograph between 1996 and 2003 selected for review Bone densitometry: scans of lumbar spine, proximal femur and whole body taken using standard dual-energy X-ray absorptiometry (DXA) on a QDR4500A model (Hologic Inc, Bedford, MA, USA) taken 2-5 times during the study BMD measurements reported as T- (adult) or Z-scores (≤19 years) Clinical/laboratory variables recorded Data analysis Analysis using SPSS v13.0 Multi-variable regression model: to estimate percent BMD change per year, with 2-	Results Overall rate of bone loss at mean 4.3 years follow-up: Lumbar spine BMD: -0.73% Proximal femur BMD: -1.93% Whole body BMD: -0.40%	Limitations The methodological limitations were assessed using a critical appraisal tool for the evaluation of the quality of prognosis studies in systematic reviews (Hayden et al. 2006): Study participation The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. YES Study attrition Loss to follow-up (from sample to study population) is not associated with key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. YES (those excluded were transplant

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
Retrospective case series Aim of the study To examine: longitudinal changes in BMD the rate of vertebral fractures in adults with CF Study dates 2002 Source of funding Ontario Thoracic Society			sided p-value of < 0.05 for significance Mann-Whitney U-test: to test differences in baseline characteristics between fracture vs non-fracture patients Fisher's exact test: to examine differences between proportions Follow-up Mean (SD): 4.03 (1.45) years (data available for n=10)		recipients or lack of scans) Prognostic factor measurement The prognostic factor of interest is adequately measured in study participants to sufficient to limit potential bias. PARTLY (clinic data was retrospective and coincident if performed within 1 year) Outcome measurement The outcome of interest is adequately measured in study participants to sufficient to limit potential bias. PARTLY (clinic data was retrospective and coincident if performed within 1 year) Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. PARTLY (wide age range in sample size

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
					and use of steroid and Vit D supplementation not controlled for) Analysis The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. YES Other information
Full citation Schulze, K. J., Cutchins, C., Rosenstein, B. J., Germain-Lee, E. L., O'Brien, K. O., Calcium acquisition rates do not support age-appropriate gains in total body bone mineral content in prepuberty and late puberty in girls with cystic fibrosis, Osteoporosis International, 17, 731-40, 2006 Ref Id 330050	Sample size N=18 Characteristics Prepubertal and pubertal girls and young females with CF Inclusion criteria Not reported Exclusion criteria Not reported	Prognostic test/ tool/ factor Baseline mean±SD gender and age matched z-scores: Lumbar spine BMD: -0.40±1.13 Whole body BMD: -0.29±1.01 Standard dual-energy X-ray absorptiometry (DXA) on a QDR4500A model (Hologic Inc, Bedford, MA, USA)	Sample selection Patients who had completed baseline assessment of bone parameters in the original study were invited to return for follow-up assessment n=18 Data collection Medical survey: fracture history, physical exercise, hospitalizations Pubertal stage assessment using Tanner stage Clinical and laboratory assessment: anthropometric measures and FEV1, hormone levels BMD: DXA using a QDR4500A model and age-matched Z-scores determined for lumbar spine and total body bone	Results Change between baseline and follow-up (mean±SD follow-up 2.13±1.16; range 1.06 to 4.10 years) Lumbar spine BMD: -0.46±0.94 Whole body BMD: -0.45±1.16	Limitations The methodological limitations were assessed using a critical appraisal tool for the evaluation of the quality of prognosis studies in systematic reviews (Hayden et al. 2006): Study participation The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. YES Study attrition Loss to follow-up (from sample to study

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
Country/ies where the study was carried out United States of America Study type Aim of the study to assess calcium accretion rates and changes in lumbar spine BND and total body mineral content to examine predictors of these parameters to understand effectors of bone health over time in children with CF Study dates Original study: July 1999 - October 2001 Follow-up: 1-4 years later Source of funding Cystic Fibrosis Foundation and National center for Research Resources/General clinical Research Center, JHH			mineral content from Hologic database Data analysis STATA v8.0 Regression analysis: to identify determinants of LS BMD Z-score, TBBMC Z-score and their changes over time ANOVA with Scheffe's multiple comparisons tests: to determine measures of BM by pubertal groups at baseline or follow-up ANCOVA: to assess changes in BM by pubertal groups Paired t-test: to assess significance in subject characteristics between baseline and follow-up measurements T-tests: within pubertal groups to determine if measures of LS and TBBMC Z-score changes over time differed from zero Follow-up Mean time: 2.13±1.14 years (range 1.6 to 4.10)		population) is not associated with key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. YES (reasons given for loss to follow-up) Prognostic factor measurement The prognostic factor of interest is adequately measured in study participants to sufficient to limit potential bias. UNSURE (clear description of prognostic factor measurement but scan follow up ranged from 1-4 years) Outcome measurement The outcome of interest is adequately measured in study participants to sufficient to limit potential bias. UNSURE (clear description of prognostic factor measurement but scan follow up ranged from 1-4 years) Confounding measurement and account

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
					Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. UNSURE (longitudinal study - treatment regimes) Analysis The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. YES Other information Although the study reported data stratified by pubertal status, this was not reported in the review as sample size was very low (range 2 to 7). Significant differences were found by pubertal stage at baseline.

G.20 Exercise

Review question: What is the effectiveness of programmes of exercise in the management of cystic fibrosis?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Enright, S., Chatham, K., Ionescu, A. A., Unnithan, V. B., Shale, D. J., Inspiratory muscle training improves lung function and exercise capacity in adults with cystic fibrosis, Chest, 126, 405-11, 2004 Ref Id 332644 Country/ies where the study was carried out See Houston 2013 Study type See Houston 2013 Aim of the study See Houston 2013 Study dates See Houston 2013 Source of funding See Houston 2013	Sample size See Houston 2013 Characteristics See Houston 2013 Inclusion criteria See Houston 2013 Exclusion criteria See Houston 2013	Interventions See Houston 2013	Details See Houston 2013	Results See Houston 2013	Limitations See Houston 2013 Other information See Houston 2013
Full citation Gruber, W., Orenstein, D. M.,	Sample size	Interventions Intervention 1: Interval-	Details Study setting.	Results FEV1 (% predicted)	Limitations The quality of this study was

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Braumann, K. M., Beneke, R., Interval exercise training in cystic fibrosis - Effects on exercise capacity in severely affected adults, Journal of Cystic Fibrosis, 13, 86-91, 2014 Ref Id 425890 Country/ies where the study was carried out Germany Study type Cohort study Aim of the study To investigate the effects of interval exercise training on lung function power and oxygen uptake (VO2) at peak performance (peak) and ventilatory anaerobic threshold (VAT) in CF patients who were unable to participate in a standard exercise program and to compare these interval exercise training	N=43 (20 in interval training group, 23 in standard exercise programme group) Characteristics Rehabilitation clinic inpatients with CF Baseline characteristics at admission: Age, mean (SD): interval training group 26.4 (7.5) vs standard exercise programme group 26.3 (9.9) FEV1 (% predicted), mean (SD): interval training group 25.5 (7.5) vs standard exercise programme group 31.6 (4.2) Inclusion criteria FEV1 < 40% predicted stability of disease throughout the study period no acute exacerbation during the 4 weeks prior to the in-patient program Exercise capacity was determined by an incremental exercise test. The participants were allocated into training groups according to results of oxygen saturation (SpO2) during incremental exercise testing. Subjects who de-saturated (SpO2 b 90%) at very low power (≤0.3 W/kg) or had a SpO2 ≤ 90%	training for 6 weeks The IT treadmill program was performed at the individual's comfortable continuous walking speed, between 3 and 4 km/h lasting 16 min, 5 times weekly and consisted of ten intervals of 20 or 30 s high intensity bouts at 50% of maximal grade achieved during steep ramp test (SRT), followed by 60 s active recovery phases at 0% grade treadmill inclination. Supplemental oxygen was administered to reach a	Study design. At admission and at discharge, all participants underwent a complete medical examination which included measurement of lung function, exercise capacity, height and bodyweight. Prior to beginning IT, the IT group performed an additional Steep Ramp Test (SRT) to determine the exercise intensity of IT. Data collection. Forced Expiratory Volume in 1 s, (FEV1%pred), and Vital Capacity (VC% pred) were measured by spirometry (Master screen, Jaeger, Wuerzburg, Germany) according to recommended techniques, and values were expressed as a percentage of age, sex and anthropometry related to normal values. Body composition was measured using the bioelectrical impedance analysis system (BIA) (Data input, Darmstadt Germany). Cardio-pulmonary exercise testing (CPET) was performed on an electro-magnetically braked cycle ergometer (Examiner, Lode B.V. Groningen, The Netherlands). Gas exchange and ventilatory measures were recorded breath by breath (Master Screen CPX, Viasys Healthcare GmbH, Hoechberg, Germany). After a period of rest (3 min) and after a 3 min phase of unloaded cycling, power was	Mean (SD): interval training group at discharge: 24.4 (6.6) and interval training group at baseline: 25.5 (7.5) vs standard exercise programme at discharge: 34.4 (5.5) and standard exercise programme at baseline: 31.6 (4.2) FVC% predicted Not reported VO2 peak (ml/kg/min) Mean (SD): interval training group at discharge: 23.4 (6.9) and interval training group at baseline: 20.9 (4.2) vs standard exercise programme at discharge: 24.6 (6.8) and standard exercise programme at baseline: 21.3 (6.5) BMI Interval training group at discharge: 17.5 (2.1) and interval training group at baseline: 17.1 (2.1) vs	assessed using the Newcastle-Ottawa scale assessment tool: Selection: High risk of bias (The participants were allocated into training groups according to results of oxygen saturation during incremental exercise testing. Patients with CF who were unable to participate in a standard exercise programme were assigned to the interval training group) Comparability: High risk of bias (The study does not control for any factor) Outcome: Low risk of bias (Description of tests is provided; results for all 43 patients are provided) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
responses with corresponding effects in CF patients performing the standard exercise program. Study dates Not reported Source of funding Not reported	at rest were allocated to IT. The other participants were assigned to SEP. Exclusion criteria untreated CF-related diabetes clinical evidence of exercise limiting cardiac, neurological or musculo-skeletal problems intravenous antibiotic therapy during the 4 weeks prior to the program ventilatory anaerobic threshold (VAT) not detectable.	haemoglobin oxygen saturation of more than 90% during exercise training. The SRT was repeated every 2 weeks to adjust 50% maximum short-time exercise capacity (MSEC) according to potential individual changes in MSEC. Intervention 2: Standard exercise program Participants exercised 5 times weekly for 6 weeks. All training sessions lasted 45 min and consisted of different sport activities depending on participants'	increased every minute by 10–20 W(Godfrey protocol) depending on the patient's height and physical fitness. Participants were encouraged to make a maximal effort, and the test was continued until the subject could no longer maintain a pedaling cadence of 60 rpm or SpO2 was below 85%. To specify the Ventilatory Anaerobic Threshold (VAT), the excess carbon dioxide method (ExCO2), and the modified V-Slope method were used. Heart rate (HR) was measured continuously using 12 lead ECG.	standard exercise programme at discharge: 18.7 (2.7) and standard exercise programme at baseline: 18.3 (2.0) Quality of life Not reported Time to next exacerbation Not reported Preference for training programme Not reported Adverse events Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		fitness level (prolonged endurance exercise in terms of walking or Nordic-Walking complemented by ball games, stretching, balance training, and resistance training). All sessions were supervised by a specially trained and experienced sport-therapist. The training intensity during endurance training was set at a HR corresponding to 80–90% of VO2VAT equivalent to 60–75% VO2peak and monitored with a portable			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		heart rate monitor.			
Full citation Hebestreit, H., Kieser, S., Junge, S., Ballmann, M., Hebestreit, A., Schindler, C., Schenk, T., Posselt, H. G., Kriemler, S., Long-term effects of a partially supervised conditioning programme in cystic fibrosis, European Respiratory Journal, 35, 578-83, 2010 Ref Id 361305 Country/ies where the study was carried out See Radtke 2015 Study type See Radtke 2015 Aim of the study See Radtke 2015 Study dates See Radtke 2015 Source of funding See Radtke 2015	Sample size See Radtke 2015 Characteristics See Radtke 2015 Inclusion criteria See Radtke 2015 Exclusion criteria See Radtke 2015	Interventions See Radtke 2015	Details See Radtke 2015	Results See Radtke 2015	Limitations See Radtke 2015 Other information See Radtke 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Hommerding, P. X., Baptista, R. R., Makarewicz, G. T., Schindel, C. S., Donadio, M. V. F., Pinto, L. A., Marostica, P. J. C., Effects of an educational intervention of physical activity for children and adolescents with cystic fibrosis: A randomized controlled trial, Respiratory Care, 60, 81-87, 2015 Ref Id 425924 Country/ies where the study was carried out See Radtke 2015 Study type See Radtke 2015 Aim of the study See Radtke 2015 Study dates See Radtke 2015 Source of funding See Radtke 2015	Sample size See Radtke 2015 Characteristics See Radtke 2015 Inclusion criteria See Radtke 2015 Exclusion criteria See Radtke 2015	Interventions See Radtke 2015	Details See Radtke 2015	Results See Radtke 2015	Limitations See Radtke 2015 Other information See Radtke 2015
Full citation	Sample size	Interventions	Details	Results	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Houston, B. W., Mills, N., Solis-Moya, A., Inspiratory muscle training for cystic fibrosis, Cochrane Database of Systematic Reviews, 11, CD006112, 2013 Ref Id 333651 Country/ies where the study was carried out Enright 2004: UK Study type Houston 2013 Cochrane systematic review Enright 2004 RCT Aim of the study Houston 2013 To determine the effects of inspiratory muscle training in the management of people with CF. Enright 2004 To investigate the effects of high-intensity inspiratory muscle training	Enright 2004 N=19 adults with CF IMT group: n=9 Control group: n=10 Characteristics Enright 2004 Age of total cohort (all adults): mean (SD) age = 22 (4.2) years. IMT at 80% of maximal effort group: mean (SD) age = 24.8 (5.5) years Control group: mean (SD) age = 21.3 (2.7) years Gender split of total cohort: 16 male, 14 female. IMT at 80% of maximal effort group: 4 males, 6 females Control group: 6 males, 4 females All had similar age, height, weight and lung function at baseline None of the participants were receiving oral steroids at the time of the study* *Information extracted from individual paper rather than from systematic review Inclusion criteria People with CF attending who were outpatients attending an adult CF centre* Stable condition, defined as: No change in symptoms or	Enright 2004 Intervention: IMT at 80% of “maximal inspiratory effort” direct supervision at home by designated training IMT is incremental maximal effort with progressively shorter rest periods 3 times a week for 8 weeks Control: no training	Enright 2004 Parallel design over 8 weeks. Study setting: single centre in the UK. Sample size calculation was undertaken and indicated that study needed at least 9 patients in each group.	Enright 2004 FEV1 % predicted Not reported FEV1 (litres) Mean (SD) at 2 to 6 months: IMT (80% of maximal effort) (n=9): 2 (1) vs control (n=10): 2 (1). Mean difference [95% CI]: 0.0 [-0.90, 0.90] FVC % predicted Not reported FVC (litres) Mean (SD) at 2 to 6 months: IMT (80% of maximal effort) (n=9): 3 (1.2) vs control (n=10): 2.9 (1). Mean difference [95% CI]: 0.10 [-0.90, 1.10] VO2 Not reported Time to next exacerbation Not reported Quality of life Not reported Preference for training programme Not reported Body composition	Houston 2013 AMSTAR checklist score: 10/11 (sources of funding or support was not indicated in relation to the included studies, only in relation to the systematic review) Enright 2004 Random sequence generation (selection bias): Unclear risk (No information provided) Allocation concealment (selection bias): Unclear risk (No information provided) Blinding (performance bias and detection bias) (all outcomes): High risk (Performance bias: the comparison was “no training”making it clear to the participants which arm they were in. Detection bias: outcome assessors

