National Collaborating Centre for
Women's and Children's Health

Diarrhoea and vomiting caused by gastroenteritis

diagnosis, assessment and management in children younger than 5 years

Clinical Guideline

April 2009

Funded to produce guidelines for the NHS by NICE

Diarrhoea and vomiting caused by gastroenteritis

diagnosis, assessment and management in children younger than 5 years

National Collaborating Centre for Women's and Children's Health

Commissioned by the National Institute for Health and Clinical Excellence

Evidence tables

April 2009

RCOG Press

Evidence tables should be read in conjunction with the full guideline.

Published by the **RCOG Press** at the Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG

www.rcog.org.uk

Registered charity no. 213280

First published 2009

ISBN 978-1-906985-14-1

NCC-WCH editor: Andrew Welsh
Original design: FiSH Books, London
Typesetting of main guideline by Andrew Welsh

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Abbreviations

AROC	area under receiver operating characteristic [curve]
BSS	bismuth subsalicylate
BUN	blood urea nitrogen
C. difficile	*Clostridium difficile*
CI	confidence interval
CRP	C-reactive protein
CRT	capillary refill time
DCRT	digital capillary refill time
E. coli	*Escherichia coli*
EL	evidence level (level of evidence)
ELISA	enzyme-linked immunosorbent assay
ESR	erythrocyte sedimentation rate
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
GDG	Guideline Development Group
HPA	Health Protection Agency
HUS	haemolytic uraemic syndrome
IM	intramuscular
iu	international unit
IV	intravenous
IVT	intravenous fluid therapy
LR	likelihood ratio
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NPSA	National Patient Safety Agency
OR	odds ratio
ORS	oral rehydration salt
ORT	oral rehydration therapy
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
RCT	randomised controlled trial
RIV	rapid intravenous hydration
RNG	rapid nasogastric hydration
ROC	receiver operating characteristic
RR	relative risk
SD	standard deviation
SMD	standardised mean difference
UK	United Kingdom
UNICEF	United Nations Children's Fund
USA	United States of America
WHO	World Health Organization
WMD	weighted mean difference

3 Diagnosis

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Khuffash FA; Sethi SK; Shaltout AA; 1988 [44] Kuwait	Study Type: Cross-sectional Evidence level: 3	595 children. 5 children with *Aeromonas hydrophilia* were excluded from the comparison because of the small number.	Children aged from under 1 year to 12 years presence of gastroenteritis hospitalised	Intervention: Clinical features of gastroenteritis Duration of gastroenteritis by aetiological agent Comparison: Comparisons of duration of diarrhoea are made between children with gastroenteritis due to different aetiological agents	Follow-up period: Clinical progress during hospitalisation and after discharge was recorded Outcome Measures: Duration of diarrhoea	Frequency of clinical characteristics by aetiological pathogen	Mean Duration Rotavirus 4.8 days Salmonellae 12.3 days *E. Coli* 6.8 days Campylobacter 7.4 days Shigellae 7.9 days Rotavirus & Salmonella 12.9 days Rotavirus & others 7.4 days No pathogen 5.6 days Overall mean 7.4 days Mortality 0.7% (all from salmonella group)	Gastroenteritis due to rotavirus follows a benign course both in the developing and developed world Although the overall number of participants is large, some of the groups have small numbers of children. Because of the higher incidence of bacterial pathogens, the cases seem to have longer durations.
Uhnoo I; Olding-Stenkvist E; Kreuger A; 1986 [51] Sweden	Study Type: Cross-sectional Evidence level: 3	416 children (228 boys and 188 girls)	Children below 15 years of age with acute gastroenteritis who attended the Department of Paediatrics. Mean age 24.9 months Median age 15 months	Intervention: Clinical features of gastroenteritis Comparison: Comparisons of symptoms and signs of rotavirus infections with those of adenovirus, bacterial, mixed and non-specific infections.	Clinical features of children in relation to enteropathogens detected in stool Mean duration of diarrhoea (in days) in relation to pathogens		Rotavirus vs. Adenovirus vs. Bacteria Frequency of clinical features (%) Diarrhoea: 98 vs. 97 vs. 100 Diarrhoea > 10 times daily: 21 vs. 22 vs. 36 Vomiting: 87 vs. 78 vs. 43 Vomiting > 5 times daily: 37 vs. 7 vs. 9 Fever: 84 vs. 44 vs. 69 Abdominal pain: 18 vs. 25 vs. 50 Blood present in stools: 1 vs. 3 vs. 41 Mucus present in stools: 17 vs. 19 vs. 26	Clinical features of gastroenteritis with rotavirus, enteric adenoviruses and bacteria each exhibit patterns that could guide the experienced clinician to a presumptive diagnosis

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
							Mean (SD) duration in days Symptoms before hospital contact: 2.9 (0.2) vs. 5.3 (0.7) vs. 5.4 (0.6) Diarrhoea: 5.9 (0.3) vs. 10.8 (1.7) vs. 14.1 (2.2) Vomiting: 2.5 (0.1) vs. 3.2 (0.8) vs. 2.1 (0.3) Hospital stay: 2.4 (0.2) vs. 3.6 (1.2) vs. 3.6 (1.2)	
Colomba C; Grazia SD; Giammanco GM; Saporito L; Scarlata F; Titone L; Arista S 2006 [52] Italy	Study Type: Cross-sectional Evidence level: 3	215 children	Children admitted with symptoms of acute diarrhoea (≥ 3 watery stools in a period of 24 hrs)	Epidemiologic and clinical features of acute viral gastroenteritis Comparison: Comparisons of symptoms and signs of viral infections with non-viral infections.	Comparison of Clinical features of children between thos with positive result and those without positive results of viral detection in stool. Mean duration of diarrhoea (in days) in relation to pathogens		Children with single viral infection vs. with dual viral infection vs. without viral infection Frequency of clinical features (%) Diarrhoea ≥ 3 days: 58.7 vs. 71.4 vs. 63.1 ($P < 0.005$) Vomiting: 71.2 vs. 61.9 vs. 43 ($P < 0.0005$) Fever: 58.7 vs. 61.9 vs. 66.7 ($P < 0.05$) Dehydrated children: 50 vs. 52.4 vs. 36.8 ($P < 0.01$) Hospitalization ≥ 3 days: 37.5 vs. 47.6 vs. 368.6 ($P > 0.05$)	
Conway SP; Phillips RR; Panday S; 1990 [53] UK	Study Type: Cross-sectional Evidence level: 3	1148 children (639 boys and 509 girls)	All children below 16 years of age admitted to a hospital over a one year period with a diagnosis of gastroenteritis 55% children less than 1 year of age, 45% belong to social class V and 17% to social class IV	Frequency of pathogens isolated Clinical features of children in relation to enteropathogens detected in stool and comparison of the features and treatment received in the hospital. Biochemical abnormalities detected according to presence/absence of			Frequency of pathogens isolated from stool examination Rotavirus: 31% Samonella: 5% Campylobacter: 3.2% Enteropathogenic *E.coli*: 2% Cryptosporidia: 1% Shigella and *C.difficile*: <1% each No pathogen: 55% Comparison of clinical features 1) Rotavirus vs. Protozoa vs.	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				dehydration			Bacteria vs. Mixed infection Mean frequency of stool/day: 5.9 vs. 6.1 vs. 7.4 vs. 7.7 Frequency of vomiting in %: 92 vs. 84 vs. 54 vs. 75 2) Bacteria + protozoa + mixed infection vs. rotavirus vs. no pathogen Stool with blood or mucus in %: 25 vs. 2.8 vs. 4.1 ($P < 0.001$) Stool frequency 4 per day in %: 30 vs. 11 vs. 7 ($P < 0.001$) % of children with diarrhoea settling in < 48 hrs: 39 vs. 52 vs. 67 % of children with diarrhoea settling in 49-96 hrs: 30 vs. 32 vs. 16 % of children with diarrhoea settling in ≥ 97 hrs: 31 vs. 16 vs. 16 Comparison of biochemical features between dehydrated children (n=101) and non-dehydrated children (n=1047) Sodium > 145 mmol/l = 11% vs. <1% ($P < 0.001$) Bicarbonate < 21 mmol/l = 72% vs. 55% ($P < 0.001$) Urea > 7 mmol/l = 30% vs. 5% ($P < 0.001$) % of gut pathogens identified in dehydrated vs. non-dehydrated children: 61% vs. 43% ($P < 0.001$)	
Deivanayagam N; Mala N; Ashok TP; Ratnam SR; Sankaranarayanan	Study Type: Case–control	170 cases	all participants were 1–23 months, admitted to the	Intervention: Risk factors for persistent diarrhoea are being	Follow-up period: this is not reported		Mother's literacy OR 1.3; 95% CI 0.8–1.9; $P = 0.28$	The risk factors strongly associated with persistent diarrhoea are:

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VS; 1993 [54] India	Evidence level: 2+	340 controls 2 controls for each case, matched for age.	Institute of Child Health Madras for diarrhoea. CASES children with diarrhoea persisting more than 14 days at admission CONTROLS children with acute diarrhoea who had recovered within 7 days	investigated. They include: mother' literacy father's literacy diarrhoea within the past 3 months pre-admission feeding pattern container used for feeding method of cleaning the bottle nature of stool frequency of stool indiscriminate use of antimicrobials dehydration persistence of dehydration for>24 hours nutritional status vitamin A deficiency associated illness weight loss during study period Comparison: Comparisons are made between cases and controls for each of the risk factors listed	Outcome Measures: Odds Ratios for mother' literacy father's literacy diarrhoea within the past 3 months pre-admission feeding pattern container used for feeding method of cleaning the bottle nature of stool frequency of stool indiscriminate use of antimicrobials dehydration persistence of dehydration for >24 hours nutritional status vitamin A deficiency associated illness weight loss during study period		Mother's literacy excluding invasive diarrhoea OR 0.8; 95% CI 0.5–1.2; *P* = 0.34 Father's literacy OR 1.0; 95% CI 0.6–1.6; *P* = 0.91 Diarrhoea within the past 3 months OR 0.5; 95% CI 0.3–1.0; *P* = 0.04 Preadmission feeding pattern OR 1.0; 95% CI 0.7–1.5; *P* = 0.97 Container used for feeding OR 0.9; 95% CI 0.6–1.5; *P* = 0.79 Method of cleaning the feeding bottle OR 0.6; 95% CI 0.1–2.3; *P* = 0.33 Method of cleaning the feeding bottle excluding invasive diarrhoea OR 0.3; 95% CI 0.03–1.7; *P* = 0.11 Nature of stool OR 2.4; 95% CI 1.3–4.3; *P* = 0.003 Adjusted OR 2.4; 95% CI 1.3–4.3; Frequency of stool OR 1.7; 95% CI 1.1–2.5; *P* = 0.01 Adjusted OR 1.8; 95% CI 1.2–2.8 Frequency of stool excluding invasive diarrhoea OR 1.6; 95% CI 1.0–2.4;	malnutrition stools with blood / mucus stool frequency of > 10 / day indiscriminate use of antimicrobials for acute diarrhoeas associated illnesses like septicaemia, pneumonia and UTI, persistence of dehydration > 24 hours with appropriate fluid therapy loss of weight during hospital stay The risk factors shown to be strongly associated with persistent diarrhoea can influence the natural history of diarrhoea and should be carefully considered in examination and history taking.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
							Adjusted OR 1.9; 95% CI 1.1–3.0 Indiscriminate use of antimicrobials OR 2.5; 95% CI 1.6–3.8; *P* < 0.001 Adjusted OR 2.4; 95% CI 1.6–3.9 Indiscriminate use of antimicrobials excluding invasive diarrhoea OR 2.6; 95% CI 1.6–4.2 Adjusted OR 2.8; 95% CI 1.7–4.8 CLINICAL FEATURES Dehydration OR 0.7; 95% CI 0.9–2.4; *P* = 0.78 Dehydration excluding invasive diarrhoea OR 0.9; 95% CI 0.2–3.9; *P* = 0.54 Persistence of dehydration > 24 hours OR 4.2; 95% CI 2.8–6.5; *P* < 0.001 Adjusted OR 1.4; 95% CI 1.2–1.7 Persistence of dehydration > 24 hours excluding invasive diarrhoea OR 3.8; 95% CI 2.4–5.9; *P* < 0.001 Nutritional status OR 2.7; 95% CI 1.9–4.1; *P* < 0.001 Adjusted OR 2.9; 95% CI 1.9–4.5	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
							Nutritional status excluding invasive diarrhoea OR 2.9; 95% CI 1.6–3.9 Adjusted OR 2.9; 95% CI 1.7–4.7 Vitamin A deficiency OR 2.3; 95% CI 1.0–5.2; *P* = 0.06 Vitamin A deficiency excluding invasive diarrhoea OR 2.3; 95% CI 1.0–5.7 Associated illness OR 4.5; 95% CI 2.7–7.4; *P* < 0.001 Adjusted OR 2.1; 95 % CI 1.5–3.1; Associated illness excluding invasive diarrhoea OR 5.9; 95% CI 3.5–10.0; Adjusted OR 2.1; 95% CI 1.4–3.1 Weight loss during study period OR 15.6; 95% CI 6.5–39.1; *P* < 0.001 Weight loss during study period excluding invasive diarrhoea OR 11.3; 95% CI 5.3–24.2; *P* < 0.001 Adjusted OR 11.5; 95% CI 5.4–25.2	
Ellis ME; Watson B; Mandal BK; Dunbar EM; Mokashi A; 1984 [57]	Study Type: Cross-sectional Evidence level: 3	447 children	Children aged under 2 years admitted to hospital with infectious gastroenteritis over a 12 month period	Frequency of pathogens isolated Biochemical abnormalities detected			Frequency of pathogens isolated from stool examination Viruses alone: 57% Bacteria alone: 6%	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				in the admitted children			Viruses & bacteria: 10% No pathogen: 23% Specific organisms isolated Rotavirus: 34% Other viruses: 53% Samonella: 4.3% Campylobacter: 5.1% Enteropathogenic *E.coli*: 6.9% Cryptosporidia: 1% Shigella: 2% *C.difficile* toxin: 4.9% Incidence of dehydration and biochemical abnormalities Moderate to severe dehydration: 14% Sodium > 150 mmol/l = 0.8% Bicarbonate < 15 mmol/l = 3% Urea > 6 mmol/l = 8%	
UK			Age distribution: ≤ 6 months: 210 7-12 months: 120 13-18 months: 86 19-24 months: 29					
Jenkins HR; Ansari BM; 1990 [58] UK	Study Type: Cross-sectional Evidence level: 3	215 children (116 boys and 99 girls)	All children admitted to four paediatric units in South Wales with acute gastroenteritis over a 12 month period Age range: 2 weeks to 9 yrs with 61% < 1 year of age Male: 54% White: 96%	Frequency of pathogens isolated Biochemical abnormalities detected in the admitted children			Frequency of pathogens isolated from stool examination Viruses alone: 30% Bacteria alone: 14% Viruses & bacteria: 5% No pathogen: 42% Specific organisms isolated Rotavirus: 25% Other viruses: 5% Samonella: 1.9% Campylobacter: 5.1% Enteropathogenic *E.coli*: 4.2% Cryptosporidia: 6% Shigella: 1.9% Incidence of dehydration and	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
							biochemical abnormalities > 5% dehydration: 7% (15/215) Sodium > 145 mmol/l = 0.9% (2/215) Bicarbonate < 15 mmol/l = 6% (13/215) Urea > 6 mmol/l = 7.9% (17/215)	
Cunliffe NA; Allan C; Lowe SJ; Sopwith W; Booth AJ; Nakagomi O; Regan M; Hart CA; 2007 [60] UK	Study Type: Survey Determination of the presence of rotavirus in stool samples by enzyme immunoassay Evidence Level: 3	stool samples from an *n* = 234 children	Children (age 1–168 months, median age 10 months) with acute gastroenteritis who had been hospitalised between January and May 2006		The presence of rotavirus	Rotavirus was detected in 17/91 cases (19%) of the healthcare -associated acute gastroenteritis and 54/152 cases (36%) of community acquired acute gastroenteritis	Rotavirus is an important cause of healthcare -associated acute gastroenteritis in a large paediatric hospital	This is survey data and thus is graded as evidence level 3. It is important to consider that this a small sample from one hospital and the data may not necessarily be extrapolated. The focus of the study was the healthcare-acquired rotavirus but this guideline is concerned with the community acquired rotavirus which was 36%
Froggatt PC; Vipond IB; Ashley CR; Lambden PR; Clarke IN; Caul EO; 2004 [59] UK	Study Type: Survey Evidence Level: 3	*n* = 3172 Sporadic stool samples (PHLS) from children under the age of seven with gastroenteritis *n* = 1,360 stool samples from outbreaks of gastroenteritis	Clinical specimens (usually stool but sometimes vomit) from cases of gastroenteritis in children under the age of seven years and from sporadic outbreaks of gastroenteritis (unclear if all paediatric) All South west and South Wales region 1999–2000 winter season	Intervention: Stool samples were tested using electron microscopy for viral pathogens Enzyme-Immuno Assay (EIA) and Polymerase Chain Reaction PCR for Norovirus EIA for rotavirus Comparison: Results of sporadic testing of stools and stools from outbreaks of gastroenteritis	Identification of causative agents focusing on norovirus	Results of sporadic cases rotavirus 21.6% norovirus 10.3% adenovirus 3.9% astrovirus 3.1% calicivirus 0.2% 62.3% were negative tests Results of the outbreaks rotavirus 3.9% norovirus 63.9% adenovirus 0.4% astrovirus 0.4% 32.6% were negative tests	Norovirus was second most common viral agent in sporadic childhood gastroenteritis indicating it has a significant role	This is a surveillance study thus is graded as evidence level 3. It must be considered that this a localised study which was conducted nearly 10 years ago. The funding of this study was not declared

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Gomara MI; Simpson R; Perault AM; Redpath C; Lorgelly P; Joshi D; Mugford M; Hughes CA; Dalrymple J; Desselberger U; Gray J; 2008 [62] UK	Study Type: Survey Evidence Level: 3	*n* = 685 stool samples of which *n* = 223 in a structured surveillance cohort (GP based) *n* = 203 in a community cohort (referred to hospital from GP) *n* = 259 in a hospital cohort (in patient)	Children under the age of 6 years with acute gastroenteritis in East Anglia UK between 2000 to 2003	Intervention: Stool samples were investigated for the presence of viruses by PCR for the detection of enteric adenovirus astrovirus norovirus Grp A & C rotavirus sapovirus Comparison: none	presence of viral pathogens in the stool samples enteric adenovirus astrovirus norovirus Grp A & C rotavirus sapovirus	A viral agent was detected in 367/685 samples (53.6%) Rotavirus was the most common in all three groups followed by norovirus and enteric adenovirus Structured surveillance *n*(%) rotavirus A 106(47.5%) norovirus 31(13.9%) adenovirus 20 (9.0%) astrovirus 11(4.9%) sapovirus 2 (0.9%) rotavirus 1(0.4%) Community cohort *n*(%) rotavirus A 60(29.6%) norovirus 18(8.9%) adenovirus 26(12.8%) astrovirus 4(2.0%) sapovirus 8(3.9%) rotavirus 2(1.0%) Hospital cohort *n*(%) rotavirus A 59(22.8%) norovirus 36(13.9%) adenovirus 20 (7.7%) astrovirus 7(2.7%) sapovirus 5(1.9%) rotavirus 2(0.8%) Multiple viruses were found in 8% of cases	Rotavirus was the most common pathogen found in all three cohorts followed by norovirus and enteric adenovirus	This was a surveillance survey and was graded as evidence level 3. It should be considered that this is a localised small study although it is fairly recent data. The study was funded by the NHS executive Eastern Region, research and Development Directorate
Van DP; Giaquinto C;	Study Type: Other	*n* = 1010 stool	Children under the	Intervention:	results were presented	No(%) of + rotavirus	Rotavirus is an important	This is a surveillance study so is

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Maxwell M; Todd P; Van der WM; REVEAL Study Group.; 2007 [61] Multi-centre Europe study	Evidence Level: 3	samples	age of 5 years with acute gastroenteritis seeking health care in UK hospitals during a 12 month period (part of multicentre pan European project)	Identification of rotavirus by ELISA and PCR Comparison: none	from three setting: Hospital Emergency department Primary care setting % of samples positive for rotavirus given as observed and expected (if ELISA test was missing, same proportion of rotavirus was assumed)	ELISA Hospital observed 39(60.9%) estimated 51(60.7%) Emergency department observed 22(59.5%) estimated 33(60%) Primary care setting observed 15 (31.9%) estimated 279(32%) Total estimated 363(35.9%)	pathogen in acute gastroenteritis in children. The incidence rate of rotavirus is ~60% in secondary health care and ~30% in the primary care setting.	graded as evidence level 3. The focus of this multicentre pan European study was to look at rotavirus genotypes across Europe in view of vaccine development The incidence rate of rotavirus is ~60% in secondary health care and ~30% in the primary care setting. However, it is important to note that the was a high proportion of estimated cases in the community data. This study was funded by Sanofi Pastuer MSD
Wheeler JG; Sethi D; Cowden JM; Wall PG; Rodriques LC; Tompkins DS; Hudson MJ; Roderick PJ 1999 [11] UK	Study Type: Survey Evidence Level: 3	*n* = 459, 975 patients served by 70 general practices in England plus community surveillance of 9776 randomly selected patients	Patients (all ages) registered at a GP practice and who either attended the practice with an infectious intestinal disease or were surveyed in the community (dates unclear)	Intervention: Incidence of infectious intestinal disease in community and reported to general practice Comparison: GP and community data is compared to the National Laboratory Surveillance data	Main outcome measure: incidence of infectious intestinal disease at 70 GP practices and in the community No of cases with identified pathogen divided into bacterial, viral or protozoan	Community data : 781 cases Incidence of 19.4/100 person years GP: 8770 cases Incidence of 3.3/100 person years Types of pathogen Community One case sent to national surveillance for every: 6.2 stools send for lab investigation 1.4 laboratory identifications 23 cases in GP 136 community cases Community cases vs national surveillance Salmonella 3.2 :1	Infectious intestinal disease occurs in 1 in 5 people each year of whom 1 in 6 presents to a GP Proportion of cases not reported by national surveillance is large and varies widely per organism	This study is described by the authors as a population based community cohort incidence study but is essentially survey data and is therefore graded as evidence level 3. The specific date of the data is unclear but is ~10 years old. Although incidence data is given for bacterial, viral and protozoan agents, the key result of this study is the disparity between the GP/community based incidence of infectious intestinal disease and that reported by the national laboratory surveillance. This study was funded by the Department of Health

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						Campylobacter 7.6 :1 Rotavirus 35 : 1 Round, structured viruses 1562 :1		
Borgnolo G; Barbone F; Guidobaldi G; Olivo G; 1996 [65] Italy	Study type: Diagnostic study Evidence Level: 2	111 children	Children aged between 1 and 60 months admitted to a hospital with acute diarrhoea lasting more than 12 hours and less than 15 days Bacterial: 53 (48%) Viral: 35 (31%) Culture-negative: 23 (21%) Exclusion: Children with chronic gastrointestinal diseases such as cow's milk protein intolerance, Crohn's disease, gastro-oesophageal reflux or chronic diseases	1) Comparison of acute phase reactant levels in bacterial, viral and culture-negative cases 2) Association and diagnostic accuracy of CRP at different thresholds in the differentiation of bacterial and viral gastroenteritis Reference standard: Stool culture		1) Comparison of mean ± SD levels for CRP (mg/l) bacterial vs. viral 44 ± 44 vs. 6.2 ± 7.0 ($P < 0.001$) bacterial vs. culture-negative 44 ± 44 vs. 19.5 ± 20 viral vs. culture-negative 6.2 ± 7.0 vs. 19.5 ± 20 Comparison of mean ± SD levels for ESR (mm/hr) bacterial vs. viral 25 ± 15 vs. 15 ± 9 ($P < 0.05$) Comparison of mean ± SD levels for blood leucocyte count (× 10^9/ l) bacterial vs. viral vs. culture-negative 9.9 ± 4.2 vs. 10.7 ± 4.7 vs. 10.1 ± 4.7 2) Association and diagnostic accuracy of CRP at different thresholds in the differentiation of bacterial and viral gastroenteritis At CRP level ≥ 12 mg/l OR: 25.8 (7.6 to 87.9) Sensitivity: 77% Specificity: 89% AROC: 0.83		Population representative with well defined exclusion Test and reference test described adequately Reference test is a standard one Blinding not specified

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						At CRP level ≥ 20 mg/l OR: 46.4 (5.9 to 364.9) Sensitivity: 58% Specificity: 97% AROC: 0.77 At CRP level ≥ 35 mg/l OR: 26.9 (3.4 to 212.1) Sensitivity: 44% Specificity: 97% AROC: 0.70		
Lin CH; Hsieh CC; Chen SJ; Wu TC; Chung RL; Tang RB; 2006 [66] Taiwan/China	Study type: Diagnostic study Evidence Level: 3	56 children	Children admitted with acute gastroenteritis, of whom 21 had rotavirus (by Rotaclone® test), 18 had bacterial infections (by stool culture with salmonella species isolated predominantly) while 17 children were recruited as controls. Mean age 2.5 years Exclusion: Children with chronic disease or history of persistent/intractable diarrhoea	1) Comparison of CRP, IL-6 and IL-8 levels in bacterial, viral and control cases 2) Diagnostic accuracy of CRP, IL-6 and IL-8 at different thresholds in the differentiation of bacterial and viral gastroenteritis Reference standard: Stool culture		Comparison of mean ± SD levels for CRP (mg/l) bacterial vs. viral 9.1 ± 6.6 vs. 1.4 ± 1.2 (P < 0.001) bacterial vs. control 9.1 ± 6.6 vs. 0.9 ± 0.8 (P < 0.001) Comparison of mean ± SD levels for IL-6 (pg/ml) bacterial vs. viral 45.3 ± 49.6 vs. 7.9 ± 2.7 (P < 0.001) bacterial vs. control 45.3 ± 49.6 vs. 5.3 ± 3.0 (P < 0.001) Comparison of mean ± SD levels for IL-8 (pg/ml) bacterial vs. viral 99.9 ± 81.9 vs. 54.3 ± 32.2 (P = 0.059) bacterial vs. control 99.9 ± 81.9 vs. 22.4 ± 6.3 (P < 0.001) 2) Diagnostic accuracy at	Population not representative Reference test not described adequately Reference test is a standard one Blinding not specified	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						different thresholds in the differentiation of bacterial and viral gastroenteritis AROC for CRP 0.897 IL-6 0.828 IL-8 0.677 At CRP level ≥ 2 mg/dl Sensitivity: 83% Specificity: 76% At IL-6 level ≥ 10 pg/ml Sensitivity: 78% Specificity: 86% At IL-8 level ≥ 70 pg/ml Sensitivity: 50% Specificity: 67%		
Marcus N; Mor M; Amir L; Mimouni M; Waisman Y; 200 [67] Israel	Study type: Diagnostic study Evidence Level: 3	44 children	Children admitted to the emergency department of a tertiary hospital with symptoms of vomiting, diarrhoea more than three episodes and fever, and who underwent laboratory testing. Age range 4 days to 17 years, median age of 2.4 years Exclusion: not defined	Comparison of mean CRP levels between bacterial and viral gastroenteritis Diagnostic accuracy of Quick-read CRP test at different thresholds in the differentiation of bacterial and viral gastroenteritis Reference standard: Stool culture		1) Comparison of mean ± SD levels for CRP (mg/l) bacterial vs. viral 223.8 ± 150.3 vs. 30.0 ± 50.0 ($P < 0.001$) 2) Diagnostic accuracy of QR-CRP at cut-off value of > 95 mg/L (best value derived from ROC curve) Sensitivity: 87% Specificity: 92%		Population not representative Reference test not described adequately and not carried out in all children Reference test is a standard one Blinding not specified

4 Assessing dehydration and shock

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Khuffash FA; Sethi SK; Shaltout AA; 1988 [44] Kuwait	Study Type: Cross-sectional Evidence level: 3	595 children. 5 children with *Aeromonas hydrophilia* were excluded from the comparison because of the small number.	Children aged from under 1 year to 12 years presence of gastroenteritis hospitalised	Intervention: Clinical features of gastroenteritis Duration of gastroenteritis by aetiological agent Comparison: Comparisons of duration of diarrhoea are made between children with gastroenteritis due to different aetiological agents	Follow-up period: Clinical progress during hospitalisation and after discharge was recorded Outcome Measures: Duration of diarrhoea	Frequency of clinical characteristics by aetiological pathogen	Mean Duration Rotavirus - 4.8 days Salmonellae 12.3 days *E. Coli* 6.8 days Campylobacter 7.4 days Shigellae 7.9 days Rotavirus & Salmonella 12.9 days Rotavirus & others 7.4 days No pathogen 5.6 days Overall mean 7.4 days Mortality 0.7% (all from salmonella group)	Gastroenteritis due to rotavirus follows a benign course both in the developing and developed world Althought the overall number of participants is large, some of the groups have small numbers of children. Because of the higher incidence of bacterial pathogens, the cases seem to have longer durations.
Bhattacharya SK; Bhattacharya MK; Manna B; Dutta D; Deb A; Dutta P; Goswami AG; Dutta A; Sarkar S; Mukhopadhaya A; 1995 [69] India	Study Type: Case–control Evidence level: 2+	*n*= 243 cases *n* = 136 controls	Infants with acute gastroenteritis (<24 hours) with either moderate or severe dehydration (cases) or non or mild dehydration (controls) and admitted into hospital.		Univariate analysis for the following factors was carried out for both groups Aetiology Feeding practices Management of diarrhoea Hygiene practices Measles in previous 6 months	Univariate analysis showed presence of vibrios in stool, withdrawal of breastfeeding during diarrhoea, not giving fluids including ORS during diarrhoea , frequent purging (>8 per day) and frequent vomiting(>2 per day) and under nutrition to be associated with dehydration The following risk factors which were significantly associated with dehydration following multivariate analysis, controlling for confounders were	Lack of fluid intake whether breast milk or other fluids by the infant during acute gastroenteritis is strongly associated with risk of dehydration. Age, severity of symptoms and nutritional status also play a part.	Well conducted case control study Good choice of control group- a source population that gave rise to the cases good structured univariate and multivariate analysis The funding of this study was undeclared

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					Clinical features on admission	Withdrawal of breastfeeding during diarrhoea OR 6.8 (95% CI 3.8 to 12.2) *P* < 0.00001		
					Followed by multivariate analysis after controlling for confounding factors including	Not giving ORS during diarrhoea OR 2.1 (95% CI 1.2 to 3.6) *P* = 0.006		
					age group gender religion nutritional status family income persons/room in family home	The confounding variables which also contributed significantly were: age (<12 months) OR 2.7 (95% CI 1.5 to 5.0) *P* = 0.001		
						Frequency of stool OR 4.1 (95% CI 2.4 to 7.0) *P* < 0.00001)		
						Frequency of vomiting OR 2.4 (95% CI 1.4 to 4.0) *P* = 0.001		
						Severe under nutrition (≤60IAP classification) OR 3.1 (95% CI 1.6 to 5.9) *P* = 0.001		
Zodpey SP; Deshpande SG; Ughade SN; Hinge AV; Shirikhande SN; 1998 [70] India	Study Type: Case–control Evidence level: 2+	*n* = 387 cases *n*= 387 controls	Children under the age of five with acute gastroenteritis (no details on duration) with severe or moderate dehydration (cases) or mild or no dehydration (controls) and admitted to hospital		Outcome Measures: Risk factors a) demographic factors e.g. age, sex b) nutritional status (IAP classification) c) hygiene practices e.g. hand washing	Data was subject to univariate analysis and multivariate analysis (shown below) Results were similar OR (95% CI) Age <12 months 1.53 (1.02–2.28) *P* = 0.038 Female sex	This study found a significant association of infancy, religion, severe under nutrition, clinical symptoms, withdrawal of breastfeeding during diarrhoea, history of measles, withdrawal of fluids during diarrhoea and not giving ORS, HAF or both during diarrhoea with the development of moderate or severe dehydration	Large case control study with appropriate control group Some of the significantly associated factors were very near the level of significance e.g. age, religion The funding of this study was not declared

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						1.18 (0.8–1.73) *P* = 0.389		
					d) clinical features on admission e.g. frequency of symptoms	Muslim religion 1.64 (1.01–2.7) *P* = 0.048		
					e) history of measles in the past 6 months	Residence in rural/urban slum 0.98 (0.77–1.24) *P* = 0.884)		
					f) management of diarrhoea e.g. breast feeding	Severe under nutrition 1.56 (1.31–1.86) *P* < 0.001)		
						Non washing of mothers hands & food prep 1.45 (0.97–2.16) *P* = 0.064		
						Non washing of mothers hands after defaecation 1.33 (0.9–1.97) *P* = 0.144		
						Non washing of mothers hands after disposal of faeces 1.44 (0.97 to2.12) *P* = 0.063		
						Freq of stool(>8 per day) 8.76 (5.88–13.04) *P* < 0.001		
						Freq of vomiting(>2 day) 2.57 1.74–3.78 *P* < 0.001		
						Temp (>99oC) 0.91 (0.47–1.76) *P* = 0.797		
						History of measles 2.87 (1.47–5.56) *P* = 0.001)		
						Withdrawal of breastfeeding 3.61 (2.11–6.16) *P* < 0.001		

