National Clinical Guideline Centre

Clinical evidence tables

Pneumonia

Diagnosis and management of community- and hospital-acquired pneumonia in adults

Clinical guideline 191

Appendix G1

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Final version

Commissioned by the National Institute for Health and Care Excellence

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

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1.1 Diagnostic tests

1.1.1 RCTs – CRP

Reference	Patient Characteristics	Experimental group	Control group	Outcomes measures	Effect sizes		Comments
Author and year: Cals 2010[16] **Study type:** RCT – unit of randomisation = patient **Selection / patient setting:** 11 family practice centres **(primary care)** in the Netherlands recruited patients with LRTI or rhinosinusitis from November 2007 until April 2008. **Addressing missing data/non reliability of data:** ITT analysis **Statistical analysis:** All analyses were performed with a multilevel approach using a 2-level logistic regression model to account and correct for	**Diagnosis:** LRTI or rhinosinusitis – results stratified. **Inclusion criteria:** All patients aged 18 years and older who consulted for the first time for a current episode of LRTI or rhinosinusitis. For LRTI, first consultation for current episode of cough (duration less than 4 weeks) regarded by the physician to be caused by an acute LRTI with at least 1 of following 4 focal signs and symptoms: (1) shortness of breath, (2) wheezing, (3) chest pain, and (4) auscultation abnormalities. At least 1 of the following systemic signs and symptoms had to be present: (1) fever, (2) perspiring, (3) headache, (4) myalgia, and (5) feeling generally unwell. **Exclusion criteria:** Immediate requirement for hospital admission, no understanding of the Dutch language, previous participation in	**N = 129** **56 LRTI** **CRP assistance (point of care test)** CRP was measured by the practice nurse Physician could use the CRP test result in addition to clinical assessment to decide on management (immediate, delayed, or no antibiotics). Education in use and purpose of CRP testing was provided and a 4-week run-in period enabled familiarisation with the devices and interpretation of CRP test results before patient	**N = 129** **51 LRTI** **No CRP assistance** Physician had to decide on a management strategy (immediate, delayed, or no antibiotics) based on clinical assessment and finish the consultation (usual care).	**LRTI subgroup**	**Exp**	**Control**	**Funding:** Orion Diagnostica **Limitations:** Unblinded; not powered to detect differences in LRTI subgroup **Additional outcomes:** N/A **Notes:** -
				Antibiotic use			
				Antibiotic use after index consultation.	21/56 (41.1%)	26/51 (51.0%	
				Antibiotic use within 28-day follow-up.	26/56 (46.4%)	30/51 (58.8%)	
				Note: the largest relative reduction in antibiotic use was seen in the 0 - 20 mg/l PCT group for the full study group (not just LRTI).			
				Mortality	0/56	0/51	
				Hospital admission	0/56	0/51	
				QoL (LRTI)			
				Feeling recovered at day 7	12/51 (23.5%)	9/49 (18.4%)	
				QoL (LRTI and rhinosinusitis)			
				Median (IQR) patient enablement score (max: 12)	2 (4)	2 (4)	
				Mean (SD) patient enablement score (max: 12)	2.5 (2.6)	2.3 (2.4)	

Reference	Patient Characteristics	Experimental group	Control group	Outcomes measures	Effect sizes	Comments
variation at the level of physician.	the study, antibiotic use or hospitalisation in the past 2 weeks, and immunocompromised status. **All patients,** N: 270 Exclusions due to: 10 did not meet inclusion criteria; 2 other reasons. **Included N:** 258 No loss to follow-up for primary outcome. **Age, mean:** CRP group – 43.0 (13.4); control group – 45.5 (14.0). **Gender (male/female):** 30.6/69.4% **Comorbidities (exp/control):** COPD: 3.9 /2.3 % Asthma: 7.8 / 7.0% Allergic rhinitis: 10.1 / 9.3 Diabetes mellitus: 7.0 / 3.1% Heart disease: 4.7 / 6.2 %	recruitment started. Guidance for using CRP to guide antibiotics prescribing: < 20 mg/L: no antibiotics > 100 mg/L: immediate antibiotics 20-99 mg/L: delayed prescription. Physicians were allowed to deviate from the proposed prescribing strategies at any time.				

Reference	Patient Characteristics	Experimental group	Control group	Outcomes measures	Effect sizes				Comments
Author and year: Cals 2007 and 2009[15,17,18] **Study type**: RCT – cluster randomised **Selection / patient setting:** 20 general practices and 2 GPs per practice Sequential eligible adult patients during regular consultation hours in general practice. **Addressing missing data/non reliability of data:** ITT analysis plus sensitivity analyses; no missing data for primary outcome. **Statistical analysis:** Three level logistic regression model	**Diagnosis:** suspected LTRI **Inclusion criteria:** Adult (> 18 years) patients presenting in general practice with an acute cough, lasting no more than 4 weeks, considered to be caused by LRTI according to the GP. Plus at least 1 of following 4 focal signs and symptoms: (1) shortness of breath, (2) wheezing, (3) chest pain, and (4) auscultation abnormalities and at least 1 of the following systemic signs and symptoms had to be present: (1) fever, (2) perspiring, (3) headache, (4) myalgia, and (5) feeling generally unwell. **Exclusion criteria:** Immediate requirement for hospital admission, no understanding of the Dutch language, previous participation in the study, current antibiotic use or use within past 2 weeks, hospitalisation in the past 6 weeks. **All patients,**	**N = 227 CRP** 1. Access to and training in point of care CRP. 2. Access to and training in the use of point of care CRP plus context-bound training in enhanced communication skills for acute cough. Guidance about interpretation of CRP results given but no instructions on what to prescribe (CRP may complement clinical findings and help in deciding on diagnosis and treatment). Training in use of point-of care test provided and technical support available by	**N = 204 no CRP** 3. Context-bound training in enhanced communication (comm) skills for acute cough 4. Usual care.		**Exp**	**Control**	**P-value***	**Intra-cluster co-efficient**	**Funding:** Netherlands Organisation for Health Research and Development. **Limitations:** cluster randomised; unclear allocation concealment. **Additional outcomes:** Patient satisfaction and future consultation intention. **Notes:** -
				Antibiotic use					
				At index consultation (overall)	70/227	108/204	0.02	0.12	
				At index consultation (stratified)	CRP alone: 39/110 CRP + comm: 23/117	Usual care: 67/120 Comm: 33/84	-	-	
				At days 1-28	102/227	119/204	<0.01	0.12	
				Re-consultation within 28 days	79/227	62/204	0.50	0.01	
				QoL					
				Median (IQR) patient enablement score (max: 12)	3 (4)	3 (4)	-	-	
				Mean (SD) patient enablement score (max: 12)	2.97 (2.59)	3.40 (2.48)	0.13	-	
				Mortality	0/227	0/204	-	-	
				Hospitalisation	0/227	0/204	-	-	
					* Calculated from multilevel logistic regression model adjusted for variance				

Reference	Patient Characteristics	Experimental group	Control group	Outcomes measures	Effect sizes	Comments
to account for variation at the practice/GP/ patient. A four-level linear regression model will be fitted to the symptom scores to account for practice, GP, patient and repeated assessments over time.	N: 431 from 20 general practices. **Age, mean:** CRP – 49.4 (14.7); no CRP – 50.3 (16.0) **Gender (male/female):** 38.5/61.5% **Comorbidities (exp/control):** COPD: 7.5 / 6.9 % Asthma: 10.1 / 7.8% Diabetes mellitus: 4.0 / 4.4% Heart disease: 4.8 / 4.4 %	telephone. There was an 8-week run-in period enabled familiarisation with the devices and interpretation of CRP test results before patient recruitment started.			at general practitioner and practice level.	

Reference	Patient Characteristics	Experimental group	Control group	Outcome measures	Effect sizes				Comments
Author and year: Little 2013[65] **Study type**: RCT – cluster randomised **Selection / patient setting:** All prescribers in eligible (not previously used interventions to reduce antibiotic prescribing and could provide at least 10 patients at baseline audit) general practices invited to participate. Practices were located in Belgium, Netherlands, Poland, Spain and the UK (Scandinavian countries not included because CRP testing already in routine use there – pers. comm.). Sequential eligible adult patients presenting in general practice – up to the first 30 with LRTI and	**Diagnosis:** suspected LTRI or URTI **Inclusion criteria:** Adult (> 18 years); first consultation for acute cough of up to 28 days duration (or main diagnosis of LRTI despite cough not being the most prominent symptom); suspected URTI (e.g. sore throat, otitis media, sinusitis, influenza, coryzal illness). **Exclusion criteria:** Working diagnosis of a non-infective disorder (e.g., pulmonary embolus, heart failure, oesophageal reflux, or allergy); use of antibiotics in the past month, inability to provide informed consent, pregnancy and immunological deficiencies. **All patients,**	**N = 2224 CRP training** (1062 without communication training and 1162 with) 1. Internet training on how to target testing using CRP (i.e. in cases of clinical uncertainty) and how to negotiate with the patient about management 2. Internet training in CRP use plus enhanced communication skills Tests were done with QuickRead CRP kits (Orion Diagnostica) and training provided by the manufacturers Guidance for using CRP to guide antibiotics prescribing: < 20 mg/l: withhold	**N = 2040 no CRP training** (870 without communication training and 1170 with). 3. Internet and video training in enhanced communication skills – focussed on patients concerns/expectation, symptoms, disease course, treatment plan agreement and when to re-consult. 4. Usual care – assessment and management according to usual practice procedures.		**Exp (CRP training)**	**Control (no CRP training)**	**Adjusted risk ratio***	**P-value**	**Funding:** European Commission Framework 6 Programme and NIHR. **Limitations:** cluster randomised. **Additional outcomes:** New or worse symptoms; symptom severity score. **Notes:** -
				CRP test performed (pers. comm.)					
					1428/ 2224 (64.2%)	94/ 2040 (4.6%)	-	-	
				Overall comparison (including with and without communication training in each arm)					
				Antibiotic prescriptions	734/2224	984/2040	0.54 (0.42-0.69)	< 0.0001	
				Median (IQR) time to resolution of symptoms	5 (3-9)	5 (3-9)	HR: 0.93 (0.83-1.04)	0.21	
				Hospital admission	22/2224	8/2040	OR: 2.91 (0.96-8.85)		
				Mortality	0/2224	0/2040	NA	NA	
				CRP training vs usual care					
				Antibiotic prescriptions	368/1062	508/870	0.53 (0.36-0.74)	< 0.001	
				Median (IQR) time to resolution of symptoms	5 (3-8)	5 (3-7)	HR: 0.87 (0.74-1.03)	0.114	
				LRTI group only; **Overall comparison (including with and**					

Reference	Patient Characteristics	Experimental group	Control group	Outcome measures	Effect sizes				Comments
5 with URTI from Feb – March 2011. **Addressing missing data/non reliability of data:** ITT analysis. **Statistical analysis:** Multi-level logistic regression model to account for a factorial study, controlled for baseline antibiotic prescribing and with allowance for clustering by physician and practice. Effects of potential confounders related to clinical severity were explored.	259/440 practices agreed to participate (13 not randomised because fewer than 10 patients). Included N: 4264 from 228 practices. **Age, mean:** 49.6 (18.6) **Gender (male/female):** 38/62% **Comorbidities (exp/control):** COPD or asthma: 19/ 17 % **Severity score (range: 1-4):** 1.8 (0.5) LRTI: N = 5355 (79.1%) URTI: N = 1416 (20.9%)	antibiotics ≥ 100 mg/l: prescribe antibiotics 21 - 50 mg/l: withhold antibiotics in most cases. 51 - 99 mg/l: withhold antibiotics in most cases but consider delayed prescription in some. There was a run-in period (several weeks) for familiarisation with the devices before data collection began.		**without communication training in each arm)**				
				Antibiotic prescriptions	620/1773	834/1625	0.53 (0.39-0.68)	< 0.001	
				Median (IQR) time to resolution of symptoms	6 (3-9)	5 (3-9)	0.92 (0.81-1.03)	0.157	
				LRTI group only; **CRP training vs usual care**					
				Antibiotic prescriptions	313/861	420/674	0.53 (0.35-0.74)	< 0.001	
				Median (IQR) time to resolution of symptoms	5 (3-8)	5 (3-8)	0.89 (0.74-1.07)	0.212	
					* Controlled for baseline prescribing and clustering by physician and practice, age, smoking, sex, major cardiovascular or respiratory com-morbidity, baseline symptoms, crepitations, wheeze, pulse > 100 beats/min, temperature > 37.8°C, respiratory rate, blood pressure, physician's rating of severity and duration of cough.				

1.1.2 RCTs – PCT

Reference	Patient Characteristics	Experimental group	Control group	Outcomes measures	Effect sizes			Comments
Author and year: Schuetz 2012[92,93] **Study type**: Systematic review and individual patient data meta-analysis. **Selection / patient setting:** Any trials in any setting meeting the protocol. **Addressing missing data/non reliability of data:** Non-event imputation (with sensitivity analysis for opposite assumption). **Statistical analysis:** All patients were analysed in the study group to which they were randomized. Multivariable hierarchical logistic regression with the following variables: use of PCT algorithm, plus important prognostic factors such as patient age and ARI diagnosis as additional fixed effects. Trial included as a random effect. Sensitivity analyses: quality	**Diagnosis:** initial suspicion of ARI (independent of final diagnosis). **Inclusion criteria:** Patients in eligible randomized or quasi-randomized trials had to be adults with a clinical diagnosis of either upper or lower ARI. **Exclusion criteria:** Trials were excluded if they exclusively focused on paediatric patients or if they used PCT for a purpose other than to guide initiation and duration of antibiotic treatment. Note: no exclusions based on language or publication status of reports. **All patients,** N: 14 trials with 4551 patients Exclusions due to: incorrect population (sepsis not related to ARI; n = 340). **Included N:** 4211 **Age, mean:** PCT group – 59.4	**N = 2085** PCT-guided antibiotics (physicians could deviate from algorithm if needed). Similar PCT algorithms used But, some trials in primary care and the ED used only a single PCT measurement on admission to guide initiation of antibiotics, whereas the most trials used repeated measurements for guiding the duration of	**N = 2126** No PCT		**Exp**	**Control**	**Adjusted OR or difference***	**Funding:** BRAHMS/Thermo Fisher scientific. **Limitations:** unclear if IPD obtained for all trials; different PCT algorithms used between trials but not differentiated in the analysis; publication bias unclear. **Additional outcomes:** Length of ICU stay. **Notes:** -
				Mortality				
				Overall	118/2085	134/2126	0.94 (0.71 – 1.23)	
				Primary care	0/507	1/501	-	
				ED	61/1291	59/1314	1.03 (0.7 – 1.5)	
				Treatment failure				
				Overall	398/2085	466/2126	0.82 (0.71 – 0.97)	
				Primary care	159/507	164/501	0.95 (0.73 – 1.24)	
				ED	182/1291	228/1314	0.76 (0.61 – 0.95)	
				Days with restricted activities (after 14 days)				
				Primary care	Median: 9 (IQR: 6-14)	Median: 9 (IQR: 5-14)	0.05 (-0.46 – 0.56)	
				Initiation of antibiotics				
				Overall	1341/2085	1778/2126	0.24 (0.2 – 0.29)	
				Primary care	116/507	316/501	0.10 (0.07 – 0.14)	
				ED	939/1291	1151/1314	0.34 (0.28 – 0.43)	
				Median (IQR) duration of antibiotics				
				Overall	7 (4 – 10)	10 (7 – 13)	-2.75 (-3.12 to -2.39)	

Reference	Patient Characteristics	Experimental group	Control group	Outcomes measures	Effect sizes			Comments
indicators, alternate definition of treatment failure, excluding trials with low adherence to PCT algorithms (< 70%), excluding all ICU trials. Pre-specified analyses stratified by clinical setting and ARI diagnosis and formally tested for potential subgroup effects by adding the clinical setting and ARI diagnosis in turn to the regression model together with the corresponding interaction term with PCT group as fixed effects. Meta-analyses with aggregate data performed to investigate inconsistency and heterogeneity of effects.	(20.1); control group – 60.1 (19.4) **Gender (male/female):** 54.2/45.8% **Comorbidities:** N/A **Clinical setting** Primary care: 24% (2 studies) Emergency department: 62% (7 studies). ICU: 14% (5 studies). **Primary diagnosis** Total upper ARI: 13% Total lower ARI: 87% (majority confirmed CAP).	treatment.		Primary care	7 (5 – 8)	7 (6 – 8)	-0.6 (-1.17 to -0.03)	
				ED	7 (4 – 10)	10 (7 – 12)	-3.7 (-4.09 to -3.31)	
				Total exposure to antibiotics in days, median (IQR)				
				Overall	4 (0 – 8)	8 (5 – 12)	-3.47 (-3.78 to -3.17)	
				Primary care	0 (0 – 0)	6 (0 – 7)	-3.06 (-3.48 to -2.65)	
				ED	5 (0 – 8)	9 (5 – 12)	-2.96 (-3.38 to -2.54)	
				*Multivariable hierarchical regression with outcome as dependent variable; PCT group, age, and ARI diagnosis as independent variables; and trial as a random effect.				
				Summary by outcome				
				Mortality	No difference between PCT and no PCT; consistent across clinical settings and ARI diagnoses.			
				Treatment failure	Lower risk in PCT group.			
				No evidence for heterogeneity or effect modification across clinical settings or ARI diagnoses for these 2 co-primary outcomes.				
				Antibiotic exposure	PCT group had lower exposure across all settings and diagnoses.			

Reference	Patient Characteristics	Experimental group	Control group	Outcomes measures	Effect sizes			Comments
Author and year: Christ-Crain 2004[23] **Study type**: RCT Cluster randomised **Selection / patient setting:** Presenting at the emergency department. **Addressing missing data/non reliability of data:** Unclear (low rate lost to follow-up). **Statistical analysis:** Adjusted for clustering using generalised estimating equations.	**Diagnosis:** LRTI **Inclusion criteria:** Suspected LRTI as the main diagnosis (cough, dyspnoea or both). **Exclusion criteria:** Severely immunocompromised, cystic fibrosis or active TB, hospital-acquired pneumonia. **Included N:** 243 **Age, mean:** PCT group – 62.8 (19.8); control group – 65.3 (17.3) **Gender (male/female):** 52.7/47.3% **Comorbidities:** Coronary artery disease – 24% Renal dysfunction – 17% Diabetes – 13% **Clinical setting** Emergency department plus follow-up on admission or discharge. **Antibiotic pre-treatment**: 23% in PCT and 18% in control groups.	**N = 124** PCT-guided antibiotics (all treatment decisions ultimately at the discretion of the physician). Advice for using PCT to guide antibiotics prescribing: ≤ 0.1 µg/l: antibiotics strongly discouraged 0.1 - 0.25 µg/l: antibiotics discouraged 0.25 - 0.5 µg/l: antibiotics advised ≥ 0.5 µg/l: antibiotics strongly recommended.	**N = 119** No PCT	**Mortality**	4/124	4/119	0.95	**Funding:** Predominantly academic. **Limitations:** Unclear adherence to PCT algorithm. **Additional outcomes:** Duration of antibiotics; length of hospital stay; VAS. **Notes:** -
				Antibiotics prescribed	55/124	99/119	<0.0001	
				Quality-of-life score (mean)	Initial: 41.3 (14.3) Final: 21.9 (14.7)	Initial: 39.3 (13.2) Final: 22.9 (15.1)	0.60	
				Hospital admission	101/124	88/119	0.16	

1.1.3 Observational studies of diagnostic test accuracy (CRP vs PCT)

1.1.3.1 Study 1

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures and effect sizes		Comments
van Vugt 2013[104]	Study type: Diagnostic, cross sectional study Data source: GRACE-09 study Setting: General practice Country: UK, Spain, France, Belgium, Germany, Italy, Poland, Finland, Norway, Sweden, The Netherlands, Slovakia, Hungary, Slovenia Recruitment:	N = 2820 Note: only a proportion of potentially eligible participants were screened owing to time constraints in practice. Inclusion criteria: Aged 18 years and over; consulting with acute cough as the main symptom (up to and including 28 days duration) or those in whom the general practitioner suspects the presence of acute lower respiratory tract infection; immunocompetent; consulting for the first time within this illness episode. Exclusion criteria: Antibiotics in the	Male: Female 40/60% Mean age: 50 (SD: 17) Prevalence of pneumonia: 5% (140/2820) Pulmonary comorbidity: 17% Cardiovascular comorbidity: 9% Diabetes: 6%	Index tests CRP and PCT – serum concentrations measured by venous blood tests in lab (not point of care test). Analysed in the following pre-specified ways: - Clinically relevant thresholds: > 20, > 30, > 50, and > 100 mg/L for CRP; > 0.25 µg/L and > 0.50 µg/L for PCT - Additional benefit of CRP and PCT when used dichotomously, if continuous results showed relevant added information. Reference standard: Pneumonia on CXR. Time between index test and reference standard: 91% patients underwent chest radiography within 5 days, and the mean duration between the first consultation for acute cough and chest radiography was 1.6 days (SD 2.6). There was no correlation between the time until radiography and presence of radiographic	**PPV for CRP as stand-alone test** CRP > 20 mg/l: 11.8% CRP > 30 mg/l: 14.8% CRP > 50 mg/l: 22.5% CRP > 100 mg/l: 35.4% **NPV for CRP as stand-alone test** CRP > 20 mg/l: 97.4% CRP > 30 mg/l: 97.2% CRP > 50 mg/l: 96.8% CRP > 100 mg/l: 96.1% **AUC (95% CI)** **'Symptoms and signs'** alone model: **0.70** (0.65 - 0.75) *Calibration test: 7.35 (df = 8; p = 0.50)* 'Symptoms and signs' model + **continuous CRP** concentration: **0.78** (0.74 - 0.82) *Calibration test: 10.69 (df = 8; p = 0.22)* 'Symptoms and signs' model + **dichotomous CRP** (30 mg/l optimum threshold): **0.77** (0.73 - 0.81) *Calibration test: 9.67 (df = 8; p = 0.29)* 'Symptoms and: **0.71** (0.67 - 0.76)	Source of funding: European Commission Framework 6 Programme and the Research Foundation in Belgium. Limitations: CRP and PCT analysed in diagnostic lab rather than as a point of care test (which may result in lower utility). CXR could have been delayed by 5 days or more after initial consultation. Additional data: Diagnostic risk classification

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures and effect sizes		Comments
	GPs in 16 primary care networks across 12 European countries (3 winters; October 2007 to April 2010).	previous month; unable to properly consent or fill out the diary (dementia, psychosis, severe depression); pregnancy; no/insufficient CXR.		pneumonia (p = 0.63). <u>Target condition</u> Pneumonia identified on chest radiograph by blinded physician. <u>Analysis</u> Possible non-random differences within countries (clusters) accounted for by using multilevel logistic regression. ROC analysis: first for symptoms and signs alone and repeated regression analyses after adding CRP and PCT concentrations as continuous offset variables, while regression coefficients of symptoms and signs were unchanged using results from all patients.	signs' model + **PCT**	*Calibration test: 7.56 (df = 8; p = 0.48)*	improvement for CRP.