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
(IMT) on inspiratory muscle function and other indicators including lung function.* * Extracted from individual paper rather than from systematic review Study dates Houston 2013 Searches were updated and run again on 01 August 2013. Enright 2004 Study dates not reported. * * Extracted from individual paper rather than from systematic review Source of funding Houston 2013 Internal sources: University of Teesside, Middlesbrough, UK. External sources: No sources of support supplied. Enright 2004 The study was supported by the Physiotherapy Research	treatment in a month preceding the study; FEV1 within 10% of the best value recorded in the previous 12 months* *Information extracted from individual paper rather than from systematic review Exclusion criteria People with cor pulmonale, liver cirrhosis, or diabetes mellitus were excluded from the study* *Information extracted from individual paper rather than from systematic review			Not reported Adverse events Not reported	at the final data collection session, although they did not state whether this was the case at the initial assessment or even if the same assessors carried out all the assessments). Incomplete outcome data (attrition bias) (all outcomes): Unclear risk (No mention is made of whether all participants completed the trial or not. Nor are there any statistical indications. Intention-to-treat: unclear.) Selective reporting (reporting bias): Unclear risk (Insufficient information available to arrive at a conclusion) Other bias: Unclear risk (Insufficient information available to arrive at a conclusion) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Foundation and the Cystic Fibrosis Trust* *Extracted from individual paper rather than from systematic review					
Full citation Klijn, P. H. C., Oudshoorn, A., Van Der Ent, C. K., Van Der Net, J., Kimpen, J. L., Helders, P. J. M., Effects of anaerobic training in children with cystic fibrosis: A randomized controlled study, Chest, 125, 1299-1305, 2004 Ref Id 425960 Country/ies where the study was carried out See Radtke 2015 Study type See Radtke 2015 Aim of the study See Radtke 2015 Study dates See Radtke 2015 Source of funding	Sample size See Radtke 2015 Characteristics See Radtke 2015 Inclusion criteria See Radtke 2015 Exclusion criteria See Radtke 2015	Interventions See Radtke 2015	Details See Radtke 2015	Results See Radtke 2015	Limitations See Radtke 2015 Other information See Radtke 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See Radtke 2015					
Full citation Kriemler, S., Kieser, S., Junge, S., Ballmann, M., Hebestreit, A., Schindler, C., Stussi, C., Hebestreit, H., Effect of supervised training on FEV1 in cystic fibrosis: a randomised controlled trial, Journal of Cystic Fibrosis, 12, 714-20, 2013 Ref Id 361395 Country/ies where the study was carried out See Radtke 2015 Study type See Radtke 2015 Aim of the study See Radtke 2015 Study dates See Radtke 2015 Source of funding See Radtke 2015	Sample size See Radtke 2015 Characteristics See Radtke 2015 Inclusion criteria See Radtke 2015 Exclusion criteria See Radtke 2015	Interventions See Radtke 2015	Details See Radtke 2015	Results See Radtke 2015	Limitations See Radtke 2015 Other information See Radtke 2015
Full citation	Sample size	Interventions	Details	Results	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Moorcroft, A. J., Dodd, M. E., Morris, J., Webb, A. K., Individualised unsupervised exercise training in adults with cystic fibrosis: a 1 year randomised controlled trial, Thorax, 59, 1074-80, 2004 Ref Id 361493 Country/ies where the study was carried out See Radtke 2015 Study type See Radtke 2015 Aim of the study See Radtke 2015 Study dates See Radtke 2015 Source of funding See Radtke 2015	See Radtke 2015 Characteristics See Radtke 2015 Inclusion criteria See Radtke 2015 Exclusion criteria See Radtke 2015	See Radtke 2015	See Radtke 2015	See Radtke 2015	See Radtke 2015 Other information See Radtke 2015
Full citation Orenstein, D. M., Hovell, M. F., Mulvihill, M., Keating, K. K., Hofstetter, C. R., Kelsey, S., Morris, K., Nixon, P. A.,	Sample size N=67 (qualified and agreed to participate). Only subjects with data at both time points were included in the comparisons: For the analysis at 6 months follow up, N=56 (26 in the	Interventions Intervention 1. Aerobic training regimen Each child was given a	Details Study setting The Children's Hospital of Pittsburgh Randomisation and blinding. Participants were assigned at random to either the aerobic or upper-body strength training	Results FEV1 (% predicted) mean (SD): Aerobic at 6 months: 89.65 (19.32) and aerobic at baseline: 92.22 (18.33) vs strength at 6 months: 86.07	Limitations The quality of this study was assessed using the Cochrane risk of bias tool: Random sequence generation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Strength vs aerobic training in children with cystic fibrosis: a randomized controlled trial, Chest, 126, 1204-14, 2004 Ref Id 333783 Country/ies where the study was carried out USA Study type Randomised Controlled Trial Aim of the study To compare the effects of a home-based, semi-supervised, upper-body strength-training regimen with a similarly structured aerobic training regimen. Study dates Data were collected during a 1-year randomized clinical trial. Source of funding The study was supported by National Heart, Lung, and	aerobic group and 30 in the strength group). For the analysis at 12 months follow up, N=53 (25 in the aerobic group and 28 in the strength group). Characteristics Age range: 8-18 Inclusion criteria People with confirmed CF diagnosis Exclusion criteria People were excluded if: they were already engaging in regular aerobic exercise or weight training for 20 min at least three times per week; their peak work capacity was 110% of predicted based on the Godfrey equation; their oxygen uptake (millimeters per minute) was 100% of predicted based on the Franklin or Rowland equation; their Vo2peak was 45 mL/kg/min; they gave a submaximal effort, which was defined as a respiratory exchange ratio of --- 1.0 or a subjective interpretation by the tester,	stair-stepping machine Participants were encouraged to exercise at least 3 times per week for 1 year Counselors conducted in-home visits once a week for the first 8 weeks followed by monthly visits for the remainder of the study Participants were instructed to exercise 5 min per session, gradually increasing their exercise to 30 min per session over the course of the study Children were taught to gradually increase their target heart	conditions following baseline strength, aerobic fitness, and pulmonary function measures. Random assignment was determined by the research coordinator from a predetermined list of random numbers. Staff members were notified of each child's assignment immediately following baseline measures, precluding advanced knowledge of assignment, and all measurement staff members remained blind to assignment through follow-up measures. Separate counseling staff remained blind to outcome measures throughout the trial. Investigators remained blind to outcome measures until all youth had completed their 12-month assessment measures. Data were transferred to coauthors in San Diego for analysis, thereby ensuring greater separation of clinical and analysis components of the trial. Data collection Measures were obtained at baseline, 6 months, and 12 months at least 2 weeks following high doses of tobramycin, ciprofloxacin, or IV treatments. Resting measures were obtained for 2 min prior to aerobic fitness testing. Progressive exercise testing was conducted on an electronically braked cycle ergometer following the Godfrey protocol. Patients began	(17.16) and strength at baseline: 90.3 (17.85) mean (SD): Aerobic at 12 months: 90.32 (17.92) and aerobic baseline: 91.51 (18.34) vs strength at 12 months: 90.29 (15.82) and strength at baseline: 91.18 (18.07) FVC% predicted Not reported VO2 peak Peak oxygen consumption (ml/min/kg), mean (SD): Aerobic at 6 months: 32.90 (6.06) and aerobic baseline: 34.81 (5.45) vs strength at 6 months: 30.38 (6.21) and strength at baseline: 32.54 (5.88) Peak oxygen consumption (ml/min/kg), mean (SD): Aerobic at 12 months: 33.69 (7.16) and aerobic baseline: 34.60 (5.46) vs strength at 12 months: 30.91 (6.73) and strength	(selection bias): Unclear risk (the authors mention a predetermined list of random numbers but do not report how the list was generated) Allocation concealment (selection bias): Unclear risk (not reported) Blinding of participants and personnel (performance bias) (all outcomes): High risk (blinding of participants was not possible; staff members were notified of each child's assignment immediately following baseline measures) Blinding of outcome assessment (detection bias) (all outcomes): Low risk (all measurement staff members remained blind to assignment through follow-up measures)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Blood Institute grant HL52306, and in-kind support from the Center for Behavioral Epidemiology and Community Health, Graduate School of Public Health, San Diego State University.	on more than one baseline testing date.	rate to 70% of their maximum heart rate Intervention 2. Upper-body strength training regimen Each child was given an upper-body-only-weight-resistance machine Participants were encouraged to exercise at least 3 times per week for 1 year Counselors conducted in-home visits once a week for the first 8 weeks followed by monthly visits for the remainder of the study Participants were instructed to perform biceps curls,	pedaling at 0 W for 1 min, with the workload increasing by 10 W, 15 W, or 20 W each minute depending on the patients' height and clinical status. Maximal effort was encouraged. The peak work capacity was defined as the highest workload (watts) sustained for 1 min, and peak work capacity percentage of predicted was determined from the equations of Godfrey based on height and gender. Metabolic equipment (Medical Graphics; St. Paul, MN) provided online, breath-by-breath measures of oxygen uptake. Peak values were determined from the last 15 s of exercise. A 12-lead ECG was monitored continuously, and heart rate was determined each minute and at peak exercise. Pulmonary Function Testing: Prior to exercise testing, participants performed pulmonary function tests according to the American Thoracic Society standards. Lung volumes were determined by body plethysmography. Spirometry, including flow volume curves both before and after inhalation of a bronchodilator (albuterol), was performed using a body plethysmograph (Sensor Medics System 6200; SensorMedics; Yorba Linda, CA), with the patient seated comfortably. FVC and FEV1 were chosen from among no fewer than	at baseline: 32.64 (6.22) Body composition Not reported Quality of life Not reported Time to next exacerbation Not reported Preference for training programme Not reported Adverse events Not reported	Incomplete outcome data (attrition bias) (all outcomes): Low risk (intention-to-treat analysis was employed. Only subjects with data at both time points were included: 56/67 and 53/67 for the 6-month and 12-month follow-up respectively) Selective reporting (reporting bias): Low risk (The authors mention that measures were obtained at baseline, at 6 months and at 12 months and report outcomes at all these follow-ups) Other bias: Low risk (not detected) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		lateral pull-downs, and military and bench presses Exercises were individually tailored to the participants' strength, and the exercise increased gradually by the number of sets and repetitions as well as by the amount of resistance per bout Children were instructed to keep their heart rate <55% of their maximum, based on the baseline exercise test. Attachments for and leg exercise were not recommended in order to decrease the likelihood of	three nor more than eight maneuvers. The "best test" was chosen on the basis of the largest sum of FVC and FEV1. Data analysis Intent-to-treat analysis, was employed. Descriptive analyses and t tests were performed. T tests were performed using the pair-wise option for missing data; therefore, only subjects with data at both points were included in the individual comparisons. The pair-wise method created different sample sizes and different means for the variables used in each comparison. The distributions were examined and adjusted using natural log transformations or squaring to improve normality.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		lower-body exercise and increase difference in training between groups			
Full citation Radtke, T., Nolan, S. J., Hebestreit, H., Kriemler, S., Physical exercise training for cystic fibrosis.[Update of Cochrane Database Syst Rev. 2008;(1):CD002768 ; PMID: 18254007], Cochrane Database of Systematic Reviews, 6, CD002768, 2015 Ref Id 426109 Country/ies where the study was carried out Hebestreit 2010: Germany Hommerding 2015: Brazil Klijn 2004: Netherlands Kriemler 2013: Switzerland Moorcroft 2004: UK	Sample size Radtke 2015 13 studies which included 402 participants, met the inclusion criteria. The numbers in each study ranged from 9 to 72 participants. Hebestreit 2010 N=38 Exercise group n=23 Control group n=15 Hommerding 2015 N=34 Exercise group n=17 Control group n=17 Klijn 2004 N=20 Intervention group n=11 Control group n=9 3 participants dropped out; 1 withdrew from the training group for practical reasons Kriemler 2013 N=39 Aerobic training group (n=17)	Interventions Radtke 2015 Any type of prescribed physical exercise training delivered to people with CF compared to usual care. Hebestreit 2010 Intervention: endurance-type and strengthening exercises Unsupervised programme Participants agreed to increase their vigorous physical activities by a minimum of 3x 60 min per	Details Radtke 2015 Relevant studies were identified from the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register using the term: exercise. The reference listso for each RCT and of review articles were searched for additional publications that may contain RCTs. Authors of studies included in this review and other experts in the field were contacted and asked for information on other published and unpublished studies. Two authors independently assessed the titles and abstracts of identified citations and selected the studies to be included in the review. Each author independently extracted data using standard data acquisition forms. Two authors independently assessed the risk of bias for each included study according to the Cochrane risk of bias tool. Hebestreit 2010	Results Hebestreit 2010 FEV1 % predicted Mean (SD) change at 3-6 months: combined aerobic and anaerobic training (n=22): -2.1 (8.4) vs no training (n=13): -4.1 (11.8). Mean difference [95% CI]: 2.00 [-5.31, 9.31] Mean (SD) change at 6 months off training for combined aerobic and anaerobic training (n=18): -6 (12.5) vs no training (n=12): -4.9 (8.7). Mean difference [95% CI]: -1.10 [-8.69, 6.49] Mean (SD) change at 12-18 months off training for combined aerobic	Limitations Radtke 2015 AMSTAR score: 10/11 (source of funding or support was given for the systematic review but not for the included studies) Hebestreit 2010 Random sequence generation (selection bias): High risk (40 folded paper tickets were put into a bag with a 3:2 ratio i.e. 24 tickets for the intervention group and 16 for the control group. Participants drew a ticket at random and the drawn ticket was then destroyed. Principal investigator was aware of the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Rovedder 2014: Brazil Santana-Sosa 2012: Spain Santana-Sosa 2014: Spain Schneiderman-Walker 2000: Canada Selvadurai 2002: Australia Study type Radtke 2015 Cochrane systematic review Hebestreit 2010 RCT Hommerding 2015 RCT Klijn 2004 RCT Kriemler 2013 RCT Moorcroft 2004 RCT Rovedder 2014 RCT Santana-Sosa 2012 RCT	Strength training group (n=12) Control group (n=10) A separate control group from a parallel study (Hebestreit 2010) was added due to an unusual deterioration of physical health in the control group in this study (n=15) Moorcroft 2004 N=51 Exercise group (n=30) Control group (n=18) 42 completed the study Rovedder 2014 N=41 Exercise group n=19 Control group n=22 Santana-Sosa 2012 N=22 Exercise group n=11 Control group n=11 Santana-Sosa 2014 N=20 Exercise group n=10 Control group n=10 Schneiderman-Walker 2000 N=65 Exercise group (n=30) Control group (n=35) 7 dropouts Selvadurai 2002 N=66	week in the first 6 months of the study. An individual exercise plan was devised for participants; activity counselling was stopped after the first 6 months and participants were encouraged to maintain or further increase their physical activity level Control: Participants told to keep their activity level constant during the first 12 months of the study. During the second year (period from 12 - 24 months) they were free to change their	Multi-centre parallel RCT; duration 24months (6-month intervention and longterm, open follow-up period) Hommerding 2015 Single-centre parallel RCT; 3-month duration Klijn 2004 Single-centre, parallel RCT, 3-month duration. Kriemler 2013 Multi-centre, parallel RCT with 3 arms; 24 month (6-month intervention and long-term, open follow-up period) Moorcroft 2004 Single-centre, parallel RCT; 1-year duration. Rovedder 2014 Single-centre, parallel RCT; 3-months home-based exercise programme Santana-Sosa 2012 Single-centre, parallel RCT; 3-month duration (8 weeks training, 4 weeks detraining) Santana-Sosa 2014	and anaerobic training (n=20): -5.5 (10.1) vs no training (n=13): -9.1 (12.2). Mean difference [95% CI]: 3.60 [-4.37, 11.57] FVC % predicted Mean Difference (SE) in change at 3-6 months for combined aerobic and anaerobic training vs no training: 0.5 (2.45). Mean difference [95% CI]: 0.50 [-4.30, 5.30] Mean Difference (SE) in change at 6 months off training for combined aerobic and anaerobic training vs no training: 2.71 (3.61). Mean difference [95% CI]: 2.71 [-4.37, 9.79] Mean Difference (SE) in change at 12-18 months off training for combined aerobic and anaerobic training vs no training: 6.06 (2.87). Mean difference	number of lots in the bag) Allocation concealment (selection bias): High risk (Participants drew a folded paper ticket from an opaque bag with closed eyes. In case that all lots have been drawn out by 1 study group, allocation concealment would no longer exist) Blinding of participants and personnel (performance bias) (all outcomes): Unclear risk (Not possible to blind participants to intervention. Unclear whether personnel was blinded) Blinding of outcome assessment (detection bias) (all outcomes): Unclear risk (Outcome assessors were not blinded with respect to the participants'

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Santana-Sosa 2014 RCT Schneiderman-Walker 2000 RCT Selvadurai 2002 RCT Aim of the study Radtke 2015 To determine the effects of physical exercise training compared to no training on aerobic exercise capacity, forced expiratory volume in one second, health-related quality of life and other patient-relevant (secondary) outcomes in cystic fibrosis. Hebestreit 2010 To determine the effects of a 6-month home-based and individualised conditioning programme on multiple outcomes	Aerobic training group (n=22) Resistance training group (n=22) Control group (n=22) No dropouts Characteristics Radtke 2015 People with CF, of any age, and any degree of disease severity, diagnosed on the basis of clinical criteria and sweat testing or genotype analysis. Hebestreit 2010 People with CF >12 years Exercise group (n = 23): mean (SD) age 19.5 (6.4) years. Control group (n = 15): mean (SD) age 19.4 (5.3) years. Hommerding 2015 Children and young people with CF Sex: 20 boys, 14 girls Exercise group (n = 17): mean (SD) age 13.4 (2.8) years. Control group (n = 17): mean (SD) age 12.7 (3.3) years. Klijn 2004 Children and young people with CF with stable disease.	activity behaviour Hommerding 2015 Intervention: aerobic exercise programme Unsupervised programme Included jogging, swimming, walking, ball games and stretching exercises. based on verbal and written guidelines twice a week for at least 20 min for 3 months participants received telephone calls every 2 weeks and instructions were provided by one of the authors	Single-centre, parallelRCT; 3-month study (8weeks training, 4weeks detraining) Schneiderman-Walker 2000 Single-centre, parallel RCT, 3-year duration. Selvadurai 2002 Single-centre, parallel RCT; hospital admission for recurrent chest infections	[95% CI]: 6.06 [0.43, 11.69] VO2 peak during maximal exercise (ml/min per kg BW) Mean Difference (SE) in change at 3-6 months for combined aerobic and anaerobic training vs no training: 2.04 (1). Mean difference [95% CI]: 2.04 [0.08, 4.00] Mean Difference (SE) in change at 6 months off training for combined aerobic and anaerobic training vs no training: 0.7 (1.18). Mean difference [95% CI]: 0.70 [-1.61, 3.01] Mean Difference (SE) in change at 12-18 months off training for combined aerobic and anaerobic training vs no training: 3.73 (1.23). Mean difference [95% CI]: 3.73 [1.32, 6.14]	group allocation for VO2 peak) Incomplete outcome data (attrition bias) (all outcomes): Unclear risk (5 participants dropped out during the first 12 months of the study: 3 gave no reason, 1 joined another study and 1 moved away At 18 and 24 months, dropout rate was 13% and 26% respectively. Dropouts were balanced between groups. Reasons for drop out were not recorded Intention-to-treat was not performed) Selective reporting (reporting bias): Unclear risk (Anaerobic capacity (PP, MP) was only reported for 18 - 24 months follow up (non significant)and results for HRQoL are only presented for the scale 'physical functioning'. No

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
at 12 and 18 months after the programme had ended.* Hommerding 2015 To evaluate the effect of an aerobic exercise programme based on verbal and written guidelines on multiple outcomes in children and young people with cystic fibrosis.* Klijn 2004 To investigate the effects of anaerobic training in children with CF.* Kriemler 2013 To determine the effects of a 6-month partially supervised aerobic training or a supervised strength training programme in comparison to no intervention on FEV1 and other secondary outcomes in people with cystic fibrosis,	Exercise group (n = 11): mean (SD) age 13.6 (1.3) years. Control group (n = 9): mean (SD) age 14.2 (2.1) years. Kriemler 2013 Participants with CF aged >12 years Aerobic training group (n = 17): mean (95% CI) age 23.8 (21.5 to 26.5) years Strength training group (n = 12): mean (95% CI) age 19.0 (16.0 to 22.0) years Control group (n = 10): mean (95% CI) age 20.3 (17.0 to 23.6) years Moorcroft 2004 Adults with CF Exercise group (n = 30): mean (SD) age 23.5 (6.4) years. Control group (n = 18): 23.6 (5.5) years. Rovedder 2014 People with CF ≥ 16 years Exercise group (n = 22): mean (SD) age 23.8 (8.3) years. Control group (n = 19): mean (SD) age 25.4 (6.9) years.	Control: usual care participants were instructed about aerobic exercises once at baseline according to the CF centre routine Klijn 2004 Intervention: anaerobic training Supervised programme 2 days per week for 30 to 45 min 12 weeks Control: normal daily activities 12 weeks Kriemler 2013 Intervention 1: aerobic training Unsupervised programme 24-months: 6-month		Time to next exacerbation Not reported Quality of life, subjective health perception (CFQ-R) Mean Difference (SE) in change at 3-6 months for combined aerobic and anaerobic training vs no training: 9.91 (4.6). Mean difference [95% CI]: 9.91 [0.89, 18.93] Mean Difference (SE) in change at 6 months off training for combined aerobic and anaerobic training vs no training: -2.31 (6.71). Mean difference [95% CI]: -2.31 [-15.46, 10.84] Mean Difference (SE) in change at 12-18 months off training for combined aerobic and anaerobic training vs no training: 9.89 (4.72). Mean difference	effects were observed for all other HRQoL scales) Other bias: Unclear risk (Financial support (max 200 Euro) was offered for intervention group participants to foster the realisation of the exercise training plan) Hommerding 2015 Random sequence generation (selection bias): Low risk (Participants were allocated to the intervention or control group in blocks of 6. A computer-based program was used for randomisation) Allocation concealment (selection bias): Unclear risk (Not discussed) Blinding of participants and personnel (performance bias) (all outcomes): Not

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and to test the long-term effects 6 and 18 months after the end of the intervention.* Moorcroft 2004 To examine the effectiveness of an individualised unsupervised home based exercise programme in adults with cystic fibrosis over a 1 year period.* Rovedder 2014 To assess the effects of a home exercise programme, based on aerobic training and muscle strength training, in people with cystic fibrosis, for a period of 3 months.* Santana-Sosa 2012 To assess the effects of an 8-week intrahospital combined circuit weight and aerobic training program performed by	Santana-Sosa 2012 Children and young people with CF Training group (n = 11): mean (SEM, range) age 11 years (3 years, 5 - 15 years) Control group (n = 11): mean (SEM, range) age 10.0 years (2 years, 6 - 14 years) Santana-Sosa 2014 Children and young people with CF Training group (n = 10): mean (SEM) age 11.1 (1.1) years. Control group (n = 10): mean (SEM) age 10.1 (1.1) years. Schneiderman-Walker 2000 People with CF 2 groups similar at baseline. Exercise group (n = 30): mean (SD) age 13.4 (3.9 years). Control group (n = 35): mean (SD) age 13.3 (3.6) years. Selvadurai 2002 Children and young people with CF aged 8 to 16 years admitted to hospital due to a pulmonary exacerbation Sex: 28 males, 38 females Aerobic training group (n = 22): mean (SD) age 13.2	intervention and long-term follow-up period 3 sessions per week of 30 to 45 minutes for 6 months and received support which was stopped thereafter Intervention 2: strength training Unsupervised programme 24-months: 6-month intervention and long-term follow-up period 3 sessions per week of 30 to 45 minutes for the first 6 months and received support which was stopped thereafter Control: no programme Participants in the control		[95% CI]: 9.89 [0.64, 19.14] Preference for training programme Not reported Body composition Mean (SD) change in body weight (kg) at 3-6 months: combined aerobic and anaerobic training (n=22): 1.1 (1.8) vs no training (n=15): 0 (2.6). Mean difference [95% CI]: 1.10 [-0.42, 2.62] Mean (SD) change in body weight (kg) at 6 months off training for combined aerobic and anaerobic training (n=19): 1.5 (4) vs no training (n=12): 1.3 (3.6). Mean difference [95% CI]: 0.20 [-2.52, 2.92] Mean (SD) change in body weight (kg) at 12-18 months off training for combined aerobic and anaerobic training (n=20): 1.8 (6) vs no	possible to blind participants to intervention. Unclear whether personnel was blinded. Blinding of outcome assessment (detection bias) (all outcomes): Unclear risk (Unclear whether outcome assessors were blinded) Incomplete outcome data (attrition bias) (all outcomes): Low risk (No drop outs were reported during the study) Selective reporting (reporting bias): Unclear risk (Blood pressure was measured prior to and after cardiopulmonary exercise testing but not reported. HR at rest and SaO2 at peak exercise were measured but results were not reported at baseline)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
children with cystic fibrosis of low-moderate severity and stable clinical conditions on multiple outcomes.* Santana-Sosa 2014 To assess the effects of an 8-week combined 'whole muscle' (resistance+aerobic) and inspiratory muscle training on multiple outcomes in paediatric outpatients with cystic fibrosis.* Schneiderman-Walker 2000 To evaluate the effects of a 3-year home exercise program on pulmonary function and exercise tolerance in mildly to moderately impaired patients with cystic fibrosis and to assess whether regular aerobic exercise is a realistic treatment option.*	(2.0) years), 9males and 13 females Resistance training group (n = 22): mean (SD) age 13.1 (2.1) years, 10 males and 12 females Control group (n = 22): mean (SD) age 13.2 (2.0) years, 9 male and 1 females Inclusion criteria Radtke 2015 All randomised and quasi-randomised controlled clinical trials comparing exercise training of any type and duration with conventional care in people with cystic fibrosis were included. Hebestreit 2010 Participants with CF; age > 12 years; FEV1 > 35 % predicted; ability to perform physical activities. Hommerding 2015 Participants with CF aged 7 - 20 years; stable disease, no signs of exacerbation of respiratory symptoms in last 15 days. Klijn 2004 Participants with CF aged 9 - 18 years; a stable clinical condition (i.e., no need for	group were told to keep their activity level constant Free access to a fitness centre for 1 year after the first study year Moorcroft 2004 Intervention: aerobic exercise Unsupervised programme Exercise based on individual preferences general aerobic exercises for lower body and weight training for upper body) 3 times per week Control: usual activities Continue with usual activities		training (n=13): 1.8 (5). Mean difference [95% CI]: 0.0 [-3.78, 3.78] Mean Difference (SE) in change in BMI (kg/m2) at 3-6 months for combined aerobic and anaerobic training vs no training: 0.4 (0.29). Mean difference [95% CI]: 0.40 [-0.17, 0.97] Mean Difference (SE) in change in BMI (kg/m2) at 6 months off training for combined aerobic and anaerobic training vs no training: 0 (0.4). Mean difference [95% CI]: 0.0 [-0.78, 0.78] Mean Difference (SE) in change in BMI (kg/m2) at 12-18 months off training for combined aerobic and anaerobic training vs no training: -0.1 (0.52). Mean difference	Other bias: Unclear risk (No validity criteria for maximal performance during cardiopulmonary exercise testing were reported in the methods. The mean (SD) peak heart rate reached during the exercise test was 157.1 (38.5) beats per min in the training group and 167.7 (20. 8) beats per min in the control group, indicative of a submaximal effort. This likely underestimates the true VO2 peak of the study participants) Klijn 2004 Random sequence generation (selection bias): Unclear risk (Described as randomised, but no details of the method) Allocation concealment (selection bias): Low risk (Allocation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Selvadurai 2002 To compare aerobic and resistance training in children with cystic fibrosis admitted to hospital with an intercurrent pulmonary infection with a control group.* *Extracted from individual paper Study dates Radtke 2015 Date of the most recent search: 10 March 2015. Hebestreit 2010 Not reported* Hommerding 2015 Data were collected from October 2010 to October 2011.* Klijn 2004 Not reported* Kriemler 2013	oral or IV antibiotic treatment in the 3 months prior to testing); the absence of musculoskeletal disorders; and an FEV1 > 30 % predicted. Kriemler 2013 Diagnosis of CF; aged 12 years and over; a FEV1 % predicted 35%; ability to perform physical activity without harm Moorcroft 2004 Participants with CF who were willing to participate were recruited from a population of 150 attending the adult CF centre inManchester at the time of the study. All participants had documented CF on the basis of clinical history plus either an increased sweat chloride or abnormal genetic testing Rovedder 2014 Participants diagnosed with CF in accordance with the criteria of the consensus;aged 16 years; 30 days of clinical respiratory disease stability Santana-Sosa 2012	Rovedder 2014 Intervention: aerobic and muscle strengthening exercises unsupervised programme 3-month home-based exercise programme printed guidance advised to perform the programme on a daily basis weekly telephone contacts were Control: no programme standard follow-up from a physiotherapist without any specific exercise instructions Santana-Sosa 2012		[95% CI]: -0.10 [-1.12, 0.92] Adverse events Not reported Hommerding 2015 FEV1 % predicted Mean (SD) change at 3 months: aerobic training (n=17): -1.8 (8.6) vs no training (n=17): 1 (14.2). FVC % predicted Mean (SD) change at 3 months: aerobic training (n=17): 0.4 (6.7) vs no training (n=17): 2 (12.2) VO2 peak during maximal exercise (ml/min per kg BW) Mean (SD) change at 3 months: Aerobic training (n=17): 1.1 (4.6) vs no training (n=17): 2.3 (11.9). Mean difference [95% CI]: -1.20 [-7.26, 4.86] Time to next exacerbation Not reported Quality of life Not reported Preference for training programme	concealed in opaque envelopes) Blinding of participants and personnel (performance bias) (all outcomes): Unclear risk (Not possible to blind participants to intervention. The primary researcher was blinded but their role in the study is unclear) Blinding of outcome assessment (detection bias) (all outcomes): Unclear risk (The primary researcher was blinded, but it is unclear whether this researcher was responsible for outcome assessment) Incomplete outcome data (attrition bias) (all outcomes): Low risk (Clear description and details about dropouts. 3 participants dropped out: 1