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						withdrawal of fluids 1.61 (1.09–2.37) *P* = 0.016 Not giving ORS 1.59 (1.08–2.34) *P* = 0.018 Not giving home available fluids(HAF) 1.62 (1.09–2.4) *P* = 0.015 Not giving either ORS of HAF 1.98 (1.34–2.91) *P* < 0.001		
Victora CG; Fuchs SC; Kirkwood BR; Lombardi C; Barros FC; 1992 [71] Brazil	Study Type: Case–control Evidence level: 2+	*n* = 192 cases *n* = 192 controls	Children (<2 years) with either gastroenteritis with moderate or severe dehydration (cases) or children without disease from the same neighbourhood		Prognostic factors for diarrhoea associated dehydration **Biological variables** Age Birth order birth interval Maternal age Maternal race **Anthropometric variables** Birth weight Height for age weight for age weight for length post rehydration body weight	Relationship between prognostic factor & diarrhoea-associated dehydration (OR 95% CI adjusted for age & father's presence/education **Biological variables** *Age* Grp of infants under 12 months: OR (95% CI) 0–1 months 2.6 (1.3–5.5) 2–3 months 7.1 (3.0–16.5) 4–5 months 3.5 (1.6–7.5) 6–8 months 2.4 (1.2–4.8) 9–11 months 1.0 *P* < 0.001 Grp of infants 12–23 months 12–17 months 3.7 (1.0–13.1) 18–23 months 1.0 *P* = 0.03 *birth order*	This study found a wide range of contributing factors to dehydration but reported that child's age, birth weight (& associated measures), low body weight (whether due to age or malnutrition), birth interval and feeding mode were the most strongly associated. More complex anthropometric indices e.g. length for age were less useful In addition, breast feeding reduces the risk of dehydration in terms of whether it is present, has been present and length of time since it has been practised. Signs and symptoms are less useful as determined by Sensitivity & specificity data (actual data not shown)	Well conducted case control study Good choice of control group This study was funded by the WHO

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						was not related to diarrhoea-associated dehydration *P* = 0.06		
					Dietary variables Type of milk			
					Feeding mode	*Birth interval (months)* <18: 1.0 ≥20–24:0.5 (0.2–1.2) ≥25–29:0.4 (0.2–1.1) ≥30:0.3 (0.1–0.7) *P* = 0.01		
					Breastfeeding status			
					Morbidity previous hospitalisations	*Maternal age* <20: 1.0 ≥20–24:0.5 (0.3–0.96) ≥25–29:1.4 (0.7–2.7) ≥30:0.7 (0.4–1.4) *P* = 0.02		
					Medicines used in last 2 weeks			
					Antibiotics used in last two weeks	*Maternal race* white: 1.0 black: 1.4 (0.8–2.6) mixed: 3.3 (1.6–6.7) *P* = 0.003		
						anthropometric variables *Birth weight (g)* <2500 1.0 >2500 0.4 (0.2–0.8) >3000 0.3 (0.1–0.5) ≥3500 0.3 (0.1–0.6) *P* < 0.001		
						Height for age, Weight for age, Weight for length showed a similar relationship *P* < 0.01, *P* < 0.001,*P* < 0.001 respectively		
						Dietary variables		

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						type of milk Breast 1.0 Breast & cows 1.3 (0.5–3.3) Breast & powdered 0.9 (0.2–4.8) Cow's 2.5 (1.1–6.0) powdered 10.3 (2.6–40.1) *P* = 0.002 *Feeding mode* Breast milk 1.0 Breast & non breast milk 1.2 (0.2–6.0) Breast & solids 0.2 (0.03–1.2) Breast & non breast & solids 0.3 (0.05–1.4) non breast milk 2.7 (0.7–10.4) Non breast & solids or solids only 0.9 (0.2–4.1) *P* < 0.001 **Morbidity** Previous hospitalisations 0: 1.0 ≥1: 2.0 (1.15–3.4) *P* = 0.01 Medicines used in past 2 weeks no 1.0 yes 2.3 (1.3–4.1) *P* = 0.002 Antibiotics used in past 2 weeks was not associated *P* = 0.5		

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						Authors provide selected data on **specificity & sensitivity** Age (months) <2 18%, 96% <4 46%, 79% Birth weight (<2500 g) 24% 91% Breast feeding None: 73%, 38% None/mixed: 91% 15% Birth interval (<18 months) 27%, 85% Clinical symptoms: 6+ stools: 71% vs 45% Reported fever 60% vs 78% Vomiting 58% vs 78% Fever or vomiting 75% vs 66%		
Fuchs SC; Victora CG; Martines J; 1996 [72] Brazil	Study Type: Case–control Evidence level: 2+	*n* = 192 cases acute gastroenteritis with moderate or severe dehydration *n* = 192 controls matched for age and neighbourhood without gastroenteritis	Children (up to 2 years old) matched for age and neighbourhood with or without dehydrating gastroenteritis		Associations between dehydrating diarrhoea and the risk factors of age type of milk consumed time since breast feeding stopped Breast feeding status	Risk factors Age Grp of infants under 12 months: OR (95% CI) 0–1 months 2.6 (1.3–5.5) 2–3 months 7.1 (3.0–16.5) 4–5 months 3.5 (1.6–7.5) 6–8 months 2.4 (1.2–4.8) 9–11 months 1.0 *P* < 0.001	These results suggest that age is related to the risk of dehydration with gastroenteritis and that breast feeding reduces the risk of dehydration in terms of whether it is present, has been present and length of time since it has been practiced.	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						Grp of infants 12–23 months 12–17 months 3.7 (1.0–13.1) 18–23 months 1.0 *P* = 0.03 Type of milk consumed OR (95% CI) adjusted for age, family income, father's presence or education, mother's education, mother's skin colour, type of housing, availability of water, number of children under 5 living in house, cleanliness of house, mothers age , presence of twins, birth weight, weight for age and previous hospitalisation Breast only 1.0 Breast & cow's 1.3 (0.3–4.9) Breast & formula 2.2 (0.3–17.2) Cows' only 6.0 (1.8–19.8) Formula only 6.9 (1.4–33.3) *P* = 0.006 Breast feeding status OR (95% CI) adjusted as above Continuing 1.0 Stopped 6.4 (2.3 to17.3) Never breast fed 0.7 (0.1 to3.7) *P* < 0.001 Interval since breast feeding stopped(months) OR (95% CI) adjusted as		

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						above Still breastfeeding 1.0 </=2 months 8.4 (2.4–29.6) 3–5 months 7.3 (2.0–26.20 ≥6 months 3.9 (1.1–14.4) Never breast fed 0.7 (0.1–3.6) *P* < 0.001		
Ahmed FU; Karim E; 2002 [73] Bangladesh	Study Type: Case–control Evidence level: 2+	*n* = 80 cases *n* = 160 controls	Children under the age of 2 years with acute gastroenteritis (<7 days) and either 'some' or severe dehydration (cases) or 'no signs' of dehydration (controls) attending hospital and having subsequent home visits		38 factors were studied for their influence on the development of dehydration which included sociodemographic e.g. age, working mother, number in family Clinical details: e.g. duration of diarrhoea, received ORS at home Environmental factors e.g. distance from hospital, clean water available	Bi-variant analysis showed that 17 factors were significantly associated with the development of dehydration OR (95% CI) Illiterate mother 2.53 (1.44–4.45) *P* < 0.05 Illiterate father 2.45 (1.37–4.42) *P* < 0.01 Father doing manual work 2.45 (1.37–4.42) *P* < 0.01 Child death in family 2.64 (1.25–5.58) *P* < 0.01 Duration of diarrhoea at hospital attendance (>3 days) 1.88 (1.05–3.36) *P* < 0.05 Stool frequency of more than 5 per day 6.22 (1.36–27.14) *P* < 0.01 Vomited during 'episode' 58.14 (16.59–243.06) *P* < 0.01 Received ORT at home 10.68 (3.05–44.64) *P* < 0.01	Along with sociodemiographic and environmental factors; duration of diarrhoea, stool frequency, vomiting , receiving ORS at home before attendance, receiving drugs before attendance and body weight were significantly associated with development of dehydration	Good case control study with appropriate control group. Logistic regression analysis not explained in full. The funding of this study was not declared

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						Drugs received before attending hospital 3.97 (2.00–797) *P* < 0.01 'wasted' child 3.84 (1.65–9.03) *P* < 0.01 Distance from hospital (>3km) 5.13 (2.61–10.13) *P* < 0.01 Thatched house 1.89 (1.02–3.49) *P* < 0.05 Mothers dirty finger nails 3.67 (1.95–6.95) *P* < 0.01 child's dirty finger nails 5.39 (2.59–10.40 *P* < 0.01 no refrigerator 3.32 (1.16–10.23) *P* < 0.05 ate unsafe leftover food 2.36 (1.11–5.06) *P* < 0.005 Followed by step wise logistic regression analysis (no detail for all factors) vomiting, ORS therapy at home , mother dirty fingernails and residing more than 3km away from hospital was the best for predicting the development of dehydration Sensitivity 77.5% Specificity 91.2 %		
Steiner MJ; DeWalt DA; Byerley JS;	Study Type: Systematic review -		Studies that contained data on the	Intervention: 3 studies that made a	Follow-up period:	Prolonged capillary refill: LR+ (95% CI): 4.1 (1.7–9.8)	The initial assessment of dehydration in young children	

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2004 [74]	meta-analysis 13 diagnostic test studies were included Evidence level: II		precision or accuracy of findings for diagnosis of dehydration in children 1 month to 5 years old.	independent, blind comparison of test with a valid gold standard; patients enrolled in a non-consecutive fashion, using a subset or smaller group who may have had the condition and generated definitive results on both test and gold standard. 10 studies with a non-independent comparison of a test with a valid gold standard among a 'grab' sample of patients believed to have the condition in question. Comparison: Test compared with a valid gold standard	Outcome Measures: Test sensitivity and specificity, positive LR and negative LR.	LR-:(95% CI): 0.57 (0.39–0.82) Sensitivity (95% CI): 0.60 (0.29–0.91) Specificity (95% CI): 0.85 (0.72–0.98) Abnormal skin turgor: LR+ (95% CI): 2.5 (1.5–4.2) LR- (95% CI): 0.66 (0.57–0.75) Sensitivity (95% CI): 0.58 (0.40–0.75) Specificity (95% CI): 0.76 (0.59–0.93) Abnormal respiratory pattern: LR+ (95% CI): 2.0 (1.5–2.7) LR- (95% CI): 0.76 (0.62–0.88) Sensitivity (95% CI): 0.43 (0.31–0.55) Specificity (95% CI): 0.79 (0.72–0.86) Sunken eyes LR+ (95% CI): 1.7 (1.1–2.5) LR- (95% CI): 0.49 (0.38–0.63) Sensitivity (95% CI): 0.75 (0.62–0.88) Specificity (95% CI): 0.52 (0.22–0.81) Dry mucous membranes: LR+ (95% CI): 1.7 (1.1–2.6) LR- (95% CI): 0.41 (0.21–0.79) Sensitivity (95% CI): 0.86 (0.80–0.92) Specificity (95% CI): 0.44 (0.13–0.74)	should focus on estimating capillary refill time, skin turgor, and respiratory pattern and using combinations of other signs. The relative imprecision and inaccuracy of available tests limit the ability of clinicians to estimate the exact degree of dehydration.	

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						Cool extremity (range): LR+: 1.5, 18.8 LR- : 0.89, 0.97 Sensitivity: 0.10, 011 Specificity: 0.93, 1.00 Weak pulse (range): LR+: 3.1, 7.2 LR- : 0.66, 0.96 Sensitivity: 0.04, 0.25 Specificity: 0.86, 1.00 Absent tears: LR+ (95% CI): 2.3 (0.9–5.8) LR- (95% CI): 0.54 (0.26–1.13) Sensitivity (95% CI): 0.63 (0.42–0.84) Specificity (95% CI): 0.68 (0.43–0.94) Increased heart rate: LR+ (95% CI): 1.3 (0.8–2.0) LR- (95% CI): 0.82 (0.64–1.05) Sensitivity (95% CI): 0.52 (0.44–0.60) Specificity (95% CI): 0.58 (0.33–0.82) Sunken fontanelle: LR+ (95% CI): 0.9 (0.6–1.3) LR- (95% CI): 1.12 (0.82–1.54) Sensitivity (95% CI): 0.49 (0.37–0.60) Specificity (95% CI): 0.54 (0.22–0.87)		

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						Poor overall appearance: LR+ (95% CI): 1.9 (0.97–3.8) LR- (95% CI): 0.46 (0.34–0.61) Sensitivity (95% CI): 0.80 (0.57–1.04) Specificity (95% CI): 0.45 (-0.1–1.02)		
Shavit I; Brant R; Nijssen-Jordan C; Galbraith R; Johnson DW; 2004 [75] Israel	Study type: Prospective cohort study Evidence Level: 2	65 children in the first phase and 83 children in the second phase The study was conducted in two phases: In the first phase Digital capillary refill time (DCRT) was used to establish a reference range in children who were not dehydrated In the second phase accuracy of DCRT was compared to conventional CRT in assessing dehydration	Children enrolled for the second phase were aged 1 month to 5 years with acute gastroenteritis admitted to an accident and emergency department Median age 18 months (IQR 11 to 34 months) Children with < 5% dehydration: 70 (84%) Children with ≥ 5% dehydration: 13 (16%) Exclusion: Children with cardiovascular or renal disease	Diagnostic accuracy of DCRT compared with conventional CRT and overall clinical assessment (using a seven-point Likert scale) in assessing severity of dehydration Reference standard: Degree of dehydration calculated by measuring the difference between the pre- and post-rehydration weight of the child		Diagnostic accuracy for predicting dehydration ≥ 5% AROC (with 95%CI) DCRT 0.99 (0.97 to 1.00) Clinical assessment 0.88 (0.78 to 0.96) Predictive accuracy DCRT (cut-off ≥ 0.4 sec) Sensitivity: 100% Specificity: 91% Conventional CRT (cut-off ≥ 2 sec)l Sensitivity: 54% Specificity: 88% Overall clinical assessment (cut-off ≥ 4 sec) Sensitivity: 77% Specificity: 81%		Population not representative Reference test described adequately Reference test is a standard one Blinding not specified
Hill ID; Mann MD; Bowie MD; 1981 [78] South Africa	Study Type: Other Prospective comparative study Evidence Level: 3	Total *n* = 197 147 children with hypernatraemia 50 children with non-hypernatreamic		Intervention: Clinical features of hypernatreamic dehydration Comparison: Children with and without hypernatreamic	Age, sex, weight, central nervous system dysfunction, underestimation of dehydration	Difference between groups: Age: Hypernatreamic group 63.9%; Non-hypernatreamic group 38.0% under the age of 6 months; *P* < 0.01.	The authors conclude that without checking serum sodium concentration a large number of hypernatreamic individuals will initially go undetected. The most useful signs for assessing hypernatreamia are those of CNS dysfunction, drowsiness being the most	There are not many studies regarding hypernatreamia. This study is not of very good quality but the only study identified that reports clinical features for hypernatreamia.

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		dehydration		dehydration.			common abnormal finding.	
						Symptoms of CNS (Drowsy, but rousable, Jittery, hypertonic or hyperreflexic, Coma and/or convulsions): Hypernatreamic group *n* = 56 (38%) Non-hypernatreamic group *n* = 2 (4%) *P* < 0.001	There are some diagnostic clinical features, but these are not specific, and without routine electrolyte estimations many with hypernatraemia would go undetected.	
						Underestimation of dehydration: Hypernatreamic group 72.5% Non-hypernatreamic group 36% *P* < 0.001		
Conway SP; Phillips RR; Panday S; 1990 [53] UK	Study Type: Cross-sectional Evidence level: 3	1148 children (639 boys and 509 girls)	All children below 16 years of age admitted to a hospital over a one year period with a diagnosis of gastroenteritis 55% children less than 1 year of age, 45% belong to social class V and 17% to social class IV	Frequency of pathogens isolated Clinical features of children in relation to enteropathogens detected in stool and comparison of the features and treatment received in the hospital. Biochemical abnormalities detected according to presence/absence of dehydration			Frequency of pathogens isolated from stool examination Rotavirus: 31% Samonella: 5% Campylobacter: 3.2% Enteropathogenic *E.coli*: 2% Cryptosporidia: 1% Shigella and *C.difficile*: <1% each No pathogen: 55% Comparison of clinical features 1) Rotavirus vs. Protozoa vs. Bacteria vs. Mixed infection Mean frequency of stool/day: 5.9 vs. 6.1 vs. 7.4 vs. 7.7 Frequency of vomiting in %: 92 vs. 84 vs. 54 vs. 75 2) Bacteria + protozoa + mixed infection vs. rotavirus vs. no	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
							pathogen Stool with blood or mucus in %: 25 vs. 2.8 vs. 4.1 ($P < 0.001$) Stool frequency 4 per day in %: 30 vs. 11 vs. 7 ($P < 0.001$) % of children with diarrhoea settling in < 48 hrs: 39 vs. 52 vs. 67 % of children with diarrhoea settling in 49-96 hrs: 30 vs. 32 vs. 16 % of children with diarrhoea settling in ≥ 97 hrs: 31 vs. 16 vs. 16 Comparison of biochemical features between dehydrated children (n=101) and non-dehydrated children (n=1047) Sodium > 145 mmol/l = 11% vs. <1% ($P < 0.001$) Bicarbonate < 21 mmol/l = 72% vs. 55% ($P < 0.001$) Urea > 7 mmol/l = 30% vs. 5% ($P < 0.001$) % of gut pathogens identified in dehydrated vs. non-dehydrated children: 61% vs. 43% ($P < 0.001$)	
Ellis ME; Watson B; Mandal BK; Dunbar EM; Mokashi A; 1984 [57] UK	Study Type: Cross-sectional Evidence level: 3	447 children	Children aged under 2 years admitted to hospital with infectious gastroenteritis over a 12 month period Age distribution: ≤ 6 months: 210 7-12 months: 120 13-18 months: 86	Frequency of pathogens isolated Biochemical abnormalities detected in the admitted children			Frequency of pathogens isolated from stool examination Viruses alone: 57% Bacteria alone: 6% Viruses & bacteria: 10% No pathogen: 23% Specific organisms isolated Rotavirus: 34%	

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			19-24 months: 29				Other viruses: 53% Samonella: 4.3% Campylobacter: 5.1% Enteropathogenic *E.coli*: 6.9% Cryptosporidia: 1% Shigella: 2% *C.difficile* toxin: 4.9% Incidence of dehydration and biochemical abnormalities Moderate to severe dehydration: 14% Sodium > 150 mmol/l = 0.8% Bicarbonate < 15 mmol/l = 3% Urea > 6 mmol/l = 8%	
Jenkins HR; Ansari BM; 1990 [58] UK	Study Type: Cross-sectional Evidence level: 3	215 children (116 boys and 99 girls)	All children admitted to four paediatric units in South Wales with acute gastroenteritis over a 12 month period Age range: 2 weeks to 9 yrs with 61% < 1 year of age Male: 54% White: 96%	Frequency of pathogens isolated Biochemical abnormalities detected in the admitted children			Frequency of pathogens isolated from stool examination Viruses alone: 30% Bacteria alone: 14% Viruses & bacteria: 5% No pathogen: 42% Specific organisms isolated Rotavirus: 25% Other viruses: 5% Samonella: 1.9% Campylobacter: 5.1% Enteropathogenic *E.coli*: 4.2% Cryptosporidia: 6% Shigella: 1.9% Incidence of dehydration and biochemical abnormalities > 5% dehydration: 7% (15/215) Sodium > 145 mmol/l = 0.9% (2/215)	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
							Bicarbonate < 15 mmol/l = 6% (13/215) Urea > 6 mmol/l = 7.9% (17/215)	
Reid SR; Losek JD; 2005 [80] USA	Study Type: Other Evidence Level: 3	Study population was 196 children	children aged 1 month to 5 years presented to hospital and received an ICD code -9 for acute gastroenteritis and dehydration	Intervention: Prevalence of hypoglycaemia among children among children with dehydration due to acute gastroenteritis Clinical variables associated with hypoglycaemia in these children Comparison: Comparisons are made between hypoglycaemic and non-hypoglycaemic children	Duration of vomiting Duration of diarrhoea systolic blood pressure (mm Hg) Glucose (mg/dL) sodium (mEq/L) bicarbonate (mEq/L) BUN (mg/dL)	Duration of vomiting in days (hypoglycaemic children) 2.6 (SD = 1.5) Duration of vomiting in days (non -hypoglycaemic children) 1.6 (SD = 1.8) Duration of diarrhoea in days for hypoglycaemic children 3.3 (SD = 1.7) Duration of diarrhoea in days for non hypoglycaemic children 2.4 (SD = 2.6)	The authors conclusions are not relevant to the clinical question being addressed	While the study is limited by its retrospective design (duration of diarrhoea and vomiting were not recorded for a number of children), the figures presented are similar to those reported from other studies
Steiner MJ; DeWalt DA; Byerley JS; 2004 [74]	Study Type: Systematic review - meta-analysis 13 diagnostic test studies were included Evidence level: II		Studies that contained data on the precision or accuracy of findings for diagnosis of dehydration in children 1 month to 5 years old.	Intervention: 3 studies that made a independent, blind comparison of test with a valid gold standard; patients enrolled in a non-consecutive fashion, using a subset or smaller group who may have had the condition and generated definitive results on both test and gold standard. 10 studies with a non-independent comparison of a test with a valid gold standard among a 'grab' sample of patients believed to		Follow-up period: Outcome Measures: Test sensitivity and specificity, positive LR and negative LR.	Prolonged capillary refill: LR+ (95% CI): 4.1 (1.7–9.8) LR-:(95% CI): 0.57 (0.39–0.82) Sensitivity (95% CI): 0.60 (0.29–0.91) Specificity (95% CI): 0.85 (0.72–0.98) Abnormal skin turgor: LR+ (95% CI): 2.5 (1.5–4.2) LR- (95% CI): 0.66 (0.57–0.75) Sensitivity (95% CI): 0.58 (0.40–0.75) Specificity (95% CI): 0.76 (0.59–0.93) Abnormal respiratory pattern: LR+ (95% CI): 2.0 (1.5–2.7) LR- (95% CI): 0.76 (0.62–0.88)	The initial assessment of dehydration in young children should focus on estimating capillary refill time, skin turgor, and respiratory pattern and using combinations of other signs. The relative imprecision and inaccuracy of available tests limit the ability of clinicians to estimate the exact degree of dehydration.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				have the condition in question. Comparison: Test compared with a valid gold standard			Sensitivity (95% CI): 0.43 (0.31–0.55) Specificity (95% CI): 0.79 (0.72–0.86) Sunken eyes LR+ (95% CI): 1.7 (1.1–2.5) LR- (95% CI): 0.49 (0.38–0.63) Sensitivity (95% CI): 0.75 (0.62–0.88) Specificity (95% CI): 0.52 (0.22–0.81) Dry mucous membranes: LR+ (95% CI): 1.7 (1.1–2.6) LR- (95% CI): 0.41 (0.21–0.79) Sensitivity (95% CI): 0.86 (0.80–0.92) Specificity (95% CI): 0.44 (0.13–0.74) Cool extremity (range): LR+: 1.5, 18.8 LR- : 0.89, 0.97 Sensitivity: 0.10, 011 Specificity: 0.93, 1.00 Weak pulse (range): LR+: 3.1, 7.2 LR- : 0.66, 0.96 Sensitivity: 0.04, 0.25 Specificity: 0.86, 1.00 Absent tears: LR+ (95% CI): 2.3 (0.9–5.8) LR- (95% CI): 0.54 (0.26–1.13) Sensitivity (95% CI): 0.63 (0.42–0.84) Specificity (95% CI): 0.68 (0.43–0.94)	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
							Increased heart rate: LR+ (95% CI): 1.3 (0.8–2.0) LR- (95% CI): 0.82 (0.64–1.05) Sensitivity (95% CI): 0.52 (0.44–0.60) Specificity (95% CI): 0.58 (0.33–0.82) Sunken fontanelle: LR+ (95% CI): 0.9 (0.6–1.3) LR- (95% CI): 1.12 (0.82–1.54) Sensitivity (95% CI): 0.49 (0.37–0.60) Specificity (95% CI): 0.54 (0.22–0.87) Poor overall appearance: LR+ (95% CI): 1.9 (0.97–3.8) LR- (95% CI): 0.46 (0.34–0.61) Sensitivity (95% CI): 0.80 (0.57–1.04) Specificity (95% CI): 0.45 (-0.1–1.02)	

5 Fluid management

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Faruque AS; 1992 [82] Study population was located in India	Study Type: Case–control Evidence level: 2+	Total *n* = 1013 Cases *n* = 285 Cases with cholera *n* = 29 (10.2%) Controls *n* = 728 Controls with cholera *n* = 19 (2.6%)	Children aged 1 and 35 months presenting with watery diarrhoea for six days or less. Only children who had been receiving breast feeding up to the time of onset of diarrhoea were included.	Intervention: Withdrawal of breastfeeding; giving ORT at home before admission to hospital Comparison: Withdrawal of breastfeeding versus continuation of breastfeeding Giving more than 250 ml or less than 250 ml of ORT solution at home versus not giving any ORT solution at home.	Follow-up period: Outcome Measures: Withdrawal of breastfeeding; Total volume of ORT before admission (ml)	Withdrawal of breastfeeding: OR 3.89 (95% CI 0.96–15.84) adjusted for confounding variables: OR 5.23 (95% CI 1.37–19.99) ORT at home: None: OR 1.34 (95% CI 0.93–1.92) compared to more than 250 ml Adjusted: OR 1.57 (95% CI 1.08–2.29) Less than 251 ml: OR 1.09 (95% 0.74–1.60) compared to more than 250 ml Adjusted: OR 1.18 (95% CI 0.84–1.66) Confounding variables were: Illiterate mother, history of vomiting, high stool frequency in any 24 hour period (11+), young age (1–9 months) and cholera (positive).	Withdrawal of breast feeding during diarrhoea was associated with a five times higher risk of dehydration compared with continued breast feeding during diarrhoea at home. Lack of ORT with either complete formula or a salt sugar solution at home was associated with a 57% higher risk of dehydration compared with receipt of a reasonable amount of ORT after controlling for several confounders.	The study does not report the number of children who were breast feed and given ORT at the same time. The use of ORT must be interpreted as start of rehydration therapy for the purpose of the guideline. 10.2% of cases and 2.6% of controls had cholera.
Hartling L; Bellemare S; Wiebe N	Study Type: Systematic review - meta-analysis	18 studies including 1811 children	Children up to 17 yrs with dehydration secondary to acute	Intervention: This is a systematic review of RCTs and quasi-RCT's		Failure to rehydrate using ORT: (RD 4%, 95% CI 1 to 7; NNT 25, 95% CI 14 to	The methodological quality of the systematic review was very high, however the	The evidence available showed that there was a slight statistical benefit of IVT compared to oral

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
2007 [83] USA (7), Peru (1), Mexico (1), Colombia (1) Canada (1), Australia (1) Panama (1), Iran (1), Afghanistan (1), Finland (1), Puerto Rico (1), Egypt (1)	Evidence level: 1++		gastroenteritis. Hospital inpatients and outpatients	Comparison: Oral rehydration therapy (oral or nasogastric tube) compared with intravenous therapy.		100; I squared 69.9%; 18 trials, 1811 participants) Failure to rehydrate using ORT: (RD 2%, 95% CI 0.08 to 5, NNT 50, 95% CI 20 to 1250, I squared 43.0%; 17 trial 1611 participants Death: (3 trials) Weight gain at discharge: (WMD -26.33g, 95% CI -206.92 to 154.26 NS, I squared 90.8% ; 6 trials, 369 participants) Percentage weight gain: (WMD -0.26%, 95% CI -1.56 to 1.05 NS, I squared 90.9%; 5 trials, 767 participants) Length of hospital stay for inpatients: (WMD -1.20 days, 95% CI -2.38 to -0.02, I squared 95.1%; 6 trials, 526 participants) NS when outlying study removed Hyponatremia: (RD 1%, 95% CI -13 to 15, NS, I squared 67.2%; 2 trials, 248 participants) Hypernatremia: (RD 0%, 95%CI -1 to 1, NS, I squared 0%; 10 trials, 1062 participants) Duration of diarrhoea: (WMD -5.90 h, 95% CI -12.70 to 0.889, NS, I	composite studies had limitations especially in the area of method of randomisation and method of allocation concealment	in relation to rehydration. The GDG did not feel that this difference was clinically significant. Moreover, the studies in the review were conducted in a secondary care setting, where disease severity was presumably higher than in patients cared for in a community setting. It therefore seemed reasonable to extrapolate the findings to children cared for outside of hospital. ORT has several advantages over IVT: it can be easily administered; and is readily available in a variety of settings.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						squared 76.3%; 8 trials, 960 participants) Total fluid intake 6 hrs after starting treatment: (WMD 32.09 mL/kg, 95% CI -26.69 to 90.88 NS, I squared 99.9%; 8 trials, 985 participants) Total fluid intake at 24 hrs: (WMD 73.45 mL/kg, 95% CI -31.78 to 178.69 NS, I squared 99.8%; 7 trials, 835 participants) 33 children (95% CI 20 to 100) need to be treated with IVT rather than ORT to prevent one case of paralytic ileus Occurence of phlebitis in IVT group (RD -2%, 95% CI -4 to -1, I squared 0%; 5 trials, 877 participants 50 children (95% CI 25 to 100) need to be treated with ORT rather than IVT to prevent 1 case of phlebitis. IVT risk for phlebitis 2.5% Sodium intake at 6 hours: (WMD 5.80 mmol/kg, 95% CI -1.48 to 13.07 NS, I squared 99%; 3 trials, 607 participants) Sodium levels at 6 hours: (WMD 1.25 mmol?kg, 95% CI -0.56 to 3.07, NS, I squared 88.5%; 7 trials, 992 participants		

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Hidayat S; Enggar S; Pardede N; Ismail R 1988 [84] Indonesia	Study Type: Randomised controlled trial Evidence level: 1-	75 children with acute diarrhoea and severe dehydration	Inclusion criteria: Palpable and countable pulse, Absence of abdominal distension and other complications Severe dehydration was not defined	ORT was compared to IVT ORT group received WHO recommended ORS solution by nasogastric infusion while the IVT group received Ringer's lactate solution. In both groups fluid administration rates were according to WHO recommendations (40ml/kg in the first hour, 30 ml/kg in the second hour, 20ml/kg in the third hour and 20ml/kg in the fourth hour)	Rehydration failure ORT: 3/36 (8.3%) and IVT: 2/39 (5.1%). RR was 1.63 (95%CI: 0.29, 9.17) Adverse effects Recurrence of dehydration ORT: 2/36 (5.5%) and IVI 4/39 (10.2%)	No significant differences were found on any outcome measure. No complication in either group		
Sharifi J 1985 [85] Iran	Study Type: Randomised controlled trial Evidence level: 1-	470 children with watery diarrhoea, vomiting and ≥ 2 signs of dehydration according to WHO criteria	Inclusion and exclusion criteria not clear Failure to rehydrate was defined as 'no change in the clinical status or worsening of signs of dehydration with first 2 hours of treatment'.	Oral treatment was compared to intravenous treatment Oral treatment group consisted of a initial phase of an electrolyte solution with osmolarity 270 mOsm/l (sodium 80mmol/l, potassium 20mmol/l, bicarbonate 35mmol/l, chloride 65mmol/l, glucose 70mmol/l) administered by nasogastric tube at a rate of 40ml/kg per hour to a maximum of 400ml/kg until clinical signs of dehydration had disappeared. Followed by a maintenance phase of another electrolyte solution with osmolarity 270 mOsm/l (sodium 40mmol/l,	Rehydration failure Oral 1/236 and IV 0/234. RR was 2.97 (95%CI: 0.12, 72.65) Duration of diarrhoea Oral 4.8 days versus IV 5.5 days. Mean difference = -0.70 days (95%CI: -1.16, -0.24) Electrolyte abnormalities 24 hours after admission Oral 14/236 and IV 29/234 Hypernatraemia Oral 12/236 and IV 1/234 Hyponatraemia Oral 13/236 and IV	No significant differences were found on any outcome measure.		