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Holm 2007[50,51]	Study type: prospective observational study Data source: (if it comes from records for instance) Setting: GP practices Country: Denmark Recruitment: Consecutive patients (Sept-Nov 2002 and Jan-April 2003)	N = 693 registered but only 369 examined and 5 of these were excluded for having pulmonary malignancy (42 of 119 GPs agreed to participate) Inclusion criteria: Age ≥ 18 years; GP diagnosis of lower respiratory tract infection (initial consultation). Exclusion criteria: Hospitalisation in the preceding 7 days; severity of illness requiring hospitalisation; pregnancy; former participation in the study.	Male: Female 47/51 Median age (range): 50 (18-94) Prevalence of pneumonia: 13.2% (48/364) Comorbidities: COPD: 9% Cardiac: 9%	Index test Blood for PCT kept at 5°C for up to 24 h before being centrifuged, and then plasma kept at –80°C until analysed. The **Kryptor®-PCT assay** (BRAHMS Diagnostica, Berlin, Germany) was used The detection limit of the Kryptor®-PCT assay is 0.02 ng/ml, and the functional sensitivity is 0.06 ng/ml Potentially clinical relevant cut-off points for PCT were chosen at the level of the functional sensitivity of the test (0.06 ng/ml) and at the two levels for suspected bacterial infection as stated by the manufacturer (0.25 and 0.50 ng/ml). Additionally, two cut-off points of 0.08 and 0.1 ng/ml between the functional sensitivity and the expected level for bacterial infection were chosen. **CRP** was evaluated at a cut-off point of 20 mg/l as a low value was thought to be optimal in the setting of primary care.	**For prediction of radiographic pneumonia** **PCT > 0.06 ng/ml** / Ref std + / Ref std - / *Total* Index test + / 33 / 106 / *139* Index test - / 14 / 204 / *218* *Total* / *47* / *310* / ***357*** **CRP ≥ 20 mg/l** / Ref std + / Ref std - / *Total* Index test + / 35 / 205 / *240* Index test - / 13 / 110 / *123* *Total* / *48* / *315* / ***363*** **Sensitivity** PCT > 0.06 ng/ml: 0.70 PCT > 0.08 ng/ml: 0.49 PCT > 0.10 ng/ml: 0.36 PCT > 0.25 ng/ml: 0.23 PCT > 0.50 ng/ml: 0.17 CRP ≥ 20 mg/l: 0.73 **Specificity** PCT > 0.06 ng/ml: 0.66	Source of funding: Academic/government. Limitations: Only 53% of those registered by GPs were examined at the out-patient clinic – majority (77%) of those missing because unable or unwilling to come to the clinic. CRP and PCT analysed in diagnostic lab rather than as a point of care test (which may result in lower utility). Additional data: predictive ORs

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
				<u>Reference standard</u> Chest radiograph – finding of transient, non-malignant infiltrate <u>Time between index test and reference standard</u>: both obtained on day of diagnosis. <u>Target condition</u> Pneumonia. <u>Analysis</u> To adjust for confounders, a logistic regression model was used for categorical outcomes. Selection of confounders was performed using the 'change in estimate' method and only factors changing the OR by at least 10% were included in the final model ROC curves were drawn and AUCs compared using χ^2 test.	PCT > 0.08 ng/ml	0.83	
					PCT > 0.10 ng/ml	0.92	
					PCT > 0.25 ng/ml	0.99	
					PCT > 0.50 ng/ml	1.00	
					CRP ≥ 20 mg/l	0.24	
					PPV		
					PCT > 0.06 ng/ml	0.24	
					PCT > 0.08 ng/ml	0.30	
					PCT > 0.10 ng/ml	0.41	
					PCT > 0.25 ng/ml	0.73	
					PCT > 0.50 ng/ml	1.00	
					CRP ≥ 20 mg/l	0.24	
					NPV		
					PCT > 0.06 ng/ml	0.94	
					PCT > 0.08 ng/ml	0.91	
					PCT > 0.10 ng/ml	0.91	
					PCT > 0.25 ng/ml	0.89	
					PCT > 0.50 ng/ml	0.89	
					CRP ≥ 20 mg/l	0.94	
					AUC *p-value for difference = 0.187*		
					CRP	0.7882	
					PCT	0.7284	
					Prediction of bacterial aetiology		
					Sensitivity		
					PCT > 0.06 ng/ml	0.51	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
					PCT > 0.08 ng/ml	0.31	
					CRP ≥ 20 mg/l	0.56	
					Specificity		
					PCT > 0.06 ng/ml	0.64	
					PCT > 0.08 ng/ml	0.81	
					CRP ≥ 20 mg/l	0.64	
					PPV		
					PCT > 0.06 ng/ml	0.25	
					PCT > 0.08 ng/ml	0.27	
					CRP ≥ 20 mg/l	0.28	
					NPV		
					PCT > 0.06 ng/ml	0.85	
					PCT > 0.08 ng/ml	0.83	
					CRP ≥ 20 mg/l	0.87	
					AUC		
					CRP	0.6346	
					PCT	0.6117	
					AUC for prediction of hospitalisation *p-value for difference = 0.944*		
					CRP	0.7518	
					PCT	0.7560	
				Mortality	4/124	4/119	0.95
				Antibiotics prescribed	55/124	99/119	< 0.0001

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes	Comments
				Quality-of-life score (mean)	Initial: 41.3 (14.3) Final: 21.9 (14.7)	Initial: 39.3 (13.2) Final: 22.9 (15.1)	0.60	
				Hospital admission	101/124	88/119	0.16	

1.2 Severity assessment tools

See Appendix G2

1.3 Microbiological tests

1.3.1 Comparative, non-multivariable studies - patient characteristics, interventions and study design

Review question	Empirical compared with targeted antibiotic therapy for CAP
Study	Benenson 2007[6]
Study type	Non-randomised comparative study (randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	1 (N = 806)
Countries and setting	Conducted in USA; Setting: Community teaching hospital
Line of therapy	Part of comparison
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ ICD-9 diagnosis
Stratum	High severity (hospital setting): Admitted via the emergency department
Subgroup analysis within study	Not applicable
Inclusion criteria	Records in hospital database for adults at least 18 years of age admitted via the ED with an ICD-9 diagnosis of pneumonia (CAP or HCAP). Patients with prior antibiotics and a history of HIV or other immunosuppressive disease or therapy were also included.
Exclusion criteria	Discharge diagnosis other than adult pneumonia
Recruitment/selection of patients	Retrospective database search of admissions in 2001 and 2002
Age, gender and ethnicity	Age - Mean (SD): Blood culture group: 71.0 (16.2); no blood culture group: 71.0 (17.4). Gender (M:F): 50/50%. Ethnicity: Not stated
Further population details	1. Comorbidities: Minority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (Of those with blood cultures (data not available for non-blood culture group), 34% had COPD; 26% CHF, 11% stroke; 17% renal disease; 3% liver disease; < 7% were immunosuppressed). 2. Predominant disease aetiology (including resistance profiles): *Streptococcus pneumoniae*

	3. Prior antibiotics: Minority with prior antibiotic use (21% of those with blood cultures had received antibiotics prior to hospitalisation (data not available for non-blood culture group)). 4. Severity: Not applicable / Not stated / Unclear
Extra comments	19% of those with blood cultures had recent hospitalisation (data not available for non-blood culture group)
Interventions	Intervention 1: Empiric then targeted antibiotic treatment ~ Targeted using blood culture results. Antibiotic regimens were based on ATS guidelines supplemented by local culture and sensitivity data. Two sets of blood cultures were to be obtained before initiating antibiotics - blood cultures positive for coagulase negative staphylococci, common skin contaminants and yeast contaminants were considered false positives. Duration NA. Concurrent medication/care: Unclear (N = 684). Further details: Intervention 2: Empirical antibiotic treatment ~ Non UK-standard empiric treatment. Antibiotic regimens were based on ATS guidelines supplemented by local culture and sensitivity data. Specific drugs not stated. Duration NA. Concurrent medication/care: Unclear(N = 122) Further details: Comments: Unclear why blood culture was not performed in these patients as it was part of the recommended clinical pathway
Study	Falguera 2010[34]
Study type	RCT (Patient randomised; Parallel)
Funding	Academic or government funding (Ciber de Enfermedades Respiratorias)
Number of studies (number of participants)	1 (N = 194)
Countries and setting	Conducted in Spain; Setting: Single hospital
Line of therapy	Part of comparison
Duration of study	Intervention + follow up: up to 1 month post-discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinical and radiological evidence of pneumonia
Stratum	High severity (formal assessment): Class IV or V of the PSI or the presence of additional circumstances that justify hospital admission

Subgroup analysis within study	Not applicable
Inclusion criteria	1. Age ≥ 18 years. 2. Clinical and radiological evidence of pneumonia consisting of two or more of the following clinical manifestations: fever, chills, cough, sputum production, pleuritic chest pain and signs of lung consolidation; along with the presence of an infiltrate in the chest radiograph that was consistent with acute infection. 3. Class IV or V of the Pneumonia Severity Index or the presence of additional circumstances that justify hospital admission. 4. Clinical stability between 2 and 6 days after admission, defined as the condition in which all the following threshold values were achieved for a 24 h period: temperature, ≤ 37.2°C; heart rate ≤ 100 beats/min; respiratory rate, ≤ 24 breaths/ min; systolic blood pressure, ≥ 90 mm Hg; and oxygen saturation of ≥ 90% or arterial oxygen partial pressure of ≥ 60 mm Hg when the patient was not receiving supplemental oxygen
Exclusion criteria	1. Misdiagnosis at admission. 2. Nosocomial-, nursing home- or healthcare-associated pneumonia. 3. Risk factors for infection due to *Pseudomonas aeruginosa*, anaerobia or other microorganisms that require alternative therapeutic regimens. 4. Infection caused by tuberculosis or opportunistic microorganisms. 5. Empyema at admission. 6. Immunosuppression, for reasons including HIV infection, haematological neoplasms, solid-organ and bone-marrow transplantation, neutropenia and immunosuppressive treatments. Patients provided written informed consent to participate in the trial. The study was approved by the scientific and ethic committees of our institution.
Recruitment/selection of patients	Prospective, April 2006 - March 2008
Age, gender and ethnicity	Age - Mean (SD): Empirical: 64 (19.2); targeted: 65 (20.1). Gender (M:F): 66/34. Ethnicity: Not stated
Further population details	1. Comorbidities: Minority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (Smoking habit 20%; alcohol abuse 7%; COPD 20%; diabetes mellitus 18%; chronic heart failure 10%; chronic liver disease 3%; chronic renal disease 5%; neoplasm 8%). 2. Predominant disease aetiology (including resistance profiles): Not stated or unclear 3. Prior antibiotics: Minority with prior antibiotic use (22%). 4. Severity: Severe (58% PSI class IV-V).

Extra comments	Note: all patients treated empirically initially and only randomised when clinically stable. In the absence of additional medical circumstances, patients were discharged between 24 and 48 h after switching from intravenous to oral treatment.
Interventions	Intervention 1: Empirical antibiotic treatment ~ Standard UK empiric treatment. Upon entry either beta-lactam (ceftriaxone, 2 g daily, or amoxicillin-clavulanate, 1 g three times daily) plus macrolide (azithromycin, 500 mg daily) or (2) fluoroquinolone (levofloxacin, 750 mg daily), according to the preferences of the attending physician. Those initially treated with beta -lactam plus macrolide were switched to a broad-spectrum oral beta-lactam (amoxicillin-clavulanate, 875/125 mg three times daily or cefditoren, 400 mg twice daily) to complete a 10 day course, plus oral macrolide (azithromycin, 500 mg daily) to complete 5 days of treatment. Alternatively, patients who had received intravenous levofloxacin completed a course of 10 days with the same antibiotic (levofloxacin, 750 mg daily). Duration 10 days (mean: 10.5 [1.3]). Concurrent medication/care: Unclear (N = 89) Further details: Comments: 22% received levofloxacin, 78% beta-lactam plus macrolide Intervention 2: Empiric then targeted antibiotic treatment ~ Targeted using urinary legionella/pneumococcal antigen results. Upon entry either beta-lactam (ceftriaxone, 2 g daily, or amoxicillin-clavulanate, 1 g three times daily) plus macrolide (azithromycin, 500 mg daily) or (2) fluoroquinolone (levofloxacin, 750 mg daily), according to the preferences of the attending physician. Switched to oral amoxicillin, 1 g three times daily, to complete a 10-day course, if the pneumococcal urine antigen test was positive or to oral azithromycin, 500 mg daily to complete a 5-day course, if the *L. pneumophila* urine antigen test was positive. Conversely, for patients with negative urinary antigen tests, oral treatment was the same as the empiric group. Duration 5 or 10 days (mean: 10.8 [1.6]). Concurrent medication/care: Unclear (N = 88) Further details: Comments: Urine for detection of antigens of *S. pneumoniae* or *L. pneumophila* was done using a rapid test (BinaxNow test, Leti Laboratories, Barcelona, Spain).
Study	Lidman 2002[63]
Study type	Non-randomised comparative study (randomised; parallel)
Funding	Funding not stated
Number of studies (number of participants)	1 (N = 605)

Countries and setting	Conducted in Sweden; Setting: Single hospital
Line of therapy	Part of comparison
Duration of study	Intervention + follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinical signs plus pulmonary infiltrate on chest x-ray
Stratum	High severity (hospital setting)
Subgroup analysis within study	Not applicable
Inclusion criteria	Admission to hospital for CAP
Exclusion criteria	Age < 15 years; known HIV; HAP; records unavailable
Recruitment/selection of patients	Consecutive patients admitted during 1995 - analysed retrospectively
Age, gender and ethnicity	Age - Median (range): 64 (16-97). Gender (M:F): 52/48. Ethnicity: Not stated
Further population details	1. Comorbidities: Minority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (32% had chronic heart or pulmonary disease). 2. Predominant disease aetiology (including resistance profiles): *Streptococcus pneumoniae* (Of 482 tested, 132 yielded results, of which 49 (10%) were *S. pneumoniae* (non-penicillin-resistant), 36 (7.5%) *M. pneumoniae* and 21 (4.4%) *H. influenzae*). 3. Prior antibiotics: Minority with prior antibiotic use (36% were antibiotic treated on admission). 4. Severity: Not applicable / Not stated / Unclear
Interventions	Intervention 1: Empiric then targeted antibiotic treatment ~ Targeted using a combination of invasive and non-invasive tests. Blood culture (n = 418) or sputum culture (n = 182) on admission; serological analysis (n = 104); culture of pleural effusion (n = 9); protected brush specimens via bronchoscopy (n = 15). Primary antibiotic treatment was penicillin-derivative, cephalosporin, macrolide, imipenem, ciprofloxacin, cephalosporin + macrolide or none; no restriction on switching reported. Duration NA. Concurrent medication/care: Unclear (N = 482). Further details: Intervention 2: Empirical antibiotic treatment ~ Non UK-standard empiric treatment. Primary antibiotic treatment was penicillin-derivative (38%), cephalosporin (36%), macrolide or doxycycline (11%), imipenem or

	ciprofloxacin (4%), cephalosporin + macrolide (8%) or none (3%). Duration NA. Concurrent medication/care: Unclear(N = 123)
Study	Piso 2012[85]
Study type	Non-randomised comparative study (randomised; parallel)
Funding	No funding
Number of studies (number of participants)	1 (N = 286)
Countries and setting	Conducted in Switzerland; Setting: Single teaching hospital
Line of therapy	Part of comparison
Duration of study	Intervention + follow-up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinical and chest x-ray diagnosis required
Stratum	High severity (formal assessment): > 50% PSI IV-V
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with definitive diagnosis of CAP (for comparative study) admitted to the emergency department. Diagnosis required: new onset of cough and one of the following: new focal chest signs, dyspnoea, tachypnoea or fever for at least 4 days; plus pulmonary infiltrates on CXR
Exclusion criteria	Alternative definitive diagnosis
Recruitment/selection of patients	Consecutive patients - Nov 2007 - Aug 2008 all had PnAG; Sept 2008 - March 2009 - PnAG discontinued at the institution
Age, gender and ethnicity	Age - Mean (SD): PnAG group: 66.9 (16.9); control: 72.3 (13.2). Gender (M:F): 62.2/37.8%. Ethnicity: Not reported
Further population details	1. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (Diabetes: 23%; coronary heart disease: 37%; alcohol abuse: 6%; chronic obstructive lung disease: 31%; renal insufficiency: 22%). 2. Predominant disease aetiology (including resistance profiles): Not stated or unclear.

	3. Prior antibiotics: Not applicable / Not stated / Unclear. 4. Severity: Moderate-severe.
Extra comments	PSI score. PnAG group: class I - 6%; II - 18%; III - 17%; IV - 32%; V - 27%. Control group: class I - 3%; II - 14%; III - 19%; IV - 40%; V - 23%
Interventions	Intervention 1: Empiric then targeted antibiotic treatment ~ Targeted using urinary pneumococcal antigen results. Blood cultures, sputum cultures, urinary Binax Now® Legionella antigen testing (LgAG) and Binax Now® pneumococcal antigen testing (PnAG) were performed in all patients when possible. Initial antibiotic treatment: 36% amoxicillin-clavulanate or cefuroxime; 37% amoxicillin-clavulanate/cephalosporin + macrolide; 8% cephalosporin; 2% macrolide; 13% other. Duration 72 hours. Concurrent medication/care: Unclear(N = 139) Further details: Comments: Decision to perform PnAG made by treating physician - only 12 patients enrolled during this period were not tested with PnAG Intervention 2: Empiric then targeted antibiotic treatment ~ Targeted using a combination of non-invasive tests. Blood cultures, sputum cultures, and urinary Binax Now® Legionella antigen testing (LgAG) were performed in all patients when possible. Initial antibiotic treatment: 37% amoxicillin-clavulanate or cefuroxime; 44% amoxicillin-clavulanate/cephalosporin + macrolide; 11% cephalosporin; 1% macrolide; 9% other. Duration 72 hours. Concurrent medication/care: Unclear(N = 147)
Study	Van der Eerden 2005[103]
Study type	RCT (patient randomised; parallel)
Funding	Funding not stated
Number of studies (number of participants)	1 (N = 303)
Countries and setting	Conducted in Netherlands; Setting: Single teaching hospital
Line of therapy	Part of comparison
Duration of study	Intervention + follow-up: up to 180 days after treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinical and radiological evidence

Stratum	Moderate to high severity (formal assessment): > 50% PSI classes III-V
Subgroup analysis within study	Not applicable
Inclusion criteria	1. Age 18 years or over 2. Clinical presentation of an acute illness with one or more of the following symptoms suggesting CAP: presence of fever (≥ 38.0°C), dyspnoea, coughing (with or without expectoration of sputum), chest pain 3. Presence of new consolidation(s) on the chest radiograph.
Exclusion criteria	Presence of severe immunosuppression (HIV infection, high dose of immunosuppressive agents such as prednisone > 35 mg/day, chemotherapy); presence of malignancy; pregnancy or breast feeding; documented severe allergy to antibiotics; presence of obstruction pneumonia; pneumonia within 8 days of hospital discharge.
Recruitment/selection of patients	Prospective; December 1998 - November 2000
Age, gender and ethnicity	Age - Mean (SD): Targeted arm: 62.0 (18.5); empiric arm: 66.7 (17.2). Gender (M:F): 54/46. Ethnicity: Not stated
Further population details	1. Comorbidities: Minority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (COPD: 37%; Asthma: 9%; Congestive heart failure: 8%; Ischaemic heart disease: 6%; Neurological disorder: 9%; Liver disease: 1%; Chronic renal disease: 2%; Diabetes mellitus: 10%). 2. Predominant disease aetiology (including resistance profiles): *S.pneumoniae* (Of 196 identified pathogens, 92 (47%) were *S. pneumoniae* - no penicillin- or macrolide-resistant strains identified). 3. Prior antibiotics: Minority with prior antibiotic use (26%). 4. Severity: Moderate-severe
Extra comments	2% nursing home residents
Interventions	Intervention 1: Immediate targeting of treatment ~ Targeted using a combination of invasive and non-invasive tests. IV treatment directed at the pathogen suspected to be the causative agent, as reported from routine microbial investigation or from clinical presentation. The results of a Gram stain (presence of > 25 polymorphonuclear leucocytes and < 10 squamous cells at 100× magnification) from sputum or pleural fluid, pneumococcal antigen detection (latex agglutination; Murex Diagnostics, Dartford, UK) in sputum or pleural fluid, and *L. pneumophila* serogroup 1 urinary antigen detection test (enzyme immunoassay, Binax-NOW, Binax, Portland, Maine, USA) could be obtained within 2 hours of admission 24 hours a day. Duration 10 days. Concurrent medication/care: Unclear(N = 152)

	Further details: Comments: Tests performed: sputum Gram stain, semi-quantitative culture, and *S. pneumoniae* antigen detection testing; blood cultures; if clinical symptoms suggested, a urine sample for *L. pneumophila* serogroup 1 antigen detection; BAL specimen and protected specimen brush (PSB) with Gram stain, semi-quantitative culture, and *S. pneumoniae* antigen detection were performed when patients did not expectorate sputum within 24 hours of admission or in case of clinical failure. Thoracentesis with Gram staining, *S. pneumoniae* antigen detection, and culture for aerobic and anaerobic bacteria was performed when pleural fluid was present. Blood samples for serology were obtained for the detection of antibodies to *M. pneumoniae*, *C. pneumoniae*, *L. pneumophila* serogroup 1–7, influenza A and B virus, parainfluenza virus 1–3, respiratory syncytial virus (RSV), and adenovirus. Clinical presentation and suspected pathogen Acute illness, lobar infiltrate, raised WBC with an increase in PMNs: *S. pneumoniae*; Mild illness, headache, upper airway tract symptoms, young age, travel to southern Europe, contact with animals: Atypical bacterial pathogen; Comorbid illness, alcohol abuse, aspiration: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, Gram negative *Enterobacteriaceae*, anaerobes; Influenza epidemic: *S. aureus* Intervention 2: Empirical antibiotic treatment ~ Standard UK empiric treatment. Antibiotic treatment according to the ATS guidelines of 1993. Beta-lactam/β-lactamase inhibitor plus erythromycin were given IV or ceftazidime and erythromycin IV for patients referred to ICU. Duration 10 days. Concurrent medication/care: Unclear (N = 151) Further details:

1.3.2 Comparative, non-multivariable studies – results

1.3.2.1 Dichotomous

Stratum	Outcome	Drug1	Drug2	Study name	No. of events group 1	No. of patients analysed group 1	No. of events group 2	No. of patients analysed group 2	Actual outcome	Comments
High severity (formal assessment)	Clinical cure	Targeted using urinary legionella/pneumococcal antigen results	Standard UK empiric treatment	Falguera 2010[34]	4	88	2	89	Clinical relapse: regained instability after starting oral treatment @ up to 30 days post-discharge	
High severity (formal assessment)	Complications (composite of empyema, effusion, abscess, metastatic infection)	Targeted using urinary legionella/pneumococcal antigen results	Standard UK empiric treatment	Falguera 2010[34]	4	88	2	89	Re-admission @ up to 30 days post-discharge	
High severity (formal assessment)	Microbiological test positive yield	Targeted using urinary legionella/pneumococcal antigen results	Standard UK empiric treatment	Falguera 2010[34]	25	88	0	0	Proportion test positive @ 2-6 days after admission	Outcome not applicable to empiric group
High severity	Mortality	Targeted using urinary legionella/pneumococ	Standard UK empiric	Falguera 2010[34]	1	88	0	89	Mortality @ 30 days post-	

Stratum	Outcome	Drug1	Drug2	Study name	No. of events group 1	No. of patients analysed group 1	No. of events group 2	No. of patients analysed group 2	Actual outcome	Comments
(formal assessment)		cal antigen results	treatment						treatment	
High severity (formal assessment)	Withdrawal due to adverse events	Targeted using urinary legionella/pneumococcal antigen results	Standard UK empiric treatment	Falguera 2010[34]	1	88	1	89	Treatment withdrawal due to adverse events @ 5-10 days	Targeted arm: leucocytoclastic vasculitis (amoxicillin-treated); empiric arm: hepatitis (levofloxacin-treated)
High severity (hospital setting)	Change in prescription	Targeted using a combination of invasive and non-invasive tests	Non UK-standard empiric treatment	Lidman 2002[63]	133	482	23	123	Change in antibiotic therapy @ NA	
High severity (hospital setting)	Change in prescription	Targeted using blood culture results	Non UK-standard empiric treatment	Benenson 2007[6]	3	684	0	122	Change in treatment @ Unclear	Not clearly reported, but all organisms isolated in blood culture group were susceptible to the empiric antibiotics used. 4 patients with positive blood cultures had treatment switched: three

Stratum	Outcome	Drug1	Drug2	Study name	No. of events group 1	No. of patients analysed group 1	No. of events group 2	No. of patients analysed group 2	Actual outcome	Comments
										had spectrum narrowed and one was switched due to allergy. However, based on the positive blood culture results 21/23 could have had antibiotic coverage narrowed
High severity (hospital setting)	Microbiological test positive yield	Targeted using a combination of invasive and non-invasive tests	Non UK-standard empiric treatment	Lidman 2002[63]	132	482	0	0	Microbiological tests positive yield @ NA	
High severity (hospital setting)	Microbiological test positive yield	Targeted using blood culture results	Non UK-standard empiric treatment	Benenson 2007[6]	77	684	0	0	Positive blood culture @ Unclear	Only 23 were true positives, 3 of whom dies in hospital, compared with 2/54 FPs and 27/607 negatives. The length of stay did not differ significantly

Stratum	Outcome	Drug1	Drug2	Study name	No. of events group 1	No. of patients analysed group 1	No. of events group 2	No. of patients analysed group 2	Actual outcome	Comments
										between the TP, FP and N groups
High severity (hospital setting)	Mortality	Targeted using a combination of invasive and non-invasive tests	Non UK-standard empiric treatment	Lidman 2002[63]	42	482	29	123	Mortality @ 3 months	OR = 3.2 (1.9 to 5.4); p = 0.001. Result independent of chronic heart or lung disease status and remained valid (p = 0.01) after adjustment for age; but identifying the pathogen had no impact on the outcome (i.e. no difference between those with positive and negative test results).
High severity (hospital setting)	Mortality	Targeted using blood culture results	Non UK-standard empiric treatment	Benenson 2007[6]	32	667	8	118	In-hospital mortality @ Unclear	Caution: non-randomised data
Moderate to high	Change in prescription	Targeted using a combination of	Standard UK empiric	Van der Eerden 2005[103]	25	134	0	0	Treatment adaptation to	N/A for empiric arm

Stratum	Outcome	Drug1	Drug2	Study name	No. of events group 1	No. of patients analysed group 1	No. of events group 2	No. of patients analysed group 2	Actual outcome	Comments
severity (formal assessment)		invasive and non-invasive tests	treatment						microbial culture results @ Unclear	
Moderate to high severity (formal assessment)	Change in prescription	Targeted using urinary pneumococcal antigen results	Targeted using a combination of non-invasive tests	Piso 2012[85]	88	139	80	147	Change in antibiotic treatment @ 72 hours	The majority of cases involved narrowing the spectrum
Moderate to high severity (formal assessment)	Clinical cure	Targeted using a combination of invasive and non-invasive tests	Standard UK empiric treatment	Van der Eerden 2005[103]	32	152	35	151	Clinical failure @ 30 days	
Moderate to high severity (formal assessment)	Microbiological test positive yield	Targeted using a combination of invasive and non-invasive tests	Standard UK empiric treatment	Van der Eerden 2005[103]	84	134	69	128	Positive test yield @ Unclear	
Moderate-to high-severity (formal assessmen	Microbiological test positive yield	Targeted using urinary pneumococcal antigen results	Targeted using a combination of non-invasive	Piso 2012[85]	39	139	15	147	Positive for pneumococcus @ 72 hours	Of the positive results in the PnAG group 22/39 were detected by