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study entry for participants was at some point in time between December 2000 and March 2001; then people were seen after 3,6,12 and 24 months.* Moorcroft 2004 Not reported* Rovedder 2014 People were invited for inclusion between April 2008 and March 2011* Santana-Sosa 2012 The study was performed between January 2010 and January 2011* Santana-Sosa 2014 The study was performed between September 2011 and July 2012* Schneiderman-Walker 2000 Not reported* Selvadurai 2002	Potential participants included 111 children previously diagnosed using a genetic test for CF and treated at the Children's Hospital Nino Jesus in Madrid. Males or females aged 5 to 15 years and living in the Madrid area (able to attend training sessions) Santana-Sosa 2014 Potential participants included 95 outpatient children previously diagnosed with CF by genetic testing and treated at the Children's Hospital Nino Jesus in Madrid. Males or females aged 6 - 17 years and living in the Madrid area (able to attend training sessions) Schneiderman-Walker 2000 Participants with CF aged 7 - 19 years with an FEV1 > 40%predicted. Selvadurai 2002 Children with CF, between ages 8-16 years, who were admitted to the Royal Alexandra Hospital for Children for the treatment of an infectious pulmonary exacerbation.	Intervention: endurance and strengthening exercises supervised programme 8-week intrahospital programme followed by a 4-week detraining period 3 times per week same chest physiotherapy Control: no programme Participants were instructed on the positive effects of regular physical activity Santana-Sosa 2014 Intervention: aerobic + anaerobic + IMT		Not reported Body composition Mean (SD) change in BMI z-score at 3 months: Aerobic training (n=17): 0.2 (0.5) vs no training (n=17): 0.1 (0.2). Mean difference [95% CI]: 0.10 [-0.16, 0.36] Adverse events Not reported Klijn 2004 FEV1 % predicted No reported FVC % predicted Not reported VO2 peak during maximal exercise (ml/min per kg BW) Mean (SD) change at 3 months: anaerobic training (n=11): 1.5 (2.6) vs no training (n=9): -2.45 (10.3). Mean difference [95% CI]: 3.95 [-2.95, 10.85] Time to next exacerbation Not reported Quality of life	participant fromthetraining group withdrew for practical reasons; 2 from the control group did not complete assessments due to pulmonary exacerbations Intention-to-treat analysis was not performed) Selective reporting (reporting bias): Unclear risk (Results for HRQoL are only presented for the scale 'physical functioning' which was significantly higher in the training group after the 12-week training period. No change in this HRQoL scale was observed in the control group after 12-weeks. No significant effects were observed for any other HRQoL scales. Data were not reported in detail)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported* *Extracted from individual paper Source of funding Radtke 2015 The systematic review was supported by the National Institute for Health Research, via Cochrane infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group. Hebestreit 2010 The study was supported by a grant from the German cystic fibrosis foundation (Mukoviszidose e.V.)* Hommerding 2015 Not reported* Klijn 2004 Not reported* Kriemler 2013	Exclusion criteria Radtke 2015 Studies which involved pure respiratory muscle training were excluded. Hebestreit 2010 Non CF-related chronic diseases and CF-related conditions posing an increased risk to the participant when exercising. These were specifically oesophageal varicosis, pulmonary bullae, a < 80% drop in arterial oxygen saturation with exercise and signs of pulmonary hypertension on electrocardiogram and/or echocardiogram Hommerding 2015 Cognitive impairment, non CF-related bone and muscle abnormalities, heart disease with haemodynamic instability Klijn 2004 Not reported Kriemler 2013 Non-CF related chronic diseases and conditions posing an increased risk to the participant when exercising	supervised programme 8-week programme followed by a 4-week detraining period whole body aerobic and weight training 3 times per week plus 2 daily IMT sessions same chest physiotherapy Control: low intensity IMT Schneiderman-Walker 2000 Intervention 1: aerobic programme unsupervised programme home programme Minimum of 20 min 3 times per week for 3-years		Mean (SD) change in HRQoL physical function (CF questionnaire) at 3 months: anaerobic training (n=11): 88.4 (9) vs no training (n=9): 87.1 (17.9). Mean difference [95% CI]: 1.30 [-11.55, 14.15] Preference for training programme Not reported Body composition Not reported Adverse events Not reported Kriemler 2013 FEV1 % predicted Mean (SD) change at 3 months: aerobic training (n=14): 4.89 (8) vs no training (n=10): -7.92 (6.7). Mean difference [95% CI]: 12.81 [6.91, 18.71] Mean (SD) change at 3 months: anaerobic training (n=11): 3.19 (7.2) vs no training (n=10): -7.92 (6.7). Mean difference	Other bias: Unclear risk (Clearly stated inclusion criteria but exclusion criteria were not reported. Described statistical methods used in analysis) Kriemler 2013 Random sequence generation (selection bias): High risk (Participants were randomly assigned by a lot that was drawn from an opaque bag with closed eyes. Investigator was aware of the number of lots in the bag) Allocation concealment (selection bias): High risk (Participants drew a lot from an opaque bag with closed eyes. In case that all lots have been drawn out by one study group, allocation concealment would no longer exist)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
The study was supported by a grant from the Swiss CF Foundation and the German Mukoviszidose e.V. * Moorcroft 2004 Not reported* Rovedder 2014 The study received financial support from the Porto Alegre Clinical Hospital Research Incentive Fund (FIPE-HCPA).* Santana-Sosa 2012 The study was funded by Fondo de Investigaciones Sanitarias (FIS, ref. no. PS09/00194) and Federación Española de Fibrosis Quística (II Convocatoria Pablo Motos). The work of I.F.G. was funded by the Van Coeverden Adriani Stichting and the	Moorcroft 2004 Participation in another clinical trial; pregnancy; transplant listing, or clinical cor pulmonale Rovedder 2014 Participants who refused to take part in the study; pregnant ladies; individuals with heart disease, orthopaedic or traumatological problems Santana-Sosa 2012 Severe lung deterioration, as defined by an FEV1 <50% predicted; unstable clinical condition (i.e. hospitalisation within the previous 3months); Burkholderia cepacia infection; musculoskeletal disease or any other disorder impairing exercise Santana-Sosa 2014 Severe lung deterioration (FEV1 < 50% predicted); unstable clinical condition (i.e., hospitalisation within the previous 3 months); Burkholderia cepacia infection or any disorder (e.g., musculoskeletal) impairing exercise	Control: maintained regular activity Selvadurai 2002 Intervention 1: aerobic training supervised programme 30 min, 5 times per week Training during hospital admission; mean (SD) duration of admission: 18.6 (3.9) days Intervention 2: resistance training supervised programme 30 min, 5 times per week Training during hospital admission; mean (SD) duration of admission:		[95% CI]: 11.11 [5.16, 17.06] Mean (SD) change at 6 months: aerobic training (n=15): 6.17 (11.6) vs no training (n=10): -11 (10.1). Mean difference [95% CI]: 17.17 [8.59, 25.75] Mean (SD) change at 6 months: anaerobic training (n=11): 8.51 (10.8) vs no training (n=10): -11 (10.1). Mean difference [95% CI]: 19.51 [10.57, 28.45] Mean (SD) change at 6 months off training: aerobic training (n=15): 1.09 (13.1) vs no training (n=8): -15.83 (12.4). Mean difference [95% CI]: 16.92 [6.07, 27.77] Mean (SD) change at 6 months off training: anaerobic training (n=11): 0.26 (12) vs no training (n=8): -15.83 (12.4). Mean difference	Blinding of participants and personnel (performance bias) (all outcomes): Unclear risk (Not possible to blind participants to intervention. Unclear whether personnel was blinded) Blinding of outcome assessment (detection bias) (all outcomes): Low risk (Outcome assessors were blinded for pulmonary function testing (primary outcome FEV1). Outcome assessors were not involved in supervision and delivery of the intervention) Incomplete outcome data (attrition bias) (all outcomes): Low risk (Clear description and details about excluded participants and drop-outs 3

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Nederlandse Cystic Fibrosis Stichting.* Santana-Sosa 2014 The study was funded by Fondo de Investigaciones Sanitarias (FIS, ref. no. PS09/00194) and Fundación Española de Fibrosis Quística (Spain).* Schneiderman-Walker 2000 Supported by a grant from the Canadian Cystic Fibrosis Foundation* Selvadurai 2002 Not reported* *Extracted from individual paper	Schneiderman-Walker 2000 Not reported Selvadurai 2002 Children with known pulmonary hypertension, or who required daytime oxygen prior to the pulmonary exacerbation which led to the hospital admission	18.8 (4.1) days Control: no specific training		[95% CI]: 16.09 [4.95, 27.23] Mean (SD) change at 18 months off training: aerobic training (n=12): 0.31 (13.2) vs no training (n=8): -12.14 (12). Mean difference [95% CI]: 12.45 [1.27, 23.63] Mean (SD) change at 18 months off training: anaerobic training (n=11): 4.87 (11.5) vs no training (n=8): -12.14 (12). Mean difference [95% CI]: 17.01 [6.27, 27.75] FVC % predicted Mean (SD) change at 3 months: aerobic training (n=14): 3.67 (7.3) vs no training (n=10): -5.57 (6.2). Mean difference [95% CI]: 9.24 [3.82, 14.66] Mean (SD) change at 3 months: anaerobic training (n=11): 1.8 (6.6) vs no training (n=10): -5.57 (6.2). Mean	participants were excluded at baseline due to FEV1 below 35% predicted. 8 participants dropped out at different time points (exacerbation n=1;non-compliance n=2; death n = 2; unclear reasons n= 3). 2 of the participants that dropped out for unclear reasons were in the control group and one was in the aerobic training group Dropout rate was 21%. Intention-to-treat analysis was not performed) Selective reporting (reporting bias): Low risk (All outcome detailed in methods were reported in results except HRQoL (secondary outcome) which was mentioned to be reported separately. In the meantime

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				difference [95% CI]: 7.37 [1.89, 12.85] Mean (SD) change at 6 months: aerobic training (n=15): 4.66 (8.9) vs no training (n=10): -7.85 (7.8). Mean difference [95% CI]: 12.51 [5.90, 19.12] Mean (SD) change at 6 months: anaerobic training (n=11): 6.2 (8.3) vs no training (n=10): -7.85 (7.8). Mean difference [95% CI]: 14.05 [7.16, 20.94] Mean (SD) change at 6 months off training: aerobic training (n=15): -0.67 (10.9) vs no training (n=8): -15.76 (10.4). Mean difference [95% CI]: 15.09 [6.01, 24.17] Mean (SD) change at 6 months off training: anaerobic training (n=11): -2.1 (9.9) vs no training (n=8): -15.76 (10.4).	published as Hebestreit et al. BMC Pulm Med. 2014, 27;14:26. HRQoL data were pooled from two intervention studies (Hebestreit 2010; Kriemler2013) and results were presented for baseline and 6-month follow up) Other bias: Unclear risk (Clearly stated inclusion and exclusion criteria and described statistical methods used in analysis. Due to the deterioration of physical health in the control group, the results of this study should be interpreted with caution Moorcroft 2004 Random sequence generation (selection bias): Unclear risk (Randomised to either active or control groups in a ratio of 3:2. A

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Mean difference [95% CI]: 13.66 [4.38, 22.94] Mean (SD) change at 18 months off training: aerobic training (n=12): -3.29 (12.1) vs no training (n=8): -12.39 (10.6). Mean difference [95% CI]: 9.10 [-0.94, 19.14] Mean (SD) change at 18 months off training: anaerobic training (n=11): 1.24 (10.2) vs no training (n=8): -12.39 (10.6). Mean difference [95% CI]: 13.63 [4.13, 23.13] VO2 peak during maximal exercise (ml/min per kg BW) Mean (SD) change at 3 months: aerobic training (n=15): 7.26 (12.1) vs no training (n=10): -2.45 (10.3). Mean difference [95% CI]: 9.71 [0.86, 18.56] Mean (SD) change at 3 months: anaerobic training	stratified randomisation in blocks (block size not stated) was used to balance the groups for FEV1, sputum colonisation by Burkholderia cepacia and gender. No details of method reported) Allocation concealment (selection bias): Unclear risk (Not discussed) Blinding of participants and personnel (performance bias) (all outcomes): Unclear risk (Not possible to blind participants to intervention. Unclear whether personnel was blinded) Blinding of outcome assessment (detection bias) (all outcomes): Unclear risk (Unclear whether outcome assessors were blinded)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(n=11): 7.5 (12.8) vs no training (n=10):-1.84 (12.1). Mean difference [95% CI]: 9.34 [-1.31, 19.99] Mean (SD) change at 6 months: aerobic training (n=15): 6.85 (12.6) vs no training (n=10): -11.48 (11.1). Mean difference [95% CI]: 18.33 [8.95, 27.71] Mean (SD) change at 6 months: anaerobic training (n=8): 6.22 (13.7) vs no training (n=10): -11.48 (11.1). Mean difference [95% CI]: 17.70 [5.98, 29.42] Mean (SD) change at 6 months off training: aerobic training (n=14): 0.16 (13.1) vs no training (n=8): -9.35 (12.1). Mean difference [95% CI]: 9.51 [-1.32, 20.34] Mean (SD) change at 6 months off training: anaerobic	Incomplete outcome data (attrition bias) (all outcomes): Unclear risk (3 participants dropped out at the start of programme: 1 from training group due to failure to attend on initial assessment; and 2 in the control group were withdrawn due to ill health. A further 6 participants dropped out during the 1-year period. Reasons for dropout were not clearly reported After 1 year, overall dropout rate was 18% and balanced among the groups (19% in the intervention and 15% in the control group) Intention-to-treat analysis was not performed. Missing data were treated by omission and only data for those who completed study presented)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				training (n=8): 2.24 (13.6) vs no training (n=8): -9.35 (12.1). Mean difference [95% CI]: 11.59 [-1.02, 24.20] Mean (SD) change at 18 months off training: aerobic training (n=11): -4.5 (13.8) vs no training (n=7): -7.36 (12.9). Mean difference [95% CI]: 2.86 [-9.70, 15.42] Mean (SD) change at 18 months off training: anaerobic training (n=8): 1.9 (13.8) vs no training (n=7): -7.36 (12.9). Mean difference [95% CI]: 9.26 [-4.26, 22.78] Time to next exacerbation Not reported Quality of life Not reported Preference for training programme Not reported Body composition Mean (SD) change in BMI (kg/m2) at 3	Selective reporting (reporting bias): Low risk (All outcome detailed in methods were reported in results. Data reported for all time-points) Other bias: Low risk (Clearly stated inclusion and exclusion criteria and describe method of statistical analysis used) Rovedder 2014 Random sequence generation (selection bias): Low risk (Participants were randomly allocated in blocks of 6 to the exercise or control group. A computer programme was used to generate randomisation sequence) Allocation concealment (selection bias): Unclear risk (Not discussed) Blinding of participants and personnel

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				months: aerobic training (n=15): 0 (0.6) vs no training (n=10): -0.3 (0.5). Mean difference [95% CI]: 0.30 [-0.13, 0.73]. Mean (SD) change in BMI (kg/m2) at 3 months: anaerobic training (n=15): 0.2 (0.6) vs no training (n=10): -0.3 (0.5). Mean difference [95% CI]: 0.50 [0.07, 0.93] Mean (SD) change in BMI (kg/m2) at 6 months: aerobic training (n=15): 0 (0.5) vs no training (n=10): -0.4 (0.5). Mean difference [95% CI]: 0.40 [0.00, 0.80]. Mean (SD) change in BMI (kg/m2) at 6 months: anaerobic training (n=15): 0.3 (0.6) vs no training (n=10): -0.4 (0.5). Mean difference [95% CI]: 0.70 [0.27, 1.13]	(performance bias) (all outcomes): Unclear risk (Not possible to blind participants to intervention. One researcher was blinded to the randomisation and intervention and was responsible for database entries) Blinding of outcome assessment (detection bias) (all outcomes): Low risk (Outcome assessors were blinded) Incomplete outcome data (attrition bias) (all outcomes): Low risk (2 participants in the exercise group could not be assessed at the 3-month visit due to submission to the lung transplant programme Intention-to-treat analysis was used and imputations for missing data were performed for these 2 participants)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Mean (SD) change in BMI (kg/m2) at 6 months off training: aerobic training (n=15): 0.1 (0.5) vs no training (n=8): -0.4 (0.6). Mean difference [95% CI]: 0.50 [0.01, 0.99]. Mean (SD) change in BMI (kg/m2) at 6 months off training: anaerobic training (n=15): 0.7 (1) vs no training (n=8): -0.4 (0.6). Mean difference [95% CI]: 1.10 [0.45, 1.75] Mean (SD) change in BMI (kg/m2) at 18 months off training: aerobic training (n=12): 0 (0.8) vs no training (n=7): -0.4 (0.9). Mean difference [95% CI]: 0.40 [-0.37, 1.17]. Mean (SD) change in BMI (kg/m2) at 18 months off training: anaerobic training (n=12): 0.9 (1.3) vs no training (n=8): -0.4 (0.9). Mean	Selective reporting (reporting bias): Low risk (All outcome detailed in methods were reported in results. Data reported for all time-points) Other bias: Unclear risk (Clearly stated inclusion and exclusion criteria and described method of statistical analysis used. Baseline between-group differences existed in BMI which could possibly impact on HRQoL (primary outcome) Santana_Sosa 2012 Random sequence generation (selection bias): Unclear risk (Participants were randomly assigned to exercise or control group with a block on gender based on the randomisation sequence. No details about how

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				difference [95% CI]: 1.30 [0.34, 2.26] Adverse events Not reported Moorcroft 2004 FEV1 % predicted Not reported FEV1 (mL) Mean difference (SE) in annual change at 12 months for combined aerobic and anaerobic training vs no training: 107 (92.34). Mean difference [95% CI]: 107.00 [-73.98, 287.98] FVC % predicted Not reported FVC (mL) Mean difference (SE) in annual change at 12 months for combined aerobic and anaerobic training vs no training: 213 (107.14). Mean difference [95% CI]: 213.00 [3.01, 422.99]	randomisation sequence was generated) Allocation concealment (selection bias): Unclear risk (Not discussed) Blinding of participants and personnel (performance bias) (all outcomes): Unclear risk (Not possible to blind participants to intervention. Personnel involved in training not blinded) Blinding of outcome assessment (detection bias) (all outcomes): Low risk (Outcome assessors were blinded to participants group assignment) Incomplete outcome data (attrition bias) (all outcomes): High risk (Clear description of missing outcome data. 5 participants