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				potassium 30nmol/l, bicarbonate 25 mmol/l, chloride 45 mmol/l, glucose 130 mmol/l) administered by bottle or nasogastric tube at a rate of 250ml/kg per day Children in the IV group were treated for shock with ringer's lactate solution at a rate of 20-30 ml/kg as rapidly as possible or within 1 hour in those with less severe illness. A second infusion of 20-30ml/kg was given if clinical signs of shock persisted. Thereafter 2/3 of the fluid deficit was replaced in first 24 hours of treatment and the remaining 1/3 on second day.	7/234 Hyperkalaemia Oral 5/236 and IV 3/234 Vomiting (1-3 episodes in first 6 hours) Oral 45/236 (19%) and IV 70/234 (30%) Deaths Oral 2/236 and IV 5/234 (all who died had completed rehydration and most had normal electrolyte levels)			
Hahn S; Kim Y; Garner P; 2007 [89] Egypt (2), Bangladesh (3), Mexico (1), Columbia (1), India (3), Panama (1), USA (1). Multicentre trial (1) conducted in Brazil, India, Mexico, Peru. A multicentre trial (1) conducted in Bangladesh, Brazil, India, Peru, Vietnam	Study Type: Systematic review - meta-analysis Evidence level: 1++	Reduced osmolarity ORS - 1004 children WHO standard ORS - 992 children the above figures refer to the outcome: need for unscheduled IV infusion	children with acute diarrhoea (history of less than 5 days). Three trials included cholera patients	Intervention: This is a systematic review of RCTs Comparison: Reduced osmolarity ORS compared with WHO standard ORS	Follow-up period: Different in individual studies Outcome Measures: Primary outcome : need for unscheduled IV fluid infusion during the course of treatment Secondary outcomes: Stool output children vomiting during rehydration asymptomatic hyponatremia (serum sodium less than 130 mmol/L) during follow up need for unscheduled IV	The review provides some evidence that dehydrated children given a solution of with a lower osmolarity were less likely to nedd an IV fluid infusion, than those given WHO standard ORS	This meta- analysis was very useful in answering this question	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
					fluid infusion - OR (fixed) 0.59 (0.45–0.79) Stool output - SMD (fixed) -0.23 (-0.33 to -0.14) episode of vomiting during rehydration - OR (Peto) 0.71 (0.55–0.92) Presence of hyponatremia after rehydration - OR (Peto) 1.44 (0.93–2.24) Sensitivity Analysis: need for unscheduled IV fluid infusion - OR (fixed) 0.61 (0.46–0.82) stool output - SMD (fixed) -0.21 (-0.31 to -0.11) Stratified by sodium concentration: need for unscheduled IV fluid infusion - OR (fixed) 0.59 (0.44–0.78) stool output - SMD (fixed) -0.20 (-0.30 to -0.10) episodes of vomiting - OR (fixed) 0.70 (0.54–0.91) presence of hyponatremia - OR (fixed) 1.45 (0.93–2.26)			
Gavin N;	Study Type: Systematic review	There was a total of 803 participants	Most studies enrolled children aged	Intervention: The efficacy of ORT in	Follow-up period: Follow up period differed for	Over the counter ORS available in the US (45–	The results of this review are consistent with other evidence	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
1996 [90] The studies were conducted in the US and in Canada. One of the US studies included children from a Panamanian hospital	- meta-analysis Evidence level: 1+	across the study. The review was not reported in a manner that allowed separation of those in the ORT arms from those in the IVT arms	3 months up to 3 years. One RCT enrolled children aged 1 month to 14 years. Most of the patients were mildly to moderately dehydrated whereas in RCTs with IVT armsseverely dehydrated children were included	comparison to IVT ORS with high sodium content is being compared to ORS with low sodium content 13 RCTs were included in the review Comparison: Oral rehydration therapy vs IV rehydration therapy High sodium glucose based ORS vs low sodium glucose based ORS Effectiveness of ORT administered outpatient vs inpatient	individual studies. In a few studies rehydration phase lasted up to 48 hours before regular feeding schedules were re-introduced Outcome Measures: Outcome measures were: Treatment failure- defined as the persistence or recurrence of signs of dehydration beyond 24 hours of ORT and other clinical indications requiring the need to revert to IV therapy weight gain; volume, frequency and duration of diarrhoea; length of stay and hospitalisation Trials with IVT arms - Failure rate 5.7% (CI 1.8% to 9.6%) Trials without IVT arms - Failure rate 3.0% (CI 0.6% to 5.4%) Overall failure rate 3.6% (CI 1.4% to 5.8%) high sodium WHO formula - Failure rate 1.9% (CI 0% to 5.4%). Difference between low and medium groups was not statistically significant	70 mEq/L with a carbohydrate to sodium ration of less than 3) are appropriate and efficacious in treating well nourished children. Only 2 of the 13 studies showed that well nourished children rehydrated with medium to low sodium solutions (50–75 mmol/L and 26–45 mmo/L respectively) may be at higher risk of iatrogenic hyponatremia	that has been retreived to answer this question	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
					low sodium formula - Failure rate 3.6% (CI 0% to 7.3%) medium sodium formula - Failure rate 5.0% (CI 1.9% to 8.1%) Hyponatremia one trial with an IVT arm reported 3 cases of hyponatremia that corrected to normal after 24 hours of treatment one trial with no IVT arm reported 1 case in the high sodium group and 6 cases each in the medium and low sodium groups Hypernatremia - one study with no IVT arm (same as above) reported one case each in the low, medium and high sodium groups.			
Fontaine O; 2007 [91] Studies were conducted in Bangladesh, Indonesia, India, Pakistan, Mexico, Chile, Peru and Egypt.	Study Type: Systematic review - meta-analysis Evidence level: 1++	Children and adults with signs of dehydration due to acute diarrhoea	Intervention: Benefit of rice-based ORS and it's relation to age of patient and aetiology of diarrhoea in comparison to WHO ORS Comparison: Standard WHO ORS was compared to rice based ORS (50–80 g/l of rice powder with electrolyte concentrations remaining	Follow-up period: Until cessation of diarrhoea Outcome Measures: Stool output during the first 24 hours total stool output from admission to study until cessation of diarrhoea duration of diarrhoea from admission to study until cessation of diarrhoea	24 hour stool otuput in cholera cases (4 trials children under 12) - WMD (g/kg) = -67.397 (95% CI -94.260 to -40.534) Total stool output (1 trial in children under 12) - WMD (g/kg) = -124.000 (95% CI -248.603–0.603) Duration of diarrhoea (1 trial in children under 12) - WMD (days) =	Based on stool outputs within the first 24 hours, rice-based ORS may be more clinically effective than WHO ORS for patients with cholera. However, it has no advantage over standard ORS in children with non-cholera diarrhoea and as it is more expensive cannot be justified in this group.	These findings are consistent with those of similar research. Given that non cholera type diarrhoea is more likely to be experienced in the UK, careful consideration must be given to the benefit that may be enjoyed from use of rice-based ORS in this country.	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
			unchanged)		-13.000 (95% CI -24.895 to -1.105) 24 hour stool output in non-cholera diarrhoea in children under 5 (15 trials) - WMD (g/kg) = -4.292 (95% CI -9.362–0.779) total stool output in non cholera diarrhoea in children under 5 (9 trials) - WMD (g/kg) = -28.162 (95% CI -52.381 to -3.944) Duration of diarrhoea in non-cholera diarrhoea in children under 5 (12 trials) - WMD (days) = -1.258 (95% CI -4.406–1.891)			
Neville KA; Verge CF; Rosenberg AR; O'Meara MW; Walker JL; 2006 [102] Australia	Study Type: RCT Evidence level: 1+	102 children were enrolled. 36% (37/102) were hyponatraemic before starting IVT	Children with gastroenteritis	0.9% saline was compared to 0.45% saline. Both groups received 2.5% dextrose (N/2). The rate of infusion was decided by the treating physician. The options used were a 'rapid replacement protocol' (RRP) consisting of 10 ml/kg per hour for 4 hours or a slow replacement protocol in which children received their fluid deficit based on estimated percentage dehydration over a 24 hour period (in addition to their maintenance fluids).	The primary outcome examined was the incidence of hyponatraemia defined as plasma sodium < 135 mmol/l. The authors presented the results separately for those with hyponatraemia and those with normal plasma sodium levels measured prior to starting IVT.	51 children were randomly assigned to each treatment group. **0.45% saline** Hyponatraemic children (*n* = 16) showed no change in mean plasma sodium after 4 hours, but in those with an initially normal plasma sodium (*n* = 35) there was a significant decrease in the mean sodium concentration after 4 hours (135 ± 1.8 mmol/l versus 137 ± 1.7 mmol/l; *P* < 0.001). **0.9% saline** Hyponatraemic children (*n* = 21) had a significant increase in mean sodium	Rehydration with 0.9% saline IVT led to a significant increase in the mean plasma sodium levels in children with hyponatraemic dehydration while the use of 0.45% saline did not correct this abnormality. Moreover, the use of 0.45% saline was associated with a significant decrease in the plasma sodium concentration in those with normal plasma sodium concentrations prior to IVT while the use of 0.9% saline was not.	

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						concentration (134 ± 2.1 mmol/l versus 132 ± 2.4 mmol/l; *P* < 0.001), but in those with an initially normal plasma sodium (*n* = 30) there was no statistically significant change.		
Phin SJ; McCaskill ME; Browne GJ; Lam LT; 2003 [103] Australia	Study Type: Comparative study with historical controls Evidence level: 2-	315	Children with gastroenteritis	Rapid rehydration was compared to IV rehydration over 24 hours All the participants were initially given a trial of oral fluids using Gastrolyte-R® or apple juice diluted to 25% (2.5 g carbohydrate, 1.25 mg sodium, 20 mg potassium) if the former was refused. Moderately dehydrated children who were unable to tolerate 100 ml of oral fluid over 1 hour (50 ml for children younger than 2 years) were given rapid rehydration. The options for administration were intravenously using N/2 saline + 2.5% dextrose over 2 hours at 20 ml/kg per hour or by nasogastric tube with Gastrolyte-R at the same rate. Following rapid rehydration, children were given another trial of 100 ml of oral fluid (50 ml for children younger than 2 years) over 1 hour. Children who tolerated and satisfied the discharge criteria were	Outcomes reported were admission to hospital discharge in 8 hours or less after presentation to the emergency department re-presentation requiring admission within 48 hours of discharge from the emergency department.	For moderately dehydrated patients only, a statistically significant reduction was observed in the hospital admission rates in the intervention group compared with the control group (55.8% versus 96.3%; *P* < 0.001). Moreover, significantly more patients in the intervention group were discharged at 8 hours or less after presentation to the emergency department (44.2% versus 3.7%; *P* < 0.001). No statistically significant difference was seen for rates of re-presentation requiring admission within 48 hours of discharge from the emergency department. For mildly dehydrated patients in the two groups, no statistically significant difference was seen for the above outcomes. In the intervention group, electrolytes were analysed for 78 children and 17 were found to be hyponatraemic on initial assessment. Two of these patients presented with serum sodium levels < 130 mmol/l (128 and		

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				discharged while those not tolerating orally were admitted to the hospital to continue rehydration. The historical control group was made of children admitted 2 years earlier in the same hospital with a similar diagnosis, and their hospital records were checked for data collection. These children were given a non-standard regimen of initial oral fluid trial, failing which they were rehydrated intravenously over a period of 24 hours.		125 mmol/l). However, they did not suffer from any complications or clinical sequelae and their serum sodium levels returned to normal levels by 12 hours		
Reid SR; Bonadio WA; 1996 [104] USA	Study Type: Prospective cohort study Evidence level: 2-	58	Children with mild or moderate dehydration The criteria for inclusion were age at least 6 months, clinical diagnosis of acute gastroenteritis with exclusion of other causes, vomiting for less than 48 hours in duration with at least five episodes in the 24 hours preceding presentation, presence of normal serum sodium levels (130–149 mEq/l) and metabolic acidosis (serum bicarbonate < 18 mEq/l) at the time of presentation.	Each patient received an infusion of 20–30 ml/kg isotonic crystalloid solution over 1–2 hours, followed by a trial of oral rehydration. Children who subsequently vomited were admitted for continued IV rehydration therapy, while those tolerating oral fluids were discharged with home-care instructions	.Re-admission rates, parent reported vomiting, urination and diarrhoea after discharge	After rapid outpatient IV rehydration, 16 patients (28%) did not tolerate oral fluids while the rest 42 (72%) tolerated orally and were discharged home. Of the discharged patients, 14% (6/42) were re-admitted owing to recurrent vomiting and dehydration. A significantly higher proportion of children who did not tolerate orally after rapid IV rehydration had metabolic acidosis (69% versus 2%; $P < 0.001$) and were moderately dehydrated (56% versus 24%; $P < 0.01$) compared with the patients discharged home. There were no differences between the two groups regarding the age and severity of diarrhoea or		

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
						vomiting		
Moineau G; Newman J; 1990 [105] Canada	Study Type: Non-comparative clinical study Evidence level: 3	17	Children with mild or moderate dehydration secondary to gastroenteritis Children were included if they had diarrhoea and/or vomiting for less than 5 days with mild to moderate dehydration, had normal nutritional status and were unable to retain small amounts of clear fluid or refused to take them. Children who had taken medication, those having an underlying disease and those with electrolyte abnormalities were excluded	A trial of rehydration was initially attempted with small amounts of clear fluids (the authors did not specify how they defined 'clear fluid'), and if the fluid was refused or vomited, the child was considered for the study. IVT was administered by giving 3.3% dextrose and 0.3% saline at a rate of 10 ml/kg per hour for 3 hours (total 30 ml/kg). During IVT, patients did not receive any oral fluid. Discharge was allowed if there were no clinical signs of dehydration, no persistent vomiting, normal central nervous system examination and if the parents felt the child had improved.	Parent report on vomiting, diarrhoea, new symptoms, visits to medical facilities and number of days before normal diets and activities were resumed	All patients improved after IVT and only 6/17 had vomited after therapy. One patient continued vomiting till 48 hours after IVT and required another course of IVT, following which there was no vomiting. None of the patients required hospital admission after discharge from the emergency department		

6 Nutritional management

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Bhattacharya SK; Bhattacharya MK; Manna B; Dutta D; Deb A; Dutta P; Goswami AG; Dutta A; Sarkar S; Mukhopadhaya A; 1995 [69] Study population was located in Burma	Study Type: Case–control Evidence level: 2+	Total *n* = 379 Cases (moderate to severe dehydration) *n* = 243 Cases having cholera *n* = 65 (26.7%) Controls (no or mild dehydration) *n* = 136 Contols having cholera *n* = 29 (21.3%)	Children aged up to 2 years of age with acute watery diarrhoea for less than 24 hours duration.	Intervention: Withdrawal of breast feeding, Not giving ORS (WHO) Comparison: Withdrawal of breast feeding during diarrhoea versus continued breast feeding. Not giving ORS versus giving ORS during diarrhoea episode.	Follow-up period: Outcome Measures: Withdrawal of breast feeding, Not giving ORS during diarrhoea Confounding variables: Age, Frequency of stools and vomiting, severe under nutrition	MULTIVARIATE ANALYSIS: Withdrawal of breast feeding: OR 6.8 (95% CI 3.8–12.2) and not giving ORS: OR 2.1 (95% CI 1.2–3.6) adjusted for age (<12 months), frequency of stool and vomiting and severe under nutrition. UNIVARIATE ANALYSIS: Stopping breast feeding compared with increased/continued breast feeding: OR 5.9 (95% CI 3.6–9.6) Not received ORS (WHO) versus received: OR 1.6 (95% CI 1.0–2.4) Not received home available fluid received versus received home available fluid: OR 1.1 (95% CI 0.9–2.0) Vibrios compared with Rota: OR 1.3 (95% CI 3.7–10.6)	Emphasis on the importance of continued breast feeding and use of oral rehydration therapy from the beginning of diarrhoea to prevent development of life-threatening dehydration and death.	The outcome is severe or moderate dehydration. The study includes cholera cases. The study investigates breast feeding and use of ORS as independent risk factors.
Khin MU; Nyunt NW; Myo K; Mu MK; Tin U; Thane T; 1985[117]	Study Type: RCT Evidence level: 1+	ORS alone *n* = 26 of which *n* = 5 (19.2%) had Vibrio cholerae in stools ORS plus breast	Inclusion: Children aged less than 2 years with acute diarrhoea of less than 48 hours with moderate or severe dehydration who had been	Intervention: Breast feeding during rehydration with ORS Comparison: ORS alone for the first 24 hours versus	Follow-up period: 48 hours Outcome Measures: Stool output No of times stools passed in hospital	Number of stools passed in hospital: ORS alone: mean 17.4 (SE 2.3) ORS plus breast feeding: mean 12.1 (SE 1.1) $P < 0.05$	There were no statistical significant differences between children receiving ORS only and those who received ORS plus breast feeding in stool and vomitus output, number of stools passed in hospital and duration of diarrhoea in	Children who required IVT where given IVT until rehydrated (usually within 4 hours of admission) and then randomly allocated. Given IVT:

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Study population was located in Bangladesh		feeding *n* = 26 of which *n* = 4 (15.4%) had Vibrio cholerae in stools	normally breastfeed. Exclusion: Children with a concomitant illness (such as bronchopneumonia, urinary tract infection, clinically evident malnutrition, or shock), bottle fed children, and children who had received antibiotics before admission.	ORS plus breast feeding thereafter ORS plus breast feeding in both comparison groups	Vomitus volume Duration of diarrhoea in hospital (hours) Total ORS required for rehydration	Non significant: Duration of diarrhoea in hospital (h) ORS alone: 45.7 (3.9) ORS plus breast feeding: 43.3 (5.0) Stool output ORS alone: (ml) 887.4 (116.0) ORS plus breast feeding: 640.9 (65.5) Vomitus volume (ml) ORS alone: 15.2 (8.5) ORS plus breast feeding: 22.9 (10.9) Total ORS (ml/patient) ORS alone: mean 2119.2 ml (SE 192.1) ORS plus breast feeding: mean 1570.4 ml (SE 112.5) *P* = 0.02	hospital. The children who received ORS plus breast feeding had on average five fewer motions than those who where not breast fed and required on average 550 ml less ORS than those not breast fed during early acute phase of diarrhoea. Breast feeding exerts a beneficial effect on the course and outcome of acute diarrhoea by reducing the number and volume of diarrhoeal stools.	8/26 (30.8%) of children receiving ORS alone and 7/26 (26.9%) of children receiving ORS and breast feeding required IVT..
Faruque AS; 1992 [82] Study population was located in India	Study Type: Case–control Evidence level: 2+	Total *n* = 1013 Cases *n* = 285 Cases with cholera *n* = 29 (10.2%) Controls *n* = 728 Controls with cholera *n* = 19 (2.6%)	Children aged 1 and 35 months presenting with watery diarrhoea for six days or less. Only children who had been receiving breast feeding up to the time of onset of diarrhoea were included.	Intervention: Withdrawal of breastfeeding; giving ORT at home before admission to hospital Comparison: Withdrawal of breastfeeding versus continuation of breastfeeding Giving more than 250 ml or less than 250 ml of ORT solution at home versus not giving any ORT solution at home.	Follow-up period: Outcome Measures: Withdrawal of breastfeeding; Total volume of ORT before admission (ml)	Withdrawal of breastfeeding: OR 3.89 (95% CI 0.96–15.84) adjusted for confounding variables: OR 5.23 (95% CI 1.37–19.99) ORT at home: None: OR 1.34 (95% CI 0.93–1.92) compared to more than 250 ml Adjusted: OR 1.57 (95% CI 1.08–2.29) Less than 251 ml: OR 1.09 (95% 0.74–1.60) compared to more than 250 ml Adjusted: OR 1.18 (95% CI	Withdrawal of breast feeding during diarrhoea was associated with a five times higher risk of dehydration compared with continued breast feeding during diarrhoea at home. Lack of ORT with either complete formula or a salt sugar solution at home was associated with a 57% higher risk of dehydration compared with receipt of a reasonable amount of ORT after controlling for several confounders.	The study does not report the number of children who were breast feed and given ORT at the same time. The use of ORT must be interpreted as start of rehydration therapy for the purpose of the guideline. 10.2% of cases and 2.6% of controls had cholera.

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						0.84–1.66) Confounding variables were: Illiterate mother, history of vomiting, high stool frequency in any 24 hour period (11+), young age (1–9 months) and cholera (positive).		
Sandhu BK; Isolauri E; Walker-Smith JA; Banchini G; van Caillie-Bertrand M; Dias JA; Guandalini S; Hoekstra JH; Juntunen M; Kolacek S; Marx D; Micetic-Turk D; Razenberg MC; Szajewska H; Tamniau J; Weizman Z; Zanacca C; Zetterstrom R; 1997 May [118]	Study Type: Comparative RCT Evidence level: 1- Pan-European 12 hospitals	*n*= 134 early feeding Grp A *n* = 96 late feeding Grp B *n* = 8 excluded from Grp B as they were given food too early. N=4 in each grp were considered treatment failures as they required IV fluids by day 4	Infants (aged 12–17 months, mean ~14 months) with acute gastroenteritis (<5 days) with mild (majority) to severe dehydration and admitted to hospital	Rehydration as appropriate for 4 hours then randomised to Grp A: usual diet (no details) Grp B: ORS continued for 20 hours followed by usual diet Extra ORS was given for each watery stool. If child was breast fed, it was continued Comparison: early vs late feeding of normal diet	Follow-up period: 14 days Outcome Measures: Total duration of diarrhoea (hours) mean weight gain (reducing sugars in stools)	Fluid intake was similar in both grps. Total duration of diarrhoea was measured by number of watery stools, there was no significant differences between the two grps (or for vomiting) (data expressed as graph, no detail) Mean weight gain Grp A vs Grp B During rehydration phase: 85 g vs 77 g *P* = 0.76 After rehydration (4–24 hours): 95 g vs 2 g *P* = 0.01 During hospitalisation No data (graph only) but higher in Grp A vs Grp B *P* = 0.001 overall weight gain was similar by day 5 and day 14 No infants had lactose intolerance on day 5 and diarrhoea and vomiting on day 14	The results show that early refeeding of infants with acute diarrhoea is of benefit in terms of higher weight gain whilst in hospital and did not worsen any symptoms of diarrhoea or vomiting compared with later feeding.	*n* = 230 recruited from 12 different European countries i.e. very mixed population No details on usual diet very sparse data, lots of graphs and no detail appropriateness of randomisation unclear

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Brown KH; Gastanaduy AS; Saavedra JM; Lembcke J; Rivas D; Robertson AD; Yolken R; Sack RB; 1988 [119] Peru	Study Type: Comparative RCT Evidence level: 1-	*n* = 31 CSO-110 formula *n* = 29 CSO-55 formula *n* = 34 GES only for 2 days, CSO-55 for 2 days, CSO-110 for 2 days *n* = 34 IV GES followed by the above diet *n* = 138 were initially enrolled of which *n* = 10 did not remain in study for at least 5 days and so were eliminated from analysis. Of the *n* = 128 remaining, *n* = 3 were withdrawn early by parents, *n* = 3 developed measles, *n* = 3 developed 2nd episode of diarrhoea/infection and *n* = 1 was eliminated as procedure was not carried out correctly 93% of infants were successfully managed (*n* = 27, *n* = 23, *n* = 31, *n* = 33), losses were equal across	Male children (aged 3–36 months, mean~10 months) with diarrhoea (<60 hours) and mild to severe dehydration (details unclear) and admitted to hospital	Rehydration was carried out according to WHO guidelines. Children in the 3 grps excluding the CSO-110 grp were rehydrated with oral GES. Children in the CSO-110 grp received IV GES almost always successful within the first 2–4 hours of admission. Children then received either a) full strength formula (CSO-110) composed of casein, sucrose: dextrin with maltose, and soybean oil: cotton seed oil (1:1) with added vitamins or b) half strength formula as for a) (CSO-55) for the first 48 hours followed by full strength or c) GES-O for the first 48 hours followed by CSO-55 for the next 48 hours and CSO -110 for the following 48 hours. or d) No oral fluids for first 48 hours, but GES-IV, then CSO-55 for the next 48 hours and CSO -110 for the following 48 hours.	Follow-up period: 14 days Outcome Measures: Duration of diarrhoea Mean increment on body weight (g)	Total energy absorbed was equal in grps by days 5–6 when therapies became equal. **Duration of diarrhoea** (hours) in successful cases (93%) Gp1vs.Gp2 vs.Gp3 vs Gp 4 143 hours+/- 67 vs 127 hours +/-85 vs 123 hours +/-58 vs 134 hours +/-59 (NS) Unsuccessful cases were also not significantly different between grps. **Mean increment on body weight (g)** (minimal data, graph presentation) Admission to day 8: Grp1 vs Gp2 vs GP3 vs GP4 were stat. signif. different $P < 0.005$ by ANOVA - Grp 1 & 2 increasing in weight, Grps 3 & 4 decreasing Admission to Day 15: Grp1 & 2 vs Grp 3 & 4 was stat. signif. different $P < 0.04$ with in the children in the former two grps gaining approximately 140 g more than the latter grps	Increase in body weight was positively related to the amounts of dietary energy consumed thus supporting the case for continued oral feeding in the early refeeding period following rehydration post acute diarrhoea in infants.	Randomisation was appropriate and successful *n* = 20 infants had Giardia lamblia (carried by 50% of Lima children asymptomatically) *n* = 13 infants had C Jejuni (carried by 10% of Lima children asymptomatically) No information on the financial support of this study

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		grps: treatment failures included recurring dehydration, hyononatremia and prolonged severe diarrhoea. There was one case of septicaemia with a positive blood culture for Alcaligenes faecalis		Thus by day 5, all grps were on the same therapy CSO-110 provides a maximum of 110 cal/kg BW per day Comparison: early vs late feeding diluted vs full strength refeeding				
Shaikh S; Molla AM; Islam A; Billoo AG; Hendricks K; Snyder J; 1991 [120] Pakistan	Study Type: Comparative RCT Evidence level: 1-	*n* = 33 WHO-ORS (24 hours) followed by khitchri & 1/2 strength formula (grp a) *n*= 36 WHO-ORS (4 hours) followed by khitchri and 1/2 strength formula & WHO-ORS (grp b) *n* = 6 did not complete due to infections or removal by parents *n* = 19 were treatment failures	Male children (aged 9–48 month, mean age 22–23 months) with acute gastroenteritis(<72 hours) with moderate and severe dehydration and admitted to hospital	Children were randomised to either Grp a) WHO-ORS only for first 24 hours followed by khitchri (rice, dal, cottonseed oil) and 1/2 strength formula freely or Grp b) WHO-ORS for 4 hours followed by khitchri and 1/2 strength formula freely Comparison: early vs late feeding	Follow-up period: mean follow up of 3 days Outcome Measures: % weight gain tolerability	Energy intake was similar in both grps Weight gain % change Grp A (*n* = 21) vs Grp B (*n* = 23) (successful cases only) After rehydration: 7.0%± 3.5 (vs. 7.1% ±4.1 24 hours post rehydration -1.4%±3.9 vs -0.6%±4.8 72 hours post rehydration -0.9%±4.3 vs -1.0%±5.0 (NS for all) Tolerability: both treatments were well tolerated	These data indicate that an early feeding of khitchri and WHO-ORS may be as tolerable as WHO-ORS alone in the first 24 hours	30% failure rate due to severity of some infants at start, reducing the power of study randomisation appropriate No blinding Thus study was supported by the Applied Diarrhoeal Disease Research Project (Harvard) with the US Agency for International Development
Gazala E; Weitzman S; Weizman Z; Gross J; Bearman JE; Gorodischer R; 1988 Mar [41]	Study Type: Comparative RCT Evidence level: 1-	*n*= 53 early feeding (6 hours) *n* = 37 late feeding (24 hours)	Infants (mean age ~7 month) with acute infantile gastroenteritis (< 7 days duration) with mild dehydration	**Early feeding:** Following an initial oral rehydration period with ORS-WHO (ORET) of 6 hours (50 ml/kg)	Follow-up period: Two weeks Outcome Measures:	**At 24 hours:** (early vs late) % weight gain 0.6% vs 1.2% (NS)	Short term clinical outcomes for infants with acute diarrhoea were not influenced by early or late refeeding. Authors advise early refeeding	There was a overall 30% loss to follow up Randomisation was inappropriate (flipping a coin)

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Israel		30% were lost to follow up 11% at 24 hours, 24% at 48 hours, 30% at 2 weeks.	(≤5%) who attended a primary care clinic.	infants were refed with either breast milk or cow's milk (parents were asked not to mix). For infants that received solids the BRAT diet was advised. Or **Late feeding:** Infants were given ORS only for the first 24 hours (200 ml/kg per day). After which they were fed in the same way as the early grp. In both grps, water supplementation was allowed Comparison: Early (6 hours) vs late feeding (24 hours)	% weight gain State of hydration Duration of diarrhoea Hospital admissions All at 24 hours & 2 weeks.	Infants with mild dehydration (≤5%) 9(20%) vs 5(15%) (NS) **Hospital admissions** 2 (4.4%) vs 3 (8.5% (NS) **At 2 weeks:** % weight gain 2.1% vs 2.4 % (NS) Duration of diarrhoea (d) 3.7± 1.9 vs 3.6±2.2 (NS) Hospital admissions 3 vs 4 (NS)	to prevent malnutrition between bouts of gastroenteritis (particularly relevant to developing countries)	Adherence to 'treatment' was under the control of family and study relied on accurate reporting by families e.g. actual/ expected ORS intake for early vs late was 67% vs 63% No information on the financial support of this study
Nanulescu M; Condor M; Popa M; Muresan M; Panta P; Ionac S; Popescu L; Sarb S; Suciu D; Corduneanu D; Rusu C; 1995 [121] Peru	Study Type: Comparative RCT Evidence level: 1-	*n* = 73 early feeding (normal feeding reached within 2–3 days) *n* = 49 late feeding (normal feeding reached within 4–6 days)	Infants (1–12 months) with acute gastroenteritis (≤ 5 days) who were not severely dehydrated (WHO criteria) and were hospitalised.	**Early refeeding**: In breast-fed children, feeding was continued throughout illness For each watery stool 50–100 ml of ORS were given For non breast fed children, regime was given adapted according to age Less than 5 years: 75 ml/kg ORS or rice water and after 3–6 hours milk formula was resumed. Ist day 1/2	Follow-up period: up to 7 days Outcome Measures: Weight measures Duration of diarrhoea	**After resolution of disease** (early vs late) % weight change +1.2 ±1.1 vs -0.01±0.9 *P* = 0.01 Weight loss recorded in 6.2% vs 37.2% (*P* < 0.01) Weight gain recorded in 76.6% vs 32.6% (*P* = 0.01) i.e. difference relates to infants with constant weight Duration of diarrhoea (d)	Authors concluded that there is a favourable effect of early feeding on body weight in the management of infantile acute diarrhoea	Loss to follow up of *n*= 21 in early grp, *n* = 13 in late grp. No comment made on this. Randomisation was inappropriate (used odd and even days) Both early and late grps contained sub grps e.g. early grp breast fed infants did not stop feeding in 1st 3–6 hours, formula fed infants were. Timings of dietary management were ranges.