Stratum	Outcome	Drug1	Drug2	Study name	No. of events group 1	No. of patients analysed group 1	No. of events group 2	No. of patients analysed group 2	Actual outcome	Comments
t)			tests							PnAG (in only 11 cases was PnAG the sole positive test)
Moderate to high severity (formal assessment)	Mortality	Targeted using a combination of invasive and non-invasive tests	Standard UK empiric treatment	Van der Eerden 2005[103]	12	152	22	151	Mortality @ 30 days	

1.3.2.2 Continuous

Drug1	Drug2	Study name	Mean group 1	Standard deviation group 1	No. of patients analysed group 1	Mean group 2	Standard deviation group 2	No. of patients analysed group 2	Actual outcome
Targeted using urinary legionella/pneumococcal antigen results	Standard UK empiric treatment	Falguera 2010[34]	7.1	4	88	7.1	3.8	89	Length of hospital stay @ Unclear
Targeted using blood culture results	Non UK-standard empiric treatment	Benenson 2007[6]	5.3	3.4	667	5	4.3	118	Length of hospital stay @ Unclear
Targeted using a combination of invasive and non-invasive tests	Standard UK empiric treatment	Van der Eerden 2005[103]	14.3	13.2	152	13.2	9.4	151	Length of hospital stay @

Drug1	Drug2	Study name	Mean group 1	Standard deviation group 1	No. of patients analysed group 1	Mean group 2	Standard deviation group 2	No. of patients analysed group 2	Actual outcome
									Unclear
Targeted using a combination of invasive and non-invasive tests	Standard UK empiric treatment	Van der Eerden 2005[103]	59.5	21.5	72	57.3	20.5	47	SF-36 @ 30 days
Targeted using a combination of invasive and non-invasive tests	Standard UK empiric treatment	Van der Eerden 2005[103]	66.7	22.9	50	67.2	30.1	35	SF-36 @ 90 days
Targeted using a combination of invasive and non-invasive tests	Standard UK empiric treatment	Van der Eerden 2005[103]	79.3	22.4	31	64.1	20.1	22	SF-36 @ 180 days

1.3.2.3 General

Stratum	Outcome	Drug1	Drug2	Study name	Summary statistic	Summary statistic value	Actual outcome	Comments
High severity (hospital setting)	Length of hospital stay	Targeted using a combination of invasive and non-invasive tests	Non UK-standard empiric treatment	Lidman 2002[63]	Other	Median (range): test group - 5 (1 to 90), n = 482; non-test group - 5 (1 to 34) days, n = 123. p-value for difference = 0.28	Length of hospital stay @ Unclear	

1.3.3 Multivariable studies

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Meehan 1997 [70] **Study type:** Retrospective medical record review **Selection / patient setting:** Medical Quality Indicator System (MQIS) pneumonia module (data collection system to assess quality of care). 3555 acute care hospital throughout USA. Potential cases selected randomly from national pool of approx. 650,000 discharges from non-federal acute care hospitals w designated ICD-9 codes using SAS random selection procedure. From Oct 1994 – Oct 1995, 500 potential cases randomly selected from Medicare Part A claims from each state, the district of Columbia and Puerto Rico. **Addressing missing data/non reliability of data:** N = 14069 used as denominator in calculating percentages regardless of missing values. **Statistical analysis (including confounders adjusted for):** Multivariable logistic regression analysis on associations between each process of care marker and 30-day mortality.	**Diagnosis:** Elderly patients (≥65) hospitalised with pneumonia. **Inclusion criteria:** Potential pneumonia identified from Medicare National Claims History File if had: • a principle discharge diagnosis of pneumonia (ICD-9-CM codes 480.0-480.9, 481, 482.0-482.9, 483.0-483.8, 485, 486, 487.0, 507.0) • a principle discharge diagnosis of respiratory failure (ICD-9-CM code 518.81) and a secondary diagnosis of pneumonia. • Patient has appropriate ICD-9-CM code, clinical document with initial working diagnosis of pneumonia, chest x-ray within 48 h reports consistent w pneumonia (terms such as: pneumonia, air bronchogram, air space disease, consolidation, infiltrate, inflammation, opacity or pneumonitis). **Exclusion criteria:** • < 65 years • Experienced acute hospitalisation w/in 10 days • HIV/AIDS • History of organ transplant	***Proportion achieving quality indicators*** (rate did not differ between those with and without prior antibiotics)		**Funding:** 500-96-P549 contract from Health Care Financing Administration of the US Department of Health and Human Services. **Limitations:** • No specific mention of CAP • Causative pathogens and antibiotic treatment choice not considered. • Retrospective diagnosis based on medical records • Multivariable analysis only adjusted for patient risk status and performance of other processes of care. • Excluded those with principle discharge diagnosis of septicaemia and a secondary
		Blood culture within 24 h (of whom 12.7% had previously received antibiotics)	**National set:** 68.7 (95% CI: 66.2-71.2)% **State or territory (range):** 45.6-82.8%	
		Blood culture before antibiotics	**National set:** 57.3 (95% CI: 54.5-60.2)% **State or territory (range):** 32.3-73.9%	
		Relationship of quality indicators to 30-day mortality – multivariable analysis		
		Overall mortality	2148 (15.3%)	
		Blood culture within 24 h compared with no blood culture within 24 h	**Aggregate study set** **AOR:** 0.90 (0.81 to 1.00) → lower 30-day mortality if BC done within 24 h	
		Blood culture before antibiotics compared with no blood before antibiotics	**Aggregate study set** **AOR:** 0.92 (0.82 to 1.02)	

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Quality indicators: 1. time from hospital arrival to initial antibiotic administration, 2. blood culture prior to initial antibiotic, 3. blood culture within 24 hours of arrival, 4. oxygenation assessment within 24 hours of arrival. Multivariable analysis adjusted for each of the above plus severity of illness details: • demographics (age, sex, nursing home residence) • comorbidities (cerebrovascular disease, congestive heart failure, neoplastic disease) • physical examination findings • lab/test results.	• Chemo or immunosuppressive therapy within previous 2 months • Transferred from another acute care facility • Died or discharged on date of admission • > 1 pneumonia hospitalisation in study period (n = 113) – only initial episode included • 30 day mortality unable to be verified (n = 33) **All patients** N: 25561 Exclusions due to: • 439 – no medical record, inadequate documentation of dates/times for hospital arrival or process-of-care performance. • 189 – Did not receive antibiotics during hospitalisation, received antibiotics > 100 hours after arrival, blood cultures drawn > 24 hours prior to hospital arrival or after discharge. • 2326 – < 65years • 1687 – Prior admission within 10 days **Included N:** Aggregate study set N = 14069 • National study set (subset to reflect relative volume of pneumonia discharges from each state/territory) n = 1343			diagnosis of pneumonia; may have systematically excluded patients with blood cultures positive for pneumonia-causing pathogens • Unclear why different outcomes reported for different sample sets **Additional outcomes:** N/A **Notes:**

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
	• State & territory study set n = 196-323 (cases per state or territory) **Age, mean:** 79.4yrs 65-74 – 4265 (30.3%) 75-84 – 5881 (41.8%) ≥ 85 – 3913 (27.8%) *Age data for 10 people missing* **Gender (male/female):** 6955/7114 **Nursing home patients:** 3289 (23.4%) (from skilled nursing facility or intermediate care facility) **Comorbidities:** 58.2% had at least one comorbid illness Congestive heart failure – 3890 (27.6%) Coronary artery disease – 3753 (26.7%) Cerebrovascular disease – 2896 (20.6%) Neoplastic disease – 1217 (8.7%) Chronic renal failure – 474 (3.4%) Chronic liver disease – 119 (0.8%) **Pneumonia severity:** Fine 1997 prediction rule for CAP – assigned 1-4 risk categories based on presence of three demographic characteristics, five comorbidities, five physical examination abnormalities and seven lab/radiographic findings. No sample breakdown by comorbidity supplied.			

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Lee 2011[59] **Study type:** Retrospective observation of prospective RCT (secondary analysis) **Selection / patient setting:** Hospitalised with pneumonia in 32 emergency departments in Connecticut & Pennsylvania in 2001. Sites were randomised to low, moderate or high intensity guideline implementation strategies to promote performance of evidence-based processes of care for pneumonia. Emergency department community-acquired pneumonia trial (EDCAP). **Addressing missing data/non reliability of data:** Patients with incomplete follow-up or medical record review were excluded from the denominator in the calculation of the frequency for these outcomes. **Statistical analysis (including confounders adjusted for):** Patient outcomes in relation to four processes of care: 1. Assessment of oxygenation	**Diagnosis:** Adult (≥18) with clinical and radiographic evidence of CAP. **Inclusion criteria:** Inpatient defined as hospital admission, transfer from ED to inpatient observation unit, admission to ED observation unit with discharge to any setting more than 24hs after presentation. **Exclusion criteria:** HAP, immunosuppression, specified conditions (pregnancy, cystic fibrosis), psychological or substance abuse problems. **All patient,** N: 4506 Exclusions due to: 891 eligible patients not enrolled (no details as to why) 414 excluded from process-of-care analysis (no details as to why) 1125 not in this particular EDCAP trial (no details as to why). **Included N:** 2076 **Age, median:** 74 **Gender (male/female):** 1013/1063	No. of patients receiving 2 blood cultures before first antibiotic = 1314 (63.3%)		**Funding:** • R01-HS10049 Agency for Healthcare Research and Quality. • National Institute of Allergy and Infectious Diseases grant (K24-AI001769) • Robert Wood Johnson Foundation Physician Faculty Scholar Award and a career development award from National Cancer Institute (K07-CA114315). **Limitations:** • No details of antibiotic treatment choice. • No details listed to explain exclusions. • Possible selection
		Association between blood culture before first antibiotic and 30-day mortality (multivariable)		
		Mortality rate – blood culture before antibiotic	88/1305 (6.7%)	
		Mortality rate – no blood culture before antibiotic	53/757 (7.0%)	
		blood culture before antibiotic compared with not	AOR 0.9 (0.6 to 1.3)	
		Secondary patient outcomes (unadjusted)		
		Median length of stay, days (IQR)	BC before antibiotic = 5 (3 to 7) No BC before antibiotic = 5 (3 to 8)	
		ITU/CCU admission	BC before antibiotic = 194/1306 (14.9%) No BC before antibiotic = 81/761 (10.6%)	
		Hospital re-admission	BC before antibiotic = 103/1238 (8.3%) No BC before antibiotic = 72/723 (10.0%)	
		Association between blood culture before first antibiotic and secondary patient outcomes (multivariable)		
		Length of stay	AOR 1.0 (0.9 to 1.2)	
		ITU/CCU admission	AOR 1.4 (1.0 to 1.9)	
		Hospital re-admission	AOR 0.8 (0.6 to 1.1)	

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
on presentation, 2. blood cultures (obtain 2 before antibiotic admin), 3. appropriate selection of antibiotic care (empiric therapy selection) and 4. rapid initiation (<4h) of antibiotics. Categorical summary of total number of individual processes of care performed (0-2, 3 and 4). Primary outcome – Mortality 30 days after presentation. Multivariable analysis adjusted for baseline severity of illness (PSI class), plus patient, provider and site characteristics (comorbidities, treatments before presentation) • Some comorbidities assumed to be covered for in PSI risk class (neoplastic, liver, cerebrovascular, congestive heart failure, renal) not adjusted for in multivariable analysis. Also accounted for clustering of patients within sites of care	**Nursing home patients:** 120 **Ethnicity:** White: 90.3% Black: 7.7% Hispanic: 1.8% **Comorbidities:** Neoplastic disease – (3.6%) Liver disease – (0.9%) Congestive heart failure – (19.5%) Cerebrovascular disease – (11.1%) Renal disease – (4.8%) Cognitive impairment – (5.9%) History of coronary artery disease – (27.7%) Chronic pulmonary disease – (38.7%) Diabetes – (24.6%) **Pneumonia severity (PSI):** Class I – 7.6% Class II – 19.5% Class III – 24.4% Class IV – 37.5% Class V – 11% **Antibiotic treatment choice:** No details **Treatment before presentation:** Home oxygen: 9.5% Oral or inhaled corticosteroid: 15.7% Antibiotic in prior 7 days: 15.5%			bias: blood cultures obtained more often for ICU/CCU patients because more severe • Small sample size- limited power to detect a difference **Additional outcomes:** Subgroup analysis: age ≥ 65 years; patients never treated in ICU or coronary care unit

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Dedier 2001[30] **Study type:** Retrospective chart (medical record) review **Selection patient/setting:** retrospectively identified from 38 US academic hospitals that participated in a University Health System Consortium–sponsored pneumonia benchmarking project **Addressing missing data/non reliability of data:** unclear. For analyses of length of stay, 66 patients who died in the hospital, 12 who left against medical advice, and 11 who were transferred to another acute-care facility were excluded. **Statistical analysis:** Outcomes were expressed as dichotomous variables: inpatient death and clinical instability were coded as occurred or not, and length of hospital stay was coded as greater than the overall median of 4 days or not. Primary analysis examined the univariate and multivariable association between achievement of blood culture within 24 hours and clinical outcomes. Multiple regression models controlled for the	**Patient group:** adults hospitalised with CAP **Inclusion criteria:** Patients hospitalized with CAP (primary International Classification of Diseases 9 code 003.22, 21.2, 39.1, 052.1, 055.1, 073.0, 112.0, 114.0, 115.05, 115.15, 115.95, 130.4, 510.0, 510.9, 511.1, 480-480.2, 480.8, 480.9, 481, 482-482.4, 482.8-483, 484.1, 484.3, 484.5-484.8, 485, or 486 or a secondary ICD 9 classification, where the primary diagnosis was respiratory in nature, septicaemia, or dehydration (code 038.0-038.9, 276.5, 490, 512.0-512.9, 518.81-518.82, or 786.0-786.9). **Exclusion criteria:** age < 18 years, initial chest radiograph > 24 h before or 48 h following hospital arrival, no infiltrate on chest x-ray film, antibiotic administration time was not identified, or antibiotics not administered within 48 h of arrival or were known to have been given before hospital arrival (medical record review of hospital records may underestimate pre-hospitalisation antibiotic use), discharge from an acute-care hospital within 10 days of admission, transfer from another acute-care hospital, active immunosuppressive therapy, known HIV seropositivity, active chemotherapy, and a diagnosis of cystic fibrosis or tuberculosis **All patients,** N: 1457 Exclusions due to : lack of evidence of pneumonia on admission CXR (n = 224); transfer	**<u>Process-marker achievement</u>**		**Funding:** none stated **Limitations:** Data were collected and coded retrospectively from medical records and based on discharge diagnosis. Causative pathogens and appropriateness of antibiotic choice not considered Only controlled for process markers and PSI class in analysis Insufficient sample size **Additional outcomes:** Clinical instability at 48 h (1.04, 0.75 to 1.44) **Notes:** 49% had at least one chronic comorbid condition and 10% had 'do not resuscitate' orders
		Median time to performing blood culture	2.6 hours (IQR: 1.1 to 5.8 hours)	
		Proportion achieving blood culture within 24 h of arrival	**Overall**: 82.5% **Range among hospitals:** 53.6-100.0% **By PSI class:** I – 79.0% II – 79.2% III – 81.9% IV – 81.4% V – 90.8%	
		Proportion achieving blood culture before antibiotic administration	**Overall**: 72.3% **Range among hospitals:** 9.5-100.0% **By PSI class:** I – 72.8% II – 72.2% III – 73.5% IV – 74.8% V – 66.8%	
		Adjusted odds ratio for blood culture within 24 h compared with after 24 h/no blood culture – multivariable		
		In patient death	0.86 (0.36 to2.07)	
		Clinical instability at 48 h	1.62 (1.13 to 2.33)	
		Length of stay longer than median	1.04 (0.72 to 1.50)	
		Adjusted odds ratio for blood culture before antibiotics compared with after/no blood culture – multivariable		

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
presence of all other process markers and pneumonia severity using the PSI.	from another acute-care hospital (n = 111); other (n = 60) **Included N:** 1062 **Age, median :** 64 (range: 47 to 78) **Gender (female):** 50% **Ethnicity:** Black: 32% White: 58% Other: 8% **Nursing home patients**: 0 **Comorbidities:** Coronary disease – 259 (24%) Diabetes – 227 (21%) COPD – 215 (20%) **PSI class:** I – 12% II – 17% III – 19% IV – 34% V – 18%	**In patient death**	1.21 (0.62 to 2.34)	
		Clinical instability at 48 h	1.06 (0.74 to 1.51)	
		Length of stay longer than median	0.84 (0.60 to 1.17)	

<table>
<tr><th>Reference</th><th>Patient Characteristics</th><th colspan="6">Outcomes measures</th><th>Comments</th></tr>
<tr><td rowspan="20">Author and year: Uematsu et al 2014[102]

Study type: Retrospective cohort study using a multicentre claim-based inpatient database

Selection / patient setting:
Adults hospitalised with CAP in different hospitals in Japan

Addressing missing data/non reliability of data:
Statistical analysis (including confounders adjusted for):
• 30-day mortality was estimated using a multivariable logistic regression model adjusted for age, sex, orientation disturbance, respiratory failure, low blood pressure, dehydration, comorbidities, emergency admission via ambulance, use of intensive care units, university-affiliated major hospital status, treatment in a pulmonary unit, hospital volume, hospital size and doctor-to-bed and nurse-to-bed ratios.
• For the outcome of length of stay, it was used a Cox proportional hazards model (adjusted for the same</td><td rowspan="20">Diagnosis: Adult (≥ 18) hose major diagnosis was pneumonia (ICD-10)

Inclusion criteria:
Inpatient defined as hospital admission, transfer from ED to inpatient observation unit, admission to ED observation unit with discharge to any setting more than 24hs after presentation.
Exclusion criteria:
HAP, HCAP, NHAP, immunocompromised status, or patients transferred to other institutions for more specialised intensive treatment

All patient,
N: 65145
Included N: 65145
Age, mean: 74.3
Gender male (%): 58%
Nursing home patients: excluded
Comorbidities:
Malignant tumour– (8.9%)
Liver disease – (2.5%)
Congestive heart disease – (18.4%)
Cerebrovascular disease – (9.3%)
Renal disease – (3.9%)
Pneumonia severity (A-DROP - excluding patients who died in</td><td colspan="6">No. of patients receiving no test: 307444
No. of patients receiving 1 test: 17086
No. of patients receiving 2 tests: 11976
No. of patients receiving 3 tests: 5339

Overall 30-day in-hospital mortality: 6.6%
Mean length of hospital stay: 18.8 days
<u>OR (95% CI) for 30-day in-hospital mortality (multivariable)</u></td><td rowspan="20">Funding:
Grants from the Ministry of health, labour and welfare, and Ministry of education and science in Japan. Grant from the Japan society for the promotion of science

Limitations:
• No detailed clinical information about the pathogens, sensitivity profile and appropriate choice of antibiotics could be obtained
• No information was available on antibiotic administration within 4 h of hospitalisation
• Observational design could have biased the results despite the adjusted analysis
• Analysis was based on electronic orders of the tests, without confirmation of their implementation
• Microbiological tests could be withheld in patients with poor prognosis (e.g. patients</td></tr>
<tr><td>Sputum tests</td><td colspan="5">1.06 (0.98-1.15)</td></tr>
<tr><td>Blood cultures</td><td colspan="5">0.78 (0.71-0.85)</td></tr>
<tr><td>Urine antigen tests</td><td colspan="5">0.75 (0.69-0.82)</td></tr>
<tr><td>1 test</td><td colspan="5">0.92 (0.85-1.00)</td></tr>
<tr><td>2 tests</td><td colspan="5">0.75 (0.68-0.83)</td></tr>
<tr><td>3 tests</td><td colspan="5">0.64 (0.56-0.74)</td></tr>
<tr><td colspan="6"><u>OR (95% CI) for 30-day in-hospital mortality (multivariable), according to severity status assessed with A-DROP</u></td></tr>
<tr><td></td><td>Very severe (n=7935)</td><td>Severe (n=8224)</td><td>Moderate (n=36,186)</td><td>Mild (n=12,213)</td></tr>
<tr><td>Mortality rate</td><td>26.1%</td><td>11.9%</td><td>3.4%</td><td>0.3%</td></tr>
<tr><td>Sputum tests</td><td>0.93 (0.82 -1.05)</td><td>1.22 (1.05-1.41)</td><td>1.11 (0.98-1.26)</td><td>1.00 (0.50-2.00)</td></tr>
<tr><td>Blood cultures</td><td>0.81 (0.70-0.93)</td><td>0.71 (0.60-0.85)</td><td>0.79 (0.68-0.93)</td><td>1.67 (0.79-3.53)</td></tr>
<tr><td>Urine antigen tests</td><td>0.75 (0.64-0.87)</td><td>0.75 (0.63-0.89)</td><td>0.80 (0.69-0.94)</td><td>0.39 (0.16-0.99)</td></tr>
<tr><td>1 test</td><td>0.97 (0.85-1.12)</td><td>1.03 (0.87-1.21)</td><td>0.81 (0.70-0.93)</td><td>1.03 (0.50-2.11)</td></tr>
<tr><td>2 tests</td><td>0.74 (0.63-0.86)</td><td>0.78 (0.64-0.94)</td><td>0.78 (0.66-0.92)</td><td>0.50 (0.17-1.47)</td></tr>
</table>

Reference	Patient Characteristics	Outcomes measures	Effect sizes			Comments
covariates as for 30-day mortality) to estimate hazard ratios for hospital discharge. Patients who died before discharge were excluded from this analysis.	**hospital):** Mild (0) – 12,213 Moderate (1 or 2)– 36,186 Severe (3) – 8224 Very severe (4 or 5) –7935 **Antibiotic treatment choice:** NR **Treatment before presentation:** NR	3 tests	0.51 (0.40-0.64)	0.70 (0.54-0.91)	0.83 (0.66-1.04)	1.08 (0.36-3.26)	with DNR orders) • Longer length of stays in Japanese hospitals may be related to a poor referral system and limit applicability to other countries • For the groups 1 test or 2 tests, it is not specified which tests were performed. **Additional outcomes:** Subgroup analysis: severity status

Length of hospital stay; HR (95% CI) for discharge (multivariable)

Sputum tests	0.98 (0.97-1.00)
Blood cultures	1.00 (0.98-1.02)
Urine antigen tests	1.07 (1.05-1.10)
1 test	1.04 (1.02-1.06)
2 tests	1.05 (1.02-1.07)
3 tests	1.04 (1.00-1.07)

*excluding patients who died in hospital.

Length of hospital stay; HR (95% CI) for discharge (multivariable), according to severity assessed with A-DROP

	Very severe (n = 5280)	Severe (n = 6880)	Moderate (n = 34,286)	Mild (n = 12,733)
Sputum tests	1.01 (0.95-1.07)	1.02 (0.97-1.08)	0.97 (0.95-0.99)	0.98 (0.94-1.01)
Blood cultures	1.02 (0.95-1.09)	1.05 (0.99-1.12)	1.03 (1.00-1.05)	0.92 (0.88-0.97)
Urine antigen tests	1.15 (1.08-1.24)	1.05 (0.99-1.11)	1.07 (1.04-1.10)	1.03 (0.98-1.07)
1 test	1.11 (1.04-1.19)	1.08 (1.02-1.15)	1.04 (1.01-1.06)	0.96 (0.92-1.00)
2 tests	1.17 (1.08-1.26)	1.09 (1.02-1.16)	1.05 (1.02-1.08)	0.94 (0.89-0.99)
3 tests	1.12 (1.01-1.23)	1.12 (1.03-1.22)	1.02 (0.98-1.07)	0.95 (0.89-1.02)

*excluding patients who died in hospital.