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				VO2 Not reported Time to next exacerbation Not reported Quality of life Not reported Preference for training programme Not reported Body composition Mean difference (SE) in annual change in BMI (kg/m2) for combined aerobic and anaerobic training vs no training: 0.54 (0.32). Mean difference [95% CI]: 0.54 [-0.09, 1.17] Adverse events Not reported Rovedder 2014 FEV1 % predicted Mean (SD) change at 3 months: combined aerobic and anaerobic training (n=19): -6 (16.1) vs no training (n=22): -2 (7.3). Mean difference [95% CI]: FVC (mL	could not be assessed at different time points (1 post-intervention and 4 after detraining) due to hospitalisations (n = 3), relocation (n = 1) and parents who declined further evaluation (n = 1). Dropout rate was unbalanced with 28% in the control group and 9% in the intervention group after the detraining period. Intention-to-treat analysis was used and missing outcome data (at post-training or detraining visit) were replaced by baseline data) Selective reporting (reporting bias): Low risk (All outcomes detailed in methods were reported in results. Data reported for all time-points) Other bias: High risk (Some raw data were made

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				FVC % predicted Mean difference (SE) in change at 3 months for combined aerobic and anaerobic training vs no training: -3.3 (4.3). Mean difference [95% CI]: -3.30 [-11.73, 5.13] VO2 Not reported Time to next exacerbation Not reported Quality of life, change* at 3 months HRQoL scale - physical (median (interquartile range)): Exercise group (n=19): 6.1 (-4 to 8) vs Control group (n=22): 2.4 (-10 to 13); p value: 0.742 HRQoL scale - body image (median (interquartile range)): Exercise group (n=19): 3.3 (-11 to 22) vs Control group (n=22): 3.0 (-2 to 11); p value: 0.915	available, but there were inconsistencies between raw data and data reported in the original publication. There were significant between-group differences in primary (VO2 peak) and secondary (strength measures) outcome measures at baseline) Santana-Sosa 2014 Random sequence generation (selection bias): Unclear risk (Randomisation to intervention or control group with block on gender. No details given for sequence generation) Allocation concealment (selection bias): Unclear risk (Not discussed) Blinding of participants and personnel (performance bias)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				HRQoL scale - digestive (median (interquartile range)): Exercise group (n=19): -1.0 (-4 to 0) vs Control group (n=22): -0.5 (0 to 0); p value: 0.953 HRQoL scale - respiratory (median (interquartile range)): Exercise group (n=19): 3.8 (0 to 11) vs Control group (n=22): -4.7 (-1 to 7); p value: 0.925 HRQoL scale - emotional (median (interquartile range)): Exercise group (n=19): 1.2 (-6 to 6) vs Control group (n=22): -4.3 (-13 to 6); p value: 0.458 HRQoL scale - social (median (interquartile range)): Exercise group (n=19): -1.1 (-11 to 5) vs Control group (n=22): -1.7 (-5 to 11); p value: 0.822 HRQoL scale - food (median	(all outcomes): Unclear risk (Not possible to blind participants to intervention. Personnel involved in training not blinded) Blinding of outcome assessment (detection bias) (all outcomes): Low risk (Outcome assessors were blinded to participants group assignment) Incomplete outcome data (attrition bias) (all outcomes): High risk (Clear description of missing outcome data. 3 participants of the control group could not be assessed at different time points (1 for post-intervention and detraining phase and 2 after detraining phase) due to hospitalisation for lung transplantation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(interquartile range)): Exercise group (n=19): -0.3 (-11 to 6) vs Control group (n=22): -2.0 (-11 to 0); p value: 0.913 HRQoL scale - treatment (median (interquartile range)): Exercise group (n=19): -2.0 (-11 to 0) vs Control group (n=22): -2.5 (-11 to 11); p value: 0.850 HRQoL scale - vitality (median (interquartile range)): Exercise group (n=19): -1.2 (-16 to 8) vs Control group (n=22): 2.6 (-8 to 10); p value: 0.579 HRQoL scale - health (median (interquartile range)): Exercise group (n=19): 1.7 (-11 to 16) vs Control group (n=22): -3.0 (-11 to 0); p value: 0.382 HRQoL scale - weight (median (interquartile	preparation (n = 1), infection with Burkholderia cepacia (n = 1) and refusal (n = 1). Unbalanced distribution of dropouts. Drop out rate in the control group was 30% versus none in the intervention group Intention-to-treat analysis was reported, but it is not clear how missing data were handled) Selective reporting (reporting bias): Low risk (All outcome detailed in methods were reported in results. Data reported for all time points) Other bias: High risk (Some raw data were made available, but there were inconsistencies between raw data and data reported in the original publication. Significant

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				range)): Exercise group (n=19): 4.6 (0 to 33) vs Control group (n=22): 12.1 (0 to 11); p value: 0.410 HRQoL scale - social role (median (interquartile range)): Exercise group (n=19): 0.8 (-8 to 8) vs Control group (n=22): 1.8 (-2 to 0); p value: 0.935 Preference for training programme Not reported Body composition Not reported Adverse events Not reported Santana-Sosa 2012 FEV1 % predicted Not reported FEV1 (litres) Mean (SE): Intervention pre-training: 1.87 (0.24); Intervention post-training: 1.94 (0.23); Intervention detraining: 1.90 (0.25) vs control pre-training: 1.77 (0.17); control post-training: 1.87 (0.15);	between-group differences in primary outcomes (VO2 peak and strength measures) existed at baseline. Schneiderman-Walker 2000 Random sequence generation (selection bias): Low risk (Computer-generated randomisation sequence) Allocation concealment (selection bias): Unclear risk (Not discussed) Blinding of participants and personnel (performance bias) (all outcomes): Unclear risk (Not possible to blind participants to intervention. Unclear whether personnel was blinded). Blinding of outcome assessment (detection bias) (all outcomes): Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				control detraining: 1.79 (0.19) FVC % predicted Not reported FVC (litres) Mean (SE): Intervention pre-training: 2.41 (0.24); Intervention post-training: 2.49 (0.25); Intervention detraining: 2.56 (0.29) vs control pre-training: 2.29 (0.19); control post-training: 2.36 (0.20); control detraining: 2.40 (0.24) VO2 peak (mean (95% CI)) ml/min per kg body weight Intervention: Intervention pre-training: n.a.; Intervention post-training: 3.9 (1.8 to 6.1); Intervention detraining: -3.4 (-5.7 to 1.7) vs control pre-training: n.a.; control post-training: -2.2 (-5.3 to 0.1); control detraining: -0.7 (-4.4 to 5.9) Time to next exacerbation	risk (Pulmonary function assessors were blinded to group assignment (primary outcome measure) Incomplete outcome data (attrition bias) (all outcomes): Unclear risk (Clear description and details about 7 dropouts were recorded Intention-to-treat analysis was reported to yield similar results for pulmonary function. Results were only reported for 65 participants who completed the 2-year follow up) Selective reporting (reporting bias): Low risk (All outcome detailed in methods were reported in results. Data reported for all time points) Other bias: Unclear risk (Groups similar at baseline. Stated the inclusion criteria but not the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Not reported Quality of life (HRQoL score) Median (range) for children's report: intervention pre-training: 696 (495 - 741); intervention post-training: 719 (550 - 734); vs control pre-training: 649 (578 - 768); control post-training: 638 (461 - 791) Median (range) for parents' report: intervention pre-training: 896 (688-1011); intervention post-training: 889 (811 - 973); vs control pre-training: 911 (842 - 1028); control post-training: 978 (684 - 1059) Preference for training programme Not reported Body composition Mean (SE) weight (kg): Intervention pre-training: 39.9 (3.5); Intervention post-training: 40.5 (3.4); Intervention detraining: 41.4	exclusion criteria. Described statistical methods used in analysis) Selvadurai 2002 Random sequence generation (selection bias): Unclear risk (Random allocation in sets of 6. No details given for generation of sequence) Allocation concealment (selection bias): Low risk (Concealed information inside opaque envelopes) Blinding of participants and personnel (performance bias) (all outcomes): Unclear risk (Not possible to blind participants to intervention. Unclear whether personnel was blinded) Blinding of outcome assessment (detection bias) (all outcomes): Unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(3.4) vs control pre-training: 34.0 (2.6); control post-training: 35.1 (2.8); control detraining: 36.2 (3.0) Mean (SE) BMI (kg/m2): Intervention pre-training: 18.4 (1.0); Intervention post-training: 18.3 (0.7); Intervention detraining 18.5 (0.7): vs control pre-training: 17.2 (0.8); control post-training: 17.1 (0.8); control detraining: 17.4 (0.9) Adverse events No adverse effects occurred during training or maximal exercise testing Santana-Sosa 2014 FEV1 % predicted Not reported FEV1 (litres) Mean (SE): Intervention pre-training: 1.65 (0.19); Intervention post-training: 1.74 (0.23); Intervention detraining: vs	risk (Unclear whether outcome assessors were blinded) Incomplete outcome data (attrition bias) (all outcomes): Low risk (Stated no dropouts) Selective reporting (reporting bias): Unclear risk (Did not report on all secondary outcomes detailed in methods (e.g. VE, VCO2, RQ) in results. Data reported for all time-points. Other bias: Low risk (Clearly stated inclusion and exclusion criteria. Described statistical methods used to analyse data). Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				control pre-training: 1.57 (0.26); control post-training: 1.55 (0.26); control detraining: 1.59 (0.26) FVC % predicted Not reported FVC (litres) Mean (SE): Intervention pre-training: 2.23 (0.27); Intervention post-training: 2.34 (0.29); Intervention detraining: 2.28 (0.28) vs control pre-training: 1.90 (0.33); control post-training: 1.85 (0.32); control detraining: 1.92 (0.32) VO2 Mean (95% CI): Intervention pre-training: n.a.; Intervention post-training: 6.9 (3.4 to 10.5); Intervention detraining: -1.5 (-2.7 to -0.4) vs control pre-training: n.a.; control post-training: n.a.; control detraining:n.a.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Time to next exacerbation Not reported Quality of life Median (min-max): Intervention pre-training: 629 (505 - 701); Intervention post-training: 688 (609 - 791); Intervention detraining: not assessed; vs control pre-training: 636 (626 - 745); control post-training: 638 (626 - 737); control detraining: not assessed Preference for training programme Not reported Body composition Mean (SE) weight (kg): Intervention pre-training: 36.4 (3.1); Intervention post-training: 37.8 (3.2); Intervention detraining: 38.3 (3.1) vs control pre-training: 31.5 (4.6); control post-training: 32.4 (4.7); control detraining: 32.7 (4.5)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Adverse events No adverse effects occurred during training or exercise testing Schneiderman-Walker 2000 FEV1 % predicted Mean (SD) annual rate of change over 36 months: aerobic training (n=30): -1.46 (3.55) vs no training (n=35): -3.47 (4.93). Mean difference: 2.01 [-0.06, 4.08] FVC % predicted Mean (SD) annual rate of change over 36 months: aerobic training (n=30): -0.25 (2.81) vs no training (n=35): -2.42 (4.15). Mean difference: 2.17 [0.47, 3.87] VO2 Not reported Time to next exacerbation Not reported Quality of life Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Preference for training programme Not reported Body composition Mean (SD) annual rate of change in ideal weight for height (%) over 36 months: aerobic training (n=30): 0.48 (2.52) vs no training (n=35): -0.04 (2.75). Mean difference: 0.52 [-0.76, 1.80] Adverse events Not reported Selvadurai 2002 FEV1 % predicted Mean (SD) change at hospital discharge: aerobic training (n=22): 6.54 (7.76) vs no training (n=22): 4.51 (6.9). Mean difference [95% CI]: 2.03 [-2.31, 6.37] Mean (SD) change at hospital discharge: anaerobic training (n=22): 10.09 (7.43) vs no training (n=22): 4.51 (6.9). Mean difference	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				[95% CI]: 5.58 [1.34, 9.82] Mean (SD) change at 1 month after hospital discharge: aerobic training (n=22): 6.25 (7.94) vs no training (n=22): 4.72 (7.15). Mean difference [95% CI]: 1.53 [-2.93, 5.99] Mean (SD) change at 1 month after hospital discharge: anaerobic training (n=22): 9.8 (7.81) vs no training (n=22): 4.72 (7.15). Mean difference [95% CI]: 5.08 [0.66, 9.50] FVC % predicted Mean (SD) change at hospital discharge: aerobic training (n=22): 2.34 (4.62) vs no training (n=22): 2.28 (4.22). Mean difference [95% CI]: 0.06 [-2.55, 2.67] Mean (SD) change at hospital discharge: anaerobic training (n=22):	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				2.45 (4.18) vs no training (n=22): 2.28 (4.22). Mean difference [95% CI]: 0.17 [-2.31, 2.65] Mean (SD) change at 1 month after hospital discharge: aerobic training (n=22): 2.2 (4.27) vs no training (n=22): 2.31 (4.29). Mean difference [95% CI]: -0.11 [-2.64, 2.42] Mean (SD) change at 1 month after hospital discharge: anaerobic training (n=22): 2.37 (4.09) vs no training (n=22): 2.31 (4.29). Mean difference [95% CI]: 0.06 [-2.42, 2.54] VO2 peak during maximal exercise (ml/min per kg BW) Mean (SD) change at hospital discharge: aerobic training (n=22): 7.31 (6.29) vs no training (n=22): -1.22 (6.15).	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Mean difference [95% CI]: 8.53 [4.85, 12.21] Mean (SD) change at hospital discharge: anaerobic training (n=22): 0.73 (5.89) vs no training (n=22): -1.22 (6.15). Mean difference [95% CI]: 1.95 [-1.61, 5.51] Mean (SD) change at 1 month after hospital discharge: aerobic training (n=22): 7.56 (6.75) vs no training (n=22): 2.65 (6.02). Mean difference [95% CI]: 8.53 [4.85, 12.21] Mean (SD) change at 1 month after hospital discharge: anaerobic training (n=22): 2.25 (6.25) vs no training (n=22): 2.65 (6.02). Mean difference [95% CI]: -0.40 [-4.03, 3.23] Time to next exacerbation Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Quality of life Mean (SD) change in health-related quality of life at 1 month after discharge: aerobic training (n=22): 0.09 (0.12) vs no training (n=22): -0.01 (0.12). Mean difference [95% CI]: 0.10 [0.03, 0.17] Mean (SD) change in health-related quality of life at 1 month after discharge: anaerobic training (n=22): 0.02 (0.1) vs no training (n=22): -0.01 (0.12). Mean difference [95% CI]: 0.03 [-0.04, 0.10] Preference for training programme Not reported Body composition Mean (SD) change in body weight (kg) at hospital discharge: aerobic training (n=22): 0.8 (0.64) vs no training (n=22): 1.03 (0.58). Mean difference	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				[95% CI]: -0.23 [-0.59, 0.13] Mean (SD) change in body weight (kg) at hospital discharge: anaerobic training (n=22): 2.76 (0.7) vs no training (n=22): 1.03 (0.58). Mean difference [95% CI]: 1.73 [1.35, 2.11] Mean (SD) change at 1 month after hospital discharge: aerobic training (n=22): 1.1 (0.78) vs no training (n=22): 1 (0.66). Mean difference [95% CI]: 0.10 [-0.33, 0.53] Mean (SD) change in body weight (kg) at 1 month after hospital discharge: anaerobic training (n=22): 2.65 (0.73) vs no training (n=22): 1 (0.66). Mean difference [95% CI]: 1.65 [1.24, 2.06] Adverse events Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				*Extracted from individual paper	
Full citation Rovedder, P. M., Flores, J., Ziegler, B., Casarotto, F., Jaques, P., Barreto, S. S., et al.,, Exercise programme in patients with cystic fibrosis: a randomized controlled trial, Respiratory Medicine, 108, 1134-40, 2014 Ref Id 426131 Country/ies where the study was carried out See Radtke 2015 Study type See Radtke 2015 Aim of the study See Radtke 2015 Study dates See Radtke 2015 Source of funding See Radtke 2015	Sample size See Radtke 2015 Characteristics See Radtke 2015 Inclusion criteria See Radtke 2015 Exclusion criteria See Radtke 2015	Interventions See Radtke 2015	Details See Radtke 2015	Results See Radtke 2015	Limitations See Radtke 2015 Other information See Radtke 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Santana-Sosa, E., Gonzalez-Saiz, L., Groeneveld, I. F., Villa-Asensi, J. R., Barrio Gomez de Aguero, M. I., Fleck, S. J., Lopez-Mojares, L. M., Perez, M., Lucia, A., Benefits of combining inspiratory muscle with 'whole muscle' training in children with cystic fibrosis: a randomised controlled trial, British Journal of Sports Medicine, 48, 1513-7, 2014 Ref Id 366701 Country/ies where the study was carried out See Radtke 2015 Study type See Radtke 2015 Aim of the study See Radtke 2015 Study dates See Radtke 2015 Source of funding See Radtke 2015	Sample size See Radtke 2015 Characteristics See Radtke 2015 Inclusion criteria See Radtke 2015 Exclusion criteria See Radtke 2015	Interventions See Radtke 2015	Details See Radtke 2015	Results See Radtke 2015	Limitations See Radtke 2015 Other information See Radtke 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Schindel, C. S., Hommerding, P. X., Melo, D. A. S., Baptista, R. R., Marostica, P. J. C., Donadio, M. V. F., Physical exercise recommendations improve postural changes found in children and adolescents with cystic fibrosis: A randomized controlled trial, Journal of Pediatrics, 166, 710-716, 2015 Ref Id 426159 Country/ies where the study was carried out Brazil Study type RCT Aim of the study To evaluate the effects of an educational guideline for physical activity on body posture in children and	Sample size N= 34 intervention: n=17 control: n=17 Characteristics People with CF. Age range: 7 to 20 years Mean (SD) age in intervention group: 13.6 (2.8) years Mean (SD) age in control group: 12.9 (3.9) years Females: 41.2% Inclusion criteria People with CF aged 7 to 20 years with clinically stable disease who were regularly followed at the CF outpatient clinic. Exclusion criteria Children and adolescents with cognitive alterations or osteomuscular changes that would make it impossible to perform the tests.	Interventions Intervention: aerobic exercise and stretching for 3 months unsupervised programme instruction handbook calendar where patients marked the days they performed exercise at least 3 times per week for a minimum of 20 minutes and perform each stretch 2 times for 20 seconds each phone calls from the researcher every two weeks Control: usual care for 3 months Verbal orientations to	Details Setting. CF outpatient clinic at Hospital São Lucas, Pontíficia Universidade Católica do Rio Grande do Sul (HSL-PUCRS). Randomization. Initially, 34 people with CF were selected, paired according to age, sex, height and weight to heathy subjects. In phase 2 people with CF were randomized to an intervention or a control group. A computer program (Random Allocation Software v 1.0; http://random-allocation-software.software.informer.com/1.0/) in blocks of 6 was used for the randomization process. Data collection. Measurements of clinical indicators were taken at the outpatient clinic at baseline and after 3 months. The researcher performing all evaluations was blinded to the group allocation.	Results FEV1 % predicted Mean (SD) change at 3 months: Intervention (n=17): -1.8 (8.6) vs control (n=17): 2.7 (12.8) FVC% predicted Mean (SD) change at 3 months: Intervention (N=17): -0.41(6.8) vs control (n=17): 1.8 (12.2) VO2 peak Not reported Quality of life Not reported Time to next exacerbation Not reported Body composition Not reported Preference for training programme Not reported Adverse events Not reported	Limitations The quality of the study was assessed using the Cochrane risk of bias tool: Random sequence generation (selection bias): Low risk (Randomization in blocks of 6 with a computer software) Allocation concealment (selection bias): Unclear risk (Not mentioned in text) Blinding of participants and personnel (performance bias) (all outcomes): Unclear risk (Not possible to blind participants to intervention. Unclear whether personnel was blinded) Blinding of outcome assessment (detection bias) (all outcomes): Low risk (Outcome