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				dilution (35–45 cal/kg per day), 2nd day 2/1 dilution (75–85 cal/kg per day) and 3rd day full strength (110–130 cal/kg per day) Greater than 5 years: 75 ml/kg ORS or rice water for the first 3–6 hours after which feeding resumed soft cheese, meat, cereals, rice, fruit and vegetables. Milk after 3 days, initially diluted, at 5 days undiluted. ORS or water given if any watery stools **Late refeeding** Breast feeding was discontinued for 24–36 hours first 6–12 hours ORS (100–150 ml/kg) Within next 24 hours carrot soup (150–200 ml/kg) or rice water. After 24–36 hours: breast feeding resumed supplemented by carrot soup/rice water to ensure 150–200 ml/kg with the amount of milk gradually being increased until normal feeding resumed at 4–6 days. For non-breast fed children The same rehydration (6–12 hours) and transition (next 24 hours) was instituted. After 24–36 hours milk formula		5.6±2.7 vs 4.9±1.8 *P* = 0.1		No information on the financial support of this study

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				was reintroduced in graduated manner with fluid requirements met with carrot soup, rice water or water. The full milk diet resumed at 5–6 days. If older than 5 month, solid foods as listed before were introduced at 24–36 hours. Comparison: Early vs late feeding adapted for age of child and whether breast or formula fed.				
Chew F; Penna FJ; Peret Filho LA; Quan C; Lopes MC; Mota JA; Fontaine O; 1993 Jan 23 [122]	Study Type: Comparative RCT Evidence level: 1- South America	*n* = 80 full strength milk *n* = 79 diluted milk	Infants (mean age ~4 months) with acute gastroenteritis (<120 hours) and no or some signs of dehydration on admission	Intervention: Following assessment and rehydration if appropriate (4–6 hours), infants were randomised to either a) Full strength milk formula immediately or b) graded feeding: 1/2 strength for 24 hours, 2/3 for next 24 hours and then full strength milk Other fluids ORS or water were given as appropriate Comparison: full strength vs regraded feeding	Follow-up period: 5 days Outcome Measures: Diarrhoea duration (hours) % Weight gain at discharge Treatment successes (diarrhoea stops before 5 days) and failures (recurrent dehydration & increased stools)	Duration of diarrhoea Full strength vs diluted milk 92(50) vs 92(50) hours 95% CI 1.0 (07–1.3) % weight gain 0.89 (0.47) vs 0.3 (4.4) at discharge 95% CI 1.0 (0.6–1.7) Treatment successes 51 (71%) vs 50 (70%) NS Treatment failures: Recurrent dehydration 6(8%) vs 6(9%) Increased stool output 8(11%) vs., 8(11%)	In infants of less than 6 months with diarrhoea whose main food is animal milk or formula, feeds should be given at full strength as soon as dehydration is corrected.	Randomisation was appropriate (block randomisation) Failures were reported This study was supported by the WHO (Diarrhoeal Diseases Control Programme)
Fox R; Leen CL; Dunbar EM; Ellis ME; Mandal BK;	Study Type: Comparative RCT	*n* = 32 graded refeeding *n* = 30 immediate full strength feeds	Infants (mean age ~11 months) with acute gastroenteritis (<7 days) with mild or	Intervention: Following rehydration for 12 hours infants were randomised to either	Follow-up period: Until discharge (up to 7 days)	No recurrence graded vs full strength	There was no difference in the incidence of recurrence of diarrhoea, effect on weight or duration of hospital stay	Randomisation was stated but not described

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1990 Sep [123] UK	Evidence level: 1-	*n* = 4 were subsequently excluded for unrelated reasons	moderate dehydration and admitted to hospital.	a) graded refeeding with cow's milk formula or breast milk at 1/4 strength for 12 hours , 1/2 strength for the next 12 hours followed by full strength or b) full strength cow's milk formula or breast milk immediately Comparison: graded vs immediate full strength refeeding	Outcome Measures: Recurrence (numbers that don't) Mean % change in weight Mean length of hospital stay (days)	19 (60%) vs 17 (57%) (NS) Mean % weight change No significant differences between grps although graded feeders lost more weight at start (data in graph form only). Mean hospital stay 4.3±1.7vs. 4.2±1.6 days (NS)	between the graded and immediate full strength feeding groups.	Dropouts were described Lack of relevant clinical data and brief description of those that were included Infants whom experienced recurrence of diarrhoea were settled on a lactose free formula The funding of the study was not declared
Rees L; Brook CG; 1979 Apr 7 [49] UK	Study Type: Comparative RCT Evidence level: 1-	*n* = 16 full strength milk *n* = 16 clear fluids and full strength milk *n* = 14 clear fluids and gradual reintroduction of full strength milk	Children (aged 6 weeks to 4 years) with gastroenteritis (<5 days duration) and mild dehydration admitted to hospital	Intervention: Children were randomly assigned to either a) full strength milk or b) Clear fluids (0.18% NaCl & 4% dextrose in water) until diarrhoea settles then full strength milk or c) Clear fluids (0.18% NaCl & 4% dextrose in water) until diarrhoea settles then milk given diluted then increased by 1/4 every 8 hours until full strength achieved Comparison: using grps	Follow-up period: ~4 days (length of hospital stay) Outcome Measures: Average length of hospital stay (days)	Average length of hospital stay Grp a vs Grp b) vs Grp c) 3.4±1.5 vs 3.2±1.0 vs 3.6± 1.4 days NS	There was no difference in hospital stay of children with acute diarrhoea receiving full strength or graded milk feeds.	Randomisation was stated but not described Lack of clinical outcomes e.g. weight, duration of diarrhoea The funding of the study was not declared

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				b) & c) Full strength vs graded feeding				
Dugdale A; Lovell S; Gibbs V; Ball D; 1982 [46] Australia	Study Type: Comparative RCT Evidence level: 1-	*n* = 28 rapid refeeding *n* = 31 graduated feeding *n* = 62 were initially enrolled but *n* = 3 were immediately excluded as they were not age matched with the other grp	Infants (mean age ~22 months) with acute gastroenteritis (<7 days) and mild or moderate dehydration, admitted into hospital	Intervention: After initial assessment and rehydration as appropriate infants were randomised to either a) Immediate resumption of normal milk and food. or b) Graduated feeding: half strength whole milk for 24 hours followed by normal feeds Clear fluids were given if deemed appropriate Comparison: Graduated vs immediate full strength feeding	Follow-up period: one week after discharge Outcome Measures: Total stay in hospital (days) Weight changes (kg) during first 24 hours of refeeding	Total stay in hospital immediate resumption vs graduated feeding 4.7(3–7) vs 5.4(3–9) days *P* > 0.05 Weight changes (24 hours) both were losses -0.02±0.25 vs.- 0.14±±0.2 kg *P* > 0.05	The rapid refeeding group with full strength milk lost less weight and went home early than the group who had graduated feeding.	Randomisation was stated but not described Short term study with short term outcome measures i.e. 24 hours although infants were checked at home a week later (no data). The funding of the study was not declared
Ransome OJ; Roode H; 1984 [124] South Africa	Study Type: Comparative RCT Evidence level: 1-	*n* = 37 full strength cow's milk *n* = 37 graduated milk *n* = 8 and *n* = 5 respectively were withdrawn from the groups because of lactose malabsorption	Children (3–36 months) with acute gastroenteritis requiring IV therapy and at least 5% dehydrated	Intervention: Following assessment and rehydration, children were randomised to either a) full strength cow's milk or b) Ist day 1/2 strength 2nd day 2/3 strength 3rd day 2/3 strength 4th day full strength cow's milk Comparison: full strength vs graded refeeding	Follow-up period: 4 days Outcome Measures: Mean duration of diarrhoea (days)	Duration of diarrhoea Full strength vs graded refeeding 2.62±0.35 vs 2.46±0.35 *P* = 0.71	Early introduction of full strength cow's milk does not prolong the course of acute gastroenteritis	Randomisation was stated but not described Children with lactose intolerance were withdrawn assumably they would have not recovered so well. Lack of clinical outcomes e.g. weight The funding of the study was not declared

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Valois S; 2005 [126]	Study Type: RCT Evidence level: 1++	90 children in total 30 - White Grape Juice 30 - Apple Juice 30 - coloured and flavoured water	male infants aged 4–18 months with severe diarrhoea and moderate dehydration.	Intervention: The effects of juice consumption during diarrhoea is being assessed. Treatment arm 1 - Apple juice Treatment arm 2 - White grape juice control arm - coloured flavoured water Comparison: Comparisons are made between the arms of duration and severity of diarrhoea as well as fecal losses througout the study. Fluid intake and vomitus losses were also compared between groups.	Follow-up period: Infants were followed up for 1 week Outcome Measures: duration of illness severity of diarrhoea (assessed by number, type and consistency of stools) amount of fecal losses (g/kg per day) vomitus losses fluid intake required to maintain fluid balance body weight changes	Total duration of diarrhoea reported as mean hours (SD) Apple juice - 111.7 (48.2) White grape juice - 105.4 (44.9) Water - 80.0 (39.6) significance not reported duration of diarrhoea in hours after randomisation Apple juice - 49.4 (32.6) White grape juice - 47.5 (38.9) Water - 26.5 (27.4) *P* < 0.05 for water vs juice groups Number of patients vomiting during the first day of treatment apple juice - 22 White grape juice - 26 water – 19	All patients recovered with appropriate treatment without anyone developing persistent diarrhoea.	Even though the study was primarily designed to compare juices with water, the fact that none of the infants had diarrhoea for more than 14 days, attests to the fact that this data can be used to answer the clinical question
Jan A; Rafi M; Mustafa S; Rasmussen ZA; Thobani S; Badruddin SH; 1997 Jan [127] Pakistan	Study Type: Comparative RCT Evidence level: 1-	*n* = 38 Dowdo grp *n* = 38 Khitchri grp *n* = 2 patients withdrew (one from each grp) due to short hospital stay and unwillingness parents to adhere *n* = 3 treatment failures (could not adhere to diet)	Children (aged 6–36 months, mean 13–14 months) with acute gastroenteritis (<7 days duration) with a range of dehydration from 'none', 'some' and 'severe.' admitted to hospital	If dehydrated (see notes) mild cases with treated with ORS, severe with IV. For 4–5 hours. Followed by randomisation to either **Dowdo diet:** atta (whole wheat flour), cow's milk, oil, salt, water cooked or	Follow-up period: 5 days Outcome Measures: Total weight change (g) Duration of hospitalisation	**Total weight change (g)** Dowdo vs Khitchri median 150 vs 140 range -500 to +640 vs -440 to +920 **Duration of hospitalisation (days)** median 69.5 vs 62 range 19–192 vs 20–216	Author's concluded that feeding Dowdo was as effective as Khitchri in children with acute diarrhoea	Over 50% of children were not dehydrated on admission Randomisation appropriate Mothers reported that the children preferred dowdo the best and that they were more likely to use this approach at home. Financial support for his was project was received from the applied Diarrhoeal Disease

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				Khitchri diet: rice, Mongdal (lentils), oil, salt, water cooked With a target intake of 110 kcal/kg per day, offering food at 3 hour intervals. Comparison: Dowdo vs Khitchri diet				Research project (Harvard)
Alarcon P; Montoya R; Rivera J; Perez F; Peerson JM; Brown KH; 1992 Jul [128] Peru	Study Type: Comparative RCT Evidence level: 1-	*n* = 25 rice, beans and vegetable oil (RB) *n*= 21 rice, soy protein isolate, corn syrup solids and vegetable oil (RS) *n* = 5 treatment failures were 8% RB vs 14% RS (*P* = 0.058) Further *n* = 3 were eliminated from analysis due to intercurrent illness.	Infants (aged 6–24 months, mean~11 months) with acute gastroenteritis (<96 hours) with a range of dehydration from mild to severe admitted to hospital	Rehydration therapy was provided according to WHO guidelines usually for the first 4 hours post admission and then the infants were randomised to either a) **RB diet:** rice, white beans (*Phaseolis vulgaris*, 'frijol canario') and soybean: cottonseed oils (55:45) or b) **RS diet:** rice, soy protein isolate, corn syrup solids and soybean: cottonseed oils, 55:45) both 80 kcal/100 g and were offered *ad libitum* in 6 divided feeds A vitamin mix was also given to both grps. Comparison: Bean vs soy component of a mixed food diet	Follow-up period: 6 days Outcome Measures: Change in body weight Duration of diarrhoea	Both grps consumed ~95 kcal/BW for 1st day after that mean intakes rose. The RS grp levelled off at 140 kcal/kg day at day 4 but Grp RB intake continued to rise. Energy consumption of RB compared to RS diet during days 4–6 was significantly greater (*P* < 0.02). **Changes in body weight** Infants in both grps gained on average 100–200 g in 1st day. After this RS grp weights did not change significantly, RB declined to towards their admission weights. Data is graph form only. Author's state that weight differences were only significant (*P* = 0.047) due to day 1rehydration. **Duration of diarrhoea** The estimated median duration of illness was 60 hours in grp Rb vs 121 hours in grp RS (*P* = 0.01) (survival analysis. Data in graph form only).	The duration of diarrhoea was significantly less in the bean diet compared to the soy diet but there were no significant difference in infant weight between the two groups.	Double-blinded study, food dye was added to diets. Randomisation was appropriate numbers of participants was small before dropouts/exclusions This study was financially supported by the Applied Diarrhoeal Disease Research project (Harvard) for the International Development Cooperation Agreement.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Mitra AK; Rahman MM; Mahalanabis D; Patra FC; Wahed MA; 1995 [129] Bangladesh	Study Type: Comparative RCT Evidence level: 1-	*n* = 32 amylase of germinated wheat flour (ARF) treated porridge diet *n* = 32 unaltered thick porridge *n*= 31 porridge diluted with extra water *n* = 102 were enrolled, 7 dropped out before being assigned to treatment	Infants (aged 6–23 months, mean ~12 months) with acute gastroenteritis (<72 hours) with 'some' (majority) or ' marked' dehydration and admitted into hospital	Infants were rehydrated with ORS or IV solution as appropriate for 224 hours before being assigned to a treatment a) ARF treated porridge b) unaltered thick porridge c) Porridge diluted with water each treatment was offered 4x daily (30 minute slots) Intake was monitored All infants received milk (breast or other) outside these periods Comparison: three porridge regimes with the assumption the ARF treated one as a test diet	Follow-up period: 5 days Outcome Measures: Weight changes (kg) Diarrhoea duration after admission (h)	The mean intake of porridge was (g/kg.d) ARS vs.thick vs diluted 44 ±13 vs 28 ±15 vs 58±17 Total energy intake:(kJ/kg.d) 414 ±97 vs.355± 120 vs 351± 73 ANOVA $P < 0.001$ in favour of test diet **Weight changes (kg)** (from admission to discharge, after 4 days of any diet) - -0.01±-0.3 vs 0.00±0.27 vs -0.06±-0.27 (NS) **Diarrhoea duration (hr)** 0.96±43 vs 0.00±-47 vs 94 ±44 (NS)	An ARS- treated porridge was more palatable (more was consumed) than the other porridge formats but this had no effect on weight of infant or length of illness	Majority of infants were mildly dehydrated and not malnourished Main result is that infants found ARS treated porridge easier to eat. Randomisation was appropriate This study was financially supported by the Swiss Development Cooperation and the International Centre for Diarrhoeal Disease Research Bangladesh.
Darling JC; Kitundu JA; Kingamkono RR; Msengi AE; Mduma B; Sullivan KR; Tomkins AM; 1995 Jul [130] Tanzania	Study Type: Comparative RCT Evidence level: 1-	*n*= 26 normal corn porridge diet *n* = 25 amylase digested (AMD) porridge diet *n* = 24 fermented and amylase digested (FAD) porridge diet *n* = 81 presented but *n* = 6 were excluded due to	Children (aged 6–25 months, mean 9–11.5 months) with acute gastroenteritis (<14 days) severe enough to warrant admission with a range of dehydration including 'none', 'some' (majority) and 'severe'	Children were entered into the study following rehydration between 4–24 hours after admission randomised to a) Normal corn porridge b) AMD porridge c) FAD porridge Study foods were prepared by staff in	Follow-up period: 9 days Outcome Measures: Duration of diarrhoea (hr) Recurrence of diarrhoea Median weight changes	Over the 4 day period, the mean daily energy intake was significantly greater in the AMD (42% more, $P = 0.003$) than the normal porridge grp. The energy intake of the FAD diet was not different from the other two at any point. **Duration of diarrhoea** (using survival analysis showed no significant differences between the grps $P = 0.54$ No difference in recurrence of	The energy intake of the AMD diet was 42% greater than the normal porridge grp but this had no bearing on the clinical outcome of diarrhoea	Children as a grp were moderately malnourished at start of study and 31% were unwell during study (infections) the trial was not blinded the randomisation was appropriate 4 deaths and 4 dropouts reduced power of study. This study was financially

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
		dysentery and not satisfying the inclusion criteria *n* = 4 left the study because they required nasogastric feeding There were 4 deaths during admission (5% mortality)		300 g portions and served *ad libitum* 5 times a day. Intake was monitored Most infants were being breast fed and this was encouraged Further IV rehydration was required in *n* = 6 infants and there was a systematic infection in *n* = 23 infants spread across the grps Comparison: Three porridge diets		diarrhoea between the grps. **Median weight changes** (as a % of admission weights were between -0.5±1.0 percent) for the 4 days of study and were no difference between the grps.		supported with the Overseas Development Administration.
Alarcon P; Montoya R; Perez F; Dongo JW; Peerson JM; Brown KH; 1991 [131] Peru	Study Type: Comparative RCT Evidence level: 1-	*n*= 29 soy-protein, lactose-free formula *n* = 28 mixed food diet plus wheat *n* = 28 mixed food diet plus potato *n* = 88 were initially admitted to study from which *n* = 3 were eliminated due to meningoencephalitis (*n* = 1) and withdrawal by parents (*n* = 2) *n* = 5 were considered treatment failures (distributed 1, 2, 2 between grps) of which *n* = 1 had	Infants (aged 5–24 months, mean ~12 months) with acute gastroenteritis (<96 hours) with mild (majority) to severe dehydration and admitted into hospital	Rehydration therapy was provided according to WHO guidelines and this was usually completed within 4 hours. The infants were then randomised to either a) (Isomil) **soy formula** (lactose free) (SP) or b) wheat peas diet (toasted wheat flour, toasted pea flour, carrot flour, soybean oil: cotton seed oil 55:45) and cane sugar (WP) or c) **potato milk diet:** potato flour, dry whole milk, carrot flour, soybean oil: cotton seed oil 55:45) and cane sugar (PM)	Follow-up period: 7 days Outcome Measures: Median duration of diarrhoea (hours) Mean cumulative increment in body weight from admission (kg)	There were no significant differences in energy intake by dietary grp. **Median duration of diarrhoea (hours)** Kaplan survival analysis PM vs WP vs SF 55 hours vs 57 hours vs 154 hours (*P* = 0.005) calculated as unadjusted and adjusted. No details given. **Mean cumulative increment in body weight from admission (kg)** There were no statistically significant differences between the 3 grps at any one point of the 7 day study. (data shown in graph form only)	Locally available, lost cost staple food mixtures (wheat & potato based) are a safe alternative to lactose free formula in the post rehydration phase following gastroenteritis in infants and in this study shortened the duration of diarrhoea.	Randomisation was appropriate Blinding was not achieved as formula was fed by bottle and solids by cup and spoon sparse description of duration of diarrhoea and weight data This study was financially supported by the Office of S & T Nutrition, US Agency for International Development and the local USAID Mission. Supplies of Isomil were provided by Ross

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
		severe diarrhoea on day 6 and *n* = 5 had recurrent dehydration		all diets were 73.3 kcal/100 ml. Formula fed by bottle. Solids by cup and spoon All diets were offered to a maximum intake of 110 cal/kg of BW per day plus a vitamin mixture for both grps Comparison: Soy formula vs solid food (wheat vs solid food (potato)				
Grange AO; Santosham M; Ayodele AK; Lesi FE; Stallings RY; Brown KH; 1994 Aug [132] Nigeria	Study Type: Comparative RCT Evidence level: 1-	*n*= 36 maize-cowpea-palm oil diet (MCP) *n*= 38 soy-protein lactose-free formula diet (SF) *n* = 5 did not remain in study of which *n* = 2 had measles/septicaemia (both SF grp) and *n* = 3 were withdrawn by parents (2 SF grp 1 MCP grp) *n* = 9 were also either withdrawn later (4–6 days) in the study by parents(*n* = 6), had recurrent diarrhoea (*n* = 2) or developed measles (*n* = 1) but their data was included in the analysis	Male infants (Aged 6–24 months, mean ~10 months) with acute gastroenteritis(<72 hours) of which 20% of the MCP grp and 42.4% of the SF grp were severely dehydrated and were admitted to hospital	Infants were rehydrated according to WHO guidelines and assessed at 4 hours and if still dehydrated treated for a further 4 hours to complete hydration Infants were then randomised to either a) **MCP grp:** fermented maize flour, toasted cowpea flour, palm oil and sugar or b) **SF grp**: lactose-free soy protein isolate formula (Isomil) Both diets were 67 kcal/100 ml a total of 150 kcal/kg bodyweight per day was	Follow-up period: 6 days Outcome Measures: Median duration of diarrhoea (hr) Mean weight change	Prior to interventions grps were not equal in terms of % severely dehydrated and this affected some of their clinical characteristics at baseline Infants on SF diet consumed significantly more than the MCP diet from day 1–6 ($P < 0.001$) **Unadjusted estimated median duration of diarrhoea** in hospital was 42 hours in grp MCP vs 104 hours in grp SF ($P < 0.001$) Data presented as graph. It was stated that adjustment did not affect result but data not presented 'Infants in the SF grp gained weight consistently, with a final increment of approximately 40 g at 6 days' 'Infants in the MCP had a less consistent weight gain with a slightly negative weight increment during the study.' These differences were stated	Less MCP diet was consumed than SF diet but MCP diet resulted in a significantly reduced duration of diarrhoea but the SF diet resulted in more steady weight gain?	Grps were not equal to start in terms of their clinical condition Lots of graphs but not enough data Confusing results Randomisation appropriate Study not blinded This study was financially supported by the Office of S & T Nutrition and the US Agency for International Development.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				offered in 5/6 feeds per day for 6 days of hospitalisation. Consumption was monitored Water was offered to a maximum of 10 ml/kg/period. A multivitamin was also given Comparison: MCP diet vs SF diet		to be statistically significant between grps at 3–6 days but data not shown (graph only)		
Maulen-Radovan I; Brown KH; Acosta MA; Fernandez-Varela H; 1994 Nov[133] Mexico	Study Type: Comparative RCT Evidence level: 1-	*n* = 44 Mixed diet (MD) *n* = 43 Soy formula (SF) *n* = 6 treatment failures all in soy grp due to recurrent dehydration and severe diarrhoea followed by recurrent dehydration	Male children (aged 5–36 months, mean~11 months) with acute dehydration (<96 hours) and a range of dehydration from mild to severe (WHO guidelines) and admitted in hospital	Rehydration therapy was provided according to WHO/UNICEF guidelines for the first 6 hours followed by either a) Mixed diet: rice, chicken, brown beans, carrots and vegetable oil blended into a puree. Feed with cup and spoon b) Soy formula fed by bottle 25 kcal/kgBW was offered by carer at 4 hour intervals A maximum intake of 150 kcal/kg was permitted per day Infants were also permitted plain boiled	Follow-up period: 6 days Outcome Measures: Duration of diarrhoea (hours) Weight change (g)	Energy consumption was similar in both grps. **Median duration of diarrhoea (survival analysis)** MD vs SF 25 hours(CI 21–29) vs 67 hours (CI 56–79) *P* < 0.001 **Cumulative weight During 6 days** 63±50 g/kg BW vs 37±60 gm/kg BW (*P* = 0.04) but if calculated from day 2 (post rehydration) to day 7 the weight changes were NS	Infants with acute diarrhoea improved quicker on a mixed solid diet as compared to soy formula diet	Impossible to blind treatments Randomisation appropriate No information on the financial support of this study.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				water Comparison: Mixed solid diet vs soy formula				
Isolauri E; Vesikari T; Saha P; Viander M; 1986 [48] Finland	Study Type: Comparative RCT Evidence level: 1-	*n* = 38 milk containing diet *n* = 27 milk free diet	Infants (mean age 14.7 months) with acute gastroenteritis (<4 days) with mild or moderate dehydration and admitted to hospital	Intervention: Following assessment and appropriate rehydration for 6–10 hours with ORS, infants were randomised to either a) Milk containing diet including plain milk, milk based gruel, sour milk, yoghurt and ice cream. Or b) Milk free diet (no details) plus both grps received an ordinary diet of broth, soup, mashed vegetable, potato, meat, porridge, strained and jellied berries, banana and juice. mean intake 800 kcal daily Comparison: lactose vs lactose free diet	Follow-up period: 3 days Outcome Measures: Duration of (watery) diarrhoea (days) Length of hospital stay (days) Weight gain (g) at day 1 & 3	Duration of diarrhoea (*n* = 8 infants had passed no stools once on ward) remaining infants lactose free vs lactose 1.3+/-0.7 vs 1.2+/-0.8 days NS Length of hospital stay 2.9+/-1.2 vs 3.1+/-1.6 days NS Weight gain (g) day 1 +313 +/-476 vs +181+/-173 NS day 3 +292+/-470 vs +175+/- 169 NS	There was no difference in the clinical recovery of infants with acute diarrhoea with either a milk free or milk diet therefore the authors recommend rapid reintroduction of feeding with no dietary restrictions in this age group.	Randomisation was stated but not described No details on dropouts Diet were under the control of parents and therefore may have deviated from the protocol The study was funded by the Finnish Foundation for Pediatric Research and the Sigrid Juselius Foundation.
Lozano JM; Cespedes JA; 1994 Mar [42] Columbia South America	Study Type: Comparative RCT Evidence level: 1-	*n* = 29 lactose free formula *n* = 28 lactose formula Of which *n* = 2 in the lactose free grp were excluded due to their disease being secondary to *E. histolytica* & *n* = 1	Infants (aged 1–24 months, mean ~11–13 months) with acute gastroenteritis(<1 we ek) with mild or moderate dehydration admitted into hospital.	All infants received parenteral fluids followed by ORS for on average the first 12 hours and were stratified for age and nutritional status and randomised to either a) lactose free formula (AL-110) or b) lactose formula (NAN	Follow-up period: up to 2 days Outcome Measures: Mean duration of diarrhoea (hours) Body weight increment (kg)	**Mean duration of diarrhoea (hours)** lactose free vs., lactose 41.9±32 vs., 54.5±-40 *P* = 0.247 **Body weight increment (kg) at third visit** (no details but mean follow up was 43 hours)	The results of this study suggest that using lactose free as opposed to a lactose formula for infants confers no benefit in the early refeeding period post acute diarrhoea.	Randomisation appropriate no blinding Small study with dropouts/withdrawals No information on the financial support of this study.

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
		in the lactose grp due to referral to another hospital. A further *n* = 1 from each grp dropped out.		1 for infant <6 months) (NAN 2 for infants>6 months) For both grps, the milk was administered at half strength for the first 24 hours by the end of the 2nd day; all infants were on full strength milk. Comparison: lactose vs., non-lactose formula		0.8 kg ±0.5 vs 0.82 kg ±0.5 *P* = 0.918		
Simakachorn N; Tongpenyai Y; Tongtan O; Varavithya W; 2004 Jun [134] Thailand	Study Type: Comparative RCT Evidence level: 1-	*n* = 40 lactose free formula *n*= 40 lactose formula *n* = 3 (*n* = 2 lactose free, *n* = 1 lactose dropped out of study. *n* = 6 unscheduled IV infusions (*n* = 2 lactose free, *n* = 4 lactose)	Male infants (aged 3–24 months, mean 11–13 months) with acute gastroenteritis (<7 days) with mild or moderate dehydration and admitted into hospital.	After appropriate rehydration by WHO guidelines infants were randomised to either a) lactose free formula or b) lactose formula Both for 90 ml/kg per day and alternated with 90 ml/kg per day of ORS for the 4–24 and 24–48 hours period to give ~180 ml/kg per day Infants were also fed rice gruel as tolerated and appropriate for age after 4 hours of rehydration Comparison: lactose free vs lactose formula	Follow-up period: 7 days Outcome Measures: Duration of diarrhoea (hours) Weight change %	**Duration of diarrhoea (hours)** lactose free vs lactose Survival analysis median duration of diarrhoea 77 vs 97.5 hours *P* = 0.002 t-test 64.2 hours±39.9 vs 92 hours±43.3 hours *P* = 0.003 **Weight change %** Day 1: 1.51±1.71 vs 0.31±1.98 *P* = 0.005 On day 2 &5 there was no stat. signif. differences in % weight changes	The use of lactose free formula for infants with acute diarrhoea significantly shortened the duration of diarrhoea compared with lactose formula. Although there was a trend towards better weight gain, this was only significant at 24 hours. Infants receiving the lactose free formula tolerated it well.	Randomisation was appropriate No details on the tolerability assume it is extrapolated from low dropout described as double-blind and details given The International Nutritional Research Institute Denmark and Dumex Ltd Thailand supplied the formula. The international Nutrition Research Institute, Denmark provided the financial support for the present study.
Gabr M; Maraghi S; Morsi S; 1979 [135]	Study Type: Comparative RCT Evidence level: 1-	*n* = 29 milk based formula *n* = 29 soy based	Well nourished infants (aged 3–18 months) with their first attack of acute	Following assessment and rehydration, infants were randomised to either	Follow-up period: 2–8 weeks Outcome Measures:	Recurrence of diarrhoea (*n*) Lactose vs no-lactose	The author's suggest that due to the recurrence if diarrhoea in the lactose group compared to the soy group, infants with	Randomisation was stated but not described No details on dropouts

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Egypt		lactose free formula	gastroenteritis (3–7 days) and moderately or severely dehydrated	a) milk formula containing lactose or b) lactose free soy formula at half strength for 3–4 days followed by full strength Comparison: lactose vs non lactose	Recurrence of diarrhoea (%)	day 1: 0 vs 0 day 6 : 15 (21%) vs 4.0 (21%) *P* < 0.05	acute diarrhoea should be given lactose-free formula for at least 8 weeks.	No other relevant clinical outcome measures reported e.g. weight The funding of the study was not declared
Haffejee IE; 1990 [43] South Africa	Study Type: Comparative RCT Evidence level: 1-	*n* = 120 milk formula *n*= 79 breast milk *n* = 35 breast & supplementation *n* = 75 soy formula *n* = 316 were initially enrolled but there *n* = 2 deaths, *n* = 5 on going diarrhoea spread across the groups	Children (age range 3 days to 28 months (mean 5.5 months) with acute gastroenteritis (< 7 days) and dehydration leading to being admitted to hospital	Following assessment and appropriate rehydration children were randomised to either a) cow's milk based formula or b) breast milk or c) breast milk plus supplementation or d) Soya formula Notes. Children on formula before study were randomised to one of two of the study formula. Breast feed	Follow-up period: until recovery Outcome Measures: Duration of diarrhoea (hours)	Duration of diarrhoea Cows vs breast vs breast & sup vs soy 70.5±60.3 vs.60.9±44.8 vs.64.8 ±43.4 vs 61.4 ±43.5 hours (NS) Sub analysis of age, duration of diarrhoea prior to admission and type of organism (rotavirus or other) did not influence duration of diarrhoea post admission	These data suggest that lactose free feeds are not required following hospital admission of children with acute gastroenteritis	Randomisation was not appropriate (sealed envelope-no details) and the feeding status of the children had to be taken into account prior to the procedure. Dropouts/exclusions were described Pragmatic study This study was funded by the South African MRC

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
				children remained on breast milk Comparison: Cow's milk (lactose) vs breast milk vs soy formula (no-lactose)				
Santosham M; Goepp J; Burns B; Reid R; O'Donovan C; Pathak R; Sack RB; 1991 May [137] USA	Study Type: Comparative RCT Evidence level: 1-	*n* = 29 early feeding *n*= 27 late feeding (*n* = 59 started of which 3 dropped out in the 1st 24 hours due to non adherence)	Infants (aged 2–12 months, mean~6 month) with acute diarrhoea (<7 days duration) and <7% dehydration (used standard criteria) under outpatient management	On presentation and following assessment infants were randomised to either Early feeding: Mothers were provided with a soy-based lactose-free formula (Nursoy) and an ORS to give their infant at ~100 ml/kg per 24 hours of each. Mothers were asked to give alternate ad libitum feedings with each liquid during a 24 hour period or Late feeding: Mothers were provided with ORS only, to alternate with water for the first 24 hours ad libitum. After 24 hours infants moved on to alternate half strength soy formula (as above) with ORS for the next 24 hours and then full strength soy formula for the following 24 hours both regimes continued until resolution of illness Comparison: Early vs late feeding	Follow-up period: Two weeks after initial presentation Outcome Measures: % resolved illness at 24,48 or post 48 hours Duration of diarrhoea (days) % weight gain at 24 hours and resolution of diarrhoea, 2 weeks later	% resolved illness (early vs.late) at 24 hours 13 (44.8%) vs 6 (22%) (NS) at 48 hours 21 (72%) vs 12 (44%) (*P* = 0.02) post 48 hours 6 (20.7%) vs 15 (55.6%) *P* < 0.01 Duration of diarrhoea (days) 2.0 ±0.2 vs 2.7±1.3 (*P* = 0.02) % weigh gain at 24 hours 1.5±3.5 vs 2.5±3.7 (NS) at resolution 1.8±3.5 vs 1.2±2.2 (NS) 2 weeks after therapy 3.0±6.2 vs 3.4±2.9 (NS)	The authors concluded that the soy-based, lactose-free formula is safe and may shorten the duration of diarrhoea in infants.	Size effects on the duration of diarrhoea are small and % resolved illness data does not support the fact this formula produces clinically relevant outcomes Randomisation method is appropriate This study was supported by a grant from Wyeth laboratories (producers of soy formula & ORS)
Bhan MK; Arora NK; Khoshoo V; Raj P;	Study Type:	*n* = 30 cows' milk	60 infants (mean age ~9 months) with mild	Intervention: Following assessment, infants	Follow-up period:	Duration of diarrhoea	Cow's milk formula was well tolerated by the infants, the	Randomisation was appropriate