1.4 Antibiotic therapy

1.4.1 Timing of antibiotic therapy

Reference	Patient Characteristics	Prognostic factors	Outcomes measures	Effect sizes		Comments
Author and year: Bordon J et al.2013 [9]. Early administration of the first antimicrobials should be considered a marker of optimal care of patients with community-acquired pneumonia rather than a predictor of outcomes. International Journal of Infectious Diseases 2013; 17: e293-e298[9] **Study type:** Retrospective **Selection / patient setting:** Consecutive adult patients hospitalised with CAP at a Veterans Affairs Medical Centre in the USA. **Addressing missing data/non reliability of data:** Not stated **Statistical analysis (including confounders adjusted for):** Multivariable* analysis was used to estimate the effects of antimicrobial timing on the outcomes, adjusting for propensity** score. *Specifically, a logistic regression analysis was performed for the outcome of	**Diagnosis:** CAP **Inclusion criteria:** new pulmonary infiltrates on X ray and either 1) a new or increased cough with/without sputum, 2) abnormal temperature (<35.6 or >37.8 deg C) or 3) an abnormal serum leukocyte count. **Exclusion criteria:** Patients who received oral or IV antimicrobial therapy before arrival at the ED, or 24 hours after arriving at the ED. **Included N:** 372 **Age, mean:** 68.9 (12.4) years in survivors and 78.0(8.4) years in those who died. **Gender (male/female):** 364 males/ 8 females **Nursing home patients:** not stated **Comorbidities (died%/survived %):** Neoplastic disease (24.1/10.2) CHF (41.4/23.9) Renal disease (27.6/14.9) Liver disease (3.4/2.6) AMI: (17.2/5.8) CVA (10.3/11.7)	Time of first antimicrobial dose (TAFD) **(died%/survived %)** **<u>≤</u> 2 hrs: (10.3/6.7)** **> 2 to 4 hrs: (31/18.1)** **> 4 to 8 hrs: (31/35)** **> 8 hrs: (27.6/40.2)** Mean (sd) administration time in hours **(died/survived)** : 5.7(3.1)/7.5(4.3)		**Effect (95% CIs)**	**p-value**	**Funding:** None reported. No conflicts of interest **Limitations:** Poor reporting of results, with no OR given for outcome of mortality **Additional outcomes**: None **Notes: -**
			Mortality (overall 8.4%)			
			unadjusted	Those dying received antimicrobials 1.8 hours earlier than those surviving (5.7 vs 7.5 hours)	0.04	
			Propensity adjusted	Not reported	0.148	
			Time to clinical stability (absence of fever, improved signs and symptoms and improved leucocyte count)			
			Propensity adjusted	HR: 1.01 (0.98-1.03)	0.604	
			Length of stay in hospital			
			Propensity adjusted	HR: 0.996 (0.97-1.02)	0.774	

mortality, and a cox regression was used for time to clinical stability and length of stay. **The propensity scores were calculated from the following variables in a separate logistic regression: age, platelet count, albumin, creatinine, diabetes mellitus, arterial hypertension, corticosteroids, blood urea nitrogen, AMI, gender, ICU admission, respiratory rate, blood pressure, sodium, O2 saturation, heart rate, nursing home residence, co-morbidities (such as cancer, liver disease, CHF, CVA, renal disease, AMI, COPD and HIV infection) and indicators of complex pneumonia such as multilobar infiltrates, pleural effusion and cavitatory lesions.	COPD: (48.3/46.6) Diabetes (34.5/35.6) Art. Hypertension (82.8/68.8) HIV (0/0.6) Nursing home resident (3.4/4.1) **Pneumonia severity: (died%/survived %)** Cavitatory lesion (3.4/0.6) Pleural effusion (31/15.20) ITU admission (24.1/17.5) Multilobar infiltrates (37.9/26.5) PSI class IV and V (86.2/53.1) CRB65 score 2-4 (20.7/15.7)				

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Houck 2004[52] **Study type:** Retrospective chart (medical records) review **Selection patient/setting:** A retrospective study using medical records from national random sample Medicare patients. Claims in each state were sampled during one of two 6-month periods: July 1 through December 31, 1998, and September 1, 1998, through March 31, 1999. There were 346 105 cases nationally during these periods. A systematic random sample of up to 850 cases was selected from each state. **Addressing missing data/non reliability of data:** Hospitals sent photocopies of medical records to 1 of 2 clinical data abstraction centers (CDACs). Inter-CDAC reliability was monitored on a monthly sample of records and averaged 92% overall. Inter-CDAC agreement on administration of antibiotics within 4 hours of arrival was 91% with a κ coefficient of 0.80 claims to identify readmission. **Statistical analysis:**	**Patient group:** Older patients with CAP **Inclusion criteria:** Patients older than 65 years who were hospitalised with CAP **Exclusion criteria:** • patients who had been hospitalised within 14 days prior to admission • lack of antibiotic timing data or radiographic evidence of pneumonia in the medical record • immunocompromised (receipt of corticosteroids or antineoplastic therapy or history of organ transplantation, leukaemia, or lymphoma) • lack of antibiotic treatment during the first 36 hours at the hospital • discharge or death on the day of admission • hospitalisation in Puerto Rico or the Virgin Islands • only the first of a patient's multiple hospitalizations was included. **All patient, N:** 39,242 cases	***PATIENTS WITHOUT PREHOSPITAL ANTIBIOTICS*** ***Antibiotic administration within 4 hours of arrival compared with later*** **All patients** Mortality during 30 days following admission Mortality during hospitalisation Hospital LOS > 5 days Readmission after discharge (within 30 days) **PSI risk classes II and III** Mortality during 30 days following admission Mortality during hospitalisation Hospital LOS > 5 days (5 days is the sample median) Readmission after discharge (within 30 days) **PSI risk classes IV and V** Mortality during 30 days following admission Mortality during hospitalisation Hospital LOS > 5 days Readmission after discharge (within 30 days) ***Antibiotic First dose timing and 30 day mortality*** ≤ 1 vs. ≥ 1 h ≤ 2 vs. ≥ 2 h	 Adjusted odds ratio, AOR (95% confidence interval): 0.85 (0.76 to 0.95) AOR: 0.85 (0.74 to 0.98) AOR: 0.90 (0.83 to 0.96) AOR: 0.95 (0.85 to 1.06) AOR: 0.62 (0.42 to 0.93) AOR: 0.77 (0.42 to 1.44) AOR: 0.86 (0.75 to 0.99) AOR: 0.87 (0.70 to 1.07) AOR: 0.87 (0.78 to 0.98) AOR: 0.86 (0.74 to 1.00) AOR: 0.92 (0.84 to 1.00) AOR: 0.99 (0.88 to 1.12) AOR: 0.99 (0.81 to 1.21) AOR: 0.94 (0.83 to 1.06)	**Funding:** Authors declared no financial interest in the article **Limitations:** Data was collected and coded retrospectively from medical records. Cases without timing were excluded from analysis - only 46.4% of all possible cases were included – most common reasons for exclusion were lack of a working diagnosis of pneumonia at the time of admission, transfer from another acute care hospital, or admission for comfort/palliative

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Multivariable logistic regression produced severity adjusted ORs (AORs), which included adjusting for antibiotic timing and factors that were independently associated with outcomes (*the PSI score, admission to an intensive care unit during the first 24 hours, and census region of hospitalization*) and factors that were associated with outcome in univariate analysis only or had been reported in previous studies to be associated with outcome (*arterial oxygenation assessment blood culture within 24 hours of arrival initial antibiotic regimen consistent with IDSA or ATS guidelines and patient ethnicity*).	**Included N:** 18,209 **Age:** 65 to 74 years – 27% 75 to 84 years – 42% ≥ 85 years – 31% **Gender (female):** 51.8%	≤ 3 vs. ≥ 3 h	AOR: 0.88 (0.79 to 0.99)	care only (n = 6531 [16.6%]), immunocompromised (n = 5015 [12.8%]), lack of radiographic evidence of pneumonia (n = 3673 [9.4%]), and age younger than 65 years (n = 3369 [8.6%]). **Additional outcomes:** Patient characteristics stratified by timing of antibiotic administration (chronic renal disease, respiration rate > 30/min, pulse > 125/min, haematocrit < 30%, arterial PO_2 <60 mmHg or SaO_2<90%) **Notes:** Confounding clinical characteristics
		≤ 4 vs. ≥ 4 h	AOR: 0.85 (0.76 to 0.95)	
		≤ 5 vs. ≥ 5 h	AOR: 0.86 (0.76 to 0.97)	
		≤ 6 vs. ≥ 6 h	AOR: 0.84 (0.73 to 0.95)	
		≤ 7 vs. ≥ 7 h	AOR: 0.87 (0.76 to 1.01)	
		≤ 8 vs. ≥ 8 h	AOR: 0.85 (0.73 to 0.99)	
		≤ 9 vs. ≥ 9 h	AOR: 0.86 (0.73 to 1.02)	
		≤ 10 vs. ≥ 10 h	AOR: 0.91 (0.76 to 1.09)	
		≤ 11 vs. ≥ 11 h	AOR: 0.93 (0.77 to 1.13)	
		≤ 12 vs. ≥ 12h	AOR: 0.97 (0.79 to 1.19)	
		PATIENTS WITH PREHOSPITAL ANTIBIOTICS		
		Antibiotic administration within 4 hours of arrival vs later		
		Mortality during 30 days following admission	AOR: 1.18 (0.97 to 1.45) Note: If antibiotic administration changed to within 8 hours vs after 8 hours, AOR 1.38 (1.02 to 1.87)	
		Mortality during hospitalisation	AOR: 1.21 (0.93 to 1.58)	
		Hospital LOS > 5 days	AOR: 0.84 (0.74 to 0.95)	
		Readmission after discharge (within 30 days)	AOR: 0.93 (0.77 to 1.12)	

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
				represented in PSI score Mortality detected using Medicare enrolment data Median length of hospitalisation was 5 days

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Battleman 2002[5] **Study type:** Retrospective chart review **Setting:** New York Presbyterian Healthcare (NYPH) system, a developing integrated health care delivery system in the New York metropolitan region. Patients for this study were identified from among 7 hospital sites in the NYPH system. Hospital sites were chosen because of a high annual incidence of pneumonia cases. Five institutions were university-based teaching hospitals; 2 were community-based non-teaching hospitals. **Selection of patients:** One hundred cases randomly selected from each of 7 network institutions between January 1998 through December 1998 using diagnosis related group (DRG) billing codes for pneumonia (DRG codes 89 and 90). This represented between 4.9% and 21.1% of the total CAP admissions for the participating study sites. **Addressing missing data/non reliability of data:** ▪ 10% the records were randomly sampled and rescored. Reliability testing indicated moderate to excellent inter abstractor reliability with a κ statistic ranging from 0.68 to 0.98: for pneumonia confirmation (κ = 0.98); exclusion criteria (κ = 0.88); and abstraction of demographic (κ = 0.94), clinical (κ = 0.91), and process (κ = 0.68) variables ▪ Each chart was reviewed and abstracted by a trained reviewer using a structured data instrument.	**Patient group:** Adult cases of CAP **Inclusion criteria:** ▪ older than 18 years ▪ the admitting diagnosis by the admitting ED physician had to be pneumonia ▪ the patient had to be admitted from either his or her home or a nursing home (Direct-to-the-floor admissions were excluded because accurate admission times could not consistently be determined for these patients, thereby invalidating the door-to-needle time calculation) ▪ admitted through the ED (direct-to-the-floor admissions were excluded). **Exclusion criteria:** ▪ known or suspected immunodeficiency (HIV, acquired immunodeficiency syndrome, or concurrent immunosuppressive therapy) ▪ suspected diagnosis of *Pneumocystis carinii* pneumonia or tuberculosis based on a physician's review of the medical record ▪ readmitted for pneumonia	**Length of hospitalisation** (LOS) > 9 days: (9 days is the 75th percentile) Variables associated with a statistically significant increased risk of prolonged LOS (AOR > 1) in the multivariable model were: ▪ increased age (per 10-year increase) ▪ ethnicity (white) ▪ presence of other comorbid illnesses ▪ higher respiratory rate at admission (per 5 units increase of breaths per minute). Variables associated with statistically significant reduction in risk of prolonged LOS (AOR > 1) were: ▪ appropriate choice antibiotics, AOR = 0.31 (0.19 to 0.48) ▪ location of antibiotics – emergency department vs. inpatient ward, AOR = 0.31 (0.19 to 0.48) ▪ both location of antibiotic and appropriateness of antibiotics were associated with timing of antibiotic administration.	**AOR:** 1.75 (1.34 to 2.29) Per 8 hour delay, time to antibiotics measured as "door to needle time" – see notes for definition.	**Funding:** None stated, study conducted New York Presbyterian Healthcare (NYPH) system **Limitations:** Retrospective chart review – however, there were adequate measures to address reliability of data. **Additional outcomes:** ▪ associations of demographic, clinical and process variables with prolonged length of stay (all reported as adjusted odd ratio, AOR), relationship between prolonged length of stay and appropriate antibiotics and predictors of initial site of antibiotic

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
▪ *Specified data collection for length of hospitalisation (measured in days) and 13 other independent variables included in the univariate analysis:* 1) *Demographic variables* : age; sex; ethnicity (white vs non-white); admission site (admitted from nursing home vs private home); payer status (Medicaid/self-pay vs Medicare/commercial insurance) 2) *Clinical variables:* COPD or history of COPD, comorbid illness adapted from the PSI (history of active neoplastic disease, renal failure, cerebrovascular disease, liver failure, congestive heart failure, or altered mental status at admission); white blood cell count (WBC) at admission; respiratory rate (RR) at admission; chest x-ray film at admission (chest x-ray film consistent with pneumonia within 48 hours of admission). Chest x-ray films were considered consistent with pneumonia if the x-ray report contained any of the following terminology: pneumonia, air bronchogram, air space disease, consolidation, infiltrate, inflammation, opacity, or pneumonitis 3) *Process-of-care variables:* site of initial antibiotic administration (ED vs floor); door-to-needle time (hours); and appropriateness of antibiotic selection (see notes for the definition of these variables) **Statistical analysis:** ▪ univariate measures of association tested between pLOS, and each of the variables listed above using the Fisher exact test, t-test or the Wilcoxon rank sum test ▪ the unadjusted mean LOS was skewed and transformed using a base-10 logarithmic transformation ▪ multivariable logistic regression model selected the	within 30 days of discharge, ▪ had antibiotic therapy initiated prior to ED presentation ▪ all in-hospital deaths and patients who left against medical advice (because the primary outcome measure of the study was LOS and because the combined death and against-medical-advice rates (3.9%)) **All patient, N:** 700 **Included N:** 609 Reason for exclusion: 18 were not admitted through the ED 24 did not have an ED physician's admitting diagnosis of pneumonia, 12 had HIV and another 8 patients had known or suspected immunodeficiency. 2 had a prior 30-day admission. There were 23 deaths and 4 patients who were discharged against medical advice **Age, mean :** 67 years **Male:** 45% **Ethnicity :** 40% were white **Other key characteristics of patients:** ▪ average door to needle time: 5.5 ± 3.5 hours (3.5 ± 1.4 in the ED, 9.5 ± 3.0 in the inpatient			treatment **Notes:** Definition of variables used in the study: ▪ door-to-needle time was measured in hours and represents the difference between the triage time and the documented time of initial antibiotic administration. ▪ appropriateness of initial antibiotic selection was scored based on the 1998 Infectious Disease Society of America (IDSA) guidelines, for the treatment of patients hospitalized with pneumonia. Antibiotic

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
best model by applying stepwise selection to any variable significant at P ≤ 0.2 from the univariate analyses ▪ interactions, correlation and co-linearity issues between variable were investigated ▪ continuous variables were rescaled as follows to maintain comparability of regression coefficients: (1) age per 10-year increase; (2) WBC per 5-unit increase; (3) RR per 5-unit increase; and (4) door-to-needle time per 8-hour period ▪ To improve the efficiency of the statistical model, power transformation to the process variable, door-to-needle time, to follow the implicit statistical assumptio of normality was done.	floor) ▪ admitted from a nursing home: 18% ▪ significant comorbid illness: 58% ▪ COPD: 26% ▪ clinical diagnosis of pneumonia from the ED physicians: All ▪ positive results on the chest x-ray examination on admission: 92% ▪ location of initial dose of antibiotics: 66% in the ED, 34% in the inpatient floor ▪ appropriate initial antibiotic selection rate: 56% ▪ mean LOS: 7.0 ± 4.1 days (the 75th percentile is 9 days)			selection within the first 24 hours of admission was determined to be consistent or inconsistent with published guidelines based on independent physician review of the medical record and recorded as per cent appropriate.

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Dedier 2001[30] **Study type:** Retrospective chart (medical record) review **Selection patient/setting:** retrospectively identified from 38 US academic hospitals that participated in a University Health System Consortium–sponsored pneumonia benchmarking project **Addressing missing data/non reliability of data:** unclear. For analyses of length of stay, 66 patients who died in the hospital, 12 who left against medical advice, and 11 who were transferred to another acute-care facility were excluded. **Statistical analysis:** Outcomes were expressed as dichotomous variables: inpatient death and clinical instability were coded as occurred or not, and length of hospital stay was coded as greater than the overall median of 4 days or not. Primary analysis examined the univariate and multivariable association between achievement of antibiotic administration within 8 hours and clinical outcomes. Multiple regression models controlled for the presence of all other process markers and pneumonia severity using the PSI.	**Patient group:** adults hospitalised with CAP **Inclusion criteria:** Patients hospitalized with CAP (primary International Classification of Diseases 9 code 003.22, 21.2, 39.1, 052.1, 055.1, 073.0, 112.0, 114.0, 115.05, 115.15, 115.95, 130.4, 510.0, 510.9, 511.1, 480-480.2, 480.8, 480.9, 481, 482-482.4, 482.8-483, 484.1, 484.3, 484.5-484.8, 485, or 486 or a secondary ICD 9 classification, where the primary diagnosis was respiratory in nature, septicaemia, or dehydration (code 038.0-038.9, 276.5, 490, 512.0-512.9, 518.81-518.82, or 786.0-786.9). **Exclusion criteria:** age > 18 years, initial chest radiograph > 24 hours before or 48 hours following hospital arrival, no infiltrate on chest x-ray film, antibiotic administration time was not identified, or antibiotics not administered within 48 hours of arrival or were known to have been given before hospital arrival (medical record review of hospital records may underestimate pre-hospitalisation antibiotic use), discharge from an acute-care hospital within 10 days of admission, transfer from another acute-care hospital, active immunosuppressive therapy, known HIV seropositivity, active chemotherapy, and a diagnosis of cystic fibrosis or tuberculosis **All patients,** N: 1457 Exclusions due to: lack of evidence of pneumonia on admission CXR (n = 224); transfer from another acute-care hospital (n = 111); other (n = 60)	<u>**Process-marker achievement**</u>		**Funding:** none stated **Limitations:** Data were collected and coded retrospectively from medical records and based on discharge diagnosis. Causative pathogens and appropriateness of antibiotic choice not considered Only controlled for process markers and PSI class in analysis **Additional outcomes:** Clinical instability at 48 hours (1.04, 0.75 to 1.44) **Notes:** Inclusion of lower severity patients may have caused the inverse
		Median time to receiving antibiotics	4.2 hours (IQR: 2.4 – 7.8 hours)	
		Proportion receiving antibiotics within 8 hours of arrival	**Overall**: 76.2% **Range among hospitals:** 53.8-100.0% **By PSI class:** I – 68.3% II – 75.3% III – 77.4% IV – 77.0% V – 79.4%	
		Adjusted odds ratio for antibiotic administration ≤ 8 h of hospital arrival		
		In patient death	1.69 (0.78 to 3.66)	
		Length of stay longer than median	0.89 (0.65 to 1.22)	
		Clinical instability at 48 h	1.04 (0.75 to 1.44)	

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
	Included N: 1062 **Age, median :** 64 (range: 47-78) **Gender (female): 50%** **Nursing home patients**: 0 **Comorbidities:** Coronary disease – 259 (24%) Diabetes – 227 (21%) COPD – 215 (20%) **PSI class:** I – 12% II – 17% III – 19% IV – 34% V – 18%			relationship between rapid antibiotic administration and favourable outcome.

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Simonetti 2012[96] **Study type:** Prospective observational study **Selection patient/setting:** Barcelona (800 bed hospital) between 2001 and 2009. Cases were identified at the emergency department by attending physicians or study investigators. **Addressing missing data/non-reliability of data:** Data prospectively recorded using a computer assisted protocol **Statistical analysis:** ▪ multivariable logistic regression analysis included variables "potentially associated" with 30-day mortality in the univariate analysis, regardless of statistical significance (age, sex, comorbidities, initial appropriate antibiotic therapy, severity , timing) ▪ discriminatory power of the logistic regression checked with area under ROC and goodness of fit. Number of variables in the multivariable analysis restricted so that there were at least 5 to 9 events per variable.	**Patient group:** ▪ Community acquired pneumonia ▪ healthcare associated pneumonia **Inclusion criteria:** ▪ presence of clinical signs and symptoms (new onset cough with and without sputum production, pleuritic chest pain, dyspnoea, fever or hypothermia, altered breath sounds on auscultation, leucocytosis) ▪ presence of new infiltrate in chest radiographs **Exclusion criteria:** ▪ immunocompromised ▪ received pre hospital antibiotics **All patient, N:** 1880 290 were excluded for receiving pre-hospital antibiotic **Included N:** 1274 for CAP, 319 for HAP **Age > 64 years:** 737 for CAP, 244 for HCAP **Death during 30 days of hospitalisation:** 70 for CAP, 43 for HCAP **Gender (male):** 875 for CAP, 201 for HCAP **Average time to antibiotic**	**Patients with Community acquired pneumonia**		**Funding:** **Limitations:** • number of events per factor analysed less than rule of thumb **Additional outcomes:** **Notes:** Timing of antibiotics administration measured as difference between time to arrival at emergency department and recorded time of initial antibiotic treatment by nursing staff. < 4 hours = "early", > 8 hours = "late" Patients defined as HCAP if they fulfilled any of the following criteria: ▪ in the 30 days before pneumonia, either 1) received any home healthcare including any IV therapy, wound care 2) attended hospital or haemodialysis clinic 3) received chemotherapy ▪ in the 90 days before
		Mortality during 30 days following admission < 4hours vs ≥ 4 hours	Adjusted odds ratio, AOR (95% CI): 1.12 (0.38 to 3.33)	
		Mortality during 30 days following admission ≤ 8 hours vs ≥ 8 hours	AOR = 1.58 (0.64 to 3.88)	
		Patients with healthcare-associated pneumonia		
		Mortality during 30 days following admission < 4 hours vs ≥ 4 hours	Adjusted odds ratio, AOR (95% CI): 1.12 (0.38 to 3.33)	
		Mortality during 30 days following admission ≤ 8 hours vs ≥ 8 hours	AOR: 0.59 (0.19 to1.83)	

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
	administration: 5.9 ± 3.6 hours overall; 5.8 ± 3.5 hours for CAP, 6.1 ± 3.9 hours for HCAP **Antibiotic treatment choice:** Beta-lactam – 698 (43.9%) Levofloxacin – 264 (16.6%) Combination – 360.5 (22.6%) Inappropriate treatment – 68 (4.3%) **Aetiology:** *Streptococcus pneumonia* – 638 (40.0%) *Legionella pneumophila* – 95 (6.0%) Aspiration pneumonia – 123 (7.7%)			pneumonia admitted to an acute care hospital ▪ residing in the long-term care facility

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Waterer 2006[107] **Study type:** Prospective observational study. **Selection patient/setting:** Patients admitted to US (Memphis) hospital between 1998 and July 2001. Unclear if random or consecutive sample. **Addressing missing data/non-reliability of data:** Not addressed. **Statistical analysis:** Logistic regression, significant interactions included at a threshold of 0 < 0.1.	**Patient group:** CAP **Inclusion criteria:** ▪ acute presentation of symptoms (< 14 days) suggested with pneumonia and confirmed chest radiographic infiltrate. ▪ clinical symptoms should be either one of fever > 37.8C , hypothermia (< 36C), cough, sputum production, or two of the following; dyspnoea, pleuritic pain, physical findings of lung consolidation, leukocyte count > 12 x 10 cells/L or < 4.5 x 10 cells/L. **Exclusion criteria:** ▪ immunosuppression (HIV infection, on chemotherapy, received immunosuppressive therapy in the past 60 days including prednisolone ≥ 20 mg/day for > 7 days) ▪ non-ambulatory nursing home residents ▪ hospitalised within past 30 days. **All patient, N:** numbers assessed not reported **Included N:** 451 **Age, mean:** 58.2 ± 19.2 **Gender (female):** 53% **Mean time to antibiotic administration:** 285 ± 202 minutes **Total number of deaths:** 36			**Funding:** Author declared no financial interest in article, was supported by national health and medical research c council Australia. **Limitations:** • main purpose of study was to study factors associated with delay in antibiotic administration. Did not describe how patients were followed up or how mortality data was collected or defined • patient selection unclear • number of events smaller than the rule of thumb for sample size. **Additional outcomes:** Factors associated with delayed antibiotic delivery were altered mental state, absence of hypoxia and, absence of fever and age.
		Mortality (not defined) > 4 hours vs ≤ 4 hours	AOR (95% CI): 1.85 (0.84 to 5.00) Unadjusted odds ratio: 2.94 (0.92 to 9.43)	

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
	Severity (PSI grades): Grade I: 11.3% Grade II: 22.2% Grade III: 18.9% Grade IV: 20.4%			