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
adolescents with CF. Study dates Not reported Source of funding C.S. was supported by a scholarship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.		perform exercise and stretching			assessor was blinded to the group allocation) Incomplete outcome data (attrition bias) (all outcomes): Low risk (Outcome data provided for all participants who were randomized) Selective reporting (reporting bias): Low risk (Lung function measurements mentioned in the method section and presented in the results section) Other bias: Low risk (none detected) Other information
Full citation Schneiderman-Walker, J., Pollock, S. L., Corey, M., Wilkes, D. D., Canny, G. J., Pedder, L., Reisman, J. J., A randomized controlled trial of a 3-year home exercise program in	Sample size See Radtke 2015 Characteristics See Radtke 2015 Inclusion criteria See Radtke 2015 Exclusion criteria See Radtke 2015	Interventions See Radtke 2015	Details See Radtke 2015	Results See Radtke 2015	Limitations See Radtke 2015 Other information See Radtke 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
cystic fibrosis, Journal of Pediatrics, 136, 304-10, 2000 Ref Id 333851 Country/ies where the study was carried out See Radtke 2015 Study type See Radtke 2015 Aim of the study See Radtke 2015 Study dates See Radtke 2015 Source of funding See Radtke 2015					
Full citation Selvadurai, H. C., Blimkie, C. J., Meyers, N., Mellis, C. M., Cooper, P. J., Van Asperen, P. P., Randomized controlled study of in-hospital exercise training programs in children with cystic fibrosis, Pediatric Pulmonology, 33, 194-200, 2002 Ref Id 331965	Sample size See Radtke 2015 Characteristics See Radtke 2015 Inclusion criteria See Radtke 2015 Exclusion criteria See Radtke 2015	Interventions See Radtke 2015	Details See Radtke 2015	Results See Radtke 2015	Limitations See Radtke 2015 Other information See Radtke 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out See Radtke 2015 Study type See Radtke 2015 Aim of the study See Radtke 2015 Study dates See Radtke 2015 Source of funding See Radtke 2015					
Full citation Santana Sosa, E., Groeneveld, I. F., Gonzalez-Saiz, L., Lopez-Mojares, L. M., Villa-Asensi, J. R., Barrio Gonzalez, M. I., Fleck, S. J., Perez, M., Lucia, A., Intrahospital weight and aerobic training in children with cystic fibrosis: a randomized controlled trial, Medicine & Science in Sports & Exercise, 44, 2-11, 2012 Ref Id 333844	Sample size See Radtke 2015 Characteristics See Radtke 2015 Inclusion criteria See Radtke 2015 Exclusion criteria See Radtke 2015	Interventions See Radtke 2015	Details See Radtke 2015	Results See Radtke 2015	Limitations See Radtke 2015 Other information See Radtke 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out See Radtke 2015 Study type See Radtke 2015 Aim of the study See Radtke 2015 Study dates See Radtke 2015 Source of funding See Radtke 2015					
Full citation Beaudoin, N., Bouvet, G. F., Coriati, A., Rabasa-Lhoret, R., Berthiaume, Y., Combined Exercise Training Improves Glycemic Control in Adult With Cystic Fibrosis, Medicine and Science in Sports and Exercise, 2016 Ref Id 537744 Country/ies where the study was carried out Canada Study type	Sample size N= 14 Exercise group: n=8 Control group: n=6 18 adults were recruited; 17 were randomized; 2 dropped out because of pulmonary exacerbations; 1 was excluded because he was noncompliant; therefore, 14 were included in the analysis Characteristics Adults with CF aged ≥18 years with glucose abnormality Exercise group (n=8): mean age 31.9; age range 24 to 41 Control group (n=6): mean age 35.5; age range 22 to 57 Inclusion criteria	Interventions Intervention: Combined aerobic and resistance training programme Unsupervised programme (supervised training session once every 4 weeks; received a phone call once a week) Both aerobic and resistance training: 3 times per	Details Study setting. CF clinic of the Centre Hospitalier de l'Universite de Montreal (CHUM) Randomization. Participants were recruited in a randomly assigned open label study. Randomization was conducted in block by gender with a ratio of 2:2. Data collection. Body weight and height were measured with light clothing and shoes removed. Pulmonary function was measured using the American Thoracic Society Standards and FEV1 (L/s-1), and the predicted % FEV1 was calculated using Nhanes III equation (Medgraphic 1870, St. Paul, MN). CPET was performed using a graded exercise test on an ergocycle, Ergoline 900 (Bitz, Germany), until voluntary exhaustion, and power output was increased by 5	Results FEV1 % predicted Mean (SD): exercise group at baseline (n=8): 70.50 (12.50); exercise group at 12 weeks (n=8): 69.25 (12.80); control group at baseline (n=6): 73.17 (14.62); control group at 12 weeks (n=6): 72.67 (17.66) FVC % predicted Mean (SD): exercise group at baseline(n=8): 87.88 (7.61); exercise group at 12 weeks (n=8): 87.50 (8.60); control group at baseline (n=6):	Limitations The quality of this study was assessed using the Cochrane risk of bias tool: Random sequence generation (selection bias): Low risk (randomization conducted in block by gender with a ratio 2:2) Allocation concealment (selection bias): Unclear risk (Not mentioned) Blinding of participants and personnel

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT Aim of the study To determine whether a combined exercise programme is beneficial to improve plasma glucose at 2h of the oral glucose tolerance test in cystic fibrosis. Study dates Participants were recruited between August 2013 and November 2014. Source of funding Not reported	sedentary (less than 100 min/wk-1 of structured exercise, assessed by physical activity questionnaire and phone interview) FEV1>40% clinically stable for the last 6 wk abnormal glucose tolerance (impaired glucose tolerance [IGT], CFRD without pharmacological treatment for diabetes, or elevated 1-h plasma glucose at the OGTT (indeterminate, 1-h OGTT >11.0 but 2-h OGTT< 7.8 mmol/L-1 [INDET]) Exclusion criteria current pulmonary exacerbation use of oral or intravenous corticosteroid known of low saturation (SpO2) during exercise history of hemoptysis in the last 6 wk	week for 12 weeks Aerobic training: 20 to 40 min; resistance training: 5 to 7 exercises for a progressively increasing number of sets and repetitions Control: no specific training	to 15 W every minute. During the CPET, expired gas samples were analyzed through a mixing chamber, and data were acquired breath by breath with 30 s time averaging, using a Moxus (AEI Technologies Inc., Naperville, IL) cardiorespiratory exercise test station. The highest 30-s average of oxygen uptake value obtained during the exercise test was considered as VO2peak. The CFQ-R was used to was administered before and after 12 weeks of protocol to measure quality of life. In order to monitor physical activity, participants wore a physical activity monitor, the SenseWear Armband Pro 3 (SWA; BodyMedia, Pittsburgh, PA), for 5 days, preintervention (before CEP) and postintervention, before the last training session. SWA was previously validated for the CF population and also against doubly labeled water for healthy adults.	97.35 (15.97); control group at 12 weeks (n=6): 93.67 (15.81) VO2 peak (ml/kg-1/min-1) Mean (SD): exercise group at baseline (n=8): 24.29 (5.16); exercise group at 12 weeks (n=8): 24.53 (4.01); control group at baseline (n=6): 22.98 (6.77); control group at 12 weeks (n=6): 25.35 (6.79) Quality of life Mean (SD) QoL physical functioning: exercise group at baseline (n=8): 72.68 (20.60); exercise group at 12 weeks (n=8): 80.20 (16.78); control group at baseline (n=6): 75.01 (26.07); control group at 12 weeks (n=6): 81.93 (16.82) Mean (SD) QoL vitality: exercise group at baseline (n=8): 55.20 (18.34); exercise group at 12 weeks (n=8): 58.33 (19.92); control	(performance bias) (all outcomes): Unclear risk (Not possible to blind participants to intervention. Unclear whether personnel was blinded)) Blinding of outcome assessment (detection bias) (all outcomes): Unclear risk (Not mentioned) Incomplete outcome data (attrition bias) (all outcomes): High risk (2 drop-outs because of pulmonary exacerbations; one patient was excluded because he was non-compliant) Selective reporting (reporting bias): Unclear risk (FVC % predicted and BMI are not mentioned in the methods section but are reported among the results in the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				group at baseline (n=6): 54.18 (20.98); control group at 12 weeks (n=6): 54.18 (20.91) Mean (SD) QoL emotional state: exercise group at baseline (n=8): 88.33 (8.53); exercise group at 12 weeks (n=8): 81.66 (12.73); control group at baseline (n=6): 82.22 (13.11); control group at 12 weeks (n=6): 83.33 (15.06) Mean (SD) QoL eating disturbances: exercise group at baseline (n=8): 100 (0); exercise group at 12 weeks (n=8): 98.61 (3.92); control group at baseline (n=6): 100 (0); control group at 12 weeks (n=6): 100(0) Mean (SD) QoL treatment burden: exercise group at baseline (n=8): 70.85 (18.72); exercise group at 12 weeks (n=8):65.29 (28.14); control	supplementary material; weight, VO2 and QoL are mentioned in the methods section but the results are only reported in the supplementary material rather than in the main text) Other bias: Low risk (None detected) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				group at baseline (n=6): 68.52 (25.75); control group at 12 weeks (n=6): 68.52 (21.59) Mean (SD) QoL health perception: exercise group at baseline (n=8): 47.23 (26.42); exercise group at 12 weeks (n=8): 58.34 (23.59); control group at baseline (n=6): 57.42 (8.39); control group at 12 weeks (n=6): 74.10 (15.17) Mean (SD) QoL social limitations: exercise group at baseline (n=8): 77.78 (11.86); exercise group at 12 weeks (n=8): 75.28 (13.02); control group at baseline (n=6): 69.43 (16.77); control group at 12 weeks (n=6): 81.50 (18.13) Mean (SD) QoL body image: exercise group at baseline (n=8): 88.90 (8.39); exercise group at 12	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				weeks (n=8): 84.74 (8.26); control group at baseline (n=6): 79.63 (20.40); control group at 12 weeks (n=6): 81.50 (18.13) Mean (SD) QoL role limitations: exercise group at baseline (n=8): 84.37 (18.08); exercise group at 12 weeks (n=8): 83.33 (25.20); control group at baseline (n=6): 90.29 (12.25); control group at 12 weeks (n=6): 84.73 (21.99) Mean (SD) QoL weight problems: exercise group at baseline (n=8): 95.84 (11.77); exercise group at 12 weeks (n=8): 87.50 (24.81); control group at baseline (n=6): 83.33 (40.82); control group at 12 weeks (n=6): 83.33 (40.82) Mean (SD) QoL respiratory symptoms: exercise group at baseline (n=8): 62.50 (14.47);	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				exercise group at 12 weeks (n=8): 62.50 (14.47); control group at baseline (n=6): 61.12 (14.48); control group at 12 weeks (n=6): 65.75 (8.17) Mean (SD) QoL digestion symptoms: exercise group at baseline (n=8): 79.19 (9.26); exercise group at 12 weeks (n=8): 84.74 (10.17); control group at baseline (n=6): 77.78 (23.31); control group at 12 weeks (n=6): 68.53 (14.79) Time to next exacerbation Not reported Body composition Mean (SD) change in weight (kg): exercise group at baseline (n=8): 65.34 (15.52); exercise group at 12 weeks (n=8): 65.14 (16.07); control group at baseline (n=6): 65.98 (15.47); control group at 12	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				weeks (n=6): 66.05 (14.92) Mean (SD) change in BMI (kg/m2): exercise group at baseline (n=8): 23.34 (3.61); exercise group at 12 weeks (n=8): 23.25 (3.76); control group at baseline (n=6): 24.24 (3.28); control group at 12 weeks (n=6): 24.09 (2.68) Adverse events Not reported	
Full citation Cox, N. S., Alison, J. A., Button, B. M., Wilson, J. W., Morton, J. M., Holland, A. E., Physical activity participation by adults with cystic fibrosis: An observational study, Respirology, 21, 511-8, 2016 Ref Id 469253 Country/ies where the study was carried out	Sample size N=61 Intervention 1: n=33 Control 1: n=28 Intervention 2: n=21 Control 2: n=40 65 adults were recruited; 4 were excluded because they wore the armband for insufficient time at baseline Characteristics Adults with CF aged ≥18 years Inclusion criteria Adults attending two specialist CF centres in	Interventions Comparison 1. Intervention 1: ≥30 minutes daily of habitual moderate-vigorous physical activity Control 1: <30 minutes daily of habitual moderate-vigorous physical activity	Details Setting. Two specialist CF centres in Melbourne. Recruitment. When attending a routine outpatient appointment, people were invited to participate in the study by a research physiotherapist not involved in their clinical care. Data collection. Physical activity was measured over 5-7 days using a portable multi-sensor armband, the SenseWear Pro3 Armband (SWA); the armband has been validated for assessing land-based PA intensity in adults with CF. Moderate physical activity intensity was classified as ≥4.8 metabolic equivalents. Data analysis. Physical activity data were	Results Need for hospitalization* Intervention 1: 16/33 vs control 1: 19/28 Intervention 2: 8/21 vs control 2: 26/40 *Please note that this was the only outcome that was extracted from this cohort study because this outcome can be considered a proxy for time to next exacerbation, which is a critical outcome	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool Selection of study population: High risk of bias Representativeness of the exposed cohort: Truly representative of the average people with CF that fit the inclusion criteria of the study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Australia Study type Prospective cohort study Aim of the study To identify if there was a relationship between objectively measured physical activity levels and clinical outcomes, specifically lung function and hospitalization, over 12 months. Study dates Not reported Source of funding NSC was the recipient of a National Health and Medical Research Council (NH&MRC) PhD scholarship, a Cystic Fibrosis Australia PhD stipend, and grants from La Trobe University and the Thoracic Society of Australia and New Zealand (TSANZ).	Melbourne, Australia, with a confirmed diagnosis of CF Exclusion criteria Intravenous antibiotics for a respiratory exacerbation in the 4 weeks preceding baseline assessment co-morbidities limiting mobilization or physical activity participation colonization of respiratory secretions with Burkholderia cepacia; pregnancy lung transplant recipient Less than 3 days wear (for ≥10 hours in each day), of the armband used to measure physical activity	Comparison 2. Intervention 2: ≥30 minutes daily of habitual moderate-vigorous physical activity accumulated in bouts of > 10 minutes Control 2: <30 minutes or ≥30 minutes not accumulated in bouts of > 10 minutes	categorized based on the recommendations in physical activity guidelines, which recommend either 30 minutes of moderate-vigorous physical activity accumulated during the course of the day or 30 minutes of moderate-vigorous activity accumulated in bouts of at least 10 minutes duration. People were considered to have reached physical activity in bouts of at least 10 minutes duration if said bouts were recorded on any one day in the monitoring period.	that was not reported in any of the included RCTs.	Selection of the non-exposed cohort: Drawn from the same community as the exposed cohort Ascertainment of exposure: the authors write that it is possible that some participants performed more activity than the norm during the days of monitoring; moreover the armband only records land-based activity; the monitoring device was considered unfashionable by a number of participants, possibly reducing wear-time Demonstration that outcome of interest was not present at the start of the study: Yes (one of the exclusion criteria was intravenous antibiotics for a respiratory exacerbation in the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					4 weeks preceding baseline assessment) Comparability: High risk of bias The study does not control for any factor in relation to the comparison of interest Assessment of outcome: Low risk of bias The outcome was assessed by record linkage. The follow-up (12 months) was long enough for the outcome to occur. All subjects (except 4 subjects excluded at baseline) accounted for during follow-up Other information

G.21 Psychsocial assessment

Review question: What strategies are effective at identifying people with cystic fibrosis for the presence of a psychological and/or behavioural problem?

Study details	Number of participants and participant characteristics	Test characteristics	Results	Comments
Full citation Daniels, T., Goodacre, L., Sutton, C., Pollard, K., Conway, S., Peckham, D., Accurate assessment of adherence: self-report and clinician report vs electronic monitoring of nebulizers, Chest, 140, 425-32, 2011 Ref Id 362988 Country/ies where the study was carried out UK Aim of the study To assess the agreement between rates of adherence to prescribed nebulizer treatments when measured by self-report, clinician report, and electronic monitoring. Study dates Not reported Source of funding	Sample size N=78 (81 participants started the study: 1 did not gave consent, 1 patient data could not be downloaded) Characteristics Adults with CF on nebulizer therapy Median (IQR) number of daily nebulizer doses: 3 (32 to 3) Median age (IQR): 26 (21 to 31) years Gender: 55.1% male (n=43) Median (IQR) FEV1 % predicted: 69.5 (54 to 86) Inclusion criteria Not reported Exclusion criteria Not reported	Details Sample selection Participants were asked to participate in the study at a routine clinic visit at the Leeds regional CF unit. Data collection A cross-sectional comparison of 3 approaches to measuring adherence: self-report, clinician report and electronic monitoring through the I-Neb Demographic and clinical data taken from patient's electronic medical record Adherence measured as % of prescribed regimen Participants: they were asked to identify their prescribed nebulizer regimen by medication, dose and frequency, and then asked about their adherence using 2 questions, in order to capture different ways of expressing adherence ((1) “On an average week, how often do you take your…” (each medication the	Results Adherence rates Adherence according to self-report: Median (IQR) = 80% (57.5% to 95%) of treatment prescribed Adherence according to electronic monitoring: Median (IQR) = 36% (5% to 84.8%) of treatment prescribed Reliability Clinician agreement: ICC = 0.95 (95% CI 0.44 to 0.66) Agreement between clinician report and electronic monitoring: ICC dietitian = 0.36 (95% CI 0.11 to 0.55) ICC liaison/ home nurse = 0.36 (95% CI 0.15 to 0.54)	Limitations The methodological limitations were assessed using a critical appraisal of outcome measures checklist (Jerosch-Herold,2005): 1. Is the purpose of the study clearly defined and focused on examining one or more measurement properties? Yes 2. Is the instrument described and is there a standardised protocol for administration and scoring which is described fully? Yes 3. Are the observers/testers appropriately trained or certified? Not relevant (important to note the observers were blinded to EM results) 4. Were the data collected on an appropriate sample which is representative of the population to whom the measure will apply? Yes 5. Is the sample size adequate? Yes (power was calculated) 6. Does the measure make intrinsic sense? Yes 7. Does the measure sample the content/domain adequately? Yes 8. Is there evidence of the test’s construct validity? Not relevant 9. What is the test-retest reliability? Not relevant

Study details	Number of participants and participant characteristics	Test characteristics	Results	Comments
This work involves an honorarium payment and began prior to this study.		patient identifi ed was questioned separately) and (2) "Overall, what percentage of your nebulizers do you think you have taken over the last 3 months?") Clinicians: they were asked to complete a questionnaire assessing adherence for each participant over the preceding 3 months. Clinicians were blinded to data from I-Neb and to all other reports of adherence. Electronic monitoring: I-Neb: chosen as it provides accurate and detailed adherence data. Currently for use in the UK. Adherence to a dose was defined as a complete dose taken at any time during the day. Statistical analysis Data analysis using SPSS Assumption was made that I-Neb had no systematic error Agreement was measured using ICC, with 95% CI	ICC physician = 0.42 (95% CI 0.21 to 0.59) ICC ward nurse = 0.34 (95% CI 0.11 to 0.54) ICC pharmacist = 0.28 (95% CI 0.07 to 0.47) ICC physiotherapist = 0.54 (95% CI 0.36 to 0.68) Validity Not reported Diagnostic accuracy data Not reported	10. What is the intertester reliability? Yes 11. Does the instrument capture clinical change? Not relevant Overall quality: moderate Other information Conflict of interest: Financial/non-financial disclosures: The authors reported the following COI: Ms Daniels provides advice as a consultant to Philips regarding nebulizer and associated technology development, to Novartis Pharmaceuticals Corporation and Pharmaxis regarding inhaled therapies, and to Air products regarding home oxygen delivery. These posts were all commenced following the completion of the present work. Ms Pollard has received assistance with travel and accommodation for a meeting from Novartis Pharmaceuticals Corporation. Dr Conway is a member of an advisory board that provides advice to Philips regarding nebulizer development. This board also has provided advice to Medic-Aid Limited and Respironics who developed AAD technology prior to being taken over by Philips. Drs Goodacre, Sutton, and Peckham have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. The authors noted that providing information about the study before asking them the

Study details	Number of participants and participant characteristics	Test characteristics	Results	Comments
				questions could have influenced the answers Complete data for 68 participants Extreme inaccuracy was observed for individual patients by clinicians and self-report adherence.
Full citation Shearer, J. E., Bryon, M., The nature and prevalence of eating disorders and eating disturbance in adolescents with cystic fibrosis, Journal of the Royal Society of Medicine, 97 Suppl 44, 36-42, 2004 Ref Id 330063 Country/ies where the study was carried out UK Aim of the study To improve previous research by using a semi-structured interview designed to assess and diagnose eating disorders in adolescent population. Study dates Not reported	Sample size N=55 children and young people with CF not undergoing psychological therapy Characteristics mean age (SD), range: centre 1: 14.2 (1.55); 11 to 16.6 centre 2: 14.14 (2.15); 11 to 17.3 gender: centre 1: 51.5% female centre 2: 45.5% female mean BMI (Sd), range centre 1: 18.1 (2.35); 14.5 to 23.4 centre 2: 18.6 (2.86) ; 13.2 to 24.1 Inclusion criteria	Details Test characteristics The Child Version of the Eating Disorder Examination (CEDE is adapted from the adult version of the Eating Disorder Examination (EDE) (considered the 'gold standard' for assessing eating disorders) It adopts the form of a semi-structured, investigator-based interview schedule designed to assess and diagnose the specific psychopathology of eating disorders in children and adolescents from 8 years of age. It produces information concerning the previous 4 weeks leading up to the interview. However, some of the questions ask about the previous 3 months, so that sufficient information can be gained to satisfy DSM-IV criteria.	Results Reliability Inter-rater reliability = 0.69 to 1 Validity Not reported	Limitations The methodological limitations were assessed using a critical appraisal of outcome measures checklist (Jerosch-Herold,2005): 1. Is the purpose of the study clearly defined and focused on examining one or more measurement properties? Yes 2. Is the instrument described and is there a standardised protocol for administration and scoring which is described fully? Yes 3. Are the observers/testers appropriately trained or certified? Unknown (it is not indicated in the study) 4. Were the data collected on an appropriate sample which is representative of the population to whom the measure will apply? Yes 5. Is the sample size adequate? Yes (power was calculated) 6. Does the measure make intrinsic sense? (Yes 7. Does the measure sample the content/domain adequately? (Yes) 8. Is there evidence of the test's construct validity? Yes (not reported in the study, but it