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
Bhatnager S; Sazawal S; Sharma K; 1988 Mar [138] India	Comparative RCT Evidence level: 1-	formula *n* = 30 lactose-free cereal based formula *n* = 3 were treatment failures or which *n* = 2 in the lactose free grp lost weight and cultures showed Salmonella and *n* = 1 in the cow's milk grp showed intolerance. All three were excluded from analysis.	acute gastroenteritis (</=7 days) and no dehydration	were randomised to either a) milk free formula (rice powder, mung bean powder, sugar, coconut oil) (Nestum, Nestle) or b) cow's milk formula (lactogen full protein, Nestle) For at least 7 days Both provide 77 kcal/100 ml ORS was given for each liquid stool passed. No other foods were allowed during the first 7 day period Comparison: Lactose free vs lactose	11 days plus Outcome Measures: Duration of diarrhoea (days) Weight gain (g/kg admission weight per day) on day 4, 7 and recovery	Non-lactose vs lactose 11.0+/-10.0 vs 7.6 +/-10.8 days NS Weight gain day 4: 1.45+/-9.9 vs 7.31+/-8.8 *P* < 0.05 day 7: 2.2+/-6.1 vs 5.4+/-7.9 NS Recovery: 2.0+/-4.2 vs 5.8+/-7.8 *P* < 0.05 (energy intake was less in the non-lactose grp vs lactose grp at day 4 & 7, statistically significantly so at day 7 *P* < 0.05)	infants who were fed the non-lactose feed showed less energy intake and gained weight less rapidly.	(block randomisation) Treatment failures were described Data suggests the non-lactose feed was less palatable The funding of the study was not declared
Romer H; Guerra M; Pina JM; Urrestarazu MI; Garcia D; Blanco ME; 1991 Jul [139] Venezuela	Study Type: Comparative RCT Evidence level: 1+	*n*= 37 cow's milk *n* = 36 chicken - based formula *n* = 4 in cow's milk grp & *n* = 2 in chicken formula grp did not have diarrhoea after admission to study. *n* = 4 in cow's milk grp and *n* = 1 in chicken formula	Male infants (aged 3–14 months) with acute gastroenteritis (<96 hours) with mild or moderate dehydration and admitted into hospital	Intervention: Following assessment, infants were given WHO-ORS for 4 hours after which they were randomised to either a) Cow's milk at normal concentration for age (8.8% for 3–6 months old, 13.5% for >6 months old) Or	Follow-up period: 1 month Outcome Measures: Duration of diarrhoea (hours) Weight increase after admission as % at 48 hours and discharge	The only difference in dietary intake between the two grps was water consumed in which the cow's milk grp drank significantly more *P* ≤ 0.025 Diarrhoea duration (hours) (cow's vs chicken formula) 75.53 (9.73) vs 55.59 (8.92) hours (NS) Weight increase after admission as %	The infants on cow milk formula had a shorter duration of diarrhoea than those on chicken formula but this difference was not statistically significant. % weight changes were similar between both groups at 48 hours and on discharge.	Randomisation was appropriate (block randomisation) Dropouts were described. Although the authors high-light the 20 hour mean difference between the groups in terms of duration of diarrhoea, this figure is rended not statistically significant by the variation in the point data. This study was financially

Bibliographic information	Study type and evidence level	Number of patients	Patient characteristics	Intervention and comparison	Follow-up and outcome measures	Effect size	Study summary	Reviewer comments
		grp did not tolerate their treatment *n* = 2 (one in each grp) had antibiotics		b) Experimental soup (59% green plantain hydrolysed with fungal alpha-amylase, 27% chicken meat with skin and 14% coconut oil (salt adjusted to same as cow's milk) at the same concentration according to age Infants also received WHO-ORS and unrestricted water as required. Breast feeding was continued as prior to study. Comparison: Cow's milk feeding versus chicken-based formula feeding		at 48 hours 2.74 (0.69) vs 5.53 (0.65) (NS) at discharge 3.39 (0.75) vs 2.19 (0.55) (NS)		supported by CONICIT PC004 and ENGAST

7 Antibiotic therapy

7.1 Salmonella

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Nelson 1980 [141]	Study Type RCT	**Total number of participants** *n* = 45	**Inclusion criteria:** Children up to 8 years with acute diarrhoea seen in hospital with Salmonella species isolated in rectal swab cultures.	**Comparison** Intervention details:	**Follow up** Daily reporting of clinical symptoms and rectal swabs by parents.	**Funding :** None stated
Location : USA	Evidence Level 1+	Randomised into three treatment arms	**Exclusion criteria :** History of adverse drug reactions to penicillins, another focus of infection, under 6 weeks age.	**Group 1:** Ampicillin 100 mg/kg per day in 4 doses daily for 5 days	Seen in clinic at day2–3 and day 5–6, then every fortnight for 2 months	Applicable to UK
		Group 1 Intervention : Ampicillin *n* = 15	**Withdrawal criteria :** Confirmation and serotyping of salmonella by rectal swab cultures. All isolates sensistive to amoxicillin and ampicillin	**Group 2:** Amoxicillin 100 mg/kg per day in 4 doses daily for 5 days	**Outcome measures:** ***Mean no days until diarrhoea stopped*** Group 1 = 8.8+-3.0 Group 2 = 7.3+-1.0 Group 3 = 7.2+-1.8 *P* > 0.20	Baseline comparability Similar for sex, duration of illness prior to therapy, Salmonella serogroups. *Children in amoxicillin group younger than other groups and no white children in placebo group*
		Group 2 Intervention : Amoxicillin *n* = 15		**Group 3:** Placebo in 4 doses daily for 5 days	***Mean no days until diarrhoea improved*** Group 1 = 1.7+-0.3 Group 2 = 1.9+-0.3 Group 3 = 2.9+-0.8 *P* > 0.20	Allocation concealment : Computer generated Sequence generation : Computer generated Blinding of outcome assessors : Yes
		Group 3 Intervention : Placebo *n* = 14			***Mean no days until 1st negative culture*** Group 1 = 18.5+-9.5	Loss to follow up 1/45 (placebo group) due to short duration of Salmonella isolation Intention to treat analysis : No Power calculation :

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					Group 2 = 20.9+-12.6 Group 3 = 28.5+-9.4 *P* > 0.10 ***Days until last positive culture*** Group 1 = 41.3+-11.7 Group 2 = 37.0+-12.7 Group 3 = 20.9+-6.8 *P* > 0.50	No
Chiu 1999 [142] Location : Taiwan	Study Type RCT Evidence Level 1+	**Total number of participants** *n* = 42 Randomised into three treatment arms Group 1 Intervention : azithromycin *n* = 14 Group 2 Intervention : Cefixime *n* = 14 Group 3 Intervention : No treatment *n* = 14	**Inclusion criteria:** All children older than 6 months age presenting to hospital with suspected Salmonella enteritis – blood and/or mucoid diarrhoea with or without fever **Exclusion criteria :** Children with toxic appearance , vomiting, abdominal distension indicative of sepsis or ileus or who had taken antibiotics in 72 hours prior to admission. Negative Salmonella stool culture **Withdrawal criteria :** Not stated Confirmation and serotyping of salmonella by stool culture.	**Comparison** Intervention details: **Group 1:** Oral azithromycin 10 mg/kg per day, in one dose daily for 5 days **Group 2:** Cefixime 10 mg/kg per day, in 2 doses daily for 5 days **Group 3 :** No treatment	**Follow up** Weekly visits to clinic after completion of therapy until two consecutive normal stools noted **Outcome measures:** Mean duration of diarrhoea post-treatment (days) Group 1 = 2.5+-2.1 Group 2 = 5.8+-5.1 Group 3 = 3.5+-3.2 Mean duration of fever post-treatment (days) Group 1 = 1.5+-1.4 Group 2 = 2.1+-2.4 Group 3 = 1.2+-1.3 Proportion of patients with positive cultures at week 3 post treatment Group 1 = 3/14 Group 2 = 3/14 Group 3 = 4/14 *P* = NS	**Funding :** Applicable to UK Baseline comparability Similar for sex, duration of diarrhoea and fever prior to treatment, Salmonella subtypes. *Children receiving cefixime were younger that children in the other two groups (P < 0.05)* Allocation concealment : Computer generated Sequence generation : Computer generated Blinding of outcome assessors : Loss to follow up None Intention to treat analysis: No Power calculation : No
Kazemi 1973 [143]	Study Type RCT	**Total number of participants**	**Inclusion criteria:**	**Comparison**	**Follow up** During treatment once daily physical	**Funding :** Partly Hoffman-LaRoche

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Location : Canada	Evidence Level 1+	*n* = 36 Randomised into three treatment arms Group 1 Intervention : Trimethoprim/sulfamethoxazole *n* = 14 Group 2 Intervention : Ampicillin *n* = 10 Group 3: Intervention : No treatment *n* = 12	Children ages 10 months to 15 years with a history of diarrhoea and fever for 3 days or more and/or mucus and blood from diarrhoeal stools. Subsequent positive culture for Salmonella **Exclusion criteria :** Antibiotics in previous 5 days or renal or hepatic disease, blood dyscrasia, or salmonella bacteraemia **Withdrawal criteria :** Not stated Confirmation and serotyping of salmonella by stool culture and all isolates sensitive to trimethoprim/sulfamethoxazole and ampicillin	Intervention details: **Group 1:** 20 mg/kg per day trimethoprim + 100 mg/kg per day sulfamethoxazole oral suspension 4times per day for 7 days **Group 2:** Ampicillin 100 mg/kg per day oral suspension or capsules 4times per day for 7 days **Group 3:** No treatment	examination and stool cultures 2 or 3 consecutive daily stool cultures at 1 week, 8 weeks and 6 months post therapy (Family contacts also had stool cultures performed at admission and as above) **Outcome measures:** ***Mean duration of diarrhoea after start of therapy*** Group 1 = 2.8 Group 2 = 3.1 Group 3 = 3 *P* = NS ***Mean duration of hospitalisation after start of therapy*** Group 1 = 5.3 Group 2 = 5 Group 3 = 6 *P* = NS ***Mean duration of fever after start of therapy*** Group 1 = 3.2 Group 2 = 1.6 Group 3 = 2.6 *P* = NS	Applicable to UK Baseline comparability Similar for age, fever, vomiting, blood in stool, initiation of therapy in relation to onset of disease, Salmonella serotypes Allocation concealment : Not stated Sequence generation : Not stated Blinding of outcome assessors : Not stated Loss to follow up None Intention to treat analysis : No Power calculation : No

7.2 Campylobacter

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Robins-Browne 1983a 152 Location : South Africa	Study Type RCT Evidence Level 1-	**Total number of participants** *n* = 25 C jejuni only *n* = 8 Randomised into two treatment arms Group 1 Intervention : Erythromycin All participants *n* = 11 C jejuni infection only *n* = 4 Group 2 Intervention : Placebo All participants *n* = 14 C jejuni infection only *n* = 4	**Inclusion criteria:** Children aged 1–24 months admitted to hospital with a history of diarrhoea of duration <96 hours, who had received no antimicrobial therapy for this illness. Confirmation of C jejuni and any other infection from microscopic and culture examination of stool samples. **Exclusion criteria :** No details **Withdrawal criteria :** No details	**Comparison** Erythromycin vs placebo Intervention details: **Group 1:** Erythromycin ethylsuccinate oral suspension, 40 mg/kg per day in divided doses for 5 days **Group 2:** Placebo oral suspension	**Follow up** Daily examination for 7 days **Outcome measures:** **Mean duration of abnormal stool frequency** All participants Group 1 = 0.77+-0.47 days Group 2 = 1.57+-1.59 days *P* = NS C jejuni only Group 1 = 0.8+-0.5 days Group 2 = 1.8+-2.5 days *P* = NS ***Mean duration of abnormal stool consistency*** All participants Group 1 = 5.27+-1.68 d Group 2 = 5.79+-1.25 d *P* = NS C jejuni only Group 1 = 5.3+-1.7 days Group 2 = 6.0+-1.2 days *P* = NS **Mean duration of vomiting** All participants Group 1 = 3.5+-0.71 d	**Funding :** South African MRC University of Natal, Abbott Laboratories Applicable to UK Baseline comparability Similar for age, sex, nutritional status, duration of illness, extent of dehydration Allocation concealment : Yes, pharmacy controlled Sequence generation : Code used Blinding of outcome assessors : Yes Loss to follow up 1/26 voluntarily withdrew Intention to treat analysis : Not stated Power calculation : None stated

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					Group 2 = 3.8+-1.3 d *P* = NS C jejuni only Group 1 = 0 Group 2 = 3.0 d **Mean duration of dehydration** All participants Group 1 = 2.91+-1.81 d Group 2 = 2.79+-1.97 d *P* = NS C jejuni only Group 1 = 1.8+-1.5 days Group 2 = 2.3+-2.5 days *P* = NS **Fever** All participants Group 1 = 3.33+-1.63 d Group 2 = 3.6+-1.52 d *P* = NS C jejuni only Group 1 = 2.0 d Group 2 = 0 d	
Pai 1983 [146] Location : Canada	Study Type RCT Evidence Level 1+	**Total number of participants** N =32, results for 27 participants with complete data presented Randomised into two treatment arms	**Inclusion criteria:** Children up to 12 years with symptomatic enteritis and their household contacts. Recruitment when stool samples from children had positive culture of erythromycin sensitive campylobacter.	**Comparison** **Erythromycin vs no treatment** Intervention details: **Group 1:** Erythromycin ethylsuccinate oral suspension, 40 mg/kg per day	**Follow up** **All participants contacted until all of the household had three consecutive negative (weekly) stool samples** Clinical symptoms assessed and reported daily by parent on telephone	**Funding :** Applicable to UK Baseline comparability Similar for age, sex, symptoms (diarrhoea, bloody diarrhoea, fever, vomiting), days ill prior to study entry.

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
		Group 1 Intervention : Erythromycin *n* = 15 Group 2 Intervention : No treatment *n* = 12	**Exclusion criteria :** Presence of other enteric pathogens in the stool, antibiotic therapy in previous 2 weeks and patients with a positive culture who were no longer symptomatic **Withdrawal criteria :** Not stated	every 6 hours for 7 days **Group 2:** No treatment	**Outcome measures:** **Mean no of days with diarrhoea** Group 1 = 3.2 +/- 1.7 Group 2 = 3.8 +/- 4.0 WMD -0.60 [95% CI -3.02–1.82] *P* = 0.63 **Range of no of days with diarrhoea** Group 1 = 1–6 Group 2 = 1–15 **Mean no of days until first negative culture** Group 1 = 2.0 +-1.3 Group 2 = 16.8 +-12.5 *P* < 0.01	Allocation concealment : Not stated Sequence generation : Not stated Blinding of outcome assessors: No Loss to follow up 5/32 participants had incomplete data Intention to treat analysis : No details Power calculation : Not stated
Salazar-Lindo 1986 [147] Location : Peru	Study Type RCT Evidence Level 1+	**Total number of participants** *n* = 30 30 participants had C. jejuni positive stool culture 2/30 had concurrent Shigella infection Randomised into two treatment arms **Group 1** Intervention : Erythromycin *n* = 14	**Inclusion criteria:** Children aged 3–60 months brought as outpatient for treatment of acute diarrhoea Five or more loose stools per day with mucous and gross blood or PMN leucocytes for no longer than 5 days, no antibiotic treatment for 7 days, no other illness necessitating antibiotics **Exclusion criteria :** Clinical signs of dehydration, separate episode of diarrhoea during 2 weeks prior to coming to hospital, weight/height ratio <3rd percentile. Concurrent Campylobacter and Shigella infection	**Comparison** Intervention details: **Group 1:** Erythromycin ethylsuccinate oral suspension, 50 mg/kg per day in 4 doses for 5 days **Group 2:** Placebo oral suspension	**Follow up** Daily stool cultures (except Sundays holidays and daily reporting of symptoms by parents for a period of 5 days Outcome measures: ***Mean duration of diarrhoea*** Group 1 = 2.4+-0.4 days Group 2 = 4.2+-0.3 days *P* < 0.01 ***Number patients with normal stools at 5 days*** Group 1 = 13/14	**Funding :** Abbott Laboratories Nestec Ltd Applicable to UK Baseline comparability **Similar for age, sex, weight/length ratio, diarrhoea symptoms, fever, vomiting, infections concurrent with Campylobacter** Allocation concealment : Pharmacy controlled Sequence generation : Pharmacy controlled Blinding of outcome assessors :

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
		Group 2 Intervention : Placebo *n* = 10	**Withdrawal criteria :** Not stated Confirmation of Campylobacter by stool culture. Confirmation received after randomisation. If treatment failed, co-trimoxazole given as therapy for dysentery.		Group 2 = 5/10 *P* < 0.02 ***Mean days to last positive stool culture*** Group 1 = 0.5+-0.3 days Range 0–5 Group 2 = 2.2+-0.6 days Range 0–5 *P* < 0.01 ***Number patients with positive stool culture at 5 days*** Group 1 = 1/11 Group 2 = 3/5 *P* < 0.05	Yes Loss to follow up 4/30 (two from each group) Intention to treat analysis : Partly Power calculation : Not stated

7.3 Yersinia

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Pai 1984 [148] Location : Canada	Study Type RCT Evidence Level 1-	**Total number of participants** *n* = 45 results for 34 participants with complete data presented Two treatment arms Group 1 Intervention : Trimethoprim/sulfamethoxazole *n* = 18 Group 2 Intervention : Placebo *n* = 16	**Inclusion criteria:** Children under 15 years with symptomatic enteritis and their household contacts. Prior to recruitment, stool samples from children had positive culture of yersinia (confirmation within 2 days of receipt of specimen) **Exclusion criteria :** Presence of other enteric pathogens in the stool, antibiotic therapy in previous 2 weeks and patients with a positive culture who were no longer symptomatic **Withdrawal criteria :** Not stated	**Comparison** Intervention details: **Group 1:** 10 mg/kg per day trimethoprim + 50 mg/kg per day sulfamethoxazole oral suspension twice per day for 7 days **Group 2:** Placebo oral suspension	**Follow up** **All participants contacted until all of the household had three consecutive negative (weekly) stool samples** Clinical symptoms assessed and reported daily by parent on telephone Stool specimens obtained for first 7 days, then weekly. **Outcome measures:** ***Median duration of diarrhoea*** Group 1 = 3.0 Range 1–67 days Group 2 = 3.5 Range 1–27 *P* = NS **(f) Diarrhoea for <7 days** Group 1 = 1 Group 2 = 1 *P* = NS ***Recurrence of diarrhoea*** Group 1 = 4 Group 2 = 2 *P* = NS ***Median no days until bacteriological cure*** Group 1 = 5.5	**Funding :** In part from National Health Research and Development (Project 605–1396–40) Drug and placebo supplied by Burroughs Wellcome Applicable to UK Baseline comparability Similar for age, sex, symptoms (diarrhoea, fever, vomiting, abdominal pain), days ill prior to study entry. Allocation concealment : Implied pharmacy controlled Sequence generation : Implied pharmacy controlled Blinding of outcome assessors : Yes Loss to follow up 11/45 Incomplete follow-up (5) Negative stool culture at admission to study (3) Appendectomy (2) Mixed infection (1) Intention to treat analysis : No Power calculation :

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					Range 2–53 Group 2 = 17.5 Range 3–62 *P* < 0.005 ***Positive stool culture at end of treatment*** Group 1 = 2 Group 2 = 13 *P* < 0.001 ***(g) Bacteriologic relapse*** Group 1 = 7 Group 2 = 0 *P* < 0.05	No

7.4 Shigella

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Garcia de Olarte 1974 [144] Location : Colombia	Study Type RCT Evidence Level 1+	**Total number of participants** *n* = 282 Randomised into two treatment arms Group 1 Intervention : Ampicillin *n* = 142 Group 2 Intervention : Placebo *n* = 140	**Inclusion criteria:** Infants and children admitted with diarrhoea as a major symptom. Subsequent culture confirmation of Shigella or Salmonella, or *E. coli* in under 2 years age required. 1 patient without recognised pathogens per 2 patients with Shigella, Salmonella, or *E. coli* were entered into study **Exclusion criteria :** Other illness requiring antibiotic therapy, age under 6 weeks, history of allergy to penicillin or its derivatives **Withdrawal criteria :** Not stated Rectal swab and stool sample examined	**Comparison** Ampicillin vs placebo Intervention details: *Year 1* **Group 1:** IM ampicillin **Group 2:** Injection of sterile fructose ***1) Year 2*** **(ii) Group 1** Oral suspension of ampicillin 100 mg/kg in equally divided doses every 6 hours for 5 days (One half Salmonella patients given 100 mg/kg in equally divided doses every 12 hours for 5 days **Group 2 :** Oral suspension of placebo in doses every 6 hours for 5 days	**Follow up** Daily rectal swabs until 10 days, thereafter if still hospitalised, every three days. Daily clinical examination **Outcome measures:** ***Mean number of days until diarrhoea improved*** Shigella *n* = 37 Group 1 = 2.4 Group 2 =4.6 Salmonella *n* = 110 Group 1 = 2.9 Group 2 = 2.4 *E. coli n* = 35 Group 1 = 2.8 Group 2 = 4.9 No Pathogens *n* = 96 Group 1 = 2.7 Group 2 = 2.9 ***Mean number of days until diarrhoea ceased*** Shigella Group 1 = 4.4 Group 2 =6.8 Salmonella	**Funding :** Applicable to UK Baseline comparability Similar for sex, race, *E. coli* group younger than other groups. Blood and mucus present in stools, lethargy and convulsions found in greater proportion of shigella group than other groups. Allocation concealment : Random number table Sequence generation : Random number table Blinding of outcome assessors : Yes Loss to follow up 4/282 Intention to treat analysis : Not stated Power calculation : Not stated

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					Group 1 = 5.2 Group 2 = 4.8 *E. coli* Group 1 = 4.2 Group 2 = 6.4 No Pathogens Group 1 = 4.2 Group 2 = 4.2 ***Mean number of days until patient afebrile*** Shigella Group 1 = <0.5 Group 2 =1.6 *P* < 0.05 Salmonella Group 1 = 0.8 Group 2 = 1.0 *E. coli* Group 1 = 0.3 Group 2 = 0.9 No Pathogens Group 1 = 0.7 Group 2 = 0.8 ***Mean number of days until culture negative*** Shigella Group 1 = 0.9 Group 2 = 2 *P* < 0.05	

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					Salmonella Group 1 = 1.8 Group 2 = 1.7 *E. coli* Group 1 = 3.4 Group 2 = 3.0 No Pathogens – not rel	

7.6 Cryptosporidium

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Amadi 2002 [149] Zambia	Study type RCT [EL = 1+]	**Total number of participants** *n* = 100 Randomised into two treatment arms Group 1 *n* = 50 25 HIV positive 25 HIV negative Group 2 *n* = 50 25 HIV positive 25 HIV negative	**Inclusion criteria:** children admitted to hospital with diarrhoea, who had C parvum oocytes identified from a pre-enrolment stool sample and whose parents consented to the child having a HIV-test. **Exclusion criteria**: age under 1 year old and receipt of a dug with antiprotozoal activity within 2 weeks of enrolment to the study. All children were stabilised with fluid therapy, antibiotics and mineral supplementation as required	**Comparison** **Group 1** : 20 g/l nitazoxanide oral suspension **Group 2** : placebo oral suspension **Both treatments** 5 ml twice daily for three consecutive days	**Follow up** In hospital for 8 days **Main outcome measures :** clinical response on day 7 (well or continuing illness) the parasitological response the time from first treatment to last unformed stool mortality by day 8 **Effect size for HIV negative participants only** **clinical response on day 7 ('well' children)** Group 1 = 14/25 Group 2 = 5/22 (*P* = 0.037) **the parasitological response** **the time from first treatment to last unformed stool** Group 1 = 13/25 Group 2 = 3/22 (*P* = 0.007) Mortality Group 1 = 0 Group 2 = 4/22 *P* = 0.041	Funding : Romark Laboratories Baseline comparability Similar for sex, age, weight, malnutrition status, laboratory abnormalities and stool frequency Allocation concealment : Code used Sequence generation : Code used Blinding of outcome assessors : Yes Loss to follow up 3/50 Power calculation : Not stated
Abdel-Maboud 2000 [150] Location : Egypt	Study Type RCT	**Total number of participants** *n* = 150	**Inclusion criteria:** Adults and children with diarrhoea attending out-patients who had a stool	**Comparison** Nitazoxanide vs Co-trimoxazole vs Placebo	**Follow up :** Samples obtained at day 7 and 10 from treatment start	**Funding :** Not stated Applicable to UK

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
	Evidence Level 1-	Results for 73 children reported here Randomised into three treatment arms Group 1 Intervention : Nitrazoxanide *n* = 24 Group 2 Intervention : Co-trimoxazole *n* = 24 Group 3 Intervention : Placebo *n* = 25	examination (MZN and IFA tests) which was positive for Cryptosporidium **Exclusion criteria :** Patients with a stool examination (MZN and IFA tests) negative for Cryptosporidium None other stated **Withdrawal criteria :** Not stated	Intervention details: **Group 1:** Nitazoxanide at 100 mg/12 hours for children≤4 years 200 mg/12 hours for children ≥4 years for 3 successive days **Group 2:** Co-trimoxazole (sulfamethoxazole 200 mg + trimethoprim 70 mg)/12 hours for children≤4 years 10 ml/12 hours for children ≥4 years for 6 successive days **Group 3:** Placebo no further details given	**Outcome measures:** ***- Proportion of individuals 'cured' (presumed within 10 days)*** Group 1 = 21/24 Group 2 = 8/24 Group 3 = 9/25 Gp1 vs Gp 3 RR 2.43 [95% CI 1.41–4.19] *P* = 0.001 Gp 2 vs Gp 3 RR 0.93 [95% CI 0.43–2.00] *P* = 0.84	Baseline comparability Not stated Allocation concealment : Not stated Sequence generation : Not stated Blinding of outcome assessors : Not stated Loss to follow up 2/75 children in Intention to treat analysis : No Power calculation : Not stated

7.7 Treatment without prior identification of a pathogen

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Wolfsdorf 1973 [151] Location : South Africa	Study Type RCT Evidence Level 1-	**Total number of participants** *n* = 34 Randomised into two treatment arms Group 1 *n* = 18 Group 2 *n* = 26	**Inclusion criteria:** Children aged 5–30 months admitted to hospital for gastroenteritis **Exclusion criteria :** Not stated **Withdrawal criteria :** Not stated	**Comparison** Trimethoprim/sulphonamide vs placebo No further details	**Follow up** **Outcome measures:** ***Mean duration of diarrhoea (days)*** Group 1 = 5.250+-3.118 Group 2 = 6.607+-9.765 *P* = NS ***Mean duration of vomiting (days)*** Group 1 = 1.812+-3.505 Group 2 = 1.607+-2.998 *P* = NS ***Mean duration of pyrexia (days)*** Group 1 = 0.437+-0.6549 Group 2 =0.642+-0.9109 *P* = NS ***Mean duration of hospital stay (hours)*** Group 1 = 156.687+-93.672 Group 2 = 177071+-99.76 *P* = NS	**Funding :** Burroughs Wellcome Applicable to UK Baseline comparability Similar for age Allocation concealment : Code used Sequence generation : Code used Blinding of outcome assessors : Yes Loss to follow up None Intention to treat analysis : Not stated Power calculation : Not stated
Robins-Browne 1983 [152] Location : South Africa	Study Type RCT Evidence Level 1+	**Total number of participants** *n* = 78 Randomised into two treatment arms	**Inclusion criteria:** Children aged 1 months-2 years admitted to hospital with a history of diarrhoea not exceeding 96 hours and who had received no antimicrobial therapy for the current illness	**Comparison** Erythromycin vs placebo Intervention details:	**Follow up** Daily examination for 7 days Distribution of pathogens similar between groups **Outcome measures:**	**Funding :** South African MRC University of Natal, Abbott Laboratories Applicable to UK No

		Group 1 Intervention : Erythromycin *n* = 39 Data presented for 32 participants Group 2 Intervention : Placebo *n* = 39 Data presented for 33 participants	**Exclusion criteria :** Not stated **Withdrawal criteria :** Not stated	**Group 1:** Erythromycin ethylsuccinate oral suspension, 40 mg/kg per day in divided doses for 5 days **Group 2:** Placebo oral suspension	**Mean duration of abnormal stool frequency** Group 1 = 1.4+-1.7 days Group 2 = 1.8+-2.1 days *P* = 0.37 ***Mean duration of abnormal stool consistency*** Group 1 = 5.0+-1.4 days Group 2 = 5.8+-1.3 days WMD -0.80 [95% CI -1.46 to -0.14] *P* = 0.02 **Mean duration of vomiting** Group 1 = 3.4+-1.4 days Group 2 = 3.7+-1.2 days *P* = 0.35 **Mean duration of dehydration** Group 1 = 3.3+-1.8 days Group 2 = 3.3+-2.1 days *P* = 1.00 **Fever** Group 1 = 3.8+-1.6 days Group 2 = 3.3+-1.5 days *P* = 0.19	Baseline comparability Similar for age, sex, nutritional status, dehydration status, duration of current illness and severity of diarrhoea. Allocation concealment : Yes, pharmacy controlled Sequence generation : Code used Blinding of outcome assessors : Yes Loss to follow up : 13/78 **2 deaths (1 in each gp)** 6 infective complications requiring antibiotics(3 in each gp) 5 voluntary withdrawals (Gp 1=3, Gp 2 =2) Intention to treat analysis : No Power calculation : None stated
Rodriguez 1989 [154] Location : Mexico	Study Type RCT Evidence Level 1+	**Total number of participants** *n* = 125 Randomised into three treatment arms Group 1	**Inclusion criteria:** Patients aged 2–59 months brought to hospital with three or more watery stools in previous 24 hours, up to 5 days diarrhoea prior to admission, and presence of PMN leucocytes d blood in stool **Exclusion criteria :**	**Comparison** Intervention details: **Group 1:** 7.5 mg/kg per day furazolidone in four equal doses a day for 5 days	**Follow up** Daily visits as outpatients to hospital. Clinical assessment at day 3, stool sample taken at days 1 and 6. **Outcome measures:**	**Funding :** Norwich Eaton Pharmaceuticals Inc, a Proctor & Gamble company Applicable to UK No Baseline comparability

	Intervention : Furazolidone *n* = 49 Group 2 Intervention : Trimethoprim/sulfamethoxazole *n* = 52 Group 3 Intervention : No treatment *n* = 24 Data presented for 22 participants	Presence of amoeba in stools, severe concomitant disease, intolerance of or allergy to study drugs, receipt of antimicrobials, antidiahorroeals, or other drugs affecting the disease course, within 48 hours prior to admission. **Withdrawal criteria :** Poor clinical response to treatment (treatment failures)	**Group 2:** 8 mg/kg per day trimethoprim + 40 mg/kg per day sulfamethoxazole in two equal doses a day for 5 days **Group 3:** No treatment Oral rehydration, antipyretics and nutritional support given as needed to all groups Treatment success = clinical cure (absence of diarrhoea and alleviation of all symptoms) at day 3 and bacteriologic cure (negative stool culture) at day 6 For patients with negative culture: Treatment success = clinical cure (absence of diarrhoea and alleviation of symptoms) at day 3 Distribution of pathogens similar between groups. 48/125 had negative stool culture	**Clinical Cure at day 3** All participants Group 1 = 43/49 Group 2 = 43/52 Group 3 = 10/22 Gp 1 vs Gp 3 RR 1.93 [95% CI 1.21–3.09] Gp 2 vs Gp 3 RR 1.82 [95% CI 1.13–2.92] Gps 1 + 2 vs Gp 3 RR 1.87 [95% CI 1.18–2.98] **Clinical Cure at day 3 pts with –ve stool cultures** Group 1 = 13/14 Group 2 = 20/23 Group 3 = 5/9 Gp 1 vs Gp 3 RR 1.67 [95% CI 0.92–3.05] Gp 2 vs Gp 3 RR 1.57 [95% CI 0.85–2.87] Gps 1 + 2 vs Gp 3 RR 1.61 [95% CI 0.89–2.91] **Bacteriologic cure at day 6 pts with +ve stool cultures** Group 1 = 20/34 Group 2 = 19/29 Group 3 = 4/12 Gp 1 vs Gp 3 RR 1.76 [95% CI 0.76–4.12] Gp 2 vs Gp 3 RR 1.97 [95% CI 0.85–4.56] Gps 1 + 2 vs Gp 3 RR 2.33 [95% CI 1.04–5.25]	Similar for age, sex, height, weight, body temp and stools per day. Patients in Gp 1 had fewer days with diarrhoea compared to patients in either 2 treatment groups ($P < 0.02$) Allocation concealment: Not stated Sequence generation : Not stated Blinding of outcome assessors: No Loss to follow up 2/24 in the control group voluntarily withdrawn Intention to treat analysis: No Power calculation: Not stated