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Huang 2006[53] **Study type:** Prospective cohort **Selection / patient setting:** Seven 'Capital Health' hospitals in Alberta, Canada from Nov 2000 – Nov 2002 implementing a pneumonia pathway guideline. **Addressing missing data/non reliability of data:** Unclear - no mention why N TFAD is different from N all suspected CAP or N definite CAP. **Statistical analysis (including confounders adjusted for):** Primary outcome measure length-of-stay (LOS): 1. Dichotomous (LOS > 7 days, LOS ≤ 7 days). 2. Continuous (days from ED presentation to discharge) Variables p < 0.1 in univariate analysis used in logistic regression model (binary data) and multiple linear regression model (continuous data). Mean LOS 8.3 ± 6.3 days Median LOS 6.4 days Age, study site (tertiary, community	**Diagnosis:** Adult patients with suspected CAP **Inclusion criteria:** Presented at ED with two or more symptoms or signs of CAP: • Cough (productive or non-productive) • Pleuritic chest pain • Shortness of breath • Temp > 38°C • Crackles or bronchial breathing on auscultation Plus radiographic evidence of pneumonia as interpreted by ED physician or internal medicine consultant. (1447/2757 confirmed definite CAP by radiologist). **Exclusion criteria:** Require admission to ICU from ED Aspiration pneumonitis Tuberculosis Cystic fibrosis Pregnant or nursing women Immunosuppressed patients HIV (if $CD_4 < 0.25x10^9/L$) Excluded from analysis: Death during hospitalisation, multiple visits or length-of-stay > 30 days, missing records @ date-of-presentation to ED or date-of-discharge.	***Mean hours from presenting to ER to first antibiotic*** (n = 2698)		**Funding:** Independent research establishment grant from Alberta Heritage Foundation for Medical Research. Grants-in-aid from Capital Health, Abbott Canada, Pfizer Canada and Jannsen-Ortho Cananda. **Limitations:** • No information detailing why N for antibiotic administration is 69 people less than total analysis N. • No information supplied about pneumonia severity.
		Overall	8.3 ± 13.5	
		LOS ≤ 7 days	7.0 ± 7.2	
		LOS > 7 days	10.2 ± 18.9	
		LOS ≤ 7 days compared to LOS > 7 days	P < 0.001	
		Multivariable analysis predicting LOS > 7days		
		TFAD 4-8 h compared to ≤ 4 h	AOR 1.28 (1.03 to 1.59)	
		TFAD > 8 h compared to ≤ 4 h	AOR 1.28 (1.03 to 1.59)	
		Multiple linear regression factors associated w median LOS (all suspected CAP, n = 2757) – univariate		
		Hours presenting to ER to first dose (per additional hour)	Ratio of 2 median LOS 1.01 (1.0 to 1.01) P < 0.001	
		Multiple linear regression factors associated w median LOS (definite CAP, n = 1447) – univariate		
		Hours presenting to ER to first dose (per additional hour)	Ratio of 2 median LOS 1.01 (1.0 to 1.01) P = 0.003	

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
and secondary care hospitals), smoking, residence on admission, weight loss, functional status, TFAD, temperature, respiratory rate, oxygen saturation, symptoms, comorbidities, antibiotic use.	**All patient,** N: 3473 Excluded due to: Death – 301 (42%) Multiple visits – 162 (22.6%) LOS > 30 days – 168 (23.4%) Missing admission/discharge dates – 86 (12.0%) **Included N:** 2757 (79.4% of total inpatient group) **Age, mean:** 68.3 (±17.8) years **Gender (male/female):** 1426/1331 **Nursing home patients:** 415 (15.1%) admitted from homecare residence 240 (8.7%) admitted from lodge/group care 245 (8.9%) admitted from subacute/continuing care facility. **Comorbidities:** Asthma – 389 (14.1%) COPD – 895 (32.5%) Diabetes – 185 (5.7%) Heart disease – 1209 (43.9%) Cancer – 356 (12.9%) Dementia – 177 (6.4%) Psychiatric disorder – 356 (12.9%) Stroke – 290 (10.5%) Neoplastic disease – 199 (7.2%)			**Additional outcomes:** N/A **Notes:** Links with Marrie 2005

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
	Liver disease – 85 (3.1%) Cerebrovascular disease – 212 (7.7%) Congestive heart failure – 461 (16.7%) Renal disease – 339 (12.3%) **Antibiotic treatment choice:** Levofloxacin (orally) Cefuroxime + erythromycin (IV) Below four listed in multiple linear regression table: Cefuroxime Ciprofloxacin Clindamycin Metronidazole			

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Lee 2011[59] **Study type:** Retrospective observation of prospective RCT (secondary analysis) **Selection / patient setting:** Hospitalised with pneumonia in 32 emergency departments in Connecticut & Pennsylvania in 2001. Sites were randomised to low, moderate or high intensity guideline implementation strategies to promote performance of evidence-based processes of care for pneumonia. Emergency department community-acquired pneumonia trial (EDCAP). **Addressing missing data/non reliability of data:** Patients with incomplete follow-up or medical record review were excluded from the denominator in the calculation of the frequency for these outcomes. **Statistical analysis (including confounders adjusted for):** Patient outcomes in relation to four processes of care: Assessment of oxygenation on presentation, blood cultures (obtain 2 before antibiotic admin), appropriate selection of antibiotic care (empiric therapy selection) and rapid initiation	**Diagnosis:** Adult (≥ 18) with clinical and radiographic evidence of CAP. **Inclusion criteria:** Inpatient defined as hospital admission, transfer from ED to inpatient observation unit, admission to ED observation unit with discharge to any setting more than 24hours after presentation. **Exclusion criteria:** HAP, immunosuppression, specified conditions (pregnancy, cystic fibrosis), psychological or substance abuse problems. **All patient,** N: 4506 Exclusions due to: 891 eligible patients not enrolled (no details as to why) 414 excluded from process-of-care analysis (no details as to why) 1125 not in this particular EDCAP trial (no details as to why). **Included N:** 2076 **Age, median:** 74 **Gender (male/female):** 1013/1063 **Nursing home patients:** 120	No. of patients receiving TFAD ≤ 4 h = 1632 (78.6%) ***TFAD ≤ 4 h and 30-day Mortality (multivariable)*** TFAD > 4 h and died TFAD ≤ 4 h and died Death TFAD > 4 h compared to death TFAD ≤ 4 h ***Secondary patient outcomes (unadjusted)*** *Median length of stay, days (IQR)* *ICU/CCU admission* *Hospital readmission* ***TFAD ≤ 4h and secondary patient outcomes (multivariable)*** Length of stay ICU/CCU admission Hospital readmission	 34/443 (7.7%) 107/1619 (6.6%) AOR 0.7 (0.5 to 1.1) TFAD ≤ 4 h = 5 (3 to 7) TFAD > 4 h = 5 (3 to 8) TFAD ≤ 4 h = 219/1623 (13.5%) TFAD > 4 h = 56/444 (12.6%) TFAD ≤ 4 h = 146/1545 (9.5%) TFAD > 4 h = 29/416 (7.0%) AOR 1.2 (1.1 to 1.4) AOR 1.0 (0.7 to 1.4) AOR 1.4 (0.9 to 2.2)	**Funding:** • R01-HS10049 Agency for Healthcare Research and Quality. • National Institute of Allergy and Infectious Diseases grant (K24-AI001769) • Robert Wood Johnson Foundation Physician Faculty Scholar Award and a career development award from National Cancer Institute (K07-CA114315). **Limitations:** • In text mention that 1632 people received TFAD ≤ 4h but in Tables 3 & 4 this number is listed as 1619 (mortality), 1623 (ICU/CCU admission) and 1545 (readmission) because patients with incomplete follow-up were excluded from the denominator in the calculation of frequency. • No details of antibiotic treatment

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
(< 4 h) of antibiotics. Categoric summary of total number of individual processes of care performed (0-2, 3 and 4). Primary outcome – Mortality 30 days after presentation. Multivariable analysis adjusted for baseline severity of illness (PSI class), plus patient, provider and site characteristics (comorbidities, treatments before presentation) • Some comorbidities assumed to be covered for in PSI risk class (neoplastic, liver, cerebrovascular, congestive heart failure, renal) not adjusted for in multivariable analysis.	**Comorbidities:** Neoplastic disease – (3.6%) Liver disease – (0.9%) Congestive heart failure – (19.5%) Cerebrovascular disease – (11.1%) Renal disease – (4.8%) Cognitive impairment – (5.9%) History of coronary artery disease – (27.7%) Chronic pulmonary disease – (38.7%) Diabetes – (24.6%) **Pneumonia severity:** Class I – 7.6% Class II – 19.5% Class III – 24.4% Class IV – 37.5% Class V – 11% **Antibiotic treatment choice:** No details			choice. • No details listed to explain exclusions. **Additional outcomes:** Subgroup analysis: For patients never treated in ICU or coronary care unit, TFAD ≤ 4 h remained independently associated with a decreased LOS.

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Meehan 1997[70] **Study type:** Retrospective medical record review **Selection / patient setting:** Medical Quality Indicator System (MQIS) pneumonia module (data collection system to assess quality of care). 3555 acute care hospital throughout USA. Potential cases selected from national pool of approx. 650,000 discharges from non-federal acute care hospitals w designated ICD-9 codes using SAS random selection procedure. From Oct 1994 – Oct 1995, 500 potential cases randomly selected from Medicare Part A claims from each state, the district of Columbia and Puerto Rico. **Addressing missing data/non reliability of data:** N = 14069 used as denominator in calculating percentages regardless of missing values. **Statistical analysis (including confounders adjusted for):** Quality indicators: 5. time from hospital arrival to initial	**Diagnosis:** Elderly patients (≥ 65) hospitalised with pneumonia. **Inclusion criteria:** Potential pneumonia identified from Medicare National Claims History File if had: • a principle discharge diagnosis of pneumonia (ICD-9-CM codes 480.0-480.9, 481, 482.0-482.9, 483.0-483.8, 485, 486, 487.0, 507.0) • a principle discharge diagnosis of respiratory failure (ICD-9-CM code 518.81) and a secondary diagnosis of pneumonia. • Patient has appropriate ICD-9-CM code, clinical document with initial working diagnosis of pneumonia, chest x-ray within 48 hrs reports consistent w pneumonia (terms such as: pneumonia, air bronchogram, air space disease, consolidation, infiltrate, inflammation, opacity or pneumonitis. **Exclusion criteria:** • < 65 yrs • Experienced acute hospitalisation w/in 10 days	***TFAD (national study set n = 1343)***		**Funding:** 500-96-P549 contract from Health Care Financing Administration of the US Department of Health and Human Services. **Limitations:** • No specific mention of CAP • Causative pathogens and antibiotic treatment choice not considered. • Retrospective diagnosis based on medical records • Multivariable analysis only adjusted for patient risk status and performance of other processes of care. • Motivation behind choice to group as ≤ 8 h and > 8 h unclear. **Additional outcomes:** N/A **Notes:**
		Patients receiving TFAD ≤ 8 hrs	75.5%	
		Median TFAD	4.3hrs	
		TFAD and 30-day mortality (multivariable) **aggregate data set n = 14069**		
		Initial antibiotics w/in 8 hrs	AOR 0.85 (0.75 to 0.96)	
		TFAD and 30-day mortality (multivariable) **aggregate data set n = 14069 with patients who received antibiotics before hospital presentation (n = 3526) removed from analysis**		
		Initial antibiotics w/in 8 h	AOR 0.78 (0.67 to 0.89)	

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
antibiotic administration, 6. blood culture prior to initial antibiotic, 7. blood culture within 24 hours of arrival, 8. oxygenation assessment within 24 hours of arrival. Multivariable logistic regression analysis on associations between each process of care and 30-day mortality. Timing of antibiotics converted to categorical variable of 2-hour increments (antibiotic w/in 2 h, 4 h, 6 h, 8 h, 10 h, 12 h). Severity of illness details included demographics (age, sex, nursing home residence), comorbidities (cerebrovascular disease, congestive heart failure, neoplastic disease), physical examination findings and lab/test results.	• HIV/AIDS • History of organ transplant • Chemo or immunosuppressive therapy w/in previous 2 months • Transferred from another acute care facility • Died or discharged on date of admission • > 1 pneumonia hospitalisation in study period (n = 113) – only initial episode included • 30 day mortality unable to be verified (n = 33) **All patient,** N: 25561 Exclusions due to: • 439 – no medical record, inadequate documentation of dates/times for hospital arrival or process-of-care performance. • 189 – Did not received antibiotics during hospitalisation, received antibiotics > 100 hours after arrival, blood cultures drawn > 24 hours prior to hospital arrival or after discharge. • 2326 – < 65 yrs • 1687 – Prior admission within 10 days **Included N:** Aggregate study set N = 14069 • National study set (subset to reflect			Figure supplied showing breakdown AOR of 30-day mortality and hours w/in which antibiotics administered (hours 1 to 10 with CIs) but raw data is not listed.

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
	relative volume of pneumonia discharges from each state/territory) n = 1343 • State & territory study set n = 196-323 (cases per state or territory) **Age, mean:** 79.4yrs 65-74 – 4265 (30.3%) 75-84 – 5881 (41.8%) ≥ 85 – 3913 (27.8%) *Age data for 10 people missing* **Gender (male/female):** 6955/7114 **Nursing home patients:** 3289 (23.4%) (from skilled nursing facility or intermediate care facility) **Comorbidities:** Congestive heart failure – 3890 (27.6%) Coronary artery disease – 3753 (26.7%) Cerebrovascular disease – 2896 (20.6%) Neoplastic disease – 1217 (8.7%) Chronic renal failure – 474 (3.4%) Chronic liver disease – 119 (0.8%) **Pneumonia severity:** Fine 1997 prediction rule for CAP – assigned 1-4 risk categories based on presence of three demographic characteristics, five comorbidities, five physical examination abnormalities and seven lab/radiographic findings. No sample breakdown by comorbidity supplied.			

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Wilson 2005[109] **Study type:** Retrospective medical record review. **Selection / patient setting:** Database search of patient case notes for 96 consecutive patients admitted to two ICU's in Australia with severe CAP between Jan 2001 – July 2003 **Addressing missing data/non reliability of data:** Unclear **Statistical analysis (including confounders adjusted for):** Multivariable analysis Comorbidities, antibiotic use prior to initial presentation, PSI	**Diagnosis:** Severe CAP **Inclusion criteria:** ≥ 18 yrs with a clinical diagnosis of pneumonia and radiological evidence of consolidation w/in 24h of presentation. **Exclusion criteria:** Hospitalisation w/in previous 10 days, HAP or emergence of alternative diagnosis during follow up. **All patient,** N: Exclusions due to : **Included N:** 96 **Age, mean:** 59.5 ± 16.6 (range 21 to 88) **Gender (male/female):** 54/42 **Nursing home patients:** **Comorbidities:** Ischaemic heart disease – 16 (17%) Heart failure – 7 (7%) Asthma – 10 (10%) COPD – 19 (20%) Interstitial lung disease – 3 (3%) Bronchiectasis – 5 (5%)	***Mean TFAD and Mortality*** (TFAD information available for 87/96 patients)		**Funding:** None **Limitations:** • Records were examined and coded by one person. • Antibiotic treatment choice empiric but appropriateness of choice not considered. **Additional outcomes:** Use of mechanical ventilation, inotropic support, dialysis, patient outcome (mortality, LOS). **Notes:** None
		Overall	3.3 ± 3.1hrs	
		Survivors	2.7 ± 1.8	
		Non-survivors	4.4 ± 4.6	
		Survivors compared to non-survivors (TFAD means).	p = 0.02	
		Early predictors of morality by logistic regression (multivariable)		
		TFAD > 4 h compared to TFAD ≤ 4 h	OR 3.45 (1.09 to 10.96)	

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
	Diabetes mellitus – 16 (17%) Immunosuppression – 14 (14%) Connective tissue disorder – 4 (4%) HIV infection – 2 (2%) Carcinoma – 7 (7%) Lymphoma – 4 (4%) Renal impairment – 7 (7%) Cerebrovascular disease – 4 (4%) Epilepsy – 3 (3%) Congenital myopathy – 3 (3%) Two or three comorbidities – 36 (38%) No major comorbidities – 21 (22%) **Pneumonia severity (PSI):** I – 0 II – 11 III – 16 IV – 40 V – 29 **Aetiology:** Aetiology determined in 44 (46%) patients. *Streptococcus pneumoniae* most frequently identified pathogen (13 patients), followed by *Influenza A* (9 patients), *Haemophilus influenzae* (5 cases), methicillin-susceptible *Staphylococcus aureus* (4 cases) and *Varicella zoster* virus (3 cases).			

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Bader 2011[4] **Study type:** Retrospective cohort **Selection / patient setting:** All diabetic patients admitted with CAP to two tertiary hospitals in Newfoundland, Canada between 2002 and2007. **Addressing missing data/non reliability of data:** Unclear **Statistical analysis (including confounders adjusted for):** Multiple logistic regression analysis variables selected into model based on their clinical and statistical importance to study outcomes. The effects of timing to first appropriate antibiotic were adjusted for risk factors such as PSI and comorbid conditions. 8 hours was the TFAD cut off time to divide patients into two groups.	**Diagnosis:** Adults (≥ 18) diabetes patients with CAP **Inclusion criteria:** CAP: Presence of acute illness with features of lower respiratory tract infections (including 2 or more of: fever, new or increasing cough or sputum production, dyspnoea, chest pain and new focal signs on chest examination) and the presence of consolidation in the chest radiograph. Diabetes: If previously diagnosed or if on insulin or oral hypoglycaemic agents on admission to hospital. **Exclusion criteria:** Cystic fibrosis, tuberculosis, opportunistic infections, absolute neutrophils count < 500 cells/µL. Patients who developed pneumonia 48 hours or later after admission. Patients requiring insulin only while in hospital (not diabetic). **All patient,** N: 596 Exclusions due to: little detail provided except "the majority of excluded patients did not have CAP by our definition" **Included N:** 206 **Age, mean:** 71.1 ± 13.1	***TFAD & in-hospital mortality (multivariable)***		**Funding:** None received. **Limitations:** • All patients had the pre-existing condition of diabetes. • 8hr cut off time slightly higher than some other studies. • No clear exclusion information. • No concise list of what multivariable analysis adjusted for (apart from PSI class and comorbid conditions) **Notes:** None
		TFAD > 8 h compared to TFAD ≤ 8h	AOR 4 (1.2 to 13.1)	
		Additional Outcomes		
		Mean TFAD & Mortality (univariate)		
		Mean TFAD (all)	6.32 ± 8.1	
		Mean TFAD (survived)	5.82 ± 8.36	
		Mean TFAD (died)	8.94 ± 5.81	
			p = 0.11	
		TFAD ≤ 8 h	n = 15	
		TFAD > 8 h	n = 18	
			p < 0.0001	
		TFAD > 8 h (survived)	n = 33	
		TFAD > 8 h (died)	n = 18	
			p < 0.0001	
		TFAD & LOS (univariate)		
		TFAD ≤ 8 h	LOS 8.7 ± 8.4	
		TFAD > 8 h	LOS 12.57 ± 12.97	
			p = 0.02	
		TFAD & Complications w/in 24h admission (univariate)		
		TFAD ≤ 8 h	n = 38	
		TFAD > 8 h	n = 21	
			p = 0.02	

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
	Gender (male/female): 107/99 **Nursing home patients:** not specified – although patients admitted from a long-term facility were included if they met inclusion criteria. **Comorbidities:** Chronic heart disease – 163 (79.1%) Chronic lung disease – 78 (37.9%) Cancer – 46 (22.3%) Neurologic disease – 50 (24.3%) Chronic renal disease – 47 (22.8%) **Pneumonia severity: PSI** I – 22 (10.7%) II – 29 (14.1%) III – 91 (44.2%) ≥ IV – 58 (28.2%) **Antibiotic treatment choice:** No information supplied **Aetiology:** *Streptococcus pneumonia* most commonly isolated organism.			

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Jo 2012[55] **Study type:** Retrospective observational study **Selection/patient setting:** Part of a prospective quality improvement study to implement the PSI in admission protocol. Conducted in an urban academic tertiary care hospital ED with 50 beds. All adult patients diagnosed at the ED between April 2008 and Sept 2009. **Addressing missing data/non reliability of data:** Unclear. Mentions that six patients mortality status could not be determined. **Statistical analysis (including confounders adjusted for):** Multivariable logistic regression analysis used to determine the adjusted effects of ED crowding on 28-day mortality, after controlling for factors that showed p-value < 0.05 and that were considered to show a trend (p-value < 0.10) in the univariate logistic regression analysis. TFAD shown to be associated with mortality in CAP by a former study	**Diagnosis:** Adults (≥ 18) CAP **Inclusion criteria:** 1. Respiratory symptoms (cough, sputum, dyspnoea and pleuritic chest pain) 2. Abnormal lung sounds (crackles on physical examination) 3. Chest x-ray abnormalities (infiltration, haziness, consolidation and associated pleural effusions. **Exclusion criteria:** 1. < 18yrs 2. Patients transferred from another facility (including ED in another hospital, an acute care facility where wither inpatient or outpatient, any distinct unit of the hospital other that ED, and ambulatory surgery centre) 3. Patients who left against medical advice or discontinued care on the day of or day after arrival. **All patient,** N: 597 Exclusions due to: < 18 yrs: n = 3 Transferred from another facility: n = 116 Left against medical advice: n = 1	***TFAD & 28-day mortality (multivariable)*** TFAD (unclear whether this is for 2 h v. 4 h v. 6 h v. 8 h)	AOR 1.000 (0.998 to 1.0002)	**Funding:** **Limitations:** • Report collecting comorbidity data (such as hypertension, diabetes, liver cirrhosis, malignancy state and congestive heart failure) but no data presented • Unclear which TFAD levels comparing in multivariable analysis. **Additional outcomes:** none **Notes:** none

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
(Houck2004) so therefore included in multivariable analysis. TFAD dichotomised using 4 different time intervals proposed by Joint Commission and Centres for Medicare/Medicaid Services – 8 h, 6 h, 4 h, 2 h.	**Included N:** 477 **Age, median (IQR):** 67 (51.0 to 76.0) **Gender (male/female):** 268/209 **Nursing home patients:** N/A **Comorbidities:** None listed. **Pneumonia severity: PSI** I – 87 II – 132 III – 98 IV – 115 V – 45 **Antibiotic treatment choice:** Not listed **Aetiology:** Not listed			

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
Author and year: Mortensen 2008[78] **Study type:** Retrospective observational cohort (chart review) **Selection / patient setting:** All patients admitted to two academic tertiary hospitals in San Antonio, Texas 1999-2002. **Addressing missing data/non reliability of data:** Unclear **Statistical analysis (including confounders adjusted for):** Multivariable logistic regression model derived with 30-day mortality as the DV, and the PSI, process of care measures (initial antibiotics w/in 8 hours), and prior receipt of antibiotics w/in 30 days prior to presentation as independent variables.	**Diagnosis:** A primary discharge diagnosis of pneumonia (ICD-9 codes 480.0–483.99 or 485–487.0) or secondary discharge diagnosis of pneumonia with a primary diagnosis of respiratory failure (518.81) or sepsis (038.xxx). **Inclusion criteria:** 1. Over 18 2. Admission diagnosis of pneumonia 3. Radiographically confirmed infiltrate or other finding consistent with pneumonia on chest x-ray or CT obtained within 24 hours of admission Both definitive and presumptive (if qualitative valid sputum sample yielded one or more predominant bacterial pathogens) pneumonia included **Exclusion criteria:** 1. Discharged from an acute care facility within 14 days of admission 2. Transfer after being admitted to another acute care hospital 3. Being a resident of a skilled nursing facility prior to admission 4. Being comfort measures only on this admission.	***TFAD & 30-day mortality (multivariable)*** Initial antibiotics within 8 hours of admission	AOR 1.2 (0.7 to 2.1)	**Funding:** Department of Veteran Affairs Veteran Integrated Service Network 17 new faculty grant. Department of Veteran Affairs Veteran grant HFP98-002. Howard Hughes Medical Institute faculty start-up grant 00378-001. NHLBI grant NOI-HR-16153. **Limitations:** • Comorbid conditions not included in multivariable analysis • Exclusion data not provided. **Additional outcomes:** none

Reference	Patient Characteristics	Outcomes measures	Effect sizes	Comments
	Included N: 733 **Age, mean:** 59 (SD 16) **Gender (male/female):** 572/161 **Nursing home patients:** N/A excluded population. **Comorbidities:** Congestive heart failure – 106 Chronic pulmonary disease – 51 History of stroke – 82 Chronic liver disease – 37 History of malignancy – 71 Renal insufficiency – 71 **Pneumonia severity: PSI** I-III – 404 IV – 243 V – 86 **Antibiotic treatment choice:** Details not provided. **Aetiology:** Four most commonly isolated organisms: *Streptococcus pneumoniae* – 60 *Staphylococcus aureus* – 38 *Pseudomonas aeruginosa* – 20 *Haemophilus influenzae* – 19			**Notes:** None.