Study details	Number of participants and participant characteristics	Test characteristics	Results	Comments
Source of funding Not reported	A diagnosis of CF and registration on the UK CF database Age 11–17 years Ability to speak English sufficiently to complete the questionnaire and interview without assistance Exclusion criteria Experience of bereavement less than 1 year prior to the study Undergoing psychological therapy or being treated for problems associated with mood	The CEDE provides either frequency or severity ratings for key behavioural and attitudinal aspects related to eating disorders. On both frequency and severity ratings, scores range from 0 to 6. The questions pertinent to a formal diagnosis are termed 'The Diagnostic sub-scale' and scores of 4–6 meet diagnostic criteria. In terms of frequency a rating of 4–6 equates with the presence of features between 16 and 30 days per month. In terms of severity a rating of 4–6 equates with moderate to supreme severity. Scores of 2–3 reveal 'eating disturbance' as the individual shows symptomatology but not to the standard required for a diagnosis. Such scores have been termed 'sub-threshold' scores. In terms of frequency a rating of 2–3 equates with the presence of features between 6 and 15 days per month. In terms of severity a rating of 2–3 equates with mild to moderate severity. Scores of 0–1 reflect concerns within the 'normal' range. Sample selection		the validity of this tool has been already established) 9. What is the test-retest reliability? No 10. What is the intertester reliability? Yes (ICC 0.69 to 1) 11. Does the instrument capture clinical change? Not reported Overall quality: moderate Other information Conflict of interest: not reported

Study details	Number of participants and participant characteristics	Test characteristics	Results	Comments
		Participants were recruited from two paediatric CF centres. Four weeks prior to their appointment, potential participants who met the inclusion criteria and their parents/legal guardians were sent an introductory letter and an invitation to participate This procedure was repeated over a 6-month period, until a minimum sample of 55 had been obtained. Power Calculator was calculated for a range of plausible values of the correlation from 0.3. This suggested that a sample size of between 24 and 68 was required. Data collection Demographic and clinical information was collected from participants' medical notes. More specific clinical information including BMI ranges (kg/m2) were categorized as follows: 17.5 or less Anorectic BMI range (AN BMI range); 17.6–18.9 Under weight; 19.0–24.9 Desirable BMI range; 25.0–29.9 Overweight; 30 or more Obese Data analysis		

Study details	Number of participants and participant characteristics	Test characteristics	Results	Comments
		The inter-rater reliability of the use of the CEDE was assessed by carrying out Pearson's bivariate correlations between the researcher and a second, trained rater who listened to tapes of 20 interviews which had been randomly selected. The correlations ranged from 0.69 to 1, which is satisfactory for the purpose of quantitative analyses.		
Full citation Siracusa, C., Clancy, J. P., Drotar, D., Electronic monitoring reveals highly variable adherence patterns in patients prescribed ivacaftor, Pediatric Pulmonology, 49, 440, 2014 Ref Id 437623 Country/ies where the study was carried out USA Aim of the study To assess self-report adherence, compared to	Sample size N=12 children, young people and adults with CF previously prescribed Ivacaftor Characteristics Mean age (SD); range: 20.8 (9.9) years (6 to 48 years) Weeks on Ivacaftor prior to the study (SD), range: 55.3 924.6); 11.9 to 89.6 Inclusion criteria Confirmed diagnosis of CF with the CFTR-G551D mutation (the only approved	Details Test characteristics Self-report adherence data was obtained using The Self-Reported Treatment Adherence & Barriers Assessment Prescription refill data were obtained from each patient's pharmacy over the study period. Electronic monitoring: the Medication Event Monitoring System (MEMS®; AARDEX Ltd. Zug, Switzerland) was used. MEMS® mimics a traditional pill bottle in both appearance and utility, and tracks the date and time of each bottle opening. Graphic	Results Adherence rates according to (mean, SD, range): self-report: 100% (14% to 100%) pharmacy refill history: 84% (31) (13% to 124% electronic monitoring: 61% (28) (4% to 99%) Electronic monitoring versus self-report rs=0.40; p=0.22 ICC=0.14; p=0.23	Limitations The methodological limitations were assessed using a critical appraisal of outcome measures checklist (Jerosch-Herold,2005): 1. Is the purpose of the study clearly defined and focused on examining one or more measurement properties? Yes 2. Is the instrument described and is there a standardised protocol for administration and scoring which is described fully? the 3 ways of assessing adherence are described, and standardised 3. Are the observers/testers appropriately trained or certified? Not applicable 4. Were the data collected on an appropriate sample which is representative of the population to whom the measure will apply? Yes

Study details	Number of participants and participant characteristics	Test characteristics	Results	Comments
pharmacy refill and electronic monitoring. Study dates Not reported Source of funding This work was supported under a training grant funded by the National Institutes of Health [Grant 5T32HD068223-02].	mutation at the time of the study) Age 6 years and older Had been prescribed ivacaftor for at least one month Exclusion criteria Patients were excluded if: there was a provider-initiated reason for them not to take their ivacafto; there was a developmental disability that prevented them from effectively monitoring their adherence or completing surveys.	feedback is provided in the form of calendars and time plots at each data download. The number of bottle openings per day are indicated in the calendar feedback, while the frequency of time points for bottle openings are indicated in time plots. Sample selection Patients were recruited from two accredited CF centers, one pediatric (250 total patients) and one adult (140 total patients). Only 16 patients met the criteria. Eligible patients were approached by trained research staff during routine CF clinic visits. Data collection Demographic and clinical data was extracted from medical charts. Self-report measures of medication adherence were completed at time of enrollment and 3-4 months later during a routine CF clinic visit. Prescription refill data: adherence rates were calculated using the medication possession ratio (MPR), a	Electronic monitoring versus pharmacy refill history rs=0.26; p=0.42 ICC-=0.26; p=0.14	5. Is the sample size adequate? No (this is a serious issue, as the study in underpowered) 6. Does the measure make intrinsic sense? Yes (It is not explicitelly indicated, but it makes sense) 7. Does the measure sample the content/domain adequately? Yes (it is not explicitely indicated, but the measures have extensively used before) 8. Is there evidence of the test's construct validity? Not applicable 9. What is the test-retest reliability? Not applicable 10. What is the intertester reliability? Not applicable 11. Does the instrument capture clinical change? Not applicable Overall quality: low Other information Conflict of interest: Dr. Clancy and Cincinnati Children's Hospital Medical Center has obtained research contract funding from Vertex Pharmaceuticals to conduct clinical trials in CF patients, that were not directly related to this present study. All other authors had no conflicts of interest to disclose. Individuals demonstrated wide variability in regards to the different measures of adherence.

Study details	Number of participants and participant characteristics	Test characteristics	Results	Comments
		widely used measurement of pharmacy-obtained adherence data. The MPR is calculated by dividing the total amount of medication obtained by the patient by the total amount of prescribed medication. Pharmacy data were measured from the fill date immediately prior to enrollment to the fill date immediately prior to the end of the study. Electronic monitoring: patients were given an electronic monitoring (EM) device and instructed to use the device to dispense their ivacaftor for the duration of the study. Data from the EM device were downloaded, and patients received feedback on their adherence data. EM data were used to calculate overall adherence rates, weekly adherence rates, and mean duration between doses. Duration between doses was also obtained. Data analysis Mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables and		

Study details	Number of participants and participant characteristics	Test characteristics	Results	Comments
		frequency/percentage for categorical variables. The primary analysis of this study modeled the trajectory pattern of the EM-derived adherence over time. The level of agreement between EM-derived adherence and MPR and self-reported adherence were evaluated using Spearman correlation coefficient (rs) and intraclass correlation coefficient (ICC). SAS 9.3 (Cary, NC, USA) and R 3.1.0 (R Core Team, 2014) were used for all the analyses.		
Full citation White, H., Denman, S., Shaw, N., Pollard, K., Peckham, D., Do longitudinal measures of clinical variation correlate with adherence in cystic fibrosis, Pediatric Pulmonology, 49, 437, 2014 Ref Id 437684 Country/ies where the study was carried out UK	Sample size N=250 young people and adults with CF pharmacy collection data available for 106 patients (42%) Characteristics Mean (SD) age: 29.7 (9.2) Gender: 58.6% males Inclusion criteria Not reported Exclusion criteria Not reported	Details Sample selection Patients attending an adult regional CF centre Data collection Patients: patients were asked to complete an adherence questionnaire (CFQ-R) Pharmacy collection: consent from patients to access pharmacy records Data analysis Correlations (Pearson)	Results Correlation between pharmacy script collection and self-report: Aerosol to open air: r=0.34; p<0.005 Aerosol to thin mucus: r=0.51; p<0.001 Inhaler: r=0.51; p<0.001 PERT: r=0.45; p<0.001 Oral nutritional supplements: r=0.51; p<0.001	Limitations The methodological limitations were assessed using a critical appraisal of outcome measures checklist (Jerosch-Herold,2005): 1. Is the purpose of the study clearly defined and focused on examining one or more measurement properties? Yes 2. Is the instrument described and is there a standardised protocol for administration and scoring which is described fully? 3. Are the observers/testers appropriately trained or certified? 4. Were the data collected on an appropriate sample which is representative of the population to whom the measure will apply?

Study details	Number of participants and participant characteristics	Test characteristics	Results	Comments
Aim of the study To determine the accuracy of self-report adherence and its relationship with clinical variation. Study dates 2007 Source of funding Supported by a grant from Gilead Sciences			Oral antibiotics: r=0.46; p<0.001 Nebulised antibiotics: r=0.55; p<0.001 Total: r=0.61; p<0.001	5. Is the sample size adequate? 6. Does the measure make intrinsic sense? 7. Does the measure sample the content/domain adequately? 8. Is there evidence of the test's construct validity? 9. What is the test-retest reliability? 10. What is the intertester reliability? 11. Does the instrument capture clinical change? Other information Abstract only Conflict of interest: not reported

G.22 Prevention of Cross-infection

Review question 1: What is the effectiveness of cohorting on the basis of pathogen status versus not cohorting on the basis of pathogen status in reducing transmission of CF pathogens?

Review question 2: What is the effectiveness of different models of segregating patients in reducing transmission of CF pathogens?

Review question 3: What is the effectiveness of individual protective equipment in reducing transmission of CF pathogens?

Review question 4: What is the effectiveness of the combination of cohorting, segregating and protective equipment in reducing transmission of CF pathogens?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Griffiths, A. L., Wurzel, D. F., Robinson, P. J., Carzino, R., Massie, J., Australian epidemic strain pseudomonas (AES-1) declines further in a cohort segregated cystic fibrosis clinic, Journal of Cystic Fibrosis, 11, 49-52, 2012 Ref Id 367562 Country/ies where the study was carried out	Sample size See Griffiths 2005 Characteristics See Griffiths 2005 Inclusion criteria See Griffiths 2005 Exclusion criteria See Griffiths 2005	Interventions See Griffiths 2005	Details See Griffiths 2005	Results See Griffiths 2005	Limitations See Griffiths 2005 Other information See Griffiths 2005

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See Griffiths 2005 Study type See Griffiths 2005 Aim of the study See Griffiths 2005 Study dates See Griffiths 2005 Source of funding See Griffiths 2005					
Full citation France, M. W., Dodd, M. E., Govan, J. R., Doherty, C. J., Webb, A. K., Jones, A. M., The changing epidemiology of Burkholderia species infection at an adult cystic fibrosis centre, Journal of Cystic Fibrosis, 7, 368-72, 2008 Ref Id	Sample size Not reported Characteristics Adults with CF Age not reported Inclusion criteria All patients cared for by the Manchester Adult CF Centre between 1986 and 2006 inclusive Exclusion criteria Not reported	Interventions Intervention 3. Cohort segregation combined with individual segregation. A policy of isolation was introduced for patients infected with all Burkholderia species. This policy involves patients not having any contact with other patients, either at an inpatient or outpatient level. Patients being admitted to single rooms during admissions and attending outpatient appointments and being immediately isolated within their own clinic room.	Details Setting. Manchester Adult CF Centre. Intervention 1 was introduced in 1991. Intervention 2 was introduced in November 1993. Intervention 3 was implemented in 2000. Data collection. All cases of respiratory infection by Burkholderia cepacia complex (Bcc) species or other Burkholderia species, including B. gladioli, have been recorded at the centre since 1983. In 2001, all Manchester Bcc isolates stored in the repository from 1983 onwards were	Results Incidence of patients infected with transmissible pathogens Incidence of infection with Burkholderia species: Post-intervention 1 (1992 data): 16.3% vs comparison 1 (1983-1990): varied from 3 to 5% Incidence of infection with Burkholderia species: Post-	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: High risk (Intervention and control group drawn from different years. Prior to 1991, there was no evidence of Burkholderia cross-infection at the centre. The first transmissible strain emerged in 1991 after a Manchester

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
367547 Country/ies where the study was carried out UK Study type Retrospective before and after study Aim of the study To review the impact of changing infection control practices at the Manchester Adult CF Centre upon the epidemiology of Burkholderia species infections. Study dates Not reported Source of funding Not reported		Patients with Burkholderia species infection were cohorted into separate wards to non-Bcc infected patients and attended a different outpatient clinic. Intervention 2. Cohort segregation. Patients with Burkholderia species infection were cohorted into separate wards to non-Bcc infected patients and each inpatient has their own single room. Patients with Burkholderia species infection attended a different outpatient clinic. Isolation policy for patients with Burkholderia species not yet implemented Intervention 1: Incomplete cohort segregation. Patients with Burkholderia species infection were admitted to inpatient beds on the opposite side of the corridor to non-Burkholderia species infected patients. There was continued patient mixing within a day-room facility on the ward and within areas such as the radiology department. Patients with Burkholderia species infection attended separate outpatient clinics to other CF patients.	identified to species level and strain typing performed by pulsed-field gel electrophoresis (PFGE). Data relating to species identification and strain typing of all available B species isolated at the centre from 1983 to 2006 inclusive were reviewed from the centre database. Data analysis. Burkholderia isolates exhibiting similar PFGE patterns and displaying evidence of cross-infection involving two or more CF patients were termed transmissible strains.	intervention 2 ("following complete cohort segregation"): <3% for all but one year vs post-intervention 1 (1992): 16.3% Prevalence of patients infected with transmissible pathogens Prevalence of Burkholderia species infection: post-intervention 3 (2005 data): 9.3% vs post-intervention 2 (1994 data): 31.2% Quality of life Not reported Emotional function including anxiety and depression (scale not specified) Not reported Patient and carer satisfaction Not reported Staff experience Not reported Staff and patient compliance Not reported	patient returned from a CF holiday camp in North America) Comparability: High risk (Study does not control for any factor, only descriptive data on incidence) Outcome: High risk (Low quality reporting. However please note that a strength of this study is that genotyping was used to understand how changes in incidence were related to cross-infection and to transmissible strains as opposed to unique strains) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		Comparison 1. No infection control measures to prevent B. cepacia complex cross-infection No details			
Full citation Frederiksen, B., Koch, C., Hoiby, N., Changing epidemiology of Pseudomonas aeruginosa infection in Danish cystic fibrosis patients (1974-1995), Pediatric Pulmonology, 28, 159-66, 1999 Ref Id 330831 Country/ies where the study was carried out Denmark Study type Retrospective before and after study Aim of the study To evaluate the impact of the	Sample size N= 107 in 1974; 256 in 1995. Characteristics Patients with CF. Median age: 9.0 in 1974, 18.5 in 1995. Inclusion criteria Patients with CF attending the Copenhagen CF centre between 1974 and 1995. Exclusion criteria Not reported	Interventions Intervention: Cohort segregation The CF centre was reconstructed, separating the wards and the outpatient clinic Patients with PA in their sputum were separated from patients without PA in the wards, in the outpatient clinic, and during social events. Comparison: No cohort segregation The wards with inpatients receiving iv treatment were near the outpatient clinic visited by all CF patients CF patients were not segregated according to presence or absence of PA in their sputum	Details Setting. Copenhagen CF centre. Cohort isolation of patients with PA started in 1981. Data collection. A database was constructed based on the monthly cultures of each patient for the period January 1974-December 1995. Precipitating antibodies were detected by crossed immunoelectrophoresis at least once a year. Each patient had an average of 10 sputum cultures per year. Data analysis. Chronic infection was defined as persistent presence of PA for at least 6 consecutive months, or less when combined with the presence of two or more PA precipitins. Intermittent PA colonization was defined as a culture of PA at least once and presence of normal levels of precipitating antibodies against PA (0-1). For yearly prevalence, a patient was categorized as PA-positive	Results Incidence of patients infected with transmissible pathogens New cases of intermittent PA/patients at risk (annual incidence): Post-intervention: 9/40 (1982 data) vs comparison 15/45 (1980 data) New cases of chronic PA/patients at risk (annual incidence): Post-intervention: 7/69 (1982 data) vs comparison 15/75 (1980 data) Prevalence of patients infected with transmissible pathogens Graphic reporting, unclear reporting in text Quality of life Not reported	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: Low risk (Intervention and comparison group were drawn from different years, however 1980 and 1982 are the closest pre- and post-intervention full years; there is uncertainty about the infection status of patients in-between cultures which means that some supposedly "at risk" patients may have had the infection when the intervention started, however cultures were performed on average 10 times per year for each patient, which reduces this uncertainty).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
following interventions on the changes in the epidemiology of PA: 1. elective antibiotics for 14 days every 3 months to patients with chronic PA infection (started in 1976); cohort isolation of patients with PA to prevent cross-infection (starting in 1981); early intensive treatment with inhaled colistin and oral ciprofloxacin from time of initial colonization (1989). Study dates Not reported. Source of funding Not reported			if just one of the yearly samples was positive for PA or if just one of the early samples was defined as chronic PA. The incidence of PA isolations was defined as the number of new cases with intermittent or chronic PA cultures during a year, divided by the total population at risk (the number of patients who never had intermittent or chronic PA).	Emotional function including anxiety and depression (scale not specified) Not reported Patient and carer satisfaction Not reported Staff experience Not reported Staff and patient compliance Not reported	Comparability: High risk (Authors do not adjust for any factor, only descriptive data on incidence are presented) Outcome: High risk (No genotyping was used so that it was not possible to assess whether new cases had the same strains and were related to cross-infection. However, the following strengths were noted: Authors mention that there was uniform data collection over the years based on monthly visits of patients to the CF centre. There is uncertainty about the infection status of patients in-between cultures, however cultures were performed on average 10 times per year for each patient, which reduces this uncertainty. Adequate follow-up

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					period for outcome of interest.) Other information
Full citation Waine, D. J., Whitehouse, J., Honeybourne, D., Cross-infection in cystic fibrosis: the knowledge and behaviour of adult patients, Journal of Cystic Fibrosis, 6, 262-6, 2007 Ref Id 366998 Country/ies where the study was carried out UK Study type Survey Aim of the study To investigate adult patients' knowledge	Sample size 184 patients were invited to participate, 94 completed the questionnaire Characteristics Demographic data was available for 90 respondents. Mean (SD) Age: 27.2 (8.5) Sex: 58.9% were males. Inclusion criteria All patients attending a clinic appointment at the West Midlands Adult CF Centre during June and July 2005 were offered a questionnaire to complete. Questionnaires were also offered to inpatients who were due to attend the clinic during the same	Interventions Intervention: Individual separation Not mixing with patients with CF Comparison:No individual separation Mixing with other CF patients	Details Setting. West Midlands Adult CF Centre, UK. Data collection. After 10 patients had completed a pilot questionnaire, the results were examined and the questionnaire updated. Data analysis. Descriptive analysis. Percentages of responses were calculated for each question.	Results Incidence of patients infected with transmissible pathogens Not reported Prevalence of patients infected with transmissible pathogens Not reported Quality of life Not reported Emotional function including anxiety and depression (scale not specified) Not reported Patient and carer satisfaction Of the 48 patients who deliberately avoided contact, 30 (62.5%) said that their quality of life did not suffer as a result.	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: High risk (51.1% response rate; comparability between respondents and non-respondents was not assessed) Comparability: High risk (Study does not control for any factor, only a descriptive summary for each group is provided) Outcome: High risk (Self-report; the questionnaire was the result of modifications on a pilot questionnaire) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
about cross-infection risk and their related behaviour. Study dates Not reported Source of funding DJW is funded by the Heart of England Foundation Trust and the Heartlands CF Appeal Charity.	period. Questionnaires were posted to 8 patients colonized with the B. cepacia complex, who attended a separate clinic Exclusion criteria Not reported			Of the 43 who did not avoid contact, 10 (23.3%) said that their quality of life would suffer a 'significant amount' or 'a great deal' if they were to begin avoiding others. Of those who mixed with others, 51.1% said their quality of life would not suffer at all if they avoided others with CF Staff experience Not reported Staff and patient compliance Not reported in relation to relevant intervention	
Full citation Griffiths,A.L., Armstrong,D., Carzino,R., Robinson,P., Cystic fibrosis patients and families support cross-infection measures, European Respiratory	Sample size N= 291 were sent the questionnaires, 190 responded (114 parents alone (60%), 75 completed the questionnaire together with a child of >=12 yrs (40%), 1 questionnaire completed by child only). Characteristics	Interventions Intervention: Combination of cohort and individual segregation. Cohort segregation was based on five separate groups: PA positive; epidemic strain PA; B. cepacia; MRSA; and PA negative. Inpatients were nursed in separate sections and attended	Details Setting. CF clinic at the Royal Children's Hospital. Data collection. A questionnaire was sent out to the families of all patients in the state of Victoria and responses were returned by reply paid post. The answer was a three-point scale: positive, negative and unsure. The	Results Incidence of patients infected with transmissible pathogens Not reported Prevalence of patients infected with transmissible pathogens Not reported	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: Unclear risk (All patients were selected; the response rate was 65%; the comparability