					Treatment cure at day 6 Group 1 = 31/49 Group 2 = 36/52 Group 3 = 5/22 Gp 1 vs Gp 3 RR 2.78 [95% CI 1.25–6.19] Gp 2 vs Gp 3 RR 3.05 [95% CI 1.38–6.72] Gps 1 + 2 vs Gp 3 RR 2.92 [95% CI 1.33–6.39]	
Oberhelman 1987 [153] Location : Mexico	Study Type RCT Evidence Level 1-	**Total number of participants** *n* = 141 Randomised into two treatment arms Group 1 Intervention : Trimethoprim/sulfamethoxazole *n* = 73 Group 2 Intervention : placebo *n* = 68	**Inclusion criteria:** Children aged 3–84 months seen in hospital with diarrhoea as chief complaint. Three or more unformed stools in previous 24 hours, <72 hours duration of diarrhoea, no antibiotic treatment in prior 7 days, absence of severe dehydration. **Exclusion criteria :** Not stated **Withdrawal criteria :** Not stated 74/141 had identifiable enteric pathogen 56/74 had a bacterial pathogen 6/31 ETEC mixed with others 25/31 ETEC only 7/10 patients had EPEC only 3/10 EPEC mixed with others	**Comparison** Intervention details: **Group 1:** 10 mg/kg per day trimethoprim + 50 mg/kg per day sulfamethoxazole oral suspension in two divided doses per day for 5 days **Group 2:** Placebo oral suspension in two doses per day for 5 days	**Follow up** **Daily assessments for 5 days except weight at day 5 and on assessment at 2 weeks post-treatment** **Outcome measures:** **Mean time to last illness stool :** All patients Group 1 = 58.2 Group 2 = 75.5 *P* = 0.021 Patients with fever Group 1 = 59.6 Group 2 = 94.6 *P* = 0.046 Patients with faecal leucocytes (>3/HPF) Group 1 = 57.7 Group 2 = 106.5 *P* = 0.025	**Funding :** Burroughs Wellcome Company Grant AI 23049 National Institutes of Health Applicable to UK Baseline comparability Similar for age, prior duration of illness, mean no stools in 24 hours prior to therapy, fever, dehydration, three faecal leucocytes per high-power field. Allocation concealment : Not stated Sequence generation : Not stated Blinding of outcome assessors : Daily assessments blinded – made by parents. Other assessments unclear Loss to follow up : None

	12 patients had Shigella 9 patients had Campylobacter 2 patients had Salmonella 4 patients had Cryptosporidium 6 patients had Giardia lablia	***Mean no of unformed stools in 5 day period :*** All patients Group 1 = 9.8 Group 2 = 12.5 *P* = NS Patients with fever Group 1 = 9.1 Group 2 = 17.3 *P* = NS Patients with faecal leucocytes (>3/HPF) Group 1 = 10.1 Group 2 = 18.1 *P* = 0.041 ***Post treatment no of unformed stools in wk1 and wk2*** All patients Patients with fever Patients with faecal leucocytes (>3/HPF) Group 1 Group 2 *P* = NS	Intention to treat analysis : Not stated Power calculation : Not stated 50/141 partipants had body weight <3rd percentile for age (Mexican standards)

7.8 Traveller's diarrhoea

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
De Bruyn 2000 [155] Location :	Study Type Cochrane systematic review Evidence Level 1+	**Total number of participants** Twelve trials included in total, nine relevant here *n* = 1174 Randomised into two treatment arms Group 1 Intervention : Antibiotic therapy *n* = 664 Group 2 Intervention : Placebo *n* = 510	**Inclusion criteria:** All trials in any language in which travellers older than 5 years were randomly allocated to treatment for acute non-bloody diarrhoea with antibiotics and where the causative organism is not known at allocation. To exclude dysentery and persistent diarrhoea at randomisation, acute bloody diarrhoea did not last more than 14 days **Exclusion criteria :** Diarrhoea lasting over 14 days **Withdrawal criteria :**	**Comparison** Antibiotic therapy vs placebo Intervention details: **Group 1:** **Antibiotics used** ***1) Ofloxacin*** Du Pont 1992 ***2) Bicozamycin*** Ericsson 1983 ***3) Ciprofoxacin*** Salam 1994 Wistrom 1992 ***4) TMP, TMP-SMX*** Du Pont 1982 ***5) Norfloxacin*** Mattila 1993 Wistrom 1989 ***6) Fleroxacin*** Steffen 1993 ***7) Atreonam*** Du Pont 1992 **Group 2:** Placebo	**Follow up** Not specified **Outcome measures:** Mean duration of diarrhoea, as assessed by time to last unformed stool 3 trials, 4 comparisons Group 1 *n* = 199 Range of means 24.8–39 hours Group 2 *n* = 264 Range of means 53.5–63.7 WMD -25.86 [95% CI -32.58 to -19.14] Also Wistrom 1992 (poorly reported) Group 1 *n* = 8 Mean 26 h Group 2 *n* = 9 Mean 60 hours Pooled SD 27.989 **Number cured at 72 hours** 6 trials included Group 1 *n*= 330	**Funding :** Applicable to UK

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					Group 2 *n*= 306 OR = 5.90 [95% CI 4.06–8.57] **Severity (no of unformed stools/24 hour period)** Baseline 1 study WMD –0.10 [95% CI –0.81–0.61] 0–24 hours 2 studies Group 1 *n* = 117 Group 2 *n* = 106 WMD –1.59 [95% CI -2.66 to –0.52] 25–48 hours 2 studies Group 1 *n* = 117 Group 2 *n* = 106 WMD –2.10 [95% CI –2.78 to –1.42] 49–72 hours 2 studies Group 1 *n* = 117 Group 2 *n* = 106 WMD –1.38 [95% CI –1.94 to –0.82] **Tolerability** 5 studies Group 1 = 10/523 Group 2 =38/339 OR 2.37 [95% CI 1.50–3.75]	

7.9 Groups for whom antibiotic treatment may be indicated

7.9.1 *E. coli* O157:H7

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Wong 2000 [156] USA	Study type: Prospective Cohort EL = 2+	Total no of patients *n*= 71/73 Cases : *n* = 10 HUS Controls : *n* = 61 no HUS	Inclusion criteria Children younger than 10 years who had diarrhoea caused by *E. coli* O157:H7 Exclusion criteria Definition HUS : A haemolytic anaemia (haematocrit < 30%, with evidence of destruction of erythrocytes on a peripheral blood-smear), thrombocytopaenia (platelet count <150,000/mm^3) and renal insufficiency (serum creatinine concentration that exceeded the upper limit of normal range for age)	Risk factors for HUS development antibiotics administered initial white blood cell count day stool culture obtained Follow up : Period of risk considered to be 14 days from the onset of diarrhoea.	**antibiotics administered** Yes 5/9 No 5/62 *P* = 0.001 Adjusted RR Within first 7 days after onset RR 17.3 [95% CI 2.2–137] *P* = 0.007 Within first 3 days after onset RR 32.3 [95% CI 1.4–737] *P* = 0.03 **initial white blood cell count** 3200–8700/mm^3 0/18 8800–11,800/mm^3 1/18 11,900–14,200/mm^3 3/18 14,200–24,600/mm^3 6/17 Significant linear trend observed. *P* = 0.005 Adjusted and analysed as a continuous outcome (RR 1.5 [95% CI 1.1–2.1] *P* = 0.02) Adjusted RR WBC count ≥ 13,000 RR 6.0 [95% CI 1.2–29.8] *P* = 0.03 **day stool culture obtained** Days 1–2 of illness 8/24 Day 2 of illness 2/22 Days 4–7 of illness 0/25 Significant linear trend observed	Applicable to UK Funding : National Institutes of Health Baseline characteristics ; Similar for age, sex, bloody diarrhoea, fever, vomiting, initial temperature readings and lab test results (serum urea nitrogen or creatinine)

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					P = 0.01 Adjusted RR RR 0.3 [95% CI 0.1–0.7] *P* = 0.008 *Significant linear trend observed for positive E. coli O157:H7 stool culture* *P* = 0.04 Days 2–4 of illness 6/24 Day 5 of illness 3/19 Days 6–10 of illness 1/28 Adjusted RR – not performed *Significant linear trend observed for day of initial white blood cell count obtained*. *P* = 0.009 Days 1–3 of illness 7/25 Days 4–5 of illness 3/25 Days 6–10 of illness 0/21 Adjusted RR - NS *Significant linear trend observed for no of medications taken for E. coli infection P* = 0.002 0 2/46 1 5/20 2 3/5 Adjusted RR – not performed	
Bell 1997 [157] USA	Study type: retrospective cohort EL = 2+	Total no of patients *n*= 278/324 (46 children did not participate –reasons noted) Cases : *n* = 37	Inclusion criteria Symptomatic, culture confirmed *E. coli* O157:H7 infection or developed HUS in Jan-Feb 1993, <16 years old and resided in Washington State. Exclusion criteria	Risk factors for HUS examined	Data collection from A telephone questionnaire by health dept staff of parents of participants within two weeks of their onset of illness. A second telephone questionnaire of parents 2–4 months later by research interviewers verifying previous data collected and collecting further data.	Applicable to UK Funding : Children's Hospital Foundation (Seattle) American College of Gastroenterology Baseline characteristics ; Similar for age, sex, and annual family income

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
			Definitions		Medical record examination	
		Controls :	Bloody diarrhoea = parental report of visible blood in stool			
		n = 241			Median age 6 years (Range 0–15)	
			Fever = temperature ≥ 38.5C at any site			
			Treatment = 2 doses of therapy within first 3 days of first symptoms		**Clinical risk factors**	
			Complete HUS – platelet count <150,000/microL, haematocrit <30% with evidence of intravascular haemolysis on peripheral blood smear and blood urea nitrogen >20 mg/dL		*Vomiting n* = 278 HUS developed - 29/153 HUS did not develop – 8/125 (RR 3.0 [95% CI 1.4–6.2])	
			Incomplete HUS = two of criteria above		*Bloody diarrhoea present n*= 271 HUS developed - 34/243 HUS did not develop – 2/28 (RR 2.0 [95% CI 0.5–7.7])	
					Fever n= 225 HUS developed – 11/56 HUS did not develop – 20/169 (RR 1.8 [95% CI 0.8–4.1])	
					Early Clinical risk factors	
					HUS development in:	
					Vomiting ≤3 days – 22/127 *No vomiting ≤ 3 days* – 13/140 RR 1.9 [95% CI 1.0–3.5]	
					Children under 5.5 years, vomiting ≤3 days (RR 3.5 [95% CI 1.4 – 9.4]) Children over 5.5 years, vomiting ≤3 days (RR 1.0 [95% CI 0.4–2.4])	
					Medication risk factors	
					Antibiotic received *n* = 50	

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					Antibiotics given, TMP-SMZ = 31/50 Ampicillin/amoxicillin = 13/50 Cephalosporin = 6/50 Metronidazole = 4/50 Tetracycline, erythromycon, ciprofloxacin, gentamicin = 1 patient each received one drug More than one antibiotic = 11/50 **Children receiving antibiotics were more likely to live in a household with annual income over $29,000 (RR 1.7 [95% CI 1.0 – 2.8])** Antimotility agent received *n* = 34 **Early medication risk factors** HUS development in: *Antibiotic given* – 8/50 *No antibiotic given* – 28/218 *P* = 0.56 *Antimotility agent given* – 6/31 *No antimotility agent* – 20/234 *P* = 0.10 *Adsorbant/antimotility given* – 8/43 *No adsorbant/antimotility agent* – 28/229 *P* = 0.26 **Laboratory risk factors** Haematocrit, platelets, BUN, segmented neutrophils and band forms - no association with development of HUS .	

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					HUS development in: *WBC Count 3rd quartile (> 10,500/microL)* – 15/63 *WBC Count 1st,2nd or 4th quartile* – 3/65 *P* < 0.01 *WBC Count 4th quartile (≥ 13,000/microL)* –13/34 *WBC Count 1st,2nd or 3rd quartile* – 5/94 *P* < 0.01	

7.9.2 Salmonella

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Lee 1998 [158] Malaysia	Study type: Retrospective review	Total no of patients *n*= 131/148 (most exclusions because of a second enteropathogen)	Inclusion criteria Children with positive stool cultures for Salmonella species seen in an outpatients department Exclusion criteria Presence of a second enteropathogen Definition Invasive Salmonellosis = presence of bacteraemia or meningitis		Demographic, clinical (diarrhoea, vomiting, fever, hydration status), blood and stool outcome measures were recorded from case notes. Sex M = 69 F = 62 Age : Range 1 month to 14 years 51/131 <6 months 37/131 between 6 and 12 months 43/131 >12 months Diarrhoea – 131/131 Fever – 60/131 Vomiting – 53/131 Bloody diarrhoea – 38/131 >5% dehydration 30/131 Abdominal colic 2/131 Fresh blood per rectum – 1/131 Risk factors for invasive complications Age<6 months Non-invasive salmonellosis = 45/124 Invasive salmonellosis = 6/7 *P* < 0.01 Fever > 38C Non-invasive salmonellosis = 53/124 Invasive salmonellosis = 7/7 *P* < 0.003 Dehydration >5% Non-invasive salmonellosis = 25/124 Invasive salmonellosis = 5/7	Applicable to UK Funding : No details

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					P < 0.01 No significant differences between groups for breast feeding and bloody diarrhoea One fatality from bacteraemia	
Nelson 2002 [159] Hong Kong	Study type: Retrospective review	Total no of patients *n*= 126 Salmonella *n*= 86 Rotavirus *n* = 55 Not specified *n* = 126	Inclusion criteria A sample of patients admitted to hospital with gastroenteritis subsequently identified as being of Salmonella, rotavirus or a non-specified aetiology Exclusion criteria Definition		Travel history Salmonella = 2/35 Rotavirus = 5/14 Not specified = 14/57 Salmonella vs rotavirus *P* = 0.02 Blood in stool Salmonella = 44/86 Rotavirus = 6/53 Not specified = 19/118 Salmonella vs rotavirus *P* < 0.0001 Salmonella vs non-specified *P* < 0.05 Mucus in stool Salmonella =60/85 Rotavirus =26/54 Not specified = 31/117 Salmonella vs rotavirus *P* < 0.0001 Rotavirus vs non-specified *P* < 0.0001 Salmonella vs non-specified *P* < 0.05 >1 episode of vomiting Salmonella =20/85 Rotavirus = 26/54 Not specified = 44/123 Salmonella vs rotavirus *P* < 0.01 Fever during admission Salmonella = 77/86 Rotavirus = 46/55 Not specified = 80/124	Applicable to UK Funding : Baseline characteristics ;

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					Rotavirus vs non-specified $P < 0.0001$ Salmonella vs non-specified $P < 0.05$ Median Age (months) Salmonella = 7.05[3.9–13.6] Rotavirus = 14.3 [7.2–25.8] Not specified = 14.9[6.2–32.3] Salmonella vs rotavirus $P < 0.0001$ Rotavirus vs non-specified $P < 0.0001$ Median Hospital stay (d) Salmonella = 3.4 [2.3–7.0] Rotavirus = 2.9[2–4] Not specified =1.8 [1.1–2.9] Rotavirus vs non-specified $P < 0.0001$ Salmonella vs non-specified $P < 0.05$ Stools (d) Salmonella = 6.2 [4.4–8.3] Rotavirus = 5.3 [3.8–7.6] Not specified = 3.6 [1.5–5.7] Rotavirus vs non-specified $P < 0.0001$ Salmonella vs non-specified $P < 0.05$ No significant differences between groups for sex, siblings at home, dehydration signs, abdominal pain, antihistamine treatment or no of infants <3 months given antibiotic treatment	

8 Other therapies

8.1 Anti-emetics

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Cubeddu 1997 [165] location: Venezuela	**Study Type** RCT **Evidence Level** 1-	**Total no. of patients** *n*= 36 Randomised in three arms: *ondansetron IV n* = 12 *metoclopramide IV n* = 12 *placebo n* = 12	Children aged 6 months to 8 years with GE with emesis, who had vomited twice within 1 hour. Patients were hospitalised for a minimum of 24 hours **Exclusion criteria** Severe dehydration, seizures, rectal T≥ 39C, parenteral anti-emetic medication in the 6 hours prior to the start of the study, parasite-induced GE	**Intervention1** *IV ondansetron (0.3 mg/kg)* ***Intervention2*** *IV metoclopramide (0.3 mg/kg)* **Comparison 1** *IV ondansetron vs* placebo **Comparison 2** *IV metoclopramide vs* placebo **Comparison 3** *IV ondansetron vs* *IV metoclopramide*	**Follow-up** 24 hours **Outcome** Emesis Episodes of diarrhoea **Effect size** <u>No emetic episodes 0–24 hours</u> *IV ondansetron 58%* *IV metoclopramide 33%* *placebo17%* <u>diarrhoea</u> 0–4 episodes *IV ondansetron 4/12* *IV metoclopramide 2/12* placebo 8/12 >4 episodes *IV ondansetron 8/12* *IV metoclopramide 10/12* placebo 4/12	**Funding** Glaxo Wellcome Research and Development **Comments** Baseline comparability between the two groups not adequate (only on gender and food intake) Method of randomisation: not reported blinding of outcome assessor: unclear power calculation: no *oral rehydration proceeded at 30 min intervals for 4 hours (WHO rec) and was given after the 30 min following the anti-emetic/placebo administration.
Freedman 2006 [163] location: USA	**Study Type** RCT **Evidence Level** 1+	**Total no. of participants** *n* = 215 Randomised in two arms: <u>Intervention group</u> *n*= 108 <u>Control group</u> *n* = 107	Children aged 6 months to 10 years with GE (at least one episode of vomiting within the 4 hours preceding triage, at least one episode of diarrhoea and mild to moderate dehydration) **Exclusion criteria**	**Intervention** *oral ondansetron (tablets)* *from 8 kg to 15 kg: 2 mg* *from 15 kg to 30 kg: 4 mg* *>30 kg: 8 mg* **Comparison**	**Follow-up** Day 3 and day 7 after randomisation **Outcome** Cessation of vomiting (vomiting episodes) IV rehydration hospitalisation	**Funding** GlaxoSmithKline National Center for Research Resources of the National Institutes of Health **Comments**

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
			Body weight<8 kg, severe dehydration, underlying disease that could affect the assessment of dehydration, history of abdominal surgery, hypersensitivity to ondansetron.	*oral ondansetron vs.* *placebo*	episodes of diarrhoea **Effect size** Cessation of vomiting *oral ondansetron 92/107* *placebo 70/107* IV rehydration *oral ondansetron 15/107* *placebo 33/107* hospitalisation *oral ondansetron 4/107* *placebo 5/107* *episodes of diarrhoea(mean)* *oral ondansetron 1.4* *placebo 0.5* *P* < 0.001	Method of randomisation and allocation concealment adequate. Loss to follow-up: 4/214 on day 3 8/214 on day 7 baseline comparability: adequate *oral rehydration: 1 hour period of intense OR was initiated 15 min after the administration of the medication, and then followed until disposition was determined (WHO rec).
Ramsook 2002 [164] Location: USA	**Study Type** RCT **Evidence Level** 1+	**Total no. of participants** *n* = 145 Randomised in two arms: Intervention group *n*= 74 Control group *n* = 71	Children aged 6 months to 12 years with GE presenting at least 5 episodes of vomiting in the preceding 24 hours and who did not receive anti-emetics **Exclusion criteria** Underlying chronic conditions, possible appendicitis, UTI, severe GE requiring immediate IV fluids.	**Intervention** *Oral ondansetron every 8 hours.* *from 6 months to 1 year:2 mg* *from 1 year to 3 years:4 mg* *from 4 years to 12 years:5 ml* **Comparison** *Oral ondansetron* *vs.* *placebo*	**Follow-up** : 48 hours **Outcome** Emesis (cessation of vomiting) IV fluids administration Frequency of diarrhoea **Effect size** Cessation of vomiting emergency department stay *oral ondansetron 64/74* *placebo 46/71* first 24 hours *oral ondansetron 37/64* *placebo 30/56* second 24 hour period *oral ondansetron 43/62* *placebo 30/51* IV rehydration (*from histogram) *oral ondansetron 8%* *placebo 22.5%*	**Funding** GlaxoWellcome Research and Development **Comments** *rehydration protocol: pedyalite first choice (if not Gatorade) randomisation and allocation concealment were adequate, the study was double-blind. Baseline comparability of the groups adequate. Power calculation: yes Loss to follow-up: none in the emergency department stay, 25/145 at 24 hours, 32/145 at 48 hours.

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					P = 0.015 hospitalisation *oral ondansetron 2/74* *placebo 11/71* *episodes of diarrhoea(mean)* *oral ondansetron 1.4* *placebo 0.5* *P* < 0.001	
Roslund 2008 [160] Location : USA	**Study Type** RCT **Evidence Level** 1+	**Total no. of participants** *n* = 106 Randomised in two arms: Intervention group *n*= 51 Control group *n* = 55	Children aged 1–10 years with acute gastritis or gastroenteritis and mild to moderate dehydration who failed oral rehydration therapy in the emergency department. **Exclusion criteria** Anitemetics in previous 6 hours, underlying chronic illness, shock state requiring immediate IV fluids, severe (≥10%) dehydration, known sensitivity to $5HT_3$ antagonists	**Intervention** *Oral ondansetron.* *Under 15 kg :2 mg(0.5tablet)* *Between 15 – 30 kgs:4 mg(1 tablet)* *Over 30 kg :6 mg (1.5 tablet)* **Comparison** *Oral ondansetron* *vs.* *placebo*	**Follow-up** Daily until symptoms resolved up to 6 days **Outcome** Emesis (cessation of vomiting) IV fluids administration Frequency of diarrhoea **Effect size** receipt of IV hydration *oral ondansetron 9/48* *placebo 30/55* *RR 0.34;95% CI 0.18–0.65* hospitalisation *oral ondansetron 3/51* *placebo 7/55* *RR 0.46; 95% CI 0.13–1.69* *episodes of diarrhoea(mean)* *oral ondansetron 1.4* *placebo 0.5* *P* < 0.001 <3 episodes of vomiting post discharge *oral ondansetron pts) 93%* *placebo pts 88%*	**Funding** GlaxoSmithKline supplied placebo tablets No other funding details **Comments** Randomisation and allocation concealment were adequate, the study was double-blind. Baseline comparability of the groups similar except significantly more children in the ondansetron group were 'moderately' dehydrated. Hence more children were mildly dehydrated in the placebo group but this was not statistically significant Power calculation: yes Loss to follow-up: 9% did not participate in follow up telephone interviews Intention to treat analysis (3 patients in ondansetron group incorrectly diagnosed)

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					median no of vomiting episodes *oral ondansetron 0 (range 0–13)* *placebo 0 (range 0–4)* *mean no of vomiting episodes* *oral ondansetron 0.71* *placebo 0.5* *<3 episodes of diarrhoea post discharge* *oral ondansetron pts 80%* *placebo pts 93%* *median no of vomiting episodes* *oral ondansetron 0 (range 0–20)* *placebo 0 (range 0–6)* *mean no of vomiting episodes* *oral ondansetron 1.76* *placebo 0.45*	

8.2 Antidiarrhoeal agents

8.2.1 Adsorbent agents

8.2.1.1 Kaolin

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Watkinson 1982 [166] location: The Gambia	Study Type quasi-RCT Evidence Level 1-	Total no. of patients *n*= 97 Randomised in two arms: *Intervention group n* = 45 *Control group n* = 52	Children between 3 and 18 months with diarrhoea Exclusion criteria Diarrhoea associated with haematologically proven malaria or with a bacterial infection necessitating ABT	Intervention *Kaolin (5 ml t.d.s.)* Comparison *GES + Kaolin vs GES*	Follow-up Not stated Outcome Duration diarrhoea after treatment in days Mean number of stools per day **Effect size** Duration diarrhoea (mean+-SD) Intervention gp 5.8+-4.7 Control gp 4.7+-4.3 number of stools per day (mean+-SD) Intervention gp 3.7+-1.2 Control gp 3.7+-1	Funding none Comments Participants allocated in the groups by birth order Compliance with the doses of Kaolin was poor in 33% of the participants the two groups were slightly different according to age allocation concealment and loss to FU: *n*.s. blinding outcome assessor: no power calculation: no

8.2.1.2 Activated charcoal

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Sebodo 1982 [167] location: Indonesia	**Study Type** RCT **Evidence Level** 1-	**Total no. of patients** *n*= 39 Randomised in two arms: *Intervention group n* = 16 *Control group n* = 23	Children with acute GE and severe dehydration aged between 1 ½ months and 10 years **Exclusion criteria** Acute GE due to Entamoeba histolytica	**Intervention** *Activated charcoal* *3x166 mg: up to 6 months* *3x250 mg: from 6 to 12 months* *3x375 mg:from 1 to 2 years* *3x500 mg: from 2 to 5 years* *3x500 mg: more than 5 years* *The activated charcoal was given until a day after the cessation of the diarrhoea* **Comparison** *Ringer lactate solution + OGE + activated charcoal vs ringer lactate solution + OGE*	**Follow-up** Not stated **Outcome** Duration diarrhoea Total ORS Total IV fluids **Effect size** (mean+-SD) <u>Duration diarrhoea (days)</u> Intervention gp 2.125+-0.8 Control gp 3+-1.17 <u>Total ORS (pack)</u> Intervention gp 3.25+-2.08 Control gp 5.43+-3.22 <u>Total IV fluids (bottle)</u> Intervention gp 3.19+-1.17 Control gp 3.74+-2.30	**Funding** none **Comments** Study poorly reported (Method of randomisation, allocation concealment, follow-up, baseline comparability of the two groups)

8.2.1.3 Smectite

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Szajewska 2006 [168] Poland	**Study Type** Systematic Review **Evidence Level** 1+	9 RCTS included in the review Total number of participants 1238 randomised in two: Intervention group: 622 Control group: 616 Gilbert 1991 (location : France)- 36 patients Guarino 2001 (location : Italy)- 804 patients Lachaux 1986 (location : France)- 36 patients Lexomboon 1994 (location : Thailand)- 66 patients Madkour 1993 (location : Egypt)- 90 patients Narkeviciute 2002 (location : Lithuania)- 54 patients Osman 1992 (location : Egypt)- 60 patients Vivatvakin 1992 (location : Thailand)- 62 patients Zong 1997 (location : China)- 30 patients	Children between 1 to 60 months of age with acute diarrhoea and treated in hospitals or as outpatients.	**Intervention** Smectite (daily doses from 3 to 6 g per day) **Comparison** *Smectite vs placebo or no additional treatment*	**Follow-up** Varied across studies: - not reported for three trials (Gilbert, Lachaux and Lexomboon) -3 days (Madkour) - 5 days (Guarino and Osman) -24 hours (Narkeviciute) -from to 48–120 hours (Vivatvakin) -3–6 days (Zong) **Outcome** duration of diarrhoea frequency of stools vomiting (number of episodes of vomiting and duration of vomiting) no symptoms by day 3 and by day 5 diarrhoea for ≥ 7 days adverse events **Results** <u>Duration of diarrhoea (h)</u> -6 trials- WMD -22.7 [95% CI -24.80 to -20.61] <u>frequency of stools</u> <u>0–6 hours</u> -2 trials- WMD -0.07 [95% CI -0.6 to 0.4] <u>6 to 24 hours</u> -2 trials- WMD -0.33; 95% CI -0.8 to 0.2 <u>24 to 48 hours</u> -2 trials- WMD -0.62 [95% CI -1 to -0.2] <u>vomiting</u>	**Funding** Partially funded by a grant from the Medical University of Warsaw **Comments** Well-conducted systematic review

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					number of episodes -2 trials- WMD -0.02 [95% CI -0.5 to 0.6] Duration of vomiting (h) -1 trial- WMD -0.1 [95% CI -0.15 to 0.3] no symptoms by day 3 -4 trials- RR 1.64 [95% CI 1.36 to 31.98] no symptoms by day 5 -4 trials- RR 1.19 (95% CI [0.93–1.53]) diarrhoea for > 7 days -1 trial- RR 0.6 [95% CI 0.42–0.85] adverse events constipation -1 trial- RR 5.8 [95% CI 0.7–47.1] * three RCTs reported no adverse events associated with short-term treatment with smectite	

8.2.2 Antisecretory agents

8.2.2.1 Racecadotril

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Salazar-Lindo 2000 [169] Location : Peru	**Study Type** RCT **Evidence** **Level** 1+	**Total number of participants** *n* = 135 Randomised into two treatment arms Group 1 Racecadotril *n* = 68 Group 2 Placebo *n* = 67	**Inclusion criteria:** Boys aged between 3–35 months admitted for dehydration, with watery diarrhoea for 5 days or less, had passed 3 or more diahorreic stools in 24 hours prior to admission and had passed 1 diarrhoeic stool within 4–6 hours post-admission. **Exclusion criteria :** Blood in the stool, severe dehydration (inability to drink because of drowsiness), any serious concomitant illness **Withdrawal criteria :** Blood in stools during first 24 hours, antibiotic treatment for concomitant illness, physician judged treatment ineffective, consent withdrawal, severe adverse events	**Comparison** racecadotril vs placebo **Group 1:** racecadotril 1.5 mg/kg body weight every 8 hours **Group 2:** placebo every 8 hours Both treatments given as saccharose-containing powders of identical taste and appearance, with small amount of water to aid swallowing. Treatment given for 5 days or until diarrhoea stopped. Standard oral rehydration given as needed to all boys (111 mmol glucose, 90 mmol sodium, 20 mmol potassium, 80 mmol chloride, 10 mmol citrate per litre)	**Follow up** every 4 hours for the first 48 hours then at 5 days or at the time of recovery if earlier **Outcome measures:** *- Mean stool output in first 48 hours* *- Hourly rate of stool production in first 48 hours* *- Mean total stool output before recovery* *- Duration of diarrhoea* *- Cure rate at 5 days* *- Oral rehydration solution intake* Effects measured for all participants and for rotavirus positive boys **Effect size :** *Mean stool output in first 48 hours* All participants Group 1 = 92 +/- 12 g/kg Group 2 = 170 +/- 15 g/kg *P* < 0.001 Rotavirus +ve Group 1 = 105 +/- 17 g/kg Group 2 = 195 +/- 20 g/kg *P* < 0.001 *Hourly rate of stool production in first 48 hours* All participants Group 1 = 1.8 +/- 0.2 g/kg/hr Group 2 = 3.1 +/- 0.3 g/kg/hr *P* < 0.001 Rotavirus +ve No details	**Funding :** grant from Bioprojet Pharma (developers of racecadotril) Applicable to UK Baseline comparability Similar for age, weight, stools in previous 24 hours, stool consistency on previous 24 hours, diarrhoea duration pre-hospitalisation, bacteria and rotavirus detected in stool. 8 boys in racecadotril group had a respiratory illness compared to one in the placebo group Allocation concealment : not stated Sequence generation : not stated Blinding of outcome assessors : not stated Loss to follow up : 9 boys in group 1, 14 boys in group 2 Intention to treat analysis : yes Power calculation : not stated

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					Mean total stool output before recovery All participants Group 1 = 157+/- 27 g/kg Group 2 = 331 +/-39 g/kg *P* < 0.001 Rotavirus +ve Group 1 = 174+/-36 g/kg Group 2 = 397+/-37 g/kg *P* < 0.001 *Duration of diarrhoea* Rotavirus +ve Group 1 = median 28 h Group 2 = median 72 hours Rotavirus –ve Group 1 = median 28 hours Group 2 = median 52 h *Cure rate at 5 days* All participants Group 1 = 57/68 Group 2 = 44/67 *Oral rehydration solution intake* @ Day 1 Group 1 = 439+/-49 ml Group 2 = 658+/-59 ml @Day 2 Group 1 = 414+/-68 ml Group 2 = 640+/-68 ml	
Cezard 2001 [170] Location :France	Study Type RCT Evidence Level 1+	**Total number of participants** *n*= 172 Randomised into two	Inclusion criteria : 172 children hospitalised for severe acute diarrhoea aged between 3 months to 4 years of both sexes. Participants had watery diarrhoea (3 watery stools per day or more) for	**Comparison** racecadotril vs placebo **Group 1:** racecadotril 1.5 mg/kg body weight 3 times daily	**Follow up for 5 days** **Outcome measures:** *-- Hourly rate of stool production in first 24 hours* *- Hourly rate of stool production in first 48 hours*	Applicable to UK **Funding** : no information supplied