1.4.2 Low-severity CAP

1.4.2.1 Single- compared with other single- antibiotic therapy

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Study	Udupa 2011[101]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 35)
Countries and setting	Conducted in India; Setting: Rural Health Training Centre
Line of therapy	1st line
Duration of study	Intervention time: 5 days
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Clinical signs plus CXR consolidation (71%) or presence of gram positive or negative bacteria on sputum microscopy
Stratum	Low severity (community setting): Out-patients
Subgroup analysis within study	Not applicable
Inclusion criteria	18 to 55 years with complaints of fever (oral temperature >98.5°F), with cough and/or breathlessness for more than 2 days. Diagnosis of pneumonia based on symptoms and signs of bronchial breathing with dull notes on percussion along with either a radiological patch on CXR or presence of gram positive or negative bacteria on sputum microscopy. An elevated neutrophil count was necessary in either of the case.
Exclusion criteria	Cough of > 1 week; symptoms of confusion, severe breathlessness, pleural effusion, or required hospitalization for either a co-morbidity or due to respiratory condition
Recruitment/selection of patients	June to September 2009
Age, gender and ethnicity	Age - Range: 18-55. Gender (M:F): 67.7/32.2. Ethnicity: Asian
Further population details	1. Age: 75 years or less 2. Comorbidities: Not stated or unclear 3. Predominant disease aetiology (including resistance profiles): Not stated or unclear
Extra comments	. Excluded those aged >55 years
Indirectness of population	Serious indirectness: Excluded those aged >55 years
Interventions	(n = 15) Intervention 1: Antibiotic alone - Macrolide. Clarithromycin (500 mg PO bid) or azithromycin (500 mg PO once, then 250 mg OD). Duration 5 days. Concurrent medication/care: Symptomatic treatment from adverse events permitted Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: Less than 7 days

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
	(n = 7) Intervention 2: Antibiotic alone - Respiratory fluoroquinolone - new. Levofloxacin (750 mg PO od). Duration 5 days. Concurrent medication/care: Symptomatic treatment from adverse events permitted Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: Less than 7 days (n = 9) Intervention 3: Antibiotic alone - Narrow spectrum beta-lactam (class 2). Amoxicillin (1 g tid). Duration 5 days. Concurrent medication/care: Symptomatic treatment from adverse events permitted Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: Less than 7 days
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MACROLIDE (CLARITHROMYCIN OR AZITHROMYCIN) versus RESPIRATORY FLUOROQUINOLONE - NEW (LEVOFLOXACIN)

Protocol outcome 1: Mortality at 30 days
- Actual outcome for Low severity (community setting): Mortality at Unclear; Mean No significant difference detected; Risk of bias: Flawed; Indirectness of outcome: No indirectness

Protocol outcome 2: Clinical cure at End of treatment
- Actual outcome for Low severity (community setting): Clinical success at 5 days; Other: No significant difference detected; Risk of bias: Flawed; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MACROLIDE (CLARITHROMYCIN OR AZITHROMYCIN) versus NARROW SPECTRUM BETA-LACTAM (CLASS 2)

Protocol outcome 1: Mortality at 30 days
- Actual outcome for Low severity (community setting): Mortality at Unclear; Mean No significant difference detected; Risk of bias: Flawed; Indirectness of outcome: No indirectness

Protocol outcome 2: Clinical cure at End of treatment
- Actual outcome for Low severity (community setting): Clinical success at 5 days; Other: No significant difference detected; Risk of bias: Flawed; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RESPIRATORY FLUOROQUINOLONE - NEW (LEVOFLOXACIN) versus NARROW SPECTRUM BETA-

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
LACTAM (CLASS 2) Protocol outcome 1: Mortality at 30 days - Actual outcome for Low severity (community setting): Mortality at Unclear; Mean No significant difference detected; Risk of bias: Flawed; Indirectness of outcome: No indirectness Protocol outcome 2: Clinical cure at End of treatment - Actual outcome for Low severity (community setting): Clinical success at 5 days; Mean No significant difference detected; Risk of bias: Flawed; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Withdrawal due to adverse events at End of treatment; Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; *C. difficile*-associated diarrhoea at End of follow-up; Clinical cure at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	Sopena 2004[98]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 70)
Countries and setting	Conducted in Spain; Setting: 5 hospitals (in and out-patients)
Line of therapy	1st line
Duration of study	Intervention + follow up: 3-10 days treatment and follow-up to day 30
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical signs and chest x-ray, but unclear how HAP excluded
Stratum	Low severity (vague description): Unclear how measured severity, included in- and out-patients
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with mild to moderate CAP; CXR showing new pulmonary infiltrate plus 2 or more of: fever ≥38°C, cough, dyspnoea (respiratory rate >20/minute), elevated leukocyte count (≥12,000/mm3) or signs of consolidation on respiratory auscultation.
Exclusion criteria	Severe pneumonia, antibiotics in the previous 72 hours, hypersensitivity to macrolides, severe asthma or cyctic fibrosis, immunosuppression or asplenia, concurrent infections requiring additional antimicrobial therapy, concurrent medication with ergotamine, theopylline or digitalics and conditions that may affect drug absorption, preganacy and breast-feeding
Recruitment/selection of patients	Prospective

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Age, gender and ethnicity	Age - Mean (SD): Azithromycin: 41.7; clarithromycin: 44.4 years. Gender (M:F): Unclear. Ethnicity: Not stated
Further population details	1. Age: All adults 2. Comorbidities: Not stated or unclear 3. Predominant disease aetiology (including resistance profiles): Mycoplasma pneumoniae (Of 16 identified pathogens, 6 (37.5%) were *M. pneumoniae*, 4 *S. pneumoniae* (25%) and 4 (25%) *L. pneumophila*).
Indirectness of population	No indirectness
Interventions	(n = 34) Intervention 1: Antibiotic alone - Macrolide. Azithromycin, oral once-daily 500 mg dose. Duration 3 days. Concurrent medication/care: Not stated Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: Less than 7 days (n = 36) Intervention 2: Antibiotic alone - Macrolide. Clarithromycin oral twice daily 250 mg dose. Duration 10 to 14 days. Concurrent medication/care: Not stated Further details: 1. Antibiotic dose: Low (BNF recommends 500 mg twice daily). 2. Duration of treatment: 7 days or more
Funding	Study funded by industry (Pfizer)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MACROLIDE (AZITHROMYCIN) versus MACROLIDE (CLARITHROMYCIN) Protocol outcome 1: Clinical cure at End of treatment - Actual outcome for Low severity (vague description): Clinical cure at 10-13 days; Group 1: 18/30, Group 2: 22/32; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Clinical cure at End of follow-up - Actual outcome for Low severity (vague description): Clinical cure at 25-30 days; Group 1: 28/30, Group 2: 28/32; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at 30 days; Withdrawal due to adverse events at End of treatment; Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; C. difficile-associated diarrhoea at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	Rizzato 1995[86]
Study type	RCT (Patient randomised; Parallel)

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Number of studies (number of participants)	1 (n = 40)
Countries and setting	Conducted in Italy; Setting: Hospital
Line of therapy	Mixed line
Duration of study	Intervention + follow up: up to 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical signs and symtpoms plus chest x-ray
Stratum	Low to moderate severity (formal assessment): Excluded patients at higher risk, according to the following criteria: 1) pneumonia in more than one lobe, as shown by posteroanterior and lateral chest roentgenogram; 2) over 75 yrs of age; 3) white blood cell count (WBC) <3 x 10(9)/l; 4) arterial oxygen tension (PaO2) <7.3 kPa (<55 mmHg); and 5) with bacteraemia
Subgroup analysis within study	Not applicable
Inclusion criteria	A diagnosis of pneumonia made on the basis of significant clinical manifestations and pulmonary opacity on the chest roentgenogram. CAP admitted to hospital
Exclusion criteria	Patients at higher risk, according to the following criteria: 1) pneumonia in more than one lobe, as shown by posteroanterior and lateral chest roentgenogram; 2) over 75 yrs of age; 3) white blood cell count (WBC) <3 x 10(9)/l; 4) arterial oxygen tension (PaO2) <7.3 kPa (<55 mmHg); and 5) with bacteraemia
Recruitment/selection of patients	All consecutive patients Oct 1992 - Aug 1993
Age, gender and ethnicity	Age - Mean (SD): Azithromycin: 48 (13); clarithromycin: 44 (19). Gender (M:F): 72.5/27.5%. Ethnicity: Not stated
Further population details	1. Age: All adults 2. Comorbidities: Minority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (Diabetes (2), COPD (3), asthma (2), small cell lung cancer (1), liver disease (3), heart disease (6), smokers (17), excessive alcohol (4)). 3. Predominant disease aetiology (including resistance profiles): Mycoplasma pneumoniae (Of 22 identified pathogens, 9 (40.9%) were M. pneumoniae and 5 (22.7%) Legionella).
Extra comments	Pre-treatment with other antibiotics was not an exclusion criterion: the failure of the previous antibiotic was ascertained from a clinical point of view, and in each case a minimum of 24 h elapsed between the last dose and enrolment. 50% had failed prior antibiotics - 8 in azithromycin and 12 in clarithromycin group. They had received 2–10 days beta-lactam antibiotics in 19 cases and with ciprofloxacin in one case; the time interval elapsed between the last dose of the previous antibiotic and the enrolment was 24 h in one case and 48 h or more in all the others.
Indirectness of population	Serious indirectness: 50% had failed prior antibiotics
Interventions	(n=20) Intervention 1: Antibiotic alone - Macrolide. Azithromycin 500 mg oral therapy in a single daily dose. Duration 3 days. Concurrent medication/care: Not stated

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
	Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: Less than 7 days (n=20) Intervention 2: Antibiotic alone - Macrolide. Clarithromycin 250 mg b.i.d. oral therapy. Duration at least 8 days. Concurrent medication/care: Not stated Further details: 1. Antibiotic dose: Low 2. Duration of treatment: 7 days or more Comments: In nine patients, clarithromycin was given for more than 8 days, as judged necessary according to clinical signs or chest roentgenogram. In the entire group, clarithromycin was given for 10±2 days (range 8–15 days).
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MACROLIDE (AZITHROMYCIN) versus MACROLIDE (CLARITHROMYCIN) Protocol outcome 1: Clinical cure at End of treatment - Actual outcome for Low to moderate severity (formal assessment): Clinical efficacy: fever, cough, volume and appearance of the sputum, physical examination, chest roentgenogram, ESR, CRP, and total and differential WBC count at unclear; Group 1: 20/20, Group 2: 17/20; Risk of bias: Very high; Indirectness of outcome: Serious indirectness Protocol outcome 2: Length of hospital stay at End of follow-up - Actual outcome for Low to moderate severity (formal assessment): Mean length of hospital stay at Unclear; Group 1: mean 12.7 days (SD 5.7); n=20, Group 2: mean 14.3 days (SD 7.6); n=20; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at 30 days; Withdrawal due to adverse events at End of treatment; Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; C. difficile-associated diarrhoea at End of follow-up; Clinical cure at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	Petitpretz 2001[84]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 411)
Countries and setting	Conducted in Argentina, Brazil, Chile, Croatia, Czech Republic, Estonia, France, Hong Kong (China), Hungary, Lithuania, Mexico, Portugal, Russia, Slovenia, South Africa, Spain, Turkey, Ukraine, United Kingdom, Uruguay; Setting: 82 centres in 20 countries
Line of therapy	1st line

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Duration of study	Intervention + follow up: 10 days treatment plus 3-4 weeks post-treatment follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical and radiological evidence
Stratum	Low to moderate severity (formal assessment): Description unclear: excluded severe infection requiring parenteral therapy and state that low-to-moderate severity status was confirmed by the low number of patients with multilobar involvement at baseline, and the low mortality rate
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients (≥ 18 years of age) presenting with CAP of suspected pneumococcal origin. Patients were classified as having CAP if they presented with fever (rectal temperature ≥ 38.5°C, oral temperature ≥ 38°C) and radiologic evidence of an infiltrate consistent with pneumonia, and at least one of the following signs or symptoms: cough, purulent sputum, dyspnea/tachypnea (> 20 breaths/min), or auscultatory findings such as rales/rhonchi, indicating pulmonary consolidation. S pneumoniae was suspected of being the causative agent of CAP if at least two of the following criteria were present: rapid onset of symptoms (≤ 48 h); high fever (rectal temperature ≥ 39.0°C, oral temperature ≥ 38.5°C) accompanied by rigors/ chills; pleuritic chest pain; localized alveolar consolidation on chest radiograph; or the presence of Gram-positive cocci on direct sputum stain.
Exclusion criteria	History of hypersensitivity to quinolones or penicillins; previous history of tendinopathy associated with quinolones; suspected aspiration pneumonia due to vomiting; a severe infection requiring parenteral therapy; any other infection necessitating the administration of a concomitant systemic antibacterial agent; concurrent disease considered likely to interfere with the clinical course of the pneumonia; AIDS (although HIV-positive patients could be included); significant renal impairment (serum creatinine level > 265 mmol/L); hepatic disease (alanine transaminase or aspartate transaminase and/or total bilirubin level more than three times the upper limit of normal); and neutropenia (neutrophil count < 1,000 cells/mL); pregnancy or lactation; known congenital or sporadic syndromes of QTc prolongation, or receiving concomitant medication reported to increase the QTc interval; hospitalized for > 48 h before the onset of pneumonia; and patients who received previous therapy with a systemic antibiotic to treat the current episode of pneumonia for > 24 h prior to enrollment. Patients who clearly failed on previous antibacterial therapy (treatment duration > 48 h) might be enrolled if the antibacterial regimen did not contain a fluoroquinolone or a beta-lactam.
Recruitment/selection of patients	June 1997 - June 1998
Age, gender and ethnicity	Age - Mean (SD): Moxifloxacin: 52.0 (20.5); amoxicillin: 49.9 (20.6). Gender (M:F): 62/38. Ethnicity: Unclear
Further population details	1. Age: All adults (13% aged >70 years). 2. Comorbidities: Not stated or unclear (16% and 22% with bronchopulmonary disease in each group, but other comorbidities not stated). 3. Predominant disease aetiology (including resistance profiles): *Streptococcus pneumoniae* (Of 147 identified pathogens, 98 (66.7%) were *S. pneumoniae*).

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Extra comments	7% had multilobar involvement and 5.5% had pleural effusion at baseline. Limited to suspected pneumococcal
Indirectness of population	Serious indirectness: Limited to suspected pneumococcal - proportion excluded unclear
Interventions	(n = 203) Intervention 1: Antibiotic alone - Respiratory fluoroquinolone - new. Moxifloxacin 400 mg/d orally. Duration 10 days. Concurrent medication/care: Unclear - not stated Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more (n = 208) Intervention 2: Antibiotic alone - Narrow spectrum beta-lactam (class 2). Amoxicillin 1g three-times daily orally. Duration 10 days. Concurrent medication/care: Unclear - not stated Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Funding	Study funded by industry (Bayer AG)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RESPIRATORY FLUOROQUINOLONE versus NARROW SPECTRUM BETA-LACTAM (CLASS 2)

Protocol outcome 1: Mortality at 30 days
- Actual outcome for Low to moderate severity (formal assessment): Mortality at up to 2-4 weeks post-treatment; Group 1: 3/200, Group 2: 4/208; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Clinical cure at End of treatment
- Actual outcome for Low to moderate severity (formal assessment): Clinical cure: disappearance of signs and symptoms or sufficient improvement that continued antibacterial therapy was not required at 13-15 days (3-5 days after end of treatment); Group 1: 173/200, Group 2: 171/208; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up
- Actual outcome for Low to moderate severity (formal assessment): Superinfection at up to 3-4 weeks post-treatment; Group 1: 0/200, Group 2: 1/208; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 4: Clinical cure at End of follow-up
- Actual outcome for Low to moderate severity (formal assessment): Clinical cure: disappearance of signs and symptoms or sufficient improvement that continued antibacterial therapy was not required at 3-4 weeks after end of treatment; Group 1: 154/200, Group 2: 164/208; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Withdrawal due to adverse events at End of follow-up
- Actual outcome for Low to moderate severity (formal assessment): Withdrawal or treatment discontinuation due to adverse events at up to 2-4 weeks post-

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
treatment; Group 1: 8/200, Group 2: 8/208; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Withdrawal due to adverse events at End of treatment; Hospital admission at End of follow-up; *C. difficile*-associated diarrhoea at End of follow-up; Length of hospital stay at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	Wiesner 1993[108]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 297 (25 with pneumonia))
Countries and setting	Conducted in Germany; Setting: 4 centres
Line of therapy	1st line
Duration of study	Intervention time: 7-14 days
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Clinical signs and symptoms alone
Stratum	Low severity (community setting): Out-patients
Subgroup analysis within study	Post-hoc subgroup analysis: Type of infection: pneumonia or bronchitis
Inclusion criteria	Outpatients with acute respiratory infections of probably bacterial aetiology
Exclusion criteria	Age < 10 or >70 years, hypersensitivity to erythromycin or tetracyclines, antibiotic treatment within prior 2 weeks, history of liver function disorders, or pregnancy
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): In full group: erythromycin: 44.1; doxycycline: 41.7 years. Gender (M:F): In full group: erythromycin: 58/42%; doxycycline: 53/47%. Ethnicity: Unclear
Further population details	1. Age: 75 years or less (Excluded those aged <10 or >70 years). 2. Comorbidities: Minority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (In full group: 44.8% had concomitant diseases (9.8% asthma, 7.4% lung fibrosis, 4.4% emphysema, 3.1% bronchiectasis, 2.4% chronic bronchitis, 8.1% CHD or HT). 3. Predominant disease aetiology (including resistance profiles): Not stated or unclear
Indirectness of population	Serious indirectness: Diagnosis not confirmed by chest x-ray; included those aged 11-17 and not aged >70 years
Interventions	(n = 11) Intervention 1: Antibiotic alone - Macrolide. Erythromycin (Orion Pharmaceutica) 800 mg daily in two doses. Duration 7-14 days. Concurrent medication/care: Concomitant symptomatic treatment permitted, but other antibiotics prohibited, as were digitalis glycosides, warfarin, ergotamine, carbamazepine and methylprednisolone Further details: 1. Antibiotic dose: Low (BNF recommends 250–500 mg every 6 hours or 0.5–1 g every 12 hours). 2.

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
	Duration of treatment: 7 days or more Comments: Number with pneumonia randomised unclear but 11 analysed. (n = 13) Intervention 2: Antibiotic plus placebo - Tetracycline + placebo. Doxycycline 100 mg daily. An identical placebo tablet was taken in the evening. Duration 7-14 days. Concurrent medication/care: Concomitant symptomatic treatment permitted, but other antibiotics prohibited, as were digitalis glycosides, warfarin, ergotamine, carbamazepine and methylprednisolone. Further details: 1. Antibiotic dose: Low (Recommended to give 200 mg initial dose). 2. Duration of treatment: 7 days or more Comments: Number with pneumonia randomised unclear but 13 analysed
Funding	Equipment / drugs provided by industry (Orion Pharmaceutical)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MACROLIDE (ERYTHROMYCIN) versus TETRACYCLINE + PLACEBO Protocol outcome 1: Clinical cure at End of treatment - Actual outcome for Low severity (community setting): Cure sufficient that no further antibiotics required at 7-14 days; Group 1: 9/11, Group 2: 12/13; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at 30 days; Withdrawal due to adverse events at End of treatment; Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; C. difficile-associated diarrhoea at End of follow-up; Clinical cure at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	Paris 2008[83]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 272)
Countries and setting	Conducted in Italy; Setting: 19 centres in Italy
Line of therapy	1st line
Duration of study	Intervention + follow up: 3-7 days treatment plus up to 19 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical and radiological assessment
Stratum	Low to moderate severity (formal assessment): Fine risk class I or II
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and female out-patients with a clinical (presence of at least 2 of the following: fever, elevated total peripheral

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
	WBC count, new or increased cough, purulent sputum or change in sputum characteristics, dyspnoea or tachypnea, pulmonary rales and/or evidence of pulmonary consolidation) and radiological (new infiltrate on CXR) diagnosis of CAP
Exclusion criteria	Pregnancy or breast-feeding, known or suspected hypersensitiviy to study drugs or to macrolides or beta-lactams in general, HAP or aspiration pneumonia, cystic fibrosis, active TB or history of TB, pneumothorax, insulin-dependent diabetes mellitus, malignancy, other infection requiring antibacterial treatment, neutropenia, known or suspected serious renal or hepatic impairment, chronic diarrhoea, GI condition that may affect study drug absorption, AIDS, history of epilepsy or seizure, receipt of any antimocrobial treatment within 72 hours prior to enrollment or any other investigational drug within 30 days prior to enrollment, treatment with warfarin, allopurinol or ergotamine and history of alcohol or drug abuse, psychosis or other emotional or intellectual problems that might impair informed consent or ability to comply with the protocol
Recruitment/selection of patients	March 2002 - October 2004
Age, gender and ethnicity	Age - Mean (range): Azithromycin: 42.4 (16-68); co-amoxiclav: 42.5 (14-76). Gender (M:F): Azithromycin: 51.5/48.5%; co-amoxiclav: 61.1/38.9%. Ethnicity: 98.5% white
Further population details	1. Age: 75 years or less (Included some patients <18 years of age; low mean age). 2. Comorbidities: Not stated or unclear (49.4% current smokers; excluded cystic fibrosis, diabetes and renal failure). 3. Predominant disease aetiology (including resistance profiles): *Mycoplasma pneumoniae* (Of 121 identified pathogens 38.8% were *M. pneumoniae* and 19.0% were *S. pneumoniae*).
Extra comments	Fine risk class: 67.4% class I and 32.6% class II
Indirectness of population	Serious indirectness: Included some aged < 18 (proportion unclear)
Interventions	(n = 136) Intervention 1: Antibiotic alone - Macrolide. Azithromycin 1g once daily. Duration 3 days. Concurrent medication/care: Not stated Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: Less than 7 days Comments: Note that outcomes were assessed at the same time for both treatment arms although the duration of treatment differed (n=132) Intervention 2: Antibiotic alone - Beta-lactamase stable penicillin. Amoxicillin-clavulanate 875/125 my twice daily. Duration 7 days. Concurrent medication/care: Not stated Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Note that outcomes were assessed at the same time for both treatment arms although the duration of treatment differed
Funding	Study funded by industry (Pfizer Italy)

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MACROLIDE (AZITHROMYCIN) versus BETA-LACTAMASE STABLE PENICILLIN (AMOXICILLIN-CLAVULANATE) Protocol outcome 1: Mortality at 30 days - Actual outcome for Low severity (formal assessment): Mortality at 22-26 days; Group 1: 0/136, Group 2: 0/132; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Clinical cure at End of treatment - Actual outcome for Low severity (formal assessment): Clinical success: complete resolution of all signs and symptoms of pneumonia or sufficient improvement so that no further antibiotic therapy was required at 8-12 days; Group 1: 126/136, Group 2: 122/131; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Withdrawal due to adverse events at End of treatment - Actual outcome for Low severity (formal assessment): Withdrawal due to adverse events at end of treatment at 8-12 days; Group 1: 1/136, Group 2: 2/132; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Clinical cure at End of follow-up - Actual outcome for Low severity (formal assessment): Clinical success: complete resolution of all signs and symptoms of pneumonia in the absence of new symptoms, or sufficient improvement so that no further antibiotic therapy was required at 22-26 days; Group 1: 125/135, Group 2: 120/129; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Withdrawal due to adverse events at End of follow-up - Actual outcome for Low severity (formal assessment): Withdrawal due to adverse events at 22-26 days; Group 1: 5/136, Group 2: 4/132; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; *C. difficile*-associated diarrhoea at End of follow-up; Length of hospital stay at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	O'Doherty 1998[81]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=203)
Countries and setting	Conducted in Multiple countries; Setting: 28 centres in 4 countries
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 3-10 day intervention plus followed-up to day 19-23

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical plus radiographic criteria
Stratum	Low severity (community setting): Out-patients
Subgroup analysis within study	Not applicable
Inclusion criteria	Out-patients with clinically diagnosed CAP based on having at least 3 of: non-productive cough, new onset of purulent sputum, change in character of sputum, sputum culture positive form gram-positive diplococci, body temperature 38C or more twice within last 24 h, and/or elevated leukocyte count
Exclusion criteria	Terminal illness or condition that could interfere with attendance schedule, condition likely to affect absorption of study drug, significant hepatic disease (serum transaminases >3-times ULN), hypersensitivity to azithromycin, clarithromycin or other macrolides, concurrent infection requiring additional microbiological therapy, known infection with organism resistant to study drugs, evidence of alcohol or drug abuse. Concurrent medication with ergotamine, cyclosporin, theophylline, astemizole, terfenadine or antacids were not permitted. Receipt of another antibiotic agent within 2 weeks unless microbiological failure was documented, treatment with another investigational drug within previous month or prior participation in this trial. Women who were pregnant, breast-feeding or of child-bearing age and not using adequate contraception.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): Azithromycin: 50.1 (14.1-75.2); clarithromycin: 51.5 (12.5-78.9) years. Gender (M:F): 58.6/41.4%. Ethnicity: Not stated
Further population details	1. Age: 75 years or less (Age range included 12-75 years). 2. Comorbidities: Not stated or unclear 3. Predominant disease aetiology (including resistance profiles): *H. influenzae* (Of 67 identified pathogens, 34 (50.7%) were *H. influenzae*, and 22 (32.8%) were *S. pneumoniae*).
Extra comments	Proportion with bronchopneumonia/lobar pneumonia: azithromycin 59/41%; clarithromycin: 49/53%
Indirectness of population	Serious indirectness: Limited age range - included children from age 12 years and nobody over 75
Interventions	(n = 101) Intervention 1: Antibiotic alone - Macrolide. Azithromycin 500 mg once daily orally. Duration 3 days. Concurrent medication/care: Concurrent medication with ergotamine, cyclosporin, theophylline, astemizole, terfenadine or antacids was not permitted. Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: Less than 7 days (n = 102) Intervention 2: Antibiotic alone - Macrolide. Clarithromycin 250 mg twice daily orally. Duration 10 days. Concurrent medication/care: Concurrent medication with ergotamine, cyclosporin, theophylline, astemizole, terfenadine or antacids was not permitted. Further details: 1. Antibiotic dose: Low (BNF recommends 500 mg q12h). 2. Duration of treatment: 7 days or more

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Funding	Study funded by industry (Pfizer)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MACROLIDE (AZITHROMYCIN) versus MACROLIDE (CLARITHROMYCIN) Protocol outcome 1: Clinical cure at End of treatment - Actual outcome for Low severity (community setting): Clinical cure: disappearance of all pre-treatment clinical signs and symptoms at 12-16 days; Group 1: 57/88, Group 2: 61/88; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Withdrawal due to adverse events at End of treatment - Actual outcome for Low severity (community setting): Discontinuation of treatment due to adverse events at 12-16 days; Group 1: 0/101, Group 2: 2/102; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Clinical cure at End of follow-up - Actual outcome for Low severity (community setting): Maintaining clinical success (among those who had improved by day 12-16) at 19-23 days; Group 1: 19/24, Group 2: 15/22; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at 30 days; Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; C. difficile-associated diarrhoea at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	Lode 1995[66]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 808)
Countries and setting	Conducted in Belgium, France, Germany, Greece, Israel, Italy, Netherlands, Spain, United Kingdom; Setting: 124 centres in 9 countries
Line of therapy	1st line
Duration of study	Intervention + follow up: 7-14 days treatment plus follow-up to 6 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Clinical and radiographic evidence - but HAP was not clearly excluded
Stratum	Low severity (vague description): Unclear how assessed - included both in-patients and out-patients (oral treatment)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged ≥ 18 years with acute CAP; diagnosis based on the presence of a new infiltrate (solid or patchy) on chest radiographic image, fever greater than 38□C, and at least one of the typical clinical signs, including cough, dyspnoea,