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Journal, 24, 449-452, 2004 Ref Id 113827 Country/ies where the study was carried out Australia Study type Survey Aim of the study To assess CF parent and patient responses to the segregation measures instituted at the hospital to determine overall support. Study dates Survey was carried out between May and December 2002, two years after the introduction of segregation measures. Source of funding	Parents of children with CF or parents together with patients with CF if aged >= 12 years. Mean age: unclear Females/males: unclear Inclusion criteria Families of all patients in the state of Victoria Exclusion criteria Not reported	physiotherapy sessions at different times. Those children infected with epidemic strain PA, MRSA or BC were isolated from each other and all other patients Those within the other groups were allowed to mix within their cohort groups. Comparison: Usual care	questionnaire was designed de novo and has not been validated. Responses were anonymous. Data analysis. Chi-squared or Fisher's exact test were used to assess individual responses and to compare responses between parents and children.	Quality of life Not reported Emotional function including anxiety and depression (scale not specified) Not reported Patient and carer satisfaction Patient satisfaction: Children with CF (>=12 yrs) overall response to segregation measures: positive: 48/76 (63%), negative: 9/76 (12%), unsure: 19/76 (25%) (p<0.001) Carer satisfaction: Parents' overall response to segregation measures: positive: 160/189 (85%), negative: 7/189 (4%), unsure: 21/189 (11%) (p<0.001) Staff experience Not reported Staff and patient compliance Not reported	between respondents and non-respondents was not established) Comparability: High risk (Study does not control for any factor) Outcome: High risk (Self-report with anonymous questionnaire (not validated); the statistical test is clearly described and appropriate, and p values are presented) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
This study was supported in part by the Royal Children's Hospital Cystic Fibrosis Research Trust (Melbourne, Australia).					
Full citation Griffiths, A. L., Jamsen, K., Carlin, J. B., Grimwood, K., Carzino, R., Robinson, P. J., Massie, J., Armstrong, D. S., Effects of segregation on an epidemic Pseudomonas aeruginosa strain in a cystic fibrosis clinic, American Journal of Respiratory & Critical Care Medicine, 171, 1020-5, 2005 Ref Id 367561	Sample size N people= 325 (1999), 291 (2002). N sputum producers: 153 (1999), 149 (2002) Characteristics Paediatric patients with CF. Number of sputum producers in each age groups: <10: 41 (2002), 39 (1999); 10-12: 34 (2002), 34 (1999); 13-15: 36 (2002), 42 (1999); >=16: 38 (2002), 38 (1999). Sex: not reported. Inclusion criteria Patients attending the CF clinic at the Royal Children's Hospital in Melbourne. Exclusion criteria Not reported	Interventions Intervention: Cohort segregation Cohorts: PA (negative, positive non-epidemic, epidemic PA (AES-1)) Separation of cohorts was maintained at outpatient visits and during hospital admissions. Standard infection control measures were reinforced, and education seminars were arranged for staff and families. Comparison: No cohort segregation. No segregation based on PA. Standard infection control measures B. Cepacia complex and MRSA strict individual segregation	Details Setting. CF clinic at the Royal Children's Hospital in Melbourne. Intervention introduced in January 2000. Data collection. The CF research database and laboratory records were surveyed for sputum culture and pulsed-field gel electrophoresis results. Children were seen every 3 months, and sputum was collected from expectorating patients. An independent laboratory scientist randomly selected a single mucoid and nonmucoid PA colony from each infected patient for molecular typing by pulsed-field gel electrophoresis. Pulsed-field-gel electrophoresis was used to identify AES-1. Data analysis. Griffiths 2005:	Results Incidence of patients infected with transmissible pathogens Not reported Prevalence of patients infected with transmissible pathogens Prevalence of PA epidemic strain AES-1 among sputum producers: post-intervention (N=149, 2002 data): 0.27 vs pre-intervention (N=153, 1999 data): 0.44. Adjusted relative risk (aRR): 0.64 (95% CI 0.47 to 0.87), P=0.004 (adjusted for age and sex)	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: High risk (Intervention and comparison groups from different years, and not the closest full years to the intervention as in other studies) Comparability: Low risk (In Griffiths 2005 authors adjust for age and sex when comparing prevalence values for 1999 and 2002 and provide an adjusted relative risk) Outcome (prevalence amongst sputum

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Australia Study type Griffiths 2005 Retrospective clinical audit (It is also a retrospective before and after study) Griffiths 2012 Retrospective before and after study Aim of the study Griffiths 2005 To determine whether strict infection control measures, including cohort segregation, interrupted cross-infection within the clinic. Griffiths 2012 To evaluate changes in prevalence of an epidemic strain of PA (AES-1, Australian			Relative risks comparing prevalence amongst sputum producers in 2002 with 1999 were adjusted for age and sex using binomial regression with a log-link function. Griffiths 2012: Prevalence amongst all patients attending was compared between 1999 and 2002. The difference in prevalence between different years was calculated. The 95% CI of the difference was estimated and statistical significance was assessed by Fisher's exact test.	Quality of life Not reported Emotional function including anxiety and depression (scale not specified) Not reported Patient and carer satisfaction Not reported Staff experience Not reported Staff and patient compliance Not reported	producers): Low risk (Although a limitation of the present study was testing only one to two sputum isolates of PA per sample from each infected patient, genotyping was used so that the prevalence of epidemic strains could be reported, separate from the prevalence of nonepidemic strains) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
epidemic strain, type 1) in a paediatric CF centre practising cohort segregation, to describe the clinical characteristics at acquisition and observe mortality rates Study dates Griffiths 2005 Not reported Griffiths 2012 Not reported Source of funding Griffiths 2005 Supported by the Royal Children's Hospital CF Research Trust Griffiths 2012 The Royal Children's CF Research Trust funded DFW in 2008					
Full citation	Sample size Not reported	Interventions	Details	Results	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Chen, J. S., Witzmann, K. A., Spilker, T., Fink, R. J., LiPuma, J. J., Endemicity and inter-city spread of Burkholderia cepacia genomovar III in cystic fibrosis, Journal of Pediatrics, 139, 643-9, 2001 Ref Id 367474 Country/ies where the study was carried out USA Study type Retrospective before and after study Aim of the study To determine whether the same Burkholderia cepacia complex strain has persisted as the	Characteristics Patients with CF at two centres. Age or sex not reported. Inclusion criteria All patients cared for in Centre A and Centre B. Exclusion criteria Not reported	Intervention 2: Individual segregation in addition to cohort segregation. Hospitalized non-colonized patients were prohibited from sharing rooms, then this policy was expanded so that all patients with CF irrespective of B cepacia colonization were in separate rooms. Separate waiting rooms were established for outpatients. Intervention 1. Cohort segregation. Cohorting of hospitalized patients with CF on the basis of B. cepacia colonization status. Comparison 1: No cohort segregation. No details. Intervention 3: Cohort segregation combined with individual segregation and with protective equipment. · Cohorting of hospitalized patients on the basis of B. cepacia colonization status. Furthermore inpatients colonized with B. cepacia were placed in contact isolation and were required to wear mask and gloves when out of their rooms. In the outpatient setting, patients infected with B. cepacia were	Setting. Intervention 1 and 2 were implemented in Centre A (large CF treatment centre in Philadelphia) in early 1990 and mid-1996 to 1998, respectively. Intervention 3 was implemented in Centre B (CF treatment centre in Washington DC) in early 1997. Data collection. All available B cepacia complex isolates from 1981 to 1987 and from 1997 to 2000 at Centre A and from 1997 to 2000 at Centre B were recovered from frozen stock. In Centre A, sputum cultures were obtained from most patients only once per year. Sputum cultures were obtained 4 to 6 times per year from patients at Centre B. Infection control policies governing B cepacia infection in patients with CF were reviewed in Centers A and B for relevant years. Data analysis. All isolates were analyzed by PCR. The incidence and prevalence of B cepacia complex infection for Centre A and Centre B were calculated for relevant years baed on the total number of patients with CF	Incidence of patients infected with transmissible pathogens Annual incidence of B. cepacia complex infection at 1 year: Post-intervention 1: 3.7% (1991 data) vs Comparison 1: 5.8% (1989 data) Annual incidence of B. cepacia complex infection (unclear follow-up): Post-intervention 3: <1% (since time of implementation) vs usual care: 8.8% (1996 data) Prevalence of patients infected with transmissible pathogens Prevalence of B. cepacia complex infection: Post-intervention 2: 7% (1999 data) vs post-intervention 1: 15% (1992 data) Quality of life Not reported Emotional function including anxiety	The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection, intervention 1 vs comparison 1: High risk (Intervention and comparison groups were drawn from different years (1991 and 1989) however these are the closest pre- and post-intervention years. There is uncertainty about the infection status of patients in-between cultures which means that some supposedly "at risk" patients may have had the infection when the intervention started, especially considering that at centre A cultures were performed for most patients only once a year) Selection, intervention 3 vs usual care: Unclear (Intervention and comparison groups

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
dominant clonal lineage among patients in a large CF treatment centre during two decades prior to the study. To investigate the inter-city spread of B cepacia through transfer of a colonized patient and the impact of infection control measures in contraining inter-patient transmission. Study dates Not reported Source of funding Supported by a grant from the CF Foundation (to Dr LiPuma).		restricted to separate clinic days during which no non-colonized patients were seen. Patients were required to wear masks while in the waiting room. A hospital-wide educational program regarding infection control measures was introduced Particular attention was given to disinfection of clinic rooms and equipment Comparison 3: Usual care No details	being cared for in the respective centre and the number reported by the respective clincal microbiology laboratory to have had at least one sputum culture positive for B cepacia.	and depression (scale not specified) Not reported Patient satisfaction Not reported Staff experience Not reported Staff and patient compliance Not reported	were drawn from different years, however years of post-intervention incidence are unclear; uncertainty of infection status (relating to time in-between cultures) is limited because cultures were obtained between 4 and 6 times a year at centre B). Selection, intervention 2 vs intervention 1: High risk (Intervention and comparison groups were drawn from different years distant in time, 1999 and 1992; there is uncertainty about the infection status of patients in-between cultures which means that some supposedly uninfected patients may have already had the infection when the intervention started, especially considering that at centre A cultures were performed for

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					most patients only once a year) Comparability: High risk (Study does not control for any factor, only descriptive data are provided). Outcome: High risk (Although genotyping was used, so that authors could show that most patients were infected with the same B cepacia genomovar III strain in both centres, the following limitations were identified: the authors analysed isolates of most patients with CF reported to have had at least one sputum culture positive for B cepacia complex and found that some pathogens had been misidentified by routine analysis and were not B cepacia complex pathogens (however they would have been counted to calculate incidence/prevalence of B. cepacia complex). This

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					problem affects all outcomes and all comparisons in the study. Moreover, with regards to comparisons relating to centre A (intervention 2 vs intervention 1, and intervention 1 vs comparison 1), cultures where performed only once a year). Other information
Full citation Savant, A. P., O'Malley, C., Bichl, S., McColley, S. A., Improved patient safety through reduced airway infection rates in a paediatric cystic fibrosis programme after a quality improvement effort to enhance infection prevention and control measures, BMJ	Sample size N= Number of patients ranged from 126 to 177 over the study years. 127 patients with cultures in 2005 at the start of the baseline monitoring period. 75 of those patients continued to be followed in the programme in 2012. Mean number of respiratory tract cultures per quarter was 169 (range 104-207 in baseline period, 173-206 in postintervention). Characteristics	Interventions Intervention: Protective equipment and individual segregation Contact precautions for all patients in the outpatient clinic, regardless of respiratory tract culture results: gowning and gloving and hand hygiene by all providers; requesting that all patients use hand gel and mask when entering the facility or when outside of the exam room Abolishing the designated communal area for taking vital sign measurements and converting to exam rooms. Re-enforcement of the "no-waiting" room policy (Immediate	Details Setting. Paediatric CF programme at Ann & Robert H. Lurie Children's Hospital of Chicago. The intervention started late in quarter 4 of 2007. Data collection. Data from 2005 to 2012 was evaluated. Data analysis. Using a before and after evaluation, data from baseline were compared to post-intervention rates. Respiratory tract culture results were tracked using a customised report from the CFF registry. At the end of each quarter, the % of patients with a positive respiratory tract culture for	Results Incidence of patients infected with transmissible pathogens Not reported Prevalence of patients infected with transmissible pathogens Mean % patients cultured each quarter with positive tract cultures for PsA: post initiation (2008-2012): 21.78% (range 31.09-12.95%) vs pre-intervention (2005-2007):	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: High risk (intervention and comparison groups drawn from different years, 2008-2012 vs 2005-2007) Comparability: High risk (Study does not adjust comparison for any factor) Outcome: High risk (No genotyping was used to assess whether acquisition

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Quality & Safety, 23, i73-i80, 2014 Ref Id 406470 Country/ies where the study was carried out USA Study type Retrospective before and after study Aim of the study To assess a quality improvement effort to reduce the risk of pathogen transmission between patients with CF and decrease the rate of acquisition of new CF pathogens. Study dates Data from 2005 to 2012 was evaluated Source of funding	Paediatric patients with CF. Age: Mean age (SD) ranged between 9.7 (5.9) and 10.6 (5.7) over the study years. (Age range was 0-21). Sex: % females ranged between 50 and 55 over the study years. Inclusion criteria All respiratory tract cultures of paediatric patients in CF programme at Ann & Robert Lurie Children's Hospital of Chicago Exclusion criteria Not reported	placement within the examination room) Education of patients and families; cleaning rooms thoroughly. Comparison: Incomplete use of protective equipment and incomplete individual separation Any patient with respiratory tract cultures revealing a multi-resistant pathogen had a flag placed on the chart to indicate the need for contact precautions. However a consistent process for the use of this indicator was not systematic or routine. Vital signs were performed in a common station in the hallway close to the exam rooms, without specific cleaning between patients. “No-waiting” room policy	a specific pathogen was defined as number of patients with a pathogen in one or more respiratory tract culture specimens divided by the total number of patients who had cultures (thus each positive respiratory tract culture for a specific pathogen only counted once per patient). A comparison between proportions was done using Student t tests. Moreover, % of patients per year with respiratory tract cultures for 2005-2007 was compared to 2008-2011 using data from the CF Patient Registry.	29.79% (range 38.74-22.94%) (p<0.0001). Mean % patients cultured each quarter with positive tract cultures for MRSA: post (2008-2012): 8.68% (range 12.78-5.38%) vs pre-intervention (2005-2007): 10.76% (range 12.5-7.34) (p=0.008). Mean % patients per year with culture positive for PsA: 2008-2011 13.95% vs 2005-2007 13.5% (data from CF Patient Registry) Mean % patients per year with culture positive for MRSA: 2008-2011 24.5% vs 2005-2007 19.1% (data from CF Patient Registry) Quality of life Not reported Emotional function including anxiety and depression (scale not specified) Not reported	of infection was related to cross-infection. However please note the following strengths: Follow-up of 4 years was long enough to detect changes; Uncertainty about infection status of patients in-between cultures is limited because cultures were obtained each quarter) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
None				Patient satisfaction Not reported Staff experience Not reported Staff and patient compliance Not reported	
Full citation Whiteford, M. L., Wilkinson, J. D., McColl, J. H., Conlon, F. M., Michie, J. R., Evans, T. J., Paton, J. Y., Outcome of Burkholderia (Pseudomonas) cepacia colonisation in children with cystic fibrosis following a hospital outbreak, Thorax, 50, 1194-8, 1995 Ref Id 426761 Country/ies where the study was carried out UK	Sample size N=115 (1992). Characteristics Children with CF. Mean age: 7.6 years. Age range: 0.6 to 15.8 years. 1 patient was already colonised with B cepacia by December 1991. Inclusion criteria Patients attending the CF Unit at the Royal Hospital for Sick Children, Glasgow. Exclusion criteria Not reported	Interventions Intervention. Cohort segregation Children with B. cepacia were admitted to a separate ward Children with B. cepacia were moved to a different waiting area and given appointment times at the end of the clinic. Recommendations to parents to avoid close physical contact outside the hospital Comparison. No cohort segregation No cohort segregation for children with B. cepacia Children with CF needing inpatient care were admitted to one ward where they had complete freedom to play together and socialise Each child had an individual peak flow meter and nebuliser for use throughout the admission Children colonised with PA had their chest physiotherapy	Details Setting. The CF Unit at the Royal Hospital for Sick Children, Glasgow. The intervention was implemented in June 1992. Data collection. Specimens for bacterial culture were either sputum samples or cough swabs in those unable to produce sputum. Bacteriocin typing of all B. cepacia organisms was performed by standard methods. Data analysis. The number of new cases of B. cepacia colonisation, disaggregated by bacteriocin type, were presented for each month of 1992.	Results Incidence of patients infected with transmissible pathogens New cases of B. cepacia / all children with CF at risk: post-intervention (Dec 1992): 1/93 vs vs pre-intervention (May 1992): 5/109 Prevalence of patients infected with transmissible pathogens Not reported Quality of life Not reported Emotional function including anxiety and depression (scale not specified) Not reported	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: Unclear (Authors do not mention how often cultures were obtained, therefore it is not clear how much uncertainty there is in the calculation of the number of people "at risk" for each month; intervention and comparison group drawn from different months in the same year, therefore there is no reason to assume they would be very different; all children attending the CF Unit were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Retrospective before and after study with regards to the outcomes of interest. Aim of the study To compare the outcomes of children with CF colonised with B. cepacia and PA to children with CF with PA but no B.cepacia. Study dates Not reported Source of funding Not reported		separately from children without PA		Patient and carer satisfaction Not reported Staff experience Not reported Staff and patient compliance Not reported	included in the analysis) Comparability: High risk (study does not adjust for any factor, only descriptive data relating to incidence pre- and post-intervention) Outcome: High risk (No genotyping was used to understand whether new cases were related to cross-infection, although bacteriocin typing was performed by standard methods. Authors do not specify how often cultures were obtained, therefore, it is unclear whether the follow-up was long enough to see a change in incidence) Other information
Full citation Jones, A. M., Dodd, M. E., Govan, J. R., Doherty, C. J., Smith, C. M., Isalska, B. J., Webb, A. K., Prospective	Sample size N= 216 (1999), 221 (2000), 228 (2001) Characteristics Adults with CF. Age not reported, sex not reported. Inclusion criteria	Interventions Intervention 1: Incomplete cohort segregation. Patients without chronic PA infection attended outpatient clinic appointments on a different day than other patients with CF.	Details Setting. Manchester CF Adult Centre. Intervention implemented in 2000. Data Collection. Over a 4-year period (2000-2003), PA isolates were prospectively typed from patients with CF. PA isolates were	Results Incidence of patients infected with transmissible pathogens Not reported for all relevant years	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: Low risk (Intervention and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
surveillance for Pseudomonas aeruginosa cross-infection at a cystic fibrosis center, American Journal of Respiratory & Critical Care Medicine, 171, 257-60, 2005 Ref Id 367609 Country/ies where the study was carried out UK Study type Retrospective before and after study. Aim of the study To assess clonality of strains amongst patients with CF attending the Manchester Adult CF Centre. Study dates 2000-2003 Source of funding	Patients with CF who attend the Manchester Adult Centre. Exclusion criteria One patient with a different transmissible PA strain transferred in late 2003 from another adult centre.	Inpatients without chronic PA infection were housed on the same CF ward as patients with chronic PA infection, but in rooms with en-suite facilities, and were advised not to socialise with other patients on the ward, however there was still some social mixing between patients on the ward. Comparison: No segregation. Purpose-built facilities: all inpatients had their own bedroom, although only 2 of 11 rooms had en-suite facilities. Treatments with door closed Practice of strict hygiene. Rooms are cleaned between patients, equipment not shared between patients, hand hygiene for staff.	retyped more frequently if they displayed unusual phenotypic features. In addition patients with multiple inpatient admissions or patients found to have been exposed to potential risk of cross-infection, e.g. through social contact, where retyped more frequently. Data analysis. Chronic PA infection was defined as the regular culture of the organism from the sputum or respiratory secretions, on two or more occasions extending over 6 months.	Prevalence of patients infected with transmissible pathogens Total number of patients with chronic PA infection/total number of patients: post-intervention: 184/228 (2001 data) vs comparison: 156/216 (1999 data) Patients chronically infected with transmissible PA strain infections/total number of patients: post-intervention 35/228 (2001 data) vs comparison: 28/216 (1999 data) Prevalence of infection with transmissible PA strains: post-intervention: 15.4% (2001 data) vs comparison: 13.0% (1999 data) Quality of life Not reported Emotional function including anxiety and depression (scale not specified)	comparison group drawn from different years, 1999 and 2001, however these are the closest pre- and post-intervention full years. All patients attending the centre were included) Comparability: High risk (Study does not adjust for any factor, only descriptive summary of outcomes for pre- and post-intervention) Outcomes: Low risk (Isolates were genotyped by pulsed-field gel electrophoresis to identify transmissible strains. However please note that authors do not report how often cultures were performed, only report that PA isolates were retyped more frequently if they displayed unusual phenotypic features. In addition patients with multiple inpatient admissions