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
		treatment arms Group 1 Racecadotril *n* = 89 Group 2 Placebo *n* = 83	a duration of less than 72 hours and had passed one watery stool post-admission Exclusion criteria: Chronic diarrhoea, weight for age deficit of 20% or more of NCHS standard, systemic illness, antibiotic or antidiarrhoeal drug or acetylsalicylic acid usage in preceding 48 hours	**Group 2:** Placebo 3 times daily Both treatments given as granules of identical taste and appearance. Oral rehydration given to all children ad libitum each hour for first 24 hours of study either orally or by gastric tube (111 mmol glucose, 49 mmol sodium, 25 mmol potassium, 25 mmol chloride, 24 mmol carbonate, 58 mmol saccharose per litre) Treatment given for 5 days or until diarrhoea stopped.	Effects measured for all participants and for rotavirus positive boys **Effect size :** *Hourly rate of stool production in first 24 hours (read from graph)* Group 1 = 11 g/hr Group 2 = 16 g/hr *P* < 0.001 *Hourly rate of stool production in first 48 hours (read from graph)* All participants Group 1 = 8 g/hr Group 2 = 16 g/hr *P* < 0.001 Rotavirus +ve Group 1 = 8 g/hr Group 2 = 19 g/hr *P* < 0.001 Rotavirus –ve Group 1 = 6 g/hr Group 2 = 13 g/hr No evidence of difference between treatments depending on rotavirus status (*P* = 0.500)	Baseline comparability Similar for age, weight, height, stools in previous 24 hours, diarrhoea duration prior to inclusion, IV rehydration prior to inclusion, antidiarrhoeal treatment prior to inclusion, abdominal circumference and temperature. Allocation concealment : not stated Sequence generation : not stated Blinding of outcome assessors : not stated Loss to follow up : 28% data presented for full dataset and for per-protocol dataset Intention to treat analysis : yes Power calculation : yes

8.2.2.2 Bismuth subsalicylate

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Chowdhury 2001 [171] location: Bangladesh	**Study Type** RCT **Evidence Level** 1+	**Total no. of patients** *n*= 451 Randomised in two arms: *Bismuth subsalicylate* *n* = 226 *placebo n* = 225	Children aged 4–36 months admitted in the Diarrhoea Hospital of the Matlab Health Research Programme and with a history of acute watery diarrhoea of less than 72 hours duration, with 3 or more watery stools in the last 24 hours. **Exclusion criteria** Use of antimicrobials within the previous 48 hours, blood in the stoll, severe malnutrition, other systemic illness, salicylates intake in the last 24 hours, allergy to salicylates, varicalla or measles in the last 3 months.	**Intervention** bismuth subsalicylate (100 mg/kg per day x 5 days) **Comparison** *bismuth subsalicylate vs* placebo	**Follow-up** for the duration of the hospitalisation + 4 days **Outcome** Onset persistent diarrhoea Duration acute diarrhoea (median) total intake of oral rehydration solution total stool+urine output **Effect size** <u>Onset persistent diarrhoea</u> bismuth subsalicylate 8% placebo 11% <u>Duration acute diarrhoea in h (median)</u> bismuth subsalicylate 36 placebo 42 *P* < 0.057 * in children with rotavirus diarrhoea (>50%) bismuth subsalicylate 56 placebo 72 *P* = 0.03 <u>total intake of oral rehydration solution ml/kg (median+-SD)</u> bismuth subsalicylate 291+-181 placebo 325+-218 *P* = 0.072 <u>total stool+urine output g/kg (median+-SD)</u> bismuth subsalicylate 386+-248 placebo 438+-272 *P* = 0.037	**Funding** Centre for Health and Population Research, via the International Child Health Foundation which received a grant from Procter & Gamble. Aid Agencies of the Government of Australia, Bangladesh, Belgium, Canada, Japan, the Netherlands, Sweden, Sri Lanka, Switzerland, UK and US and international organisations including the UN Children's Fund. **Comments** Well conducted RCT Loss follow-up 8% (lost participants not included in the analysis, initially 489 patients enrolled) * Diarrhoea=3 or more liquid stools in 24 hours PD=diarrhoeal episodes for or more than 14 days
Figueroa-Quintanilla 1993 [172] location: Peru	**Study Type** RCT **Evidence Level** 1+	**Total no. of participants** *n* = 215 Randomised in three arms: <u>BSS 100 mg/kg per day group</u> *n*= 108	Boys from 6 to 59 months that had presented 3 or more watery stools in the preceding 24 hours (acute diarrhoea). **Exclusion criteria** Blood in the stools, diarrhoea for more than 5 days, antibiotics or antidiarrhoeal medication or any treatment with AAS in the 72 hours	**Intervention** BSS (bismuth subsalicylate) 100 mg/kg per day or 150 mg/kg per day, every 4 hours for 5 days or until the diarrhoea stopped. **Comparison1** *BSS (100 mg/kg per day) vs. placebo*	**Follow-up** Hospital stay **Outcome** Duration of diarrhoea (proportion of patients with diarrhoea by day 5) Total stool output (ml/kg) Total volume of vomitus (ml/kg)	**Funding** Grant from the International Child Foundation and Procter&Gamble **Comments** Loss follow-up 8% (lost participants not included in the analysis, initially 275 patients

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
		BSS 150 mg/kg per day group *n*= 108 placebo group *n* = 107	before admission, clinical evidence of another illness requiring ABT, severe malnutrition, allergy to salicylate or bismuth, exclusively breastfed.	**Comparison2** *BSS (150 mg/kg per day) vs. placebo* **Comparison3** *BSS (100 mg/kg per day) vs. BSS (150 mg/kg per day)*	Total intake of rehydration (ml/kg) Hospital stay (days) **Effect size** Duration of diarrhoea BSS (100 mg/kg per day) 89% BSS (150 mg/kg per day) 88% placebo 74% Total stool output (mean+-SD) BSS (100 mg/kg per day) 182+-197 BSS (150 mg/kg per day) 174=-159 placebo 260+-254 Total volume of vomitus (mean+-SD) BSS (100 mg/kg per day) 11.6+- 19.6 BSS (150 mg/kg per day) 8.7+- 18.3 placebo 16.2+- 27 Total intake of rehydration (mean+-SD) BSS (100 mg/kg per day) 239+-177 BSS (150 mg/kg per day) 236+-152 placebo 314+- 234 Hospital stay (mean+-SD) BSS (100 mg/kg per day) 3.3+- 1.5 BSS (150 mg/kg per day) 3.4+- 1.5 placebo 4.1+- 2.1	enrolled) Well conducted RCT (outcomes other than duration of diarrhoea might refer to the whole stay in hospital but not clear)
Soriano-Brucher 1991 [173] location: Chile	**Study Type** RCT **Evidence Level** 1+	**Total no. of participants** *n* = 142 Randomised in two arms: Intervention group *n*= 72 Control group *n* = 70	Children 4–36 months of age with diarrhoea and dehydration <72 hours and who needed hospitalisation for therapy and rehydration **Exclusion criteria** Symptoms >72 hours, blood in stools, severe malnutrition, antibiotics use in the previous 48 hours, salicylate intake>20 mg/kg in the previous 12 hours, allergy to bismuth/salicylate, acute illness not consistent with diarrhoeal state.	**Intervention** bismuth subsalicylate (100 mg/kg per day x 5 days) **Comparison** *bismuth subsalicylate vs* placebo	**Follow-up :** 8 days -patients were monitored in hospital for at least 5 days and then were followed for 3 more days (whether they remained in hospital or were discharged) **Outcome** Disease duration in h: time to last abnormal stool weight, time to last loose/watery stool, time until last unformed stool. Duration of hospital stay IV fluids intake (mL/kg) **Effect size** Disease duration: last loose/watery stool	**Funding** Procter&Gamble Company **Comments** Patients lost in the follow-up (13.4%) were excluded from the analysis Method of randomisation not reported. *treatment regimes were in accordance with WHO recommendations, with initial IV fluids (for at least 8 hours) and followed by oral rehydration

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					bismuth subsalicylate 73.4 placebo 107.5 *P* < 0.02 time until last unformed stool *bismuth subsalicylate 130.4* placebo 170 *P* < 0.01 Duration of hospital stay *bismuth subsalicylate 6.93* placebo 8.48 *P* < 0.02 IV fluids intake *The authors reported that the group receiving BSS required less IV fluids (day 3 and day 5). than the placebo group, the difference being statistically significant. No data but an histogram is provided.* Day 3 *bismuth subsalicylate ap. 30* mL/kg placebo approx. 45 mL/kg day 5 *bismuth subsalicylate ap. 20 m*L/kg placebo *42 m*L/kg	

8.2.3 Antimotility agents

8.2.3.1 Loperamide

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Su-Ting TL 2007 [174] USA	**Study Type** Systematic Review **Evidence Level** 1+	13 RCTS included in the review Total number of participants 1788 randomised in two arms across all the studies: Intervention group: 975 Control group: 813 Prakash 1980 (location: India)- 472 patients Owens 1981 (location: Lybia)- 100 patients Kassem 1983 (location: Egypt)- 100 patients Anderson 1984 (location: Mexico)- 56 patients Anonymous 1984 (location: UK)- 303 patients Chavarria 1984 (location: Costa Rica)- 34 patients Vesikari 1985 (location: Finland)- 31 patients Cordier 1987 (location: France)- 50 patients Ghisolfi 1987 (location: France)- 63 patients Karrar 1987 (location:	Children aged between 0–132 months suffering from acute diarrhoea (inpatients -10 trials- and outpatients -3 trials-included).	**Intervention** Loperamide (daily doses varied across studies) **Comparison** *Loperamide vs placebo*	**Follow-up** Varied among the studies **Outcome** Proportion of children with diarrhoea at 24 and 48 h Duration acute diarrhoea (median) Stool count (mean count at 24 hours) Adverse events **Results** <u>Diarrhoea at 24 hours</u> -4 trials- RR 0.66 [95% CI 0.57–0.78] -3 trials with same definition for diarrhoea resolution (=last unformed stool)- RR 0.66 [95% CI 0.56–0.77] <u>Diarrhoea at 48 hours</u> -4 trials- RR 0.59 [95% CI 0.45–0.78] <u>Duration diarrhoea (mean +- SD)</u> -6 trials- WMD -0.80 [95% CI -0.87 to -0.74] -5 trials with loperamide dose ≤ 0.25 mg/kg per day- WMD -0.7 [95% CI -0.6 to -0.8] <u>Stool count at 24 hours (mean +- SD)</u> -4 trials- count ratio 0.84 [95% CI 0.77–0.92] *The results reported favoured significantly the use of loperamide in shortening the duration of diarrhoea and reducing the number of stools <u>Adverse events</u> -12 trials- **ileus, lethargy, death**	**Funding** No specific funding received **Comments** Well-conducted systematic review The authors concluded that in children under 3 years, malnourished, moderately/severely dehydrated or with blood in the stools the risk of adverse events from loperamide outweighs the benefits.

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
		Saudi Arabia)- 59 patients Motala 1990 (location: South Africa)- patients 60 Bowie 1995 (location: South Africa)- 200 patients Kaplan 1999 (location: Mexico)- 258 patients			intervention group 8/927 control group 0/764 **ileus, abdominal distension, lethargy/sleepiness, death** intervention group 21/927 control group 4/764 * serious adverse events occurred among children under 3 years	

8.3 Micronutrients and fibre

8.3.1 Zinc

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Al-Sonboli 2003 [181] Location: Brazil Setting: hospital	**Study Type** RCT **Evidence Level** 1-	**Total no. of participants** *n* = 74 Randomised in two arms: Intervention group *n*= 37 Control group *n* = 37	Children aged 3–60 months with acute diarrhoea for <7 days or 1 or more loose stool with blood in the previous 24 hours and at least mild dehydration **Exclusion criteria** Severe systemic infection, antimicrobials/ anti-diarrhoeals in the 72 hours prior to admission, severe malnutrition (<60%WFA, NCHS).	**Intervention** Zinc sulfate - 22.5 mg 3–6 months - 45 mg 7–60 months **Control** Vitamin C - 250 mg 3–6 months - 500 mg 7–60 months **Comparison** *zinc vs control*	**Follow-up** 5 days (or until resolution of diarrhoea, defined by clinical judgement) **Outcome** 1.mean duration of diarrhoea (d) 2.stool frequency (number of stools) **Effect size** 1.mean (SD) duration of diarrhoea *intervention group 1.2 (0.8)* *placebo group 2.5 (1.8)* *P* < 0.*001* 2. mean (SD) number of stools *intervention group 4.1(4.1)* *placebo group 10 (10.2)* *P* < 0.*01*	**Funding** *n*.s. **Comments** *all children in the trial received Ringer's lactate before ORS -Lost to follow-up:8.6% -Method of randomisation: random numbers -Baseline comparability of the two groups at the start of the study adequate -Double-blinded (assessor and patient) -Allocation concealment non stated -Power calculation *n*.s.
Fisher Walker 2006 [183] Location: Ethiopia, India, Pakistan Setting: community-based	**Study Type** RCT **Evidence Level** 1+	**Total no. of participants** *n* = 1110 Randomised in two arms: Intervention group *n*= 538 Control group *n* = 536	infants from 1 to 5 months with acute diarrhoea for < 72 hours **Exclusion criteria** Severe malnutrition, pneumonia, required hospitalisation for any reason, major congenital malformation, or other serious pre-existent medical condition, live out or plan to move out of study area.	**Intervention** Zinc sulfate 10 mg per day per 14 days **Comparison** *zinc vs placebo*	**Follow-up** until the infant had passed <3 watery stools per 24 hours for at least 48 hours and until the mother confirmed the cessation of the diarrhoea * patients with diarrhoea>9 days were referred to the HC facility for additional clinical assessment **Outcome** 1.mean duration of diarrhoea (h) 2.proportion of diarrhoea d7 3.stool frequency (mean number of stools per day) 4.hospitalisation 5.vomiting 6.death **Effect size** 1.geometric mean (-1SD,+1SD) duration of diarrhoea *intervention group 3.80(1.84, 7.85)* *placebo group 3.59(1.82, 7.10)*	**Funding** Johns Hopkins Family Health and Survival and Global Research Activity Cooperative Agreement with the US Agency for International Development **Comments** -Method of randomisation: adequate -Allocation concealment: yes -power calculation: yes -Baseline comparability of the two groups at the start of the study was not adequate for gender and breast-feeding -Double-blinded (assessor and patient)

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					2.proportion (95% CI) of diarrhoea >7 days *intervention group 25.1(21.5, 29.0)* *placebo group 20.3(17.0, 24,0)* 3. mean (SD) number of stools per day *intervention group 5(2.3)* *placebo group 5(2.4)* 4.hospitalisation, 1st 3 days of study *intervention group 0/554* *placebo group 1/556* 5.vomiting *intervention group 8.7%* *placebo group 6.2%* 6.death (Ethiopia), 1st 3 days of study *intervention group 1/554* *placebo group 1/556*	-Lost to follow-up: 36/1074 during the 1st 3 days of the study (and were excluded from the analysis)
Bhatnagar 2004 [182] Location: India Setting: hospital	**Study Type** RCT **Evidence Level** 1+	**Total no. of participants** *n* = 287 Randomised in two arms: Intervention group *n*= 143 Control group *n* = 144	boys aged 3–36 months with acute diarrhoea for <72 hours with mild dehydration **Exclusion criteria** Severe malnutrition (<65% WFH, NCHS), visible blood in stool, severe systemic illness	**Intervention** Zinc sulfate per 14 days - 15 mg: <12 months - 30 mg: > 12 months **Comparison** *zinc vs control* * both groups received multivitamin	**Follow-up** Until cessation of diarrhoea= time of the last abnormal stool before a 12 hour period when no stool had been passed or before the passage of two consecutive formed stools) **Outcome** 1. duration of diarrhoea (h) 2.diarrhoea at d5 3.diarrhoea at d7 4.stool output (g/kg) 5.vomiting **Effect size** 1.mean (SD) duration of diarrhoea *intervention group 55.8 (37)* *placebo group 64.6 (45.6)* 2.diarrhoea at d5 *intervention group 17/132* *placebo group 27/134* 3.diarrhoea at d7 *intervention group 1/132* *placebo group 9/134* 4.total stool output GM (CI) *intervention group 111 (86,147)* *placebo group 148 (116,190)*	**Funding** WHO and the Indian Council of Medical Research **Comments** -Method of randomisation: random numbers -Allocation concealment yes -Power calculation: yes -Double-blinded (assessor and patient) -Baseline comparability of the two groups at the start of the study adequate -Lost to follow-up: 21/287 (7%), not included in the final analysis

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					5.vomiting (at any time in the study) *intervention group 65%* *placebo group 59%*	
Brooks 2005 [212] location: Bangladesh Setting: hospital	**Study Type** RCT **Evidence Level** 1+	**Total no. of patients** *n* = 275 Randomised in two arms: *Intervention 1 group n* = 91 *Intervention 2 group n* = 91 *Placebo group n* = 93	males aged 1–6 months with diarrhoea <72 hours and ≥3 watery stools in the preceding 24 hours, some dehydration or ≥ 100 ml of watery stool within 4 hour observation period **Exclusion criteria** Clinical signs of zinc deficiency, kwashiorkor, weight-to-age <60%WFA (NCHS), bloody stool, other comorbidity that required to be managed in another ward or proven or suspected cholera. * patients dehydration was corrected before enrolment: some (moderate) dehydration with 100 ml/kg ORS for 4 hours; severe dehydration with initial IVT and then ORS *Those who remained dehydrated were treated as cholera patients and therefore not enrolled in the study	**Intervention 1** 5 mg zinc acetate/5 ml **Intervention 2** 20 mg zinc acetate/5 ml ***placebo*** *5 ml placebo* *treatment given for the duration of illness* **Comparison** *20 mg zinc vs placebo* *5 mg zinc vs placebo* *20 mgzinc vs.5 mg zinc*	**Follow-up** Duration of illness **Outcome** 1.total duration of diarrhoea after start intervention (d) 2.total stool output (ml) 3.frequency of diarrhoeal stools (number per day) 4. vomiting volume (ml) 5.total IV fluids (ml) 6.total fluid intake (ml) 1.total duration of diarrhoea after start intervention (d) Intervention1 gp 5 (4,6) Intervention2 gp 5 (4,6) Placebo gp 5 (4,6) 2.total stool output (ml) Intervention1 gp 229 (180,256) Intervention2 gp 240 (200,266) Placebo gp 202 (180,246) 3.frequency of diarrhoeal stools (number per day) Intervention1 gp 5 (5,6) Intervention2 gp 5 (5,6) Placebo gp 5 (4,6) 4. vomiting volume (ml) Intervention1 gp 26 (11.8,36.8) Intervention2 gp 18.5 (5.4,34.9) Placebo gp 37 (7.7,63.9) 5.total IV fluids (ml) Intervention1 gp 300 (200,400) Intervention2 gp 240 (213,504) Placebo gp 300 (100,500) 6.total fluid intake (ml) Intervention1 gp 500 (500,527) Intervention2 gp 500 (500,500) Placebo gp 500 (500,572) **There were no significant differences found**	**Funding** Supported by Johns Hopkins Family Health and Chld Survival Cooperative Agreement with the US Agency for International Development, by a cooperative agreement between the International Centre for Diarrhoeal Diseases Research, Bangladesh and US AID and by core donors to the ICDDR,B. **Comments** End of diarrhoea=formation of 3 soft stools or the absence of stools for ≥12 hours -all the study members and patients were blinded to group assignment -adequate method of randomisation, baseline comparability between groups, power calculation done -allocation concealment unclear -15/275 lost at follow-up (95% of the enrolled participants included in the analysis)

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					between the groups	
Larson 2005 [184] Location: Bangladesh Setting: outpatients and inpatients	**Study Type** RCT **Evidence Level** 1+	**Total no. of participants** *n* = 1067 Randomised in two arms: <u>Intervention group</u> *n*= 534 <u>Control group</u> *n* = 533	Children aged 3–59 months with acute diarrhoea, having taken ORS as instructed, no vomiting reported in the past 2 hours for the short-stay ward or 30 min in the outpatient clinic, and no longer dehydrated **Exclusion criteria** Returning to the hospital with an ongoing episode of diarrhoea, zinc supplementation	**Intervention** Zinc sulphate 20 mg per dayay per 10 days **Control** placebo **Comparison** *zinc vs placebo*	**Follow-up** 60 minutes from the administration of the study intervention (at the termination of the study observation period all children received zinc as per diarrhoea-management protocol of the hospital or clinic) **Outcome** Vomiting (=the forceful emptying of stomach contents) **Effect size** Short-stay ward treatment group <u>1.post-treatment vomiting</u> *intervention group(N=267): 71 (26.6%)* *placebo group(N=266): 37 (13.9%)* outpatient clinic treatment group <u>1.post-treatment vomiting</u> *intervention group (N=267): 68 (25.5%)* *placebo group (N=267): 27 (10.1%)*	**Funding** Bill and Melinda Gates Foundation-funded project **Comments** -All participants enrolled were included in the analysis (lost to follow-up reported 0%) -Method of randomisation: adequate -power calculation: yes -Baseline comparability of the two groups at the start of the study adequate -Double-blinded (assessor and patient) -Allocation concealment yes
Sachdev 1988 [185] Location: India Setting: hospital	**Study Type** RCT **Evidence Level** 1-	**Total no. of participants** *n* = 50 Randomised in two arms: <u>Intervention group</u> *n*= 25 <u>Control group</u> *n* = 25	Children aged 6–18 months with dehydration secondary to acute diarrhoea for < 4 days duration **Exclusion criteria** ABT, severe malnutrition, pneumonia, concomitant features (meningitis, pneumonia, liver disease, otitis media, fever>39C)	**Intervention** Zinc 20 mg twice daily day **Comparison** *zinc vs placebo*	**Follow-up** Period of illness **Outcome** 1.mean duration of diarrhoea (h) 2.stool frequency (number of stools per 24 hours) 3.vomiting **Effect size** <u>1 mean (SD) duration of diarrhoea</u> *intervention group 82(42.9)* *placebo group 90.5(40)* <u>2.stool frequency (number of stools per 24 hours)</u> *intervention group 7.6(4.0)* *placebo group 9.3(4.3)* <u>5.vomiting</u> *none of the infants developed emesis secondary to zinc intake*	**Funding** *n*.s. **Comments** -Method of randomisation: no details -no details on the proportion of the participants enrolled and included in the analysis -Baseline comparability of the two groups at the start of the study was adequate -Blinding: unclear -Allocation concealment unclear *AB were given after completion of the rehydration therapy
Sazawal [177]	**Study Type** RCT	**Total no. of participants**	Children aged 6–35 months with four unformed stools in the previous 24 hours and with diarrhoea for	**Intervention** Zinc gluconate 20 mg daily	**Follow-up** Period of illness	**Funding** WHO, Diarrhoeal Disease

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
1995 Location: India Setting: community-based	**Evidence Level** 1+	*n* = 947 Randomised in two arms: Intervention group *n*= 462 Control group *n* = 485	<7 days, with dehydration >7%, permanent resident of Kalkaji **Exclusion criteria** Second visit, malnutrition requiring hospitalisation	(until recovery?) **Comparison** *zinc vs control* * both groups received multivitamin supplements * children who had diarrhoea for 10 days or more were given ABT	(cessation of diarrhoea= the last day of diarrhoea followed by a 72 hours diarrhoea-free period) **Outcome** 1.diarrhoea at d7 2.stool frequency **Effect size** 1.diarrhoea > d7 *intervention group(N=456): 15.4* *placebo group(N=481): 18.5* **children enrolled by day 4 of D* *intervention group (N=284) 10.2* *placebo group (N=285) 16.8* 2. mean (sd) watery stools per day *intervention group 3.1 (9.9)* *placebo group 5.1(14.9)*	Control Programme, the Thrasher Research Fund and the Indian Research Council for Medical Research **Comments** -Lost to follow-up: 10 children were excluded from all the final analysis of the study and 6 other the duration of diarrhoea was unknown (and were excluded from the analysis of duration of diarrhoea) -Method of randomisation: random numbers -Baseline comparability of the two groups: adequate -Double-blinded (assessor and patient) -Allocation concealment yes
Strand 2002 [186] location: Nepal setting: community-based	**Study Type** RCT **Evidence Level** 1+	**Total no. of patients** *n* = 891 *Zinc group n* = 442 *Placebo group n* = 449	children aged 6–35 months with acute diarrhoea for <96 hours **Exclusion criteria** massive dose of vitamin A, had an illness requiring hospitalisation, family intended to leave Bhaktapur within 2 months	**Intervention** zinc gluconate: 15 mg for infants and 30 mg for older children (for +- 10 days) until 7 days after recovery **Comparison** *Zinc vs placebo*	**Follow-up** 1 month **Outcome** 1.diarrhoea at day 3 2. diarrhoea at day 7 3. diarrhoea at day 14 (recovery from diarrhoea= the first of the first 2 consecutive diarrhoea-free days-<3 loose and no watery stools) **Effect size * (mean and 95% CI)** 1.diarrhoea at day 3 RR 0.75 (95% CI 0.61–0.91) *placebo gp 159/449 2. diarrhoea at day 7 RR 0.57 (95% CI 0.38–0.86) *placebo gp 58/449 3. diarrhoea at day 14 RR 0.0.55 (95% CI 0.20–1.47) *placebo gp 11/449	**Funding** EU-INCO-DC and NUFU **Comments** -Lost to follow-up:1% -Method of randomisation: adequate -Baseline comparability of the two groups: adequate -Double-blinded (assessor and patient) -Allocation concealment: yes -power calculation: yes *some of the children were enrolled twice or even three times (if >4 monthd had lapsed from recovery from the previous enrolment episode)

8.3.2 Vitamin A

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Henning 1992 [187] location: Bangladesh setting: Hospital	**Study Type** RCT **Evidence Level** 1+	**Total no. of patients** *n* = 83 Randomised in two arms: *Intervention group n* = 46 *Placebo group n* = 37	Male children aged 1–5 years with watery non-cholera diarrhoea for less than 48 hours. **Exclusion criteria** Children with cholera, those with serious illness (such as pneumonia or severe malnutrition) and those receiving vitamin A within the past 3 months were excluded. *Children with a history of night blindness or clinical signs of vitamin A deficiency were given high-dose vitamin A and excluded from further study.	**Intervention** *Vitamin A 200 000 UI + vitamin E 25 UI* ***placebo*** *vitamin E 25 iu* **Comparison** *Vitamin A vs placebo* ** rehydration therapy and maintenance: rice-based oral rehydration solution* *IV fluids (5%dextrose) were administered if the child had excessive vomiting or inability to take fluids orally*	**Follow-up** Until discharge from hospital when cessation of diarrhoea occurred (= the last liquid stool after which two normal stools occurred or after no stool for 24 hours) **Outcome** 1.total duration of diarrhoea after start intervention (h) 2.total stool output (g/kg/episode) 3.stool output 1st 24 hours (g/kg/h) 4.emetic episodes 1st 24 hours (g per day) 5.Diarrhoea >10 days 6.treatment failures (=children who needed IV fluids after initial rehydration) **Effect size** 1. total duration of diarrhoea * *intervention group 52.1(29.4)* *placebo group 54.6(41.7)* 2.total stool output * *intervention group 143(133.2)* *placebo group 143.6(160.7)* 3.stool output 1st 24 hours* *intervention group 5.8(4.2)* *placebo group 5.5(3.9)* 4.emetic episodes 1st *24 hours* * *intervention group 24.9(59.8)* *placebo group 16.5(46.1)* 5. diarrhoea >10 days *intervention group 0/46* *placebo group 1/37* 6.treatment failures *intervention group 5/46* *placebo group 4/37* *** (mean and SD)**	**Funding** Office of Health, the United States Agency for International Development, and the Institute for International Programs, the Johns Hopkins University and the International Centre for Diarrhoeal Diseases Research, Bangladesh **Comments** *the groups in the final analysis were of unequal sizes because more children in the placebo group had to be excluded after enrolment (reasons for exclusion after enrolment: development of other illnesses like pneumonia, meningitis, measles-, identification of Giardia lamblia, parental refusal to continue). - 9 children in the intervention group and 7 in the placebo group (15/83) withdrew from the study before the episode of diarrhoea was over. All withdrawals occurred when the subjects' clinical status had already improved. Total lost to follow-up: unclear -Method of randomisation: yes -allocation concealment yes -Power calculation: *n*.s. -Baseline comparability: yes
Hossain 1998	**Study Type** RCT	**Total no. of participants**	Children aged 1–7 years with Shigella infection, bloody diarrhoea for < 72 hours (proved by culture of	**Intervention** Single oral dose of	**Follow-up** 5 days	**Funding** United States Agency for International

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
[188] location: Bangladesh setting: hospital	**Evidence Level** 1+	*n* = 83 Randomised in two arms: Intervention group *n*= 42 Control group *n* = 41	the stool or rectal swab) and with no other illnesses. **Exclusion criteria** Children with other acute or chronic illnesses, microscopic stool examination showing trophozoites of Entamoeba histolytica, antibiotic therapy, vitamin A administration within tha last 3 months, weight ≤75% of the national health statistics growth reference median.	vitamin A 200 000 iu plus 25 iu of vitamin E ***placebo*** *vitamin E 25 iu* **Comparison** *Vitamin A vs placebo* * medical care: each child was given nalixidic acid (55 mg/kg every 6 hours). Children were admitted to hospital for 5 study days after receiving the trial treatment.	**Outcome** Clinical cure Bacteriological cure **Effect size** 1.Clinical cure *intervention group 19/42* *placebo group 8/41* 2.Bacteriological cure *intervention group 16/42* *placebo group 16/41*	Development with the International Centre for Diarrhoeal Disease Research, Bangladesh **Comments** Subjects were considered **clinically cured** when: 3 or < formed stools per day without blood or mucus, afebrile, no abdominal pain, no abdominal tenderness. **Bacteriological cure** was defined as: absence of Shigella spp in both stools and rectal swab samples from study day 3 onwards. Method of randomisation: adequate Allocation concealment: yes Power calculation: yes Baseline comparability: adequate Lost to follow-up: 7/90 (Seven subjects were excluded after enrolment: 3 in the control group and four in the intervention group).
Yurdakok 2000 [189] Location: Turkey Setting: community-based	**Study Type** quasi-RCT **Evidence Level** 1-	**Total no. of participants** *n* = 120 Randomised in two arms: Intervention group *n*= 60 Control group *n* = 60	Children aged 6–12 months with diarrhoea <5 days duration. **Exclusion criteria** Chronic diseases, malnutrition (<WFA 10th percentile according to NCHS), associated infectious disease, prior antibiotic use, dysentery.	**Intervention** Single oral dose of vitamin A 100 000 iu **Comparison** *Vitamin A vs placebo*	**Follow-up** until recovery from diarrhoea (=passage of formed stool as described by the mother for at least 24 hours). Infants were then evaluated at 2 weeks and 1 month from the study enrolment. **Outcome** 1.total duration of diarrhoea after start intervention (d) 2.persistent diarrhoea **Effect size** 1.total duration of diarrhoea after start intervention (d)-mean(SD) *intervention group 3.8 (2.3)* *placebo group 3.9 (1.9)* 2.persistent diarrhoea *intervention group 2/60* *placebo group 2/60*	**Funding** Grant from the Scientific and Technical Research Council of Turkey **Comments** *dehydration was assessed and treated according to WHO guidelines (G-ORS) -Method of randomisation: based on patients file numbers (odd or even) -allocation concealment: yes -baseline comparability: yes -power calculation: yes -double-blind -Lost to follow-up: none until cessation of diarrhoea, 19/120 at the 2nd assessment and 40/120 at the follow-up visit one month later

8.3.3 Glutamine

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Songul Yalcin 2004 [178] Location: Turkey Setting: community-based	**Study Type** quasi-RCT **Evidence Level** 1-	**Total no. of participants** *n* = 159 Randomised in two arms: Intervention group *n*= 79 Control group *n* = 80	Children aged 6–24 months with diarrhoea < 10 days duration. **Exclusion criteria** Chronic diseases, severe malnutrition (<60%WFA according to NSCHS), associated infectious disease, prior antibiotic or anti-diarrhoeal use, dysentery.	**Intervention** 0.3 g/kg per day of glutamine for 7 days **Comparison** *Glutamine vs placebo* *non compliant children were excluded (less than 3 days or less than ½ of the prescribed supplementation)	**Follow-up** until recovery from diarrhoeal episode and further assessments monthly for the next 3 months **Outcome** 1.mean duration of diarrhoea after treatment(d) 2. Proportion of persistent diarrhoea 3. total duration of diarrhoea (d) after start intervention in children with: <8stools per day on admission ≥8stools per day on admission -<90%WFA ->90%WFA **Effect size** 1.mean (SD)duration of diarrhoea *intervention group 3.4 (1.96)* *placebo group 4.57 (2.48)* 2.mean (SD) total duration of diarrhoea *intervention group 6.90 (3.24)* *placebo group 8.29 (3.39)* 3. Proportion of persistent diarrhoea *intervention group 2/63* *placebo group 6/65*	**Funding** Supported by the Scientific and Technical Research Council of Turkey **Comments** **Clinical recovery**=the passage of a soft-formed stool as described by the mother for at least 24 hours. **Persistent diarrhoea**=an episode lasting 14 or more days. -Lost to follow-up: 31/159 Lost patients were not included in the final analysis -Method of randomisation: based on patients file numbers (odd or even) -allocation concealment: yes -power calculation: yes -double-blind -baseline comparability: yes