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
	chills, sputum production and/or chest pain, or a white blood cells (WBC) count of 10,000–30,000 cells•µL-1, or purulent respiratory secretion (greater than 25 polymorphonuclear cells per low-power microscopic field (LPF)).
Exclusion criteria	Pregnancy, lactation, severe concomitant disease, allergy, photosensitivity, prior use of antibacterials, need for parenteral antibacterial therapy, and concomitant therapy which may interfere with absorption. Patients with human immunodeficiency virus (HIV) infection were not excluded but those with frank acquired immune deficiency syndrome (AIDS) were.
Recruitment/selection of patients	December 1990 - March 1992
Age, gender and ethnicity	Age - Mean (SD): Erythromycin: 55 (14.4); co-amoxiclav: 52 (14.1). Gender (M:F): Erythromycin: 62/38; co-amoxiclav: 64/36. Ethnicity: 98% white
Further population details	1. Age: All adults (Proportion >65 years: 37%). 2. Comorbidities: Minority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD (Chronic bronchitis: 34/30%; asthma: 25/22%; smoker: 27/22%). 3. Predominant disease aetiology (including resistance profiles): *Streptococcus pneumoniae* (Of 166 identified pathogens 85 (51.2%) were *S. pneumoniae* and 46 (27.7%) H. influenzae).
Extra comments	Age greater than 65 years, concomitant bronchopulmonary disease, diabetes, malnutrition, alcohol/drug abuse were not exclusion criteria but such patients were monitored carefully. 89% had unilateral pneumonia and 11% had pleural effusion at baseline
Indirectness of population	No indirectness: Did not exclude those who had been hospitalised within the previous 3 days (but only 2.5% had >3 days hospitalisation - excluded from evaluable population)
Interventions	(n = 208) Intervention 1: Antibiotic alone - Macrolide. Erythromycin (August Wolff Laboratories, Germany), 1,000 mg b.i.d.. Duration 7-14 days. Concurrent medication/care: Not stated Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Mean duration 9-10 days (range: 1-16 days) (n=199) Intervention 2: Antibiotic alone - Beta-lactamase stable penicillin. Amoxicillin-clavulanate (SmithKline Beecham Laboratories, France) (500/125 mg t.i.d). Duration 7-14 days. Concurrent medication/care: Not stated Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Mean duration 9-10 days (range: 1-16 days)
Funding	Study funded by industry (Rhône DPC Europe)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MACROLIDE (ERYTHROMYCIN) versus BETA-LACTAMASE STABLE PENICILLIN (AMOXYCILLIN-CLAVULANATE)	

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Protocol outcome 1: Mortality at 30 days - Actual outcome for Low to moderate severity (formal assessment): Mortality at 6 weeks; Group 1: 10/208, Group 2: 4/199; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Clinical cure at End of treatment - Actual outcome for Low to moderate severity (formal assessment): Overall efficacy (clinical cure and resolution or improvement on chest radiography, or clinical improvement and resolution on chest radiography) at 7-14 days; Group 1: 154/208, Group 2: 154/199; Risk of bias: High; Indirectness of outcome: Serious indirectness Protocol outcome 3: Clinical cure at End of follow-up - Actual outcome for Low to moderate severity (formal assessment): Overall efficacy (clinical cure and resolution or improvement on chest radiography, or clinical improvement and resolution on chest radiography) at 6 weeks; Group 1: 129/208, Group 2: 130/199; Risk of bias: High; Indirectness of outcome: Serious indirectness Protocol outcome 4: Withdrawal due to adverse events at End of follow-up - Actual outcome for Low to moderate severity (formal assessment): Discontinuation due to adverse events at Unclear if end of treatment or follow-up; Group 1: 16/208, Group 2: 5/199; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Withdrawal due to adverse events at End of treatment; Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; C. difficile-associated diarrhoea at End of follow-up; Length of hospital stay at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	Hoeffken 2001[48]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 678)
Countries and setting	Study is a prospective, randomised, double blind trial carried out in 50 centres in 15 countries: Australia, Austria, Germany, Greece, Hong Kong (China), Indonesia, Israel, New Zealand, Norway, Philippines, South Africa, Sweden, Switzerland, Taiwan, United Kingdom; Setting: Secondary care centres
Line of therapy	Mixed line
Duration of study	Intervention + follow up: Patients were assessed at baseline, during treatment (day 3-5), after the end of treatment (day 13-15) and at follow-up (21-28 days) after the end of treatment.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CAP was diagnosed clinically on the basis of chest radiographs and signs and symptoms
Stratum	Low severity (community setting)
Subgroup analysis within study	Not applicable

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Inclusion criteria	Outpatients of either sex, aged 18 years or older, with CAP. Female patients of childbearing age had to be using a reliable contraceptive method. CAP was diagnosed clinically on the basis of chest radiographs and the presence of fever (core temp >38.5C or oral temp >38C) and leukocytosis (>10000mm3), together with one or more of: productive cough, purulent sputum, dyspnoea or tachypnoea, rigors/chills, pleuritic chest pain or rales/rhonchi indicating consolidation.
Exclusion criteria	Patients were excluded if they presented with a history of hypersensitivity to study drugs or related compounds; suspected aspiration pneumonia due to vomiting; neutropenia; liver disease or renal insufficency; AIDs; any severe infection or severe cardiac failure; severe life threatening disease or a history of tendinopathy with fluoroquinones; if they required concomitant systemic anitbacterial treatment or had recieved systemtic antibacterial therapy for more than 24 hours prior to enrolment. Female patients were excluded if they were pregnant or breast feeding. Patients with congenital or sporadic syndromes of QTc prolongation or receiving concomitant medication known to increase the QTc interval were also excluded.
Recruitment/selection of patients	Nov 1996 - Feb 1998
Age, gender and ethnicity	Age - Mean (SD): Moxifloxacin 400mg od 48.0 (20.8). Clarithromycin 500mg bid 48.2 (19.2) years. Gender (M:F): Moxifloxacin 400mg 61.2/38.8%. Clarithromycin 500mg bid 62.1/37.8%. Ethnicity: Not reported
Further population details	1. Age: All adults 2. Comorbidities: Not stated or unclear (Said to be comparable between groups). 3. Predominant disease aetiology (including resistance profiles): *Streptococcus pneumoniae* (Of 117 identified pathogens, 53 (45.3%) were *S. pneumoniae* and 45 (38.5%) *H. influenzae* or *H. parainfluenzae*).
Indirectness of population	Serious indirectness: Patients recruited from 15 countries. Therefore, results may not be generalisable to the UK population
Interventions	(n = 224) Intervention 1: Antibiotic plus placebo - Respiratory fluoroquinolone (new) + placebo. Oral moxifloxacin (400 mg once daily for 10 days) - one active and one placebo capsule in the morning and two placebo capsules in the evening. Duration 10 days. Concurrent medication/care: Concomitant anti-bacterials not permitted Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Also included a 200 mg dose arm but not reported as this is not a licenced dose. All medications taken orally with meals and 100 ml water. (n = 222) Intervention 2: Antibiotic alone - Macrolide. Oral clarithromycin 500 mg, twice daily. Duration 10 days. Concurrent medication/care: Concomitant anti-bacterials not permitted Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: All medications taken orally with meals and 100 ml water

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Funding	Study funded by industry (Bayer AG)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RESPIRATORY FLUOROQUINOLONE (NEW; MOXIFLOXACIN) + PLACEBO versus MACROLIDE (CLARITHROMYCIN) Protocol outcome 1: Mortality at 30 days - Actual outcome for Low severity (community setting): Mortality at 21-28 days after the end of treatment (31-38 days); Group 1: 2/224, Group 2: 5/222; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Clinical cure at End of treatment - Actual outcome for Low severity (community setting): Clinical cure: resolution of clinical signs and symptoms related to infection not requiring further antibacterial treatment at 3-5 days after end of study treatment; Group 1: 167/177, Group 2: 164/174; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Withdrawal due to adverse events at End of treatment - Actual outcome for Low severity (community setting): Discontinuation due to adverse events at 10 days; Group 1: 11/224, Group 2: 11/222; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Clinical cure at End of follow-up - Actual outcome for Low severity (community setting): Clinical cure: resolution of clinical signs and symptoms maintained throughout follow-up and not requiring further antibacterial treatment at 21-28 days after end of study treatment; Group 1: 141/152, Group 2: 141/153; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; *C. difficile*-associated diarrhoea at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	Higuera 1996[47]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 162)
Countries and setting	Conducted in Argentina, Dominican Republic, Mexico, USA; Setting: 31 centres throughout USA and Latin America
Line of therapy	1st line
Duration of study	Intervention + follow up: 10 days plus 14 days post-treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical signs/symptoms confirmed by CXR
Stratum	Low severity (community setting): Outpatients

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatients 12 years of age or older with community-acquired pneumonia. Diagnosis confirmed by a chest X-ray (read by a radiologist) showing localised infiltrates with or without pleural effusion, the presence of two of five clinical symptoms (fever ≥100.5°F (oral), chills, recent onset of productive cough, shortness of breath, or pleuritic chest pain), and the presence of at least two of five physical signs (tachypnoea, egophony, rales, dullness to percussion, and bronchial breath sounds). Patients also had to have either leucocytosis (> 10 x 10[9]/L white blood cells) or > 15% band cells, and/or a positive culture of a susceptible pathogen from bronchopulmonary secretions.
Exclusion criteria	Pregnancy or lactation, history of a hypersensitivity reaction to any of the study drugs, received other antibiotics within 72 h before enrolment, or neutropenia or significant underlying disease, including pulmonary disease marked by abnormal baseline pulmonary function tests (pO2 < 60 mmHg or pCO2 > 55 mmHg), or an underlying condition known to compromise their ability to eradicate bacterial infections.
Recruitment/selection of patients	Prospective: November, 1988 and June, 1991. 58% were enrolled at the three Latin American centres and 42% at centres in the USA. A majority of the USA centres did not begin enrolling patients until December, 1990, when the study had already been under way for 2 years
Age, gender and ethnicity	Age - Median (range): Cefuroxime group: 39.9 (12-89); amoxicillin-clavulanate group: 41.7 (12-89). Gender (M:F): 49.4/50.6%. Ethnicity: 63.0% white; 32.7% hispanic; 4.3% black
Further population details	1. Age: All adults (Also included children from 12 years). 2. Comorbidities: Not stated or unclear 3. Predominant disease aetiology (including resistance profiles): *Streptococcus pneumoniae* (Of 97 patients with pathogens isolated the most common were S. pneumonia (38%) and *H. influenzae* (18%)).
Indirectness of population	Serious indirectness: Included 12-18 year olds
Interventions	(n = 84) Intervention 1: Antibiotic alone - Cephalosporin. Cefuroxime axetil 500 mg b.i.d (oral). Duration 10 days. Concurrent medication/care: Unclear Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Mean duration: 10 days (range: 3-12 days) (n = 78) Intervention 2: Antibiotic alone - Beta-lactamase stable penicillin. Amoxicillin-clavulanate 500 mg/125 mg t.i.d. Duration 10 days. Concurrent medication/care: Unclear Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Mean duration: 10 days (range: 3-13 days)
Funding	Study funded by industry (Glaxo Wellcome Inc.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEPHALOSPORIN (CEFUROXIME AXETIL) versus BETA-LACTAMASE STABLE PENICILLIN (AMOXICILLIN-CLAVULANATE)	

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Protocol outcome 1: Clinical cure at End of follow-up - Actual outcome for Low severity (community setting): Clinical cure: complete resolution of clinical signs and symptoms at 14 days post-treatment; Group 1: 49/55, Group 2: 46/51; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at 30 days; Clinical cure at End of treatment; Withdrawal due to adverse events at End of treatment; Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; *C. difficile*-associated diarrhoea at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	Gotfried 2002[44]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 299)
Countries and setting	Conducted in Canada, USA; Setting: 51 sites
Line of therapy	1st line
Duration of study	Intervention + follow up: 7 day's treatment plus 14-21 days post-treatment follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Signs and symptoms plus chest radiograph (within 48 hours of drug initiation)
Stratum	Low severity (community setting): Ambulatory patients
Subgroup analysis within study	Not applicable
Inclusion criteria	Ambulatory male and female patients aged ≥18 years with signs and symptoms suggestive of CAP plus chest radiograph (within 48 hours of drug initiation) consistent with CAP. Signs and symptoms suggestive of CAP included: cough, purulent sputum production or change in character of sputum, rales or consolidations, dyspnoea or tachypnoea, fever of hypothermia, elevated total peripheral WBC count, hypoxemia
Exclusion criteria	Residents of chronic care facility, hospitalised within 4 weeks of study entry, active TB (or other mycobacterial infections), empyema, lung abscess, pulmonary embolism, lung tumour, bronchial obstruction, history of post-obstructive pneumonia or known/suspected P. carinii pneumonia. Underlying condition that would interfere with absorption of study drug or evidence of alcohol/drug abuse within 12 months. Uncontrolled clinically significant cardiovascular, pulmonary, renal, haemostatic, metabolic, gastrointestinal, neurologic or endocrine disease or malignancy. Received treatment with long-lasting anti-microbial agent within 2 weeks or another systemic antibiotic within 7 days or investigational drug within 4 weeks. History of hypersensitivity or allergic reactions to macrolides or quinolones or infection that required concomitant anti-microbial. Pregnancy, lactation, immunocompromised or known HIV infection.

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Recruitment/selection of patients	November 1999 to July 2000
Age, gender and ethnicity	Age - Mean (range): 50 (18-91) years. Gender (M:F): 55.2/44.8%. Ethnicity: 92% white; 4.3% black; 3.3% Asian
Further population details	1. Age: All adults 2. Comorbidities: Not stated or unclear 3. Predominant disease aetiology (including resistance profiles): *Mycoplasma pneumoniae* (of 280 identified pathogens, 65 (23%) were *M pneumoniae*, 63 (23%) *C pneumoniae* and 60 (21%) *H influenzae*).
Extra comments	It was necessary to have obtained a Gram-stain qualified sputum sample to be included. Very extensive exclusion criteria.
Indirectness of population	Serious indirectness: Required qualified sputum sample to be included
Interventions	(n = 143) Intervention 1: Antibiotic alone - Respiratory fluoroquinolone - new. Levofloxacin - two 250-mg tablets once daily. Duration 7 days. Concurrent medication/care: Not stated Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more (n = 156) Intervention 2: Antibiotic alone - Macrolide. Clarithromycin extended release - two 500 mg tablets. Duration 7 days. Concurrent medication/care: Not stated Further details: 1. Antibiotic dose: 2. Duration of treatment:
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RESPIRATORY FLUOROQUINOLONE - NEW (LEVOFLOXACIN) versus MACROLIDE (CLARITHROMYCIN ER) Protocol outcome 1: Withdrawal due to adverse events at End of treatment - Actual outcome for Low severity (community setting): Withdrawal due to adverse events at 7 days; Group 1: 1/143, Group 2: 5/156; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Clinical cure at End of follow-up - Actual outcome for Low severity (community setting): Clinical cure - resolution or improvement of all signs and symptoms, plus improvement or lack of progression on CXR; or no pneumonia or extrapulmonary infection requiring antimicrobial therapy other than study drug) at 14-21 days post treatment (test-of-cure); Group 1: 107/124, Group 2: 113/128; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at 30 days; Clinical cure at End of treatment; Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; C. difficile-associated diarrhoea at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	Fogarty 1999[39]

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=474 patients from 51 medical centres)
Countries and setting	Conducted in USA; Setting: Patients recruited from 51 medical centres.
Line of therapy	Unclear
Duration of study	Intervention + follow up: 14 to 35 days post-therapy
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical signs and symptoms and radiological evidence
Stratum	Low severity (community setting): 99% out-patients and excluded severe pneumonia
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients 18 years or older with CAP (documented by presence of fever, elevated white blood cell count (greater than 10,000/mL), leukocytosis, signs or symptoms of pneumonia (productive cough, purulent sputum, dyspnoea or tachypnoea, chills, pleuritic chest pain, or signs of pulmonary consolidation), and a new or progressive infiltrate on chest X-ray).
Exclusion criteria	Patients with any of the following: allergy due to fluoroquinolones, pregnancy or lactation, presence of severe pneumonia requiring parenteral antimicrobials or mechanical ventilation, suspected aspiration pneumonia due to vomiting, hospitalisation for more than 48 hours, significant liver or renal impairment, or severe heart failure, neutropenia or low CD4 count, history of fluoroquinolone tendinopathy, previous therapy with systemic antibiotic for more than 24 hours or requirement for concomitant antibacterial therapy, rapidly fatal underlying disease, other confounding respiratory disease (e.g. lung cancer), history of prolonged QTc interval or requirement for concomitant medication associated with increased QTc interval, administration of another investigational drug within 30 days of study enrolment, or previous enrolment in study.
Recruitment/selection of patients	Prospective (November 1996 - May 1998)
Age, gender and ethnicity	Age - Mean (range): 48 years (18-88) in the moxifloxacin group and 49years (18-88) in the clarithromycin group . Gender (M:F): 46/54% in the moxifloxacin group and 49/51% in the clarithromycin group . Ethnicity: American
Further population details	1. Age: All adults 2. Comorbidities: Not stated or unclear (62.3% current or former smokers). 3. Predominant disease aetiology (including resistance profiles): Not applicable (Of 277 identified pathogens, 100 (36%) were *C. pneumoniae*, 44 (16%) *M. pneumoniae*, 39 (14%) *H influenzae* and 36 (13%) *S pneumoniae*).
Extra comments	Pre-therapy anti-bacterials taken in 14/382 (4%); 8 in moxifloxacin and 6 in clarithromycin groups. 86% had unilateral infiltrates, 5% had pleural effusion, 67% had rales.
Indirectness of population	Serious indirectness: High proportion *C. pneumoniae*
Interventions	(n = 241) Intervention 1: Antibiotic plus placebo - Respiratory fluoroquinolone (new) + placebo. Moxifloxacin 400 mg

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
	OD plus placebo OD (oral). Duration 10 days. Concurrent medication/care: Unclear Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Number randomised not stated - estimated based on available data. (n = 233) Intervention 2: Antibiotic alone - Macrolide. Clarithromycin, 500 mg BD (oral). Duration 10 days. Concurrent medication/care: Unclear Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Number randomised not stated - estimated based on available data
Funding	Study funded by industry (Bayer Corporation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RESPIRATORY FLUOROQUINOLONE (NEW; MOXIFLOXACIN) + PLACEBO versus MACROLIDE (CLARITHROMYCIN) Protocol outcome 1: Clinical cure at End of treatment - Actual outcome for Low severity (community setting): Clinical cure: disappearance or sufficient improvement in signs/symptoms (including radiological) that additional or alternative antimicrobial therapy was not required at 10-16 days; Group 1: 177/194, Group 2: 173/188; Risk of bias: High; Indirectness of outcome: Serious indirectness Protocol outcome 2: Withdrawal due to adverse events at End of treatment - Actual outcome for Low severity (community setting): Drug discontinued due to adverse events at 10 days; Group 1: 6/241, Group 2: 12/232; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Clinical cure at End of follow-up - Actual outcome for Low severity (community setting): Continued resolution: maintaining resolution/improvement in signs/symptoms (including radiological) at 14-35 days post-treatment; Group 1: 184/194, Group 2: 178/188; Risk of bias: ; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Mortality at 30 days; Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; *C. difficile*-associated diarrhoea at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	Antani 1991[3]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 72)
Countries and setting	Conducted in India; Setting: Single office practice

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
Line of therapy	1st line
Duration of study	Intervention time: 10 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Signs and symptoms of pneumonic consolidation (e.g. high grade pyrexia, cough, expectoration, chest pain or discomfort, dullness or percussion, rales) plus radiological confirmation
Stratum	Low severity (community setting): Domiciliary study in office practice
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients presenting with signs and symptoms of pneumonic consolidation (e.g. high grade pyrexia, cough, expectoration, chest pain or discomfort, dullness or percussion, rales) plus radiological confirmation
Exclusion criteria	Not all stated, but for example, presence of other major illnesses such as TB leprosy, diabetes, liver and kidney disease
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Tetracycline: 36.3 (2.43); cephalosporin: 38.6 (2.81). Gender (M:F): 75/25%. Ethnicity: Asian
Further population details	1. Age: All adults (Low mean age). 2. Comorbidities: Not stated or unclear 3. Predominant disease aetiology (including resistance profiles): *Streptococcus pneumoniae* (Of 65 identified pathogens 39 (60%) were S. pneumonia).
Indirectness of population	No indirectness
Interventions	(n = 31) Intervention 1: Antibiotic alone - Cephalosporin. Cephalexin 500 mg (BD). Duration 10 days. Concurrent medication/care: Not stated Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more (n = 38) Intervention 2: Antibiotic alone - Tetracycline. Demeclocycline 300 mg BD. Duration 10 days. Concurrent medication/care: Not stated Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Funding	Study funded by industry (Cyanamid India)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEPHALOSPORIN (CEPHALEXIN) versus TETRACYCLINE (DEMECLOCYCLINE) Protocol outcome 1: Clinical cure at End of treatment - Actual outcome for Low severity (community setting): Overall efficacy (clinical and radiological) - highly effective at 10 days; Group 1: 9/31, Group 2: 9/29; Risk of bias: High; Indirectness of outcome: Serious indirectness Protocol outcome 2: Withdrawal due to adverse events at End of treatment - Actual outcome for Low severity (community setting): Withdrawal due to adverse events at 10 days; Group 1: 1/31, Group 2: 0/29; Risk of bias: Low; Indirectness of	

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at 30 days; Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; C. difficile-associated diarrhoea at End of follow-up; Clinical cure at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up.
Study	Bonvehi 2003[8]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 327)
Countries and setting	Conducted in Argentina, Italy, Mexico, South Africa, Spain, Turkey; Setting: 45 sites in primary care and referral centre settings [12 in Argentina, four in Italy, three in Mexico, 11 in South Africa, four in Spain, and 11 in Turkey]
Line of therapy	Mixed line
Duration of study	Intervention + follow up: & days treatment plus up to 28-35 days after treatment completion
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical signs plus radiographic confirmation
Stratum	Low severity (community setting)
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatients aged 12-85 years with a diagnosis of community-acquired pneumonia verified by the presence of acute pulmonary infiltrates (i.e. lobular pattern or alveolar infiltrates) on a chest radiograph. Patients were selected for inclusion on the basis of having a positive pre-treatment sputum culture, although this was not required; a qualified sputum sample, defined as Gram-stained sputum specimens containing fewer than ten squamous epithelial cells and >25 leucocytes per low field (100x). Patients must have had at least three of the following signs and symptoms consistent with bacterial pneumonia: cough; purulent sputum production or a change in the character of the sputum; history of or current fever (>38.0°C or >100.4°F); and an elevated white blood cell (WBC) count (>10,000/mm3). Alternatively, the investigator could enrol patients with other clinical findings. For example, >15% bands (regardless of total WBC count), leukopenia (WBC count <4500/mm3), and development of, or increase in, dyspnoea or tachypnoea (respiratory rate consistently >22/min). Also included were auscultatory findings such as rales and/or evidence of pulmonary consolidation, development of, or increase in, chest discomfort and/or congestion, and rigors or shaking chills. Gram-stain findings consistent with *S. pneumoniae* or a urine specimen positive for *S. pneumoniae* antigen at the pre-treatment visit were recommended (to increase the probability of enrolling patients with pneumococcal pneumonia), but were not required
Exclusion criteria	Pregnant or lactating females; patients hospitalised for more than 48 hours and/or within 4 weeks of study enrolment; residents at a chronic care facility; immunocompromised patients; patients with pulmonary diseases other

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
	than pneumonia (i.e. active tuberculosis, bronchiectasis, lung abscess, pulmonary embolism, pulmonary oedema, cystic fibrosis, pulmonary tumour, bronchial obstruction, history of post-obstructive pneumonia, evidence of Legionella pneumonia, or known or suspected *Pneumocystis carinii* pneumonia); patients with clinically significant renal impairment (serum creatinine ≥ 2.0 mg/dL) or hepatic impairment/disease, or other medical conditions likely to interfere with the evaluation of treatment response; CD4 count of ≤500 cells/mm3; patients receiving antiretroviral therapy
Recruitment/selection of patients	Prospective; March 2000 and May 2002
Age, gender and ethnicity	Age - Mean (SD): Clarithromycin: 43.3 (18.2); co-amoxiclav: 46.7 (18.5). Range: 12-85 years. Gender (M:F): 55/45%. Ethnicity: 81% Caucasian; 5.8% black
Further population details	1. Age: Not stated or unclear (12-85 years). 2. Comorbidities: Not stated or unclear (Pulmonary disease history reported: CAP (17%); chronic bronchitis/COPD (9%); bronchial asthma: 7%; acute bronchitis (7%)). 3. Predominant disease aetiology (including resistance profiles): *Haemophilus influenzae* (A respiratory tract pathogen was isolated from sputum in 192 patients. *H. influenzae* was 35% of isolated pathogens; S. pneumonia 29% and *H. parainfluenzae* 21%. Of 85 strains of *S. pneumoniae* isolated pre-treatment, 4 were resistant to clarithromycin and 2 to co-amoxyclav).
Indirectness of population	Serious indirectness: Children included and excluded known Legionella
Interventions	(n=160) Intervention 1: Antibiotic alone - Macrolide. Clarithromycin immediate-release 500mg twice daily (Klaricid®, Abbott Laboratories, Ltd) orally. Duration 7 days. Concurrent medication/care: The use of systemic antibacterial agents within 2 weeks (4 weeks for benzathine benzylpenicillin) of enrolment, or concomitant use during the study, for another infection was not allowed. Likewise, concomitant use of an antiretroviral, systemic corticosteroid at a dose equal or greater than 10mg of prednisone or any other immunosuppressant was not permitted. To avoid a potential drug interaction, patients were to avoid taking terfenadine, astemizole, cisapride or pimozide concurrently with the study medication. For the same reason, patients were not allowed to take theophylline, carbamazepine, ergotamine, dihydroergotamine mesylate, triazolam, diazepam, disulfiram, digoxin, benzodiazepine, phenytoin or hexobarbital unless they were carefully assessed for toxicity Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more (n=167) Intervention 2: Antibiotic alone - Beta-lactamase stable penicillin. Amoxicillin/clavulanic acid 875mg/125mg twice daily (Augmentin®, GlaxoSmithKline) orally. Duration 7 days. Concurrent medication/care: The use of systemic antibacterial agents within 2 weeks (4 weeks for benzathine benzylpenicillin) of enrolment, or concomitant use during the study, for another infection was not allowed. Likewise, concomitant use of an antiretroviral, systemic corticosteroid at a dose equal or greater than 10mg of prednisone or any other immunosuppressant was not permitted. To avoid a potential drug interaction, patients were to avoid taking terfenadine, astemizole, cisapride or

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
	pimozide concurrently with the study medication. For the same reason, patients were not allowed to take theophylline, carbamazepine, ergotamine, dihydroergotamine mesylate, triazolam, diazepam, disulfiram, digoxin, benzodiazepine, phenytoin or hexobarbital unless they were carefully assessed for toxicity Further details: 1. Antibiotic dose: High 2. Duration of treatment: 7 days or more
Funding	Study funded by industry (Abbott Laboratories)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MACROLIDE versus BETA-LACTAMASE STABLE PENICILLIN Protocol outcome 1: Clinical cure at End of treatment - Actual outcome for Low severity (community setting): Clinical cure: resolution or marked improvement of all signs and symptoms with no need for antimicrobial therapy other than the study drug and ability to perform usual activities at 4-7 days after treatment completion; Group 1: 114/124, Group 2: 117/129; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Withdrawal due to adverse events at End of treatment - Actual outcome for Low severity (community setting): Premature discontinuation due to adverse events at 7 days; Proportion Clarithromycin: 1.9%; co-amoxiclav: <1%; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at 30 days; Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; C. difficile-associated diarrhoea at End of follow-up; Clinical cure at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	Carbon 1999[21]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 518)
Countries and setting	Conducted in Argentina, Finland, France, Germany, Irish Republic, Italy, Netherlands, South Africa, United Kingdom; Setting: Multicentre - 50 centres in 9 countries
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 7-10 days intervention plus 14-21 days after treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical signs and symptoms plus chest x-ray (HAP excluded)
Stratum	Low severity (vague description): Mild to moderate pneumonia - those with one or more indications of severe pneumonia were excluded
Subgroup analysis within study	Not applicable
Inclusion criteria	In- or out-patients, aged 18-65 years, with clinical signs and symptoms of mild-to-moderate pneumonia and physical

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
	examination findings consistent with the clinical diagnosis plus chest X-ray results confirming the clinical diagnosis
Exclusion criteria	Pregnant or of childbearing potential and not taking adequate contraceptive measures; pneumonia occurring more than 72 h after hospitalisation; pneumonia requiring parenteral antibiotic treatment; one or more indicators of severe pneumonia; pneumonia expected to be a terminal event; glucose-6-phosphate deficiency; hypersensitivity to ofloxacin or other fluoroquinolones or penicillin/b-lactams; or any concomitant clinical condition likely to interfere with the conduct of the study; had received ofloxacin or amoxicillin/clavulanic acid for this infectious episode; required probenecid or maintenance systemic corticosteroid therapy or a systemic antibiotic for another infection; or had received antibiotic pre-treatment for more than 24 h in the 5 days before study entry or azithromycin in the 7 days before study entry.
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): Levofloxacin 1x500mg: 41.19(15.78); Levofloxacin 2x500mg: 40.96(14.20); amoxiclav: 40.93(14.23). Gender (M:F): Levofloxacin: 58.3/41.7%; Amoxiclav: 67.9/32.1%. Ethnicity: 74.6% white; 16.3% black; 0.4% Asian; 8.7% other
Further population details	1. Age: 75 years or less (Excluded those aged >65 years). 2. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (297 (57.6%) patients had concomitant illnesses, mostly respiratory. Surgical history was positive in 171 patients (33.1%), and a history of drug/alcohol abuse and smoking was observed in 14 (2.7%) and 295 (57.2%) patients, respectively.). 3. Predominant disease aetiology (including resistance profiles): *Streptococcus pneumoniae* (Of 161 identified pathogens, 39.1% were *S. pneumoniae* and 34.2% *H. influenzae*).
Extra comments	Excluded those aged >65 years; 10.5% had prior antibiotic treatment; the majority had lobar pneumonia and the split between mild and moderate pneumonia was approximately 50/50
Indirectness of population	Serious indirectness: Excluded those aged >65
Interventions	(n=348) Intervention 1: Antibiotic alone - Respiratory fluoroquinolone - new. Levofloxacin 500 mg once or twice daily. Duration 7-10 days (mean 8.1 days). Concurrent medication/care: In total, 42.2% received concomitant non-anti-infective medications (break down by group not stated) Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Note: randomised to one of two doses (n=168) Intervention 2: Antibiotic alone - Beta-lactamase stable penicillin. Amoxicillin/clavulanic acid 625 mg three times daily. Duration 7-10 days (mean 8.1 days). Concurrent medication/care: In total, 42.2% received concomitant non-anti-infective medications (break down by group not stated)

Review question	Single- compared with single-antibiotic therapy for low-severity CAP managed in the community
	Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Funding	Study funded by industry (Hoechst Marion Roussel)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RESPIRATORY FLUOROQUINOLONE (LEVOFLOXACIN) versus BETA-LACTAMASE STABLE PENICILLIN (AMOXYCILLIN/CLAVULANIC ACID) Protocol outcome 1: Mortality at 30 days - Actual outcome for Low severity (vague description): Mortality at Up to 42 days after end of treatment; Group 1: 0/348, Group 2: 2/168; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Clinical cure at End of treatment - Actual outcome for Low severity (vague description): Clinical cure (no remaining signs/symptoms and CXR improved or CXR improved and no subsequent antibiotic treatment started) at 2-5 days after end of treatment; Group 1: 286/348, Group 2: 144/168; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Withdrawal due to adverse events at End of treatment - Actual outcome for Low severity (vague description): Withdrawal due to adverse events at 7-10 days; Group 1: 13/348, Group 2: 5/168; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Clinical cure at End of follow-up - Actual outcome for Low severity (vague description): Clinical cure (no remaining signs/symptoms and CXR improved or CXR improved and no subsequent antibiotic treatment started) at 14-42 days after end of treatment; RR No data reported, but states no differences seen between the treatment groups; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; C. difficile-associated diarrhoea at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up

Review question	Single compared with single antibiotics for low-severity CAP (managed in hospital)
Study	Bohte 1995-1[7]
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Pfizer)
Number of studies (number of participants)	1 (N = 64)
Countries and setting	Conducted in Netherlands; Setting: 6 hospitals
Line of therapy	1st line
Duration of study	Intervention + follow up: Up to 21 days after discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Chest x-ray and clinical signs and symptoms
Stratum	High severity (hospital setting)
Subgroup analysis within study	Stratified then randomised: Pneumococcal or non-pneumococcal
Inclusion criteria	Diagnosis of CAP based on chest x-ray, aged ≥18 years and not hospitalised at onset of illness
Exclusion criteria	Living in a nursing home or hospitalised within 1 week of admission, age > 75 years, parenteral therapy administered (e.g. for tachypnoea, confusion or diastolic hypertension), known hypersensitivity to study drug, antimicrobial therapy within 2 weeks prior to admission, history of gastrointestinal disease that could affect drug absorption, terminal illness or other condition that could interfere with drug therapy or its evaluation
Recruitment/selection of patients	Jan 1991 - April 1993
Age, gender and ethnicity	Age - Mean (SD): Azithromycin: 51 (17); benzylpenicillin: 50 (16). Gender (M:F): 50/50%. Ethnicity: Not stated
Further population details	1. Age: 75 years or less 2. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (42% and 62% with CVD, COPD, renal insufficiency, diabetes, malignancy, GI diseases and autoimmune diseases). 3. Predominant disease aetiology (including resistance profiles): *S. pneumoniae* (Of 38 identified pathogens 21 (55.3%) were *S. pneumoniae*).
Extra comments	Pneumococcal criterion: having at least one of sudden onset of illness, cold chills, purulent sputum or Gram stain revealing positive diplococci.
Interventions	Intervention 1: Antibiotic alone ~ Macrolide. Azithromycin 500 mg orally twice on first day and once daily for the next 4 days. Duration 5 days. Concurrent medication/care: Unclear(N = 36)

	Further details: 1. Antibiotic dose: High (High dose on day 1). 2. Duration of treatment: Less than 7 days Intervention 2: Antibiotic alone ~ Narrow spectrum beta-lactam (class 1). Benzylpenicillin 1 x 10^6 IU four times daily IV until 5 days after body temperature had normalised. Duration Unclear. Concurrent medication/care: Unclear(N = 30) Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: Not stated or unclear Comments: Route of administration differs between treatment arms
Study	Bohte 1995-2[7]
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Pfizer)
Number of studies (number of participants)	1 (N = 40)
Countries and setting	Conducted in Netherlands; Setting: 6 hospitals
Line of therapy	1st line
Duration of study	Intervention + follow up: Up to 21 days after discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Chest x-ray and clinical signs and symptoms
Stratum	High severity (hospital setting)
Subgroup analysis within study	Stratified then randomised: Pneumococcal and non-pneumococcal
Inclusion criteria	Diagnosis of CAP based on chest x-ray, aged ≥ 18 years and not hospitalised at onset of illness
Exclusion criteria	Living in a nursing home or hospitalised within 1 week of admission, age > 75 years, parenteral therapy administered (e.g. for tachypnoea, confusion or diastolic hypertension), known hypersensitivity to study drug, antimicrobial therapy within 2 weeks prior to admission, history of gastrointestinal disease that could affect drug absorption, terminal illness or other condition that could interfere with drug therapy or its evaluation
Recruitment/selection of patients	Jan 1991 - April 1993
Age, gender and ethnicity	Age - Mean (SD): Azithromycin: 51 (17); erythromycin: 54 (17). Gender (M:F): 55/45%. Ethnicity: Not stated
Further population details	1. Age: 75 years or less

	2. Comorbidities: Minority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (43% and 31% with CVD, COPD, renal insufficiency, diabetes, malignancy, GI diseases and autoimmune diseases). 3. Predominant disease aetiology (including resistance profiles): *S. pneumoniae* (Of 18 identified pathogens 5 (27.8%) were *S. pneumoniae*, 4 (22.2%) *M. pneumoniae*, 4 (22.2%) viruses and 3 (16.7%) *L. pneumophila*).
Extra comments	Non-pneumococcal criteria: not having any of sudden onset of illness, cold chills, purulent sputum or Gram stain revealing positive diplococci.
Interventions	Intervention 1: Antibiotic alone ~ Macrolide (azithromycin). Azithromycin 500 mg orally twice on the first day then once daily for 4 further days. Duration 5 days. Concurrent medication/care: Not stated(N = 20) Further details: 1. Antibiotic dose: High (High initial dose on day 1). 2. Duration of treatment: Less than 7 days Intervention 2: Antibiotic alone ~ Macrolide. Erythromycin 500 mg orally four times daily. Duration 10 days. Concurrent medication/care: Not stated(N = 22) Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Study	Brambilla 1992[11]
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Glaxo Group Research UK)
Number of studies (number of participants)	1 (N = 512)
Countries and setting	Conducted in Belgium, France, Germany, Greece, Israel, Netherlands, New Zealand, Switzerland; Setting: 22 hospitals across 8 countries
Line of therapy	Unclear
Duration of study	Intervention + follow up: At least 7 day treatment and 7-28 day post-treatment follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinical signs and symptoms and chest x-ray confirmation
Stratum	High severity (hospital setting)
Subgroup analysis within study	Not stratified but pre-specified: Pneumonia or bronchitis
Inclusion criteria	Adults hospitalised and requiring initial intravenous therapy for pneumonia or acute exacerbations of chronic bronchitis

	or bronchiectasis. Pneumonia was defined as acute LRTI associated with fever and focal signs of infection on examination confirmed radiographically by new pulmonary infiltrates.
Exclusion criteria	Known hypersensitivity to penicillins or cephalosporins, received antibiotics within prior 48 hours unless had clinically failed to respond, pathogens resistant to study drug isolated prior to entry, and those considered terminally ill or who required assisted ventilation. Also, those with bronchial carcinoma, pulmonary tuberculosis, atypical pneumonia (due to legionella or mycoplasma) or left ventricular failure, pregnant and breast-feeding women.
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): 63.5 years in full study sample (not given for pneumonia group). Gender (M:F): 68/32% in full study sample (not given for pneumonia group). Ethnicity: Not stated
Further population details	1. Age: All adults (Age range 18 to 97 years). 2. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (50% with concurrent disease in full study sample (not given for pneumonia group). This included CVD (18%), other respiratory diseases (14%), GI diseases (8%), diabetes (5%) and neurological disorders (4%)). 3. Predominant disease aetiology (including resistance profiles): *S. pneumoniae* (Of 57 identified pathogens, 21 (37%) were *S. pneumoniae*, 18 (32%) *H. influenzae*, 8 (14%) *M. catarrhalis* and 7 (12%) *S. aureus*).
Extra comments	In the pneumonia group 91.5% CAP and 8.5% HAP
Interventions	Intervention 1: Antibiotic alone ~ Cephalosporin. Cefuroxime 750 mg by slow IV infusion or injection three times daily for 48-72 hours, followed by cefuroxime axetil tablets 500 mg twice daily for at least 5 days. Duration At least 7 days. Concurrent medication/care: Concurrent antibiotics were not permitted(N = 137) Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Intervention 2: Antibiotic alone ~ Beta-lactamase stable penicillin. Co-amoxiclav 1.2 g three-times daily IV, followed by 625 mg three-times daily orally. Duration At least 7 days. Concurrent medication/care: Concurrent antibiotics were not permitted(N = 134) Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Study	Genne 1997[43]

Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Abbott AG)
Number of studies (number of participants)	1 (N = 127)
Countries and setting	Conducted in Switzerland; Setting: Single hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: Up to 2-3 weeks after the end of treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ New symptoms plus a new infiltrate on chest radiograph
Stratum	High severity (hospital setting): CAP requiring hospital admission
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults (> 18 years of age) with newly occurring cough and/or sputum production and/or dyspnoea associated with a new infiltrate on chest radiograph on admission or within 24 hours, and a leukocyte count of > 10 x 10^9/l or < 4 x 10^9/l
Exclusion criteria	People with pulmonary infiltrates clearly due to cardiac failure; antibiotic therapy or hospitalisation within 7 days prior to enrolment; documented allergy to macrolides or beta-lactams; immunocompromised status; presence of active pulmonary TB, bronchiectasis or cystic fibrosis; transaminase levels > twice ULN; concomitant treatment with carbamazepine or terfenadine; pregnancy.
Recruitment/selection of patients	All patients admitted with CAP between May 1993 and April 1995
Age, gender and ethnicity	Age - Mean (SD): Clarithromycin: 71 (16); co-amoxiclav: 69 (16) years. Gender (M:F): 61.6/38.4%. Ethnicity: Unclear
Further population details	1. Age: All adults 2. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (280 recorded cases across 8 different comorbidities (average of 31% with each comorbidity)). 3. Predominant disease aetiology (including resistance profiles): *S. pneumoniae* (Of 77 identified pathogens 34 (44%) were *S. pneumoniae*; 14 (18%) *H. influenzae*, and 6 (8%) each of *C. pneumoniae* and *L. pneumophila*. Note that 5 of the *H. influenzae* strains were resistant to clarithromycin).
Extra comments	Physician was free to change treatment according to the patient's condition
Interventions	Intervention 1: Antibiotic alone ~ Macrolide. Clarithromycin lactobionate 500 mg IV twice daily for 3-5 days followed by 500 mg orally twice daily . Duration At least 10 days. Concurrent medication/care: Concomitant treatment with carbamazepine or terfenadine not permitted(N = 56) Further details:

	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Oral therapy could be continued as an out-patient in cases of rapid clinical improvement Intervention 2: Antibiotic alone ~ Beta-lactamase stable penicillin. Amoxicillin plus clavulanic acid 1.2 g IV four times daily for 3-5 days followed by 625 mg orally three-times daily. Duration At least 10 days. Concurrent medication/care: Concomitant treatment with carbamazepine or terfenadine not permitted (N = 56) Further details: 1. Antibiotic dose: High (High dose but likely to achieve similar results to recommended doses based on likely pathogens and MICs). 2. Duration of treatment: 7 days or more Comments: Oral therapy could be continued as an out-patient in cases of rapid clinical improvement
Study	Harazim 1987[46]
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	1 (N = 230 (131 with pneumonia))
Countries and setting	Conducted in Austria; Setting: Unclear
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinical presentation and radiological symptoms
Stratum	High severity (hospital setting)
Subgroup analysis within study	Not stratified but pre-specified: Type of infection
Inclusion criteria	Adults hospitalised with LRTI
Exclusion criteria	History of hypersensitivity to nalidixic acid and its derivatives or to doxycycline; pregnant or nursing women; other antibiotics within prior 3 days (unless infecting organism shown to be resistant); likely to receive additional antimicrobials concurrently; use of investigational drug within 2 weeks; probenicid within 2 weeks; significant renal impairment; serious hepatic disease; rapidly progressing terminal disease
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Other: Not stated. Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	1. Age: All adults

	2. Comorbidities: Not stated or unclear 3. Predominant disease aetiology (including resistance profiles): Not stated or unclear
Interventions	Intervention 1: Antibiotic alone ~ Non-respiratory Fluoroquinolone. Ofloxacin 200 or 400 mg twice daily orally. Duration 10 days. Concurrent medication/care: Not stated(N = 62) Further details: 1. Antibiotic dose: BNF/SPC concordant (400 mg daily dose need not be divided into two 200 mg doses). 2. Duration of treatment: 7 days or more Comments: Number randomised not stated Intervention 2: Antibiotic alone ~ Tetracycline. Doxycycline 100 mg twice daily orally. Duration 10 days. Concurrent medication/care: Not stated(N = 69) Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Number randomised not stated
Study	Leuenberger 1983[62]
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	1 (N = 38)
Countries and setting	Conducted in Switzerland; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention time: 8 days
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis ~ Either clinical signs and symptoms or infiltrate on CXR (but all had CXR evidence documented)
Stratum	High severity (hospital setting)
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with either a history of acute onset of fever and cough, physical signs of pulmonary infection, purulent sputum with Gram stain showing monomorphic bacteria in the presence of neutrophils, or an infiltrate on CXR.
Exclusion criteria	Known allergy to beta-lactam antibiotics, pregnancy, pulmonary oedema, diabetic acidosis, severe renal or hepatic

	failure, and antibiotic therapy within previous 48 hours.
Recruitment/selection of patients	September 1981 to June 1982 - all patients developed pneumonia outside the hospital
Age, gender and ethnicity	Age - Mean (SD): Amoxicillin: 67.6 (4.3); cefaclor: 64.8 (3.5). Gender (M:F): Define. Ethnicity: White
Further population details	1. Age: All adults 2. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (COPD: 10/18 and 8/16; heart failure: 11/18 and 5/16; bronchial carcinoma: 2/18 and 2/16; alcoholism: 2/18 and 2/16; diabetes: 0/18 and 1/16). 3. Predominant disease aetiology (including resistance profiles): *S. pneumoniae*.
Extra comments	'Severe' infection: 14/18 and 15/16; 'moderate' in 4/18 and 1/16
Interventions	Intervention 1: Antibiotic alone ~ Cephalosporin. Cefaclor 500 mg three-times daily before meals. Duration 8 days. Concurrent medication/care: Unclear (N = 16) Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Route of administration unclear; number randomised unclear (overall 4 were not analysed but unclear how many of these were randomised to each group) Intervention 2: Antibiotic alone ~ Narrow spectrum beta-lactam (class 2). Amoxicillin 750 mg three-times daily before meals. Duration 8 days. Concurrent medication/care: Unclear(N = 18) Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Route of administration unclear; number randomised unclear (overall 4 were not analysed but unclear how many of these were randomised to each group)
Study	Oh 1996[82]
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Assistance from Glaxo Singapore, Smith Kline and Beecham (unclear if only provided drugs or fully funded the study)
Number of studies (number of participants)	1 (N = 48)
Countries and setting	Conducted in Singapore; Setting: Single hospital

Line of therapy	1st line
Duration of study	Intervention + follow up: 7 to 14 days treatment plus 1 to 2 weeks post-treatment follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ New pulmonary infiltrate and confirmatory clinical findings
Stratum	High severity (hospital setting): Admitted to department of General Medicine
Subgroup analysis within study	Not applicable
Inclusion criteria	New pulmonary infiltrate on chest X-ray on admission or within 24 hours; confirmatory clinical findings including at least 2 of the following: fever over 37.5°C, cough, sputum production, pulmonary consolidation by examination, WBC count > 10,000/mm^3
Exclusion criteria	Hypersensitivity to penicillins or cephalosporins, antimicrobial therapy in the 3 days before study entry, GI disorders likely to interfere with study drug absorption, pregnancy or lactation, and serious underlying disease or other circumstances making availability for follow-up unlikely
Recruitment/selection of patients	All patients admitted were evaluated
Age, gender and ethnicity	Age - Mean (SD): Co-amoxiclav: 39.3 (17.2); cefuroxime: 43.3 (19.8). Gender (M:F): Define. Ethnicity: 68.8% Chinese; 16.7% Indian; 12.5% Malay, 2% other
Further population details	1. Age: Not stated or unclear 2. Comorbidities: Minority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (Bronchiectasis (6 patients); chronic obstructive airways disease (5), bronchial asthma (2), hypertension (4), heart disease (4), diabetes (1), alcoholic liver disease (1)). 3. Predominant disease aetiology (including resistance profiles): No dominant pathogen (Only 16 pathogens identified (in 13 patients), 3 *M. pneumoniae*, 2 *P. aeruginosa*, 2 *Klebsiella* and 2 *Legionella*).
Extra comments	Unclear if any children were included
Interventions	Intervention 1: Antibiotic alone ~ Beta-lactamase stable penicillin. Co-amoxiclav 1.2 g IV every 8 hours for 48 hours followed by 750 mg orally three-times daily . Duration 7-14 days. Concurrent medication/care: Unclear (N = 24) Further details: 1. Antibiotic dose: High (Oral dose: 750 mg, presumably as 2 x 250 mg amoxicillin + 125 mg clavulanic acid. The amount of amoxicillin is equivalent to the UK dose and a greater amount of clavulanic acid in the preparation is unlikely to produce better results than the standard dose used in the UK.). 2. Duration of treatment: 7 days or more Comments: Oral dosing slightly high but unlikely to produce different results than the standard dose used in the UK. Mean duration 7 days (range: 7-28 days)

	Intervention 2: Antibiotic alone ~ Cephalosporin. Cefuroxime 750 mg IV every 8 hours for 48 hours followed by 500 mg orally twice daily. Duration 7-14 days. Concurrent medication/care: Unclear (N = 24) Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Mean duration 7 days (range: 7-28 days)

1.4.2.1.1 *Results*

Dichotomous

Study	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl
Stratum: High severity (hospital setting). Comparison: Macrolide (azithromycin) vs macrolide														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	
Bohte 1995-2[7]			Mortality @ up to 21 days post-discharge Azithromycin: carcinoma of the oesophagus (died on day 2); erythromycin: bronchus carcinoma with obstruction of right primary bronchus (died on day 5).		Cure: complete resolution of all signs and symptoms @ Discharge or 10-12 days 4 in azithromycin and 5 in erythromycin groups switched treatment due to fever or side effects									
	20	22	1/20	1/22	14/19	14/21	NR	NR	NR	NR	NR	NR	NR	NR
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**		**Withdrawal due to adverse events @ End of follow-up**									
Bohte 1995-2[7]			Cure: complete resolution of all signs and symptoms @ up to 21 days post-		Withdrawal or switching treatment due to adverse events @ up to 21 days post-									

			discharge		discharge Switched due to adverse events									
	20	22	15/19	15/21	0/19	2/21								
Stratum: Moderate to high severity (formal assessment). Comparison: Cephalosporin vs beta-lactamase stable penicillin														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	
Brambilla 