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported				Not reported Patient satisfaction Not reported Staff experience Not reported Staff and patient compliance Not reported	or patients found to have been exposed to potential risk of cross-infection where retyped more frequently) Other information Authors mention that the new cases of transmissible PA infection since 2000 are cases of super-infection among patients already infected with sporadic strains of PA. The latter were not segregated from the former. As a consequence of the results of the study all inpatients were required to remain in their own rooms at all times and not to mix with other patients irrespective of their microbiological status.
Full citation Hayes, D., Jr., West, S. E., Rock, M. J., Li, Z., Splaingard, M. L., Farrell, P. M.,	Sample size N= 39 infants and children with CF (21 in intervention group, 18 in comparison group) Characteristics	Interventions Intervention. Cohort segregation: Segregated clinics (free of patients with PsA). The segregated clinics were held on a separate day in the same clinic space used for mixed clinics;	Details Study setting. University of Wisconsin Hospital and Clinics in Madison, WI and Children's Hospital of Wisconsin in Milwaukee, WI. Data collection. A	Results Incidence of patients infected with transmissible pathogens Incidence of PA infection over 10	Limitations The quality of this trial was assessed using the Cochrane risk of bias assessment tool:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pseudomonas aeruginosa in children with cystic fibrosis diagnosed through newborn screening: assessment of clinic exposures and microbial genotypes, Pediatric Pulmonology, 45, 708-16, 2010 Ref Id 367574 Country/ies where the study was carried out United States Study type Randomized clinical trial of two clinic types (subjects randomized to either segregated clinics or mixed clinics) with enrollment, longitudinal cohort follow-up observation	Infants and children with CF. Age: not reported Sex: Intervention: 9 females (43%), 12 males (57%) vs comparison: 7 females (39%), 11 males (61%) Inclusion criteria Positive newborn screen; informed consent provided by parents or legal guardians. Exclusion criteria Not reported	large clinics and waiting rooms, and hygienic precautions. Comparison. No cohort segregation: Mixed clinics that included PsA positive patients; large clinics and waiting rooms, and hygienic precautions.	cotton-tipped swab was used to collect the specimen from the oropharynx at each clinic visit using standardized methods previously employed at each CF center. Confirmation of PA was performed by standard biochemical testing. Arbitrarily primed polymerase chain reaction (AP-PCR) was used for genetic analysis. Data analysis. The incidence over 10 years was calculated for each group.	years: Intervention: 13/21 vs Comparison: 14/18. Prevalence of patients infected with transmissible pathogens Not reported Quality of life Not reported Emotional function including anxiety and depression (scale not specified) Not reported Patient and carer satisfaction Not reported Staff experience Not reported Staff and patient compliance Not reported	Random sequence generation: Unclear risk of bias (authors do not describe how the allocation sequence was generated). Allocation concealment: Unclear risk of bias (authors do not describe whether any method was used to conceal the allocation sequence). Blinding: Unclear risk of bias (Blinding is not mentioned. It may not be possible with this intervention). Incomplete outcome data: Unclear risk of bias (no attrition; authors do not mention how many children did not fit the study's inclusion criteria). Selective reporting: Unclear risk of bias (Authors do not mention the possibility of selective outcome reporting).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and data collection during approximately 10 years. Randomization in 1996 occurred between two centres, but due to an IRB requirement during the reapproval process after one year, the assignments changed to within-centre randomization for 1997-2001. Aim of the study The project was designed to address several goals: To compare PsA acquisition in segregated and mixed clinics; To compare PsA acquisition in a new clinic with adequate hygiene precautions					Other bias: Low risk of bias (None identified) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
versus the small, old clinic in Miwaukee; To examine PsA isolates through genotyping for patterns that might imply cross-infection. Study dates 1996-2005 Source of funding The National Institutes of Health (grant NIDDK 5 R01 DK34108-17)					
Full citation Thomassen, M. J., Demko, C. A., Doershuk, C. F., Stern, R. C., Klinger, J. D., Pseudomonas cepacia: decrease in colonization in patients with cystic fibrosis, American Review of Respiratory	Sample size N= 389 (admissions post-segregation); 453 (admissions pre-segregation); Characteristics Paediatric patients with CF. Age: not reported Inclusion criteria Inpatients and outpatients at the Rainbow Babies and Children's Hospital. Exclusion criteria	Interventions Intervention: Incomplete cohort segregation All patients with Pseudonomas cepacia recovered from sputum or throat culture were admitted to one floor of the hospital - other patients with CF were not admitted to this floor. Siblings of patients with P. cepacia colonization were also admitted to this ward The patients on this ward were not permitted to visit other inpatient wards but were not isolated in any other way. They	Details Setting. Rainbow Babies and Children's Hospital. Intervention was introduced in August 1983. Data collection. Sputum or deep throat cultures after cough were obtained at admission and weekly thereafter for inpatients. Strains of P. cepacia were serotyped. Data analysis. To investigate possible modes of transmission, patient-to-patient contact was examined. Hospital-	Results Incidence of patients infected with transmissible pathogens Incidence (Number of patients with hospital-associated colonization/at-risk patients): Post-intervention: 2.6% (6/235) vs pre-intervention: 7.8% (24/308), OR (pre vs post)=3.1, p=0.012	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: Low risk (Cultures from all admitted patients were included; intervention and comparison groups were drawn from two different time periods however these time intervals were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Disease, 134, 669-71, 1986 Ref Id 332134 Country/ies where the study was carried out USA Study type Retrospective before and after study Aim of the study To compare colonization patterns after precautionary measures were instituted to the patterns before the measures were introduced. Study dates Not reported Source of funding Supported by Public Health Service Grant AM-27651 from the National Institutes of Health and by grants from the	Not reported	had free access to the elevators, hospital cafeteria, and other common areas. No special precautions were taken to totally avoid chance meetings of the 2 groups of patients in the radiology department, outpatient areas, pulmonary function laboratory, or other hospital areas. Equipment in pulmonary function lab was sterilized or changed between patients. Hand washing was emphasized. In some cases medical staff advised patients to avoid out-of-hospital contact with colonized patients. Masks or other isolation equipment were not used by patients or hospital personnel. Summer camp facility was reserved for patients free of P. cepacia, another camp site was provided for colonized patients. Comparison: No cohort segregation in hospital Basic infection control procedures (no details) No segregation in camp facility	associated colonization was considered if a patient's first positive culture occurred 10 or more days after admission. This was generally the patient's third culture since admission. This interval was chosen to account for patients colonized with P. cepacia at subdetectable amounts prior to hospitalization. Patients hospitalized within 3 months prior to colonization were also considered to have a hospital-associated acquisition. Patients with a positive culture prior to 10 days after admission were considered precolonised. The number of patients who were precolonised was subtracted from the number of admissions to calculate the number of patients at risk. Incidence of hospital-associated colonization was calculated for 1 year and 5 months before the intervention (1 Mar 1982- 31 Jul 1983) and 1 year and 5 months afterwards (1 Aug 1983- 31 Dec 1984). Chi-square analysis of the 2x2 contingency table was	Prevalence of patients infected with transmissible pathogens Not reported Quality of life Not reported Emotional function including anxiety and depression (scale not specified) Not reported Patient and carer satisfaction Not reported Staff experience Not reported Staff and patient compliance Not reported	reasonably close: the pre- intervention interval was 1 Mar 1982- 31 Jul 1983 and the post-intervention interval was 1 Aug 1983- 31 Dec 1984; authors made sure that the outcome of interest was not present in the group considered "at risk" by defining hospital-associated colonization as an infection that showed for the first time in a positive culture 10 or more days after admission. This interval was chosen to account for patients colonized with P. cepacia at subdetectable amounts prior to hospitalization) Comparability: High risk (Study does not control for any factor) Outcome: High risk (There was an attempt to assess the relationship between incidence and cross-infection because serotyping was used

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
CF Foundation, the C.H. Ivey Foundation, and United Way Services of Cleveland.			performed and the OR was calculated.		to identify strains of P cepacia, patient-to-patient contact was examined and environmental reservoirs for P. cepacia were examined. However, no genotyping was used. Please note the following strength: Authors focused on incidence of hospital-associated colonization, which would be more closely related to cross-infection than overall incidence amongst all patients.) Other information
Full citation Lee, T. W., Brownlee, K. G., Denton, M., Littlewood, J. M., Conway, S. P., Reduction in prevalence of chronic Pseudomonas aeruginosa infection at a regional pediatric cystic	Sample size N=232 patients (76 in January 1990, 152 in December 2000); 17,230 patient months Characteristics Paediatric patients with CF. Mean age: 7.73 (January 1990), 9.42 (December 2000). Inclusion criteria All patients attending the clinic between	Interventions Intervention: Cohort segregation. Separate clinics for patients chronically infected with PA and uninfected patients. Improved hygienic measures in a purpose-built CF centre Comparison: No cohort segregation Various management strategies over the years to reduce the prevalence of chronic PA, including:	Details Setting. Leeds Regional CF Unit. Intervention implemented in 1991. Data collection. Patients had a sputum or cough swab sample taken at every clinic visit, with not more than 12 weeks between visits. Patients were defined each successive calendar month as: PA culture-positive; PA culture-negative; no culture	Results Incidence of patients infected with transmissible pathogens Graphic reporting, authors mention: "the annual incidence of new growths of PA, while fluctuating, showed no downward trend, despite segregation"	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: High risk (Intervention and comparison groups drawn from different and distant years, namely 1990 and 2000; the post-intervention group

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
fibrosis center, Pediatric Pulmonology, 37, 104-10, 2004 Ref Id 331318 Country/ies where the study was carried out UK Study type Retrospective before and after study Aim of the study To assess the impact of subsequent interventions implemented at Leeds Regional CF Unit over the years on reducing the prevalence of PA infection, including separate clinics for patients chronically infected with PA and uninfected	January 1990 and December 2000. Exclusion criteria Not reported	Neonatal screening (1975) Regular microbiological monitoring (1975) Early antibiotic treatment of first isolations of PA (1985) Intensive iv antibiotic treatment where nebulized antibiotics failed to eradicate PA (1988)	performed. All patients in the clinic were categorized each successive month according to their PA culture status over the preceding 12 months on the following basis: Chronic: chronic PA infection, with more than 50% of months when samples had been taken being PA culture-positive. Intermittent: 50% or less of months when samples had been taken being PA culture-positive. Free: Free of PA with no growth of PA for the previous 12 months, having previously been PA culture-positive. Never: Never grown PA. Data analysis. A monthly prevalence of "chronic", "intermittent", "free" and "never" status was calculated. Statistical analysis was performed, using a t-test for proportions.	Prevalence of patients infected with transmissible pathogens Yearly prevalence of chronic PA infection at 9 years: post-intervention (2000): 18.1% (326/1803 patient months) vs. pre-intervention (1990): 24.5% (237/966 patient months), P<0.05 Yearly prevalence of intermittent PA infection at 9 years: post-intervention (2000): 34.5% (622/1803 patient months) vs pre-intervention (1990): 26.2% (253/966 patient months), P<0.02 Quality of life Not reported Emotional function including anxiety and depression (scale not specified) Not reported Patient satisfaction Not reported Staff experience	was not only exposed to segregation, but also to an additional intervention: in 1998 the duration of eradication therapy was increased to 3 months of oral ciprofloxacin and nebulized colomycin, and this change was associated with a further fall in the prevalence of PA infection; according to the authors, the rise in intermittent PA infection is probably due to the successful eradication of new PA infection) Comparability: High risk (Study does not control for any factor; however please note that increase in average age of the clinic and in the mean culture frequency would both tend to bias towards an increase in diagnosis of chronic PA infection) Outcome: High risk (No genotyping was

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
patients in 1991. Study dates Not reported Source of funding Not reported				Not reported Staff and patient compliance Not reported	done to see if PA infections had been acquired through cross-infection; cultures were performed at least once every 12 weeks, however it is not clear if the denominator for prevalence (patient months) excludes patients that did not have a culture for a specific month) Other information
Full citation McKay, K. O., Cooper, P. J., van Asperen, P. P., Segregation of children with CF diagnosed via newborn screening and acquisition of Pseudomonas aeruginosa, Journal of Cystic Fibrosis, 8, 400-4, 2009 Ref Id 331487	Sample size N=Between 72 and 90 children were seen in each year of the study. The results of 2837 sputum cultures were analysed for the study. Characteristics Infants and children with CF. Age <=5. Sex: "There were equal numbers of male and female children in each group" Inclusion criteria All children aged <=5 for whom culture results	Interventions Intervention: Cohort segregation by age. Outpatients clinics were designated by colour as "red" (children 5 and under who were PA-free), "blue" (primary school age or children under 5 already colonised with PA) or "green" (secondary school age). Additional infection measures (e.g. removal of toys from the waiting room and hand cleansing). All inpatients were treated in single rooms or in rooms shared with children without CF.	Details Setting. Segregation policy was introduced in the hospital April and May 2003 and outcome data are provided for 1999-2002 vs 2004-2007. Data collection. Culture results were obtained between 1999-2002 and 2004-2007. Mean+-SE of sputum cultures analysed each year for each child: post-intervention: 4.63+-0.07 (median=4) and pre-intervention: 4.53+-0.08 (median=4). All cultures performed from 1st January to 31st December	Results Incidence of patients infected with transmissible pathogens Not reported Prevalence of patients infected with transmissible pathogens 4-year prevalence of MRSA at 1-4 years: Post-intervention (2004-2007): 1.0% vs pre-intervention (1999-2002): 1.3%, P= ns	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: High risk (Adherence to the "coloured" clinic booking scheme was high, ranging between 94.4% and 97.5%, however not complete, so that some people who were supposed to be in the intervention group may have not been in the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Australia Study type Retrospective before and after study Aim of the study To investigate the effect of segregation on acquisition of respiratory pathogens Study dates Not reported Source of funding Not reported	were obtained between 1999-2002 and 2004-2007. Exclusion criteria Not reported	Comparison: No cohort segregation One all age (0-18) clinic Free mixing of patients in waiting area	each year were included for that year's results. Few of the children were able to successfully expectorate so sputum samples were collected by experienced nurses using a deep pharyngeal suction technique. Data analysis. Prevalence was defined as the percentage of children isolating the organism in question at least once during the relevant period (pre-intervention or post-intervention). Comparison of rates of infection before and after the introduction of segregation was done using Chi-square analysis.	4-year prevalence of non-mucoid PA at 1-4 years: Post-intervention (2004-2007): 22.7% vs pre-intervention (1999-2002): 22.3%, P= ns 4-year prevalence of mucoid PA at 1-4 years: Post-intervention (2004-2007): 1.0% vs pre-intervention (1999-2002): 5.9%, P<=0.001 Quality of life Not reported Emotional function including anxiety and depression (scale not specified) Not reported Patient and carer satisfaction Not reported Staff experience Not reported Staff and patient compliance Adherence to the "coloured" clinic booking scheme: % of children attending the red clinic who were 5 and under:	intervention group in practice. Intervention and comparison groups were drawn from different time intervals, 1999-2002 and 2004-2007. However, authors mention that the use of antibiotics did not change significantly after segregation. Similarly there were no changes in respiratory consultants) Comparability: High risk (Study does not control for any factor) Outcome: High risk (Although the frequency of at least 4 cultures per child per year would be sufficient to assess prevalence over 4 years, no genomic fingerprinting was carried out to see if prevalence was related to cross-infection. Moreover, authors mention that while deep suction via the oropharynx was used in the study to obtain

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				2004: 96.8%; 2005: 97.5%; 2006: 94.4%; 2007: 95.9%	sputum samples rather than oropharyngeal swabs for microbiological culture, such specimens do not always predict the presence of bacterial pathogens, particularly PA, in the lower airways of young children with CF.) Other information
Full citation Russo, K., Donnelly, M., Reid, A. J., Segregation--the perspectives of young patients and their parents, Journal of Cystic Fibrosis, 5, 93-9, 2006 Ref Id 367784 Country/ies where the study was carried out UK Study type	Sample size N= 192 parents, 101 patients. Characteristics Mean age of eligible patients: 13 (range 10-17). Sex:Male to female ratio: 49:52. Infection status of patients: 13 did not have an infection, 2 had an unknown status, 47 cultured one organism, 34 cultured two organisms, 5 cultured three or more organisms. Inclusion criteria	Interventions Intervention: individual segregation. Policy of segregation requiring all patients to remain in their individual rooms for the duration of their hospital stay Comparison: Usual care	Details Setting. Belfast Paediatric CF centre. In mid-2004 views were elicited in preparation for the process of implementing the intervention. Data collection. Semi-structured questionnaires were anonymous and included both open-ended and closed-ended questions. Two versions of the questionnaire were devised - a child friendly version and a version for parents/carers. A pilot exercise was undertaken to test the relevance and acceptability of the child and parent questionnaire,	Results Incidence of patients infected with transmissible pathogens Not reported Prevalence of patients infected with transmissible pathogens Not reported Quality of life Not reported Emotional function including anxiety and depression (scale not specified) Not reported	Limitations The quality of this study was assessed using the Newcastle-Ottawa scale assessment tool: Selection: High risk (43% of parents and 23% of children returned questionnaires. The authors mention that the main limitation of this study is the low response rate, particularly from patients. Comparability between respondents and non-respondents was assessed for

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Survey with questionnaire including closed-ended and open-ended questions Aim of the study To elicit patients and carers' views and to involve them in the process of introducing segregation in a paediatric CF centre Study dates Mid-2004 Source of funding The study was partly supported by the Belfast Royal Group of Hospitals Multidisciplinary Research Fellowship.	All parents and patients over 10 years cared for by the Belfast Paediatric CF centre. Questionnaires received within 2 months from initial posting were included in the analysis. Exclusion criteria Not reported		respectively, as well as the data collection procedures. Questionnaires were mailed along with a covering note and an information sheet. A reminder letter was posted after three weeks. Data analysis. A content analysis identified common themes. The percentage of parents and children who supported segregated treatment was calculated. A chi-squared analysis and a logistic regression analysis were undertaken to investigate systematic differences between respondents and non-respondents.	Patient and carer satisfaction % of parents who supported segregated treatment: 91%. N of parents who disagreed: 4. N of parents who were unsure: 3 % of children who supported segregated treatment: 92%. N of children who disagreed though their parents agreed with the policy: 1. N of children who were unsure though their parents agreed with the policy: 1 Staff experience Not reported Staff and patient compliance Not reported	parents, indicating that more parents of younger children than of older children tended to respond (p=0.01). The relatively small number of child respondents did not permit a meaningful statistical comparison). Comparability: High risk (The study does not control for any factor) Outcome: High risk (Self-report, questionnaires had been tested in a pilot exercise) Other information
Full citation Hoiby, N., Pedersen, S.	Sample size N= Range: 54-226 (between 1970 and	Interventions	Details Setting. Danish CF centre at Rigshospitalet,	Results Incidence of patients infected	Limitations The quality of this study was assessed

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
S., Estimated risk of cross-infection with Pseudomonas aeruginosa in Danish cystic fibrosis patients, Acta Paediatrica Scandinavica, 78, 395-404, 1989 Ref Id 451979 Country/ies where the study was carried out Denmark Study type Retrospective before and after study Aim of the study To further analyse data on PA cross-infection at the Danish CF Centre and to try to estimate the risk of cross-infection in various periods of time in the Centre.	1987). Subgroup of patients with PA infection in 1983, segregated between patients with multiply resistant PA and patients with sensitive strain of PA: N=119 Characteristics People with CF Age: Not reported Sex: Not reported Inclusion criteria Patients attending the CF centre at Rigshospitalet in Copenhagen. Exclusion criteria Not reported	Intervention 2: Cohort segregation of patients with multiply resistant PA strain Three groups: Patients with multiply resistant PA strain; cohort with normally sensitive strains of chronic PA infection; PA negative patients Improved hygienic precautions Intervention 1. No cohort segregation of patients with multiply resistant PA strain (although there was segregation of PA positive patients - same intervention and setting (i.e. same population) as in the Frederiksen 1999 study) Two cohorts, cohort with chronic PA infection separated from PA negative patients Segregated from each other in different wards and seen on different days in the outpatient clinic.	Copenhagen. Intervention 2 was implemented in April 1983. Data Collection. Once a month patients are seen at the outpatient clinic, the examinations include microscopy and culture of bacteria and fungi from sputum or tracheal secretion obtained by endolaryngeal suction. Data analysis. Authors calculated incidence and prevalence. Incidence and prevalence of multiply-resistant PA was calculated using the number of PA positive patients as denominator.	with transmissible pathogens Incidence per month of multiply resistant strain (new patients with multiply resistant strain/patients with PA at risk): intervention 2: 6.5% (5/77) (May 1983) vs intervention 1: 20.6% (22/107) (March 1983) Prevalence of patients infected with transmissible pathogens Prevalence per month of multiply resistant strain (patients with multiply resistant strain/patients with PA): intervention 2: 37% (44/119)* (May 1983) vs intervention 1: 33% (39/119)* (March 1983) Quality of life Not reported Emotional function including anxiety and depression (scale not specified)	using the Newcastle-Ottawa scale assessment tool: Selection, intervention 2 vs intervention 1: Low risk (All patients with PA, comparison and intervention group drawn from different months of the same year) Comparability: High risk (Study does not adjust for any factor) Outcome: High risk (No genotyping was used to assess the relationship between incidence or prevalence and cross-infection. Please note that follow up (either 1 month or 2-4 years depending on the comparison) was long enough for changes to occur because culture of bacteria was obtained once a month) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported Source of funding Not reported				Not reported Patient satisfaction Not reported Staff experience Not reported Staff and patient compliance Not reported * Numerator calculated by the NGA technical team	