8.3.4 Folic acid

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Ashraf 1998 [179] Location: Bangladesh Setting: hospital	**Study Type** RCT **Evidence Level** 1+	**Total no. of participants** *n* = 106 Randomised in two arms: Intervention group *n*= 54 Control group *n* = 52	Male children aged 6–23 months with watery diarrhoea < 72 hours duration and with some signs of dehydration. **Exclusion criteria** *n*.s.	**Intervention** Folic acid in a dose of 5 mg at 8 hour intervals for 5 days. **Comparison** *Folic acid vs placebo*	**Follow-up** 5 days **Outcome** 1. Total diarrhoea output g/kg 2. Total intake ORS g/kg 3. Duration of diarrhoea h 4. Proportion of patients with diarrhoea beyond 5 days 5. Proportion of patients that received IV fluids **Effect size** 1.mean (SD) total diarrhoea output *intervention group 532 (476)* *placebo group 479 (354)* 2.mean (SD) total intake ORS *intervention group 511(457)* *placebo group 456 (355)* 3. mean (SD) duration of diarrhoea *intervention group 108 (68)* *placebo group 103 (53)* 4. proportion of patients with diarrhoea beyond 5 days *intervention group 24/54* *placebo group 22/52* 5. proportion of patients that received IV fluids *intervention group 2/54* *placebo group 5/52*	**Funding** *n*.s. **Comments** Cessation of diarrhoea=the passage of a minimum of two soft stools or no stools in at least two consecutive 8 hour periods without recurrence of watery/liquid stool. * patients were rehydrated using a rice-based oral rehydration solution according to WHO guidelines -Method of randomisation: *n*.s. -Baseline comparability of the two groups at the start of the study adequate -Allocation concealment *n*.s. -Double-blinded -Power calculation done -Lost to follow-up: none

8.3.5 Fibre

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Brown 1993 [190] location: Peru setting: hospital	**Study Type** RCT **Evidence Level** 1-	**Total no. of patients** *n* = 34 *Intervention group n* = 19 *Control group n* = 15	Male children aged 2–24 months with acute diarrhoea for <96 hours **Exclusion criteria** systemic infection, dysentery, previous diarrhoea episode within the last 14 days, breast-fed >1 per day	**Intervention** Soy protein lactose free formula + added fibre **Control** Soy protein lactose free formula **Comparison** *Intervention vs control*	**Follow-up** **Outcome** 1.mean duration of diarrhoea (h) 2. mean stool output 3. treatment failure **Effect size** <u>1.median duration of diarrhoea</u> intervention gp 43 hours control gp 163 hours *P* = 0.003 <u>2. mean (sd) stool output 1st d hospitalisation</u> intervention gp 84 (70)g/kg control gp 77 (46) g/kg *stool output declined significantly in both groups during subsequent days of follow-up but there were no significant differences reported between the two groups <u>3. treatment failure</u> intervention gp 4/19 control gp 2/15	**Funding** Pediatric Nutrition Research and Development Division of Ross Laboratories UC Davis Clinical Nutrition Research Unit **Comments** *duration of diarrhoea=number of hours postadmission until excretion of the last liquid stool not followed by another abnormal stool within 24 hours *Treatment failure= recurring dehydration >5%, or electrolyte disorders after initial rehydration or faecal excretion >350 g/kg for 1 day, >250 g/kg for 2 consecutive days, or >100 g/kg on day 6 of treatment -Lost to follow-up:6/40 -Method of randomisation: adequate -Baseline comparability of the two groups at the start of the study adequate -Allocation concealment unclear
Vanderhoof 1997 [191] location: USA setting: community-based	**Study Type** RCT **Evidence Level** 1+	**Total no. of patients** *n* = 55 *Intervention group n* = 30 *Control group n* = 25	Infants <24 months with acute diarrhoea (≤3 days), ≥ watery stools/24 hours, or 3 times the normal number of stools in 24 hours **Exclusion criteria** Other GI disorders, infection disease	**Intervention** Soy-fibre supplemented formula for the first 10 days **Control** Soy formula without fibre For the first 10 days **Comparison** *Intervention vs control*	**Follow-up** 24 days (the study addressed first 10 days) **Outcome** 1.duration of diarrhoea **Effect size** <u>1. median duration of diarrhoea (h)</u> *Intervention group* 12.2	**Funding** *n*.s. **Comments** Lost to follow-up:19/74 *55 infants completed the study, the analysis included 67. Method of randomisation: random numbers

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					Control group 16.9 *P* > 0.5 *infants > 6 months (*n* = 44) *Intervention group* 9.7 *Control group* 23.1 *P* < 0.5	Baseline comparability of the two groups at the start of the study adequate Double-blinded (assessor and patient) Allocation concealment unclear

8.4 Alternative and complementary therapies

Homeopathy

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Jacobs 2003 [192] USA	Study type Systematic review with meta-analysis Evidence Level 1+	3 trials were identified for inclusion (Total *n* = 230/247 participants) Quality varied but all the studies were RCTs Nicaragua 2 RCTs pilot study (*n* = 33) main study (*n* = 81)) Nepal 1 RCT - *n* = 116	Inclusion criteria : Childrenaged 6 months to 5 years with a history of diarrhoea (defined as 3 or more unformed stools per day) for no more than 7 days (Nicaragua) or 5 days (Nepal). Exclusion Criteria Children were excluded if they had received antidiarrhoeal treatment within 24–48 hours prior to enrolment or if they had severe diarrhoea requiring hospitalisation or intravenous hydration. ORT given as required to all children	**Group 1 : one of 19 prescribed homeopathic remedies (**liquid homeopathic dilution in the 30C potency) *n* = **120** **Group 2 : placebo** **Both administered by parent :** 1 tablet from the prescribed tube after each unformed stool to be dissolved in mouth *n* = 110	Outcome measures Duration of diarrhoea No of stools per day Effect size Duration of diarrhoea (days) Group 1 = 3.1± 2.0 Group 2 = 3.8 ± 1.9 *P* = 0.008 No of stools per day Group 1 = 2.7 ± 2.0 Group 2 = 3.4 ± 2.0 *P* = 0.004 Follow up By parents and auxiliary nurses for 5 days (for 6 days in the pilot Nicaraguan trial)	**Funding : Boiron Research Foundation** Baseline comparability Children in the placebo group were significantly younger, shorter and lighter than those receiving homeopathy treatments Allocation concealment : adequate Sequence generation : adequate Blinding of outcome assessors: Yes Loss to follow up 17/247
Jacobs 2006 [193] Honduras setting	**Study type** <B>RCT [EL = 1+]</B>	**Total number of participants** *n* = 292 Randomised into two treatment arms Group 1 *n* = 131 Group 2 *n* = 134	**Inclusion criteria** children between 5 months and 6 years old who presented to a municipal acute care clinic in Honduras **Exclusion criteria** Children were excluded if the diarrhoea had lasted more than 4 days, if there was visible blood in the stool, if they were severely dehydrated or if they lived outside the catchment area of the clinic	**Comparison** **Group 1** : combination homeopathic therapy containing the five most common single remedies - *Arsenicum album*, *Calcarea carbonica*, *Chamomilla*, *Podophyllum* and sulphur in a liquid homeopathic dilution in the 30C potency **Group 2** : placebo	**Follow up** by parents and auxiliary nurses for 7 days after the initial visit or until symptoms resolved, if sooner **Outcome measures:** Duration of diarrhoea Only Hazard Ratio provided Crude HR = 1.02 [95% CI 0.79–1.33] mean rate of unformed stool passage per day	**Funding :** **Boiron Research Foundation** Baseline comparability Similar for age, sex, height, weight, body temperature, vomiting, dehydration status, vomiting, and duration of diarrhoea and unformed stools prior to study entry Allocation concealment :

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					during follow up Group 1 = 2.6 [95% CI : 2.2–2.9] Group 2 = 2.8 [95% CI 2.4–3.1] *P* = 0.43 total number of unformed stools during follow up Group 1 = median of 7 stools per day Group 2 = median of 8 stools per day *P* = 0.41	Code used Sequence generation : Code used Blinding of outcome assessors : Yes Loss to follow up 27/292 Power calculation : Not stated

8.5 Probiotics

Systematic reviews

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Allen SJ 2004 [196] UK	Study type Systematic review with meta-analysis Evidence Level 1++	23 trials were identified for inclusion (Total *n* = 1917 participants) Quality varied but all the studies were RCTs	Participants were adults and children with acute diarrhoea (<14 days), proven or presumed to be caused by an infectious agent. 18 trials reported exclusively on children (*n* = 1449)	Any probiotic preparation regime vs placebo or no probiotic administration (Intervention and control arm to be otherwise treated identically in relation to other treatments and drugs)	**Outcomes** Diarrhoea lasting 3 or more days, 4 or more days Duration of diarrhoea Stool frequency Adverse events **Comparison 1** ***Probiotic vs control*** <u>1.Diarrhoea lasting 3 or more days</u> significantly favoured probiotic 15 RCTs (*n* = 1341): RR 0.66 [0.55–0.77] *infants and children 11 RCTs (*n* = 1008): RR 0.68 [0.54–0.85] <u>2.Diarrhoea lasting 4 or more days</u> significantly favoured probiotic 13 RCTs (*n* = 1228): RR 0.31 [0.19–0.50] *infants and children 9 RCTs (*n* = 895): RR 0.41 [0.24–0.68] <u>3.Duration of diarrhoea</u> significantly favoured probiotic 12 RCTs (*n* = 970): WMD -30.48 [-42.46 to -18.51] <u>4.Stool frequency on day 2</u> significantly favoured probiotic 5 RCTs (*n* = 417): WMD -1.51 [-1.85 to -1.17] *infants and children 4 RCTs (*n* = 232): WMD -1.01 [-1.66 to -0.36] <u>5.Stool frequency on day 3</u> significantly favoured probiotic 4 RCTs (*n* = 447): WMD -1.31 [-1.56 to -1.07]	**Sources of support** Department for International Development UK Medical Research Council Laboratories Gambia University of Oxford UK **Comments** Well-conducted systematic review Despite the great variability between studies (setting, participants recruited, probiotic tested, treatment regimens and definitions of outcome measures), nearly all trials reported that probiotics had a beneficial effect in reducing diarrhoea , and this was statistically significant in many studies.

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					*infants and children 2 RCTs (*n* = 170): WMD -1.12 [-1.79 to -0.46] **Comparison 2** ***Probiotic vs control, in children with rotavirus diarrhoea*** Duration of diarrhoea No statistically significant difference 4 RCTs (*n* = 231): WMD -38.10[-68.10 to 8.10] **Comparison 3** ***Live Lactobacillus GG vs control*** 1.Diarrhoea lasting 3 or more days No statistically significant difference 2 RCTs (*n* = 329): RR 0.51 [0.14–1.83] 2.Diarrhoea lasting 4 or more days significantly favoured probiotic 1 RCT (*n* = 287): RR 0.61 [0.43–0.85] 3.Duration of diarrhoea significantly favoured probiotic 5 RCTs (*n* = 578): WMD -31.18[-51.62 to -10.75] 4.Stool frequency on day 2 significantly favoured probiotic 2 RCTs (*n* = 62): WMD -1.50 [-2.83 to -0.17] **Comparison 4** ***Live Lactobacillus reuteri vs control*** 1.Diarrhoea lasting 3 or more days significantly favoured probiotic 2 RCTs (*n* = 106): RR 0.49 [0.26–0.94] 2.Diarrhoea lasting 4 or more days No statistically significant difference 2 RCTs (*n* = 106): RR 0.29 [0.06–1.51] 3.Duration of diarrhoea significantly favoured probiotic 5 RCTs (*n* = 86): WMD -25.33 [-40.70 to -9.95] 4.Stool frequency on day 2 significantly favoured probiotic 1 RCT (*n* = 40): WMD -1.50 [-2.93 to -0.07]	

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					5.Stool frequency on day 3 No statistically significant difference 1 RCT (*n* = 40): WMD -1.2 [-2.60–0.20] **Comparison 5** ***Live Enterococcus LAB strain SF68 vs control*** 1.Diarrhoea lasting 3 or more days significantly favoured probiotic 5 RCTs (*n* = 372): RR 0.59 [0.47–0.74] 2.Diarrhoea lasting 4 or more days significantly favoured probiotic 5 RCTs (*n* = 372): RR 0.23 [0.11–0.49] 3.Stool frequency on day 2 significantly favoured probiotic 1 RCT (*n* = 185): WMD -1.70 [-2.10 to -1.30] 4.Stool frequency on day 3 significantly favoured probiotic 1 RCT (*n* = 185): WMD -1.40 [-1.67 to -1.13] **Comparison 6** ***Live L. acidophilus and L. bifidus vs control*** 1.Diarrhoea lasting 3 or more days No statistically significant difference 2 RCTs (*n* = 164): RR 0.52 [0.21–1.28] 2.Diarrhoea lasting 4 or more days significantly favoured probiotic 2 RCTs (*n* = 164): RR 0.06 [0.01–0.31] **Comparison 7** ***Live Streptococcus thermophilus and Lactobacillus. bulgaricus vs control*** 1.Diarrhoea lasting 3 or more days No statistically significant difference 1 RCT (*n* = 96): RR 1.08 [0.76–1.55] 2.Diarrhoea lasting 4 or more days No statistically significant difference 1 RCT (*n* = 96): RR 1.04 [0.61–1.79] **Comparison 8** ***Killed Lactobacillus acidophilus LB vs control***	

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					1.Diarrhoea lasting 3 or more days No statistically significant difference 2 RCTs (*n* = 144): RR 0.77 [0.40–1.46] 2.Diarrhoea lasting 4 or more days significantly favoured probiotic 1 RCT (*n* = 73): RR 0.11 [0.01–0.81] 3.Duration of diarrhoea No statistically significant difference 1 RCT (*n* = 73): WMD -13.60 [-28.10 to 0.90]	
					Comparison 9 ***Saccharomyces boulardii vs control*** 1.Diarrhoea lasting 3 or more days significantly favoured probiotic 1 RCT (*n* = 130): RR 0.71 [0.58–0.87] 2.Diarrhoea lasting 4 or more days significantly favoured probiotic 1 RCT (*n* = 130): RR 0.41 [0.26–0.66] 3.Stool frequency on day 2 No statistically significant difference 1 RCT (*n* = 130): WMD -0.62 [-1.49 to 0.25] 4.Stool frequency on day 3 significantly favoured probiotic 2 RCTs (*n* = 222): WMD -0.92 [-1.52 to -0.32]	
					Comparison 10 ***Live Lactobacillus casei vs control*** 1.Duration of diarrhoea significantly favoured probiotic 1 RCT (*n* = 27): WMD -36.00 [-65.87 to -6.13]	
					Comparison 11 ***Live L. rhamnosus and L. reuteri vs control*** 1.Duration of diarrhoea significantly favoured probiotic 2 RCTs (*n* = 112): WMD -23.43 [-41.47 to -5.40]	
					***Adverse events** 12 RCTs reported that clinical observations of	

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					the participants revealed no adverse events, 8 did not collect or report information on adverse events and 3 studies reported that an adverse event occurred: Pant 1996, 1/19 children in the control group vomited one dose of the medication (0/20 in the probiotic group) Raza 1995, frequency of vomiting on the 2nd day of intervention was statistically significant less in children in the probiotic group than in the placebo group. Shornikova-a 1997, fewer children in the probiotic than in the control group had vomiting from the 2nd day of treatment (stat. sig. on day 2 and 4) No authors reported an adverse effect that they considered to be attributable to the probiotic	
Szajewska 2007 198 Poland	Study type Systematic review with meta-analysis Evidence Level 1+	5 RCTs were identified for inclusion (Total *n* = 619 participants) The quality varied across the studies 2 RCTs were located in Pakistan, One in Mexico, one in Turkey and one in Argentina	Participants were children (from 2 months to 12 years) with acute diarrhoea, inpatients and outpatients.	*S. boulardii* compared to placebo or no additional intervention in treating acute diarrhoea.	**Outcomes** Duration of diarrhoea Cure on day 2 and 8 Presence of diarrhoea at different time intervals Diarrhoea lasting > 7 days Frequency of stool output Vomiting Hospitalisation * definition criteria for resolution of the diarrhoea, when reported, was different across studies **Comparison** ***S.boulardii vs control*** 1.Duration of diarrhoea (days) significantly favoured Sb 4 RCTs (*n* = 473): WMD -1.1 [-1.3 to -0.83] 2. Cure on day 2 significantly favoured Sb 1 RCT (*n* = 130): RR 4 [1.8–9.1] 3. Cure on day 8 significantly favoured Sb 1 RCT (*n* = 130): RR 1.9 [1.4–2.8] 4.Diarrhoea on day 3 significantly favoured Sb	**Sources of funding** Medical University of Warsaw **Comments** All the studies included presented methodological limitations (only two RCTs reported an adequate method of randomisation, only one had an adequate allocation concealment, two were not blinded and three did not apply the intention-to-treat analysis). Duration of intervention: was between 4 and 6 days (and one study had 14 days follow-up)

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					1 RCT (*n* = 101): RR 0.71 [0.56–0.9] 5.Diarrhoea on day 4 No statistically significant difference 1 RCT (*n* = 88): RR 0.73 [0.5–1.1] 6.Diarrhoea on day 6 'significantly' favoured Sb 1 RCT (*n* = 101): RR 0.49 [0.24–0.99] 7.Diarrhoea on day 7 significantly favoured Sb 1 RCT (*n* = 88): RR 0.39 [0.20–0.75] 8.Diarrhoea > 7 days significantly favoured Sb 1 RCT (*n* = 88): RR 0.25 [0.08–0.83] 9.number of stools on day 1 No statistically significant difference 1 RCT (*n* = 130): WMD -0.32 [-1.1 to 0.43] 10.number of stools on day 3 significantly favoured probiotic 3 RCTs (*n* = 331): WMD -1.3 [-1.9 to -0.63] 11.number of stools on day 4 significantly favoured probiotic 2 RCTs (*n* = 218): WMD -1.1 [-1.6 to -0.64] 12.number of stools on day 6 significantly favoured probiotic 2 RCTs (*n* = 201): WMD -1.7 [-2.4 to -1] 13.number of stools on day 7 significantly favoured probiotic 1 RCT (*n* = 88): WMD -0.9 [-1.4 to -0.62] 14.Hospitalisation (days) significantly favoured probiotic 1 RCT (*n* = 200): WMD -1 [-1.4 to -0.62] 15.Duration of vomiting (days) No statistically significant difference 1 RCT (*n* = 200): WMD -0.1 [-0.34 to 0.14] ***Adverse events** Adverse events associated with the administration of Sb were not reported in any of the trials	

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Szajweska 2007 [213] Poland	Study type Systematic review with meta-analysis Evidence Level 1+	8 RCTs were included (Total *n* = 988 participants) The quality varied across the studies 4 RCTs were located in Europe, 1 in Brazil, 1 in Uruguay, 1 in Peru and 1 in Pakistan.	Participants were children (from 1–36 months) with acute diarrhoea, inpatients and outpatients *5 trials included inpatients participants and 1 outpatient. 2 trials included inpatient and outpatient participants *The RCT located in Pakistan included undernourished children.	*Lactobacillus rhamnosus* GG compared to placebo or no additional intervention. *The daily dose of the probiotic, preparation and the duration of the intervention varied across studies	**Outcomes** Duration of diarrhoea Total stool output Presence of diarrhoea at different time intervals hospitalisation * definition criteria for resolution of diarrhoea, when reported, was different across studies **Comparison** ***Lactobacillus rhamnosus* GG *vs control*** 1.Duration of diarrhoea (days) significantly favoured LGG 7 RCTs (*n* = 876): WMD -1.08 [-1.87 to -0.28] * Duration diarrhoea rotavirus + children 3 RCTs (*n* = 201): WMD -2.08 [-3.55 to -0.6] 2.total stool output ml/kg significantly favoured LGG 2 RCTs (*n* = 303): WMD 24.2 [-86.26 to 104.2] 3. Diarrhoea on day 3 significantly favoured LGG 2 RCTs (*n* = 329): RR 0.56 [0.4–0.78] 4.Diarrhoea >7 days significantly favoured LGG 1 RCT (*n* = 287): RR 0.25 [0.09–0.75] 5.Diarrhoea >10 days No statistically significant difference 1 RCT (*n* = 97): RR 0.23 [0.03–1.91] 6.Hospitalisation (days) No statistically significant difference (random EM) 3 RCTs (*n* = 535): WMD -0.43 [-1.32 to 0.46]	**Sources of funding** Medical University of Warsaw **Comments** All the studies included presented methodological limitations and were significantly heterogenous. Only studies carried out in Europe consistently showed a beneficial effect of the administration of LGG Duration of intervention was not specified in two trials, was ad libitum in two others, was 2 days in one and 5 days in the remaining three.

Randomised controlled trials

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Henker 2007 [214] Location: Ukraine, Russia, Germany	**Study Type** Multicentre-RCT **Evidence Level** 1+ **Setting:** outpatient	**Total no. of participants** *n* = 113 Randomised in two arms: Intervention group *n*= 55 Control group *n* = 58	Children, aged between 2 and 47 months, treated for acute diarrhoea (< than 3 days of >3 watery-to-loose stools per dayay of non-bloody diarrhoea) in the paediatric outpatient wards of 11 centres **Exclusion criteria** Dehydration (>5% loss of BW), participation in another trial, intake of EcN within the previous 3 months, intake of food supplements or drugs with live micro-organisms, antibiotics, other antidiarrhoeal drugs, breast-feeding, premature birth, severe or chronic GI illness, other concomitant diseases.	**Intervention** Oral suspension E.coli Nissle 1917 Infants<1 year: 1 ml per day 1–3 years:1 ml x2 per day 3–4 years:1 mlx3 per day **Control** placebo **Comparison** *EcN vs control*	**Follow-up** 10 days **Outcome** 1.median duration of diarrhoea (d) 2.patients with no diarrhoea d3 3.patients with no diarrhoea d10 4.adverse events **Effect size** 1.median duration of diarrhoea (d) *intervention group 2.5* *placebo group 4.8* *P < 0.001* 2.patients with no diarrhoea d3 *intervention group 34/55* *placebo group 24/55* 3.patients with no diarrhoea d10 *intervention group 52/55* *placebo group 39/58* 4.adverse events *intervention group 2/55* **rhinitis and abdominal pain* *placebo group 2/58* *acute otitis media	**Funding** ARDEYPHARM . **Comments** Lost to follow-up: 12.3% Method of randomisation: random numbers Baseline comparability of the two groups at the start of the study adequate Double-blinded (assessor and patient) Allocation concealment yes Intention-to-treat: yes
Salazar-Lindo 2007 [201] Location: Peru	**Study Type** Multicentre-RCT **Evidence Level** 1+ **Setting** outpatients	**Total no. of participants** *n* = 80 Randomised in two arms: Intervention group *n*= 40 Control group *n* = 40	Children with acute diarrhoea presumed to be of infectious origin, <72 hours and with ≥3 watery stools within the previous 24 hours. **Exclusion criteria** Signs of dehydration requiring hospitalisation according to WHO guidelines, bloody stools, chronic GI disease, chronic immunological condition, lactose or fructose intolerance, haemodynamic abnormalities, neurological disturbance, rectal body temperature >39C.	**Intervention** 20 billion units of killed Lactobacillus LB 2 sachets per day x 4.5 days **Comparison** *L LB vs placebo*	**Follow-up** 4.5 days **Outcome** 1.median duration of diarrhoea (h) 2.proportion of children with diarrhoea at the end of the study 3.total ORS intake 4.vomiting 5.adverse events **Effect size**	**Funding** Axcan Pharma SA **Comments** End of diarrhoea episode=time to the first normal stool followed by 2 consecutive normal stools or time to the last diarrhoeic stool followed by 12 hours without stool Lost to follow-up:3/80

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					1 median duration of diarrhoea *intervention group 10(6/56.7)** *placebo group 16.6(7.1/50.3)** **(quartile1/quartile3)* 2.proportion of children with diarrhoea at the end of the study *intervention group 1/40* *placebo group 5/40* 3.total ORS intake reported as similar in both groups The authors reported that the findings were non statistically significant 4.vomiting *intervention group 12/40* *placebo group 6/40* 5.adverse events *intervention group 1/40* *placebo group 1/40*	Method of randomisation: *n*.s. Baseline comparability of the two groups at the start of the study was addequate Double-blinded (assessor and patient) Allocation concealment unclear
Sarker 2005 [200] Location: Bangladesh	**Study Type** RCT **Evidence Level** 1+ **Setting:** hospital	**Total no. of participants** *n* = 230 Randomised in two arms: Intervention group *n*= 115 Control group *n* = 115	Male infants and young children aged 4–24 months with acute diarrhoea (≥4liquid stools during 24 hours) for <48 hours **Exclusion criteria** Severe malnutrition, systemic infection requiring ABT, bloody diarrhoea, children whose stool sample resulted + (dark-field microscopy) to *Vibrio cholerae*, ABT within the previous 2 weeks	**Intervention** Lyophilised L. paracasei strain ST11 (5x10 9 CFU) twice daily for 5 days **Comparison** *L.ST11 vs placebo*	**Follow-up** 6 days or until cessation of diarrhoea **Outcome** 1. mean duration of diarrhoea (h) after first dose therapy 2.cessation of diarrhoea 3. total stool output (g/kg) 4.total ORS intake (ml/kg) 5.children requiring IVT **Effect size** 1.mean (SD) duration of diarrhoea *intervention group 90.4 (45)* *placebo group 94.2 (43.3)* 2.cessation of diarrhoea *intervention group 81/115* *placebo group 73/115* 3.total stool output (g/kg) *intervention group 385(330)* *placebo group 389(259)*	**Funding** Swedish agency for research in developing countries, the Karolinska Institute, the Nestle Research Centre **Comments** *cessation of diarrhoea =passage of the last watery or loose stool before passage of 2 consecutive soft or formed stools or no stool in >2 consecutive 8 hour periods Lost to follow-up: 11.8% Method of randomisation: random numbers Baseline comparability of the two groups at the start of the study adequate

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					4.total ORS intake (ml/kg) *intervention group 334 (280)* *placebo group 343 (230)* 5.children requiring IVT *intervention group 1/115* *placebo group 4/115* ***children rotavirus-infected** 1.mean (SD) duration of diarrhoea *intervention group 94 (43)* *placebo group 95 (37.9)* 2.cessation of diarrhoea *intervention group 56/75* *placebo group 45/65* 3.total stool output (g/kg) *intervention group 421(345)* *placebo group 417(273)* 4.total ORS intake (ml/kg) *intervention group 370 (288)* *placebo group 366 (229)* ***children non rotavirus-infected** 1.mean (SD) duration of diarrhoea *intervention group 77 (48)* *placebo group 99 (51)* 2.cessation of diarrhoea *intervention group 19/27* *placebo group 17/18* 3.total stool output (g/kg) *intervention group 225(218)* *placebo group 318(240)* 4.total ORS intake (ml/kg) *intervention group 180 (207)* *placebo group 331 (236)*	Double-blinded (assessor and patient) Allocation concealment yes Power calculation
Szymanski 2006 [40] location: Poland	**Study Type** RCT **Evidence Level** 1+	**Total no. of patients** *n* = 87 Randomised in two arms:	Children aged 2 months to 6 years with acute diarrhoea treated either at the paediatric ward or at the outpatient department. **Exclusion criteria**	**Intervention 1** 1.2x10*10CFU L.rhamnosus strains (573L/1 ; 573L/2 ; 573L/3)	**Follow-up** 5 days **Outcome** 1.total duration of diarrhoea after start	**Funding** Wellcome travel Award **Comments**

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
	Setting: hospital	*Intervention group n* = 49 *Placebo group n* = 44	Organic GI disease, underlying chronic disease, immuno-suppressive condition or treatment and exclusively breast-fed infants.	**Comparison** *Probiotic vs placebo*	intervention (d) 2.diarrhoea lasting >7 days 3.duration IV therapy (h) 4.adverse events **Effect size * (mean and 95% CI)** 1.total duration of diarrhoea after start intervention (h)* Intervention gp 83.6 (55.6) Placebo gp 96 (71.5) 2.diarrhoea lasting >7 days Intervention gp 3/46 Placebo gp 7/41 3.duration IV therapy (h)* Intervention gp 16 (19.3) Placebo gp 24.3 (29.1) ***children with rotaviral diarrhoea** 1.total duration of diarrhoea after start intervention (h)* Intervention gp 77.5 (35.4) Placebo gp 115 (66.9) 2.diarrhoea lasting >7 days Intervention gp 1/22 Placebo gp 1/17 3.duration IV therapy (h)* Intervention gp 14.9 (13.7) Placebo gp 37.7(32.9) 4.adverse events No adverse events were reported	diarrhoea= 3 or more bowel movements per day of stools that are looser than normal and may contain blood, pus or mucus, for more than 1 but less than 5 days study members and patients blinded to group assignment adequate method of randomisation, baseline comparability between groups, allocation concealment yes 6.5% lost at follow-up (<90% of the enrolled participants included in the analysis)
Berni Canani 2007 [215] Location: Italy	**Study Type** RCT **Evidence Level** 1+ **Setting:** outpatient	**Total no. of participants** *n* = 571 Randomised in six arms: Intervention group1 *n*= 92 Intervention group2	Children aged 3–36 months visiting a family paediatrician for acute diarrhoea **Exclusion criteria** Returning to the hospital with an ongoing episode of diarrhoea, zinc supplementation	Interventions and placebo administered twice daily **Intervention1** LGG 6x10*9CFU/dose **Intervention2** S boulardii 5x10*9live micro-org. **Intervention3**	**Follow-up** **Outcome** 1.duration of diarrhoea(h) 2.daily stool output 3.*n*. admitted to hospital 4.vomiting	**Funding** None` **Comments** *duration of diarrhoea= time in hours from the last abnormal (loose or liquid) stools preceding a normal stool

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
		n= 100 Intervention group3 *n*= 91 Intervention group4 *n*= 100 Intervention group5 *n*= 97 Control group *n* = 91		Bacillus clausii 10*9CFU/dose **Intervention4** L bulgaricus 10*9CFU, L acidophilus 10*9CFU, S thermophilus 10*9CFU, B bifidum5X10*8/CFU **Intervention5** E faecium 7.5x10*7CFU/dose **Control** Placebo (ORS) **Comparison** *Intervention1 vs placebo* *Intervention2 vs placebo* *Intervention3 vs placebo* *Intervention4 vs placebo* *Intervention5 vs placebo*	**Effect size** 1.median duration of diarrhoea (IQR) *intervention 1 gp 78.5 (56.5–104.5)* **P < 0.001* *intervention 2 gp 105 (90–104.5)* *intervention 3 gp 118 (95.2–128.7)* *intervention 4 gp 70 (49–101)* **P < 0.001* *intervention 5 gp 115 (89–144)* *placebo gp 115.5 (95.2–127)* 2.median daily stool output(IQR) ***day2*** *intervention 1 gp 4 (4–6)* **P < 0.001* *intervention 2 gp 5 (4–7)* *intervention 3 gp 5 (4–7)* *intervention 4 gp 4 (4–6)* **P < 0.001* *intervention 5 gp 5 (4–7)* *placebo gp 5 (4–7)* ***day5*** *intervention 1 gp 2 (2–3)* **P = 0.003* *intervention 2 gp 3 (2–4)* *intervention 3 gp 3 (2–4)* *intervention 4 gp 2 (2–3)* **P = 0.002* *intervention 5 gp 3 (2–4)* *placebo gp 3 (2–4)* 3.n. admitted to hospital (%) *intervention 1 gp 1 (1.0)* *intervention 2 gp 4 (4.4)*	output. Method of randomisation: computer generated sequence Allocation concealment yes Blinding: No Sample size power calculation yes

Bibliographic information	Study type and evidence level	Study details	Participant characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					intervention 3 gp 4 (4.0) *intervention 4 gp 2 (2.1)* *intervention 5 gp 4 (4.4)* *placebo gp 4 (4.3)* Reported as no statistically sig. 4.vomiting (%) *intervention 1 gp 31 (31)* *intervention 2 gp 24 (26.4)* *intervention 3 gp 32 (32)* *intervention 4 gp 34 (35.1)* *intervention 5 gp 36 (39.6)* *placebo gp 34 (37)`* Reported as no statistically sig.	

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ISBN 978-1-906985-14-1
9 781906 985141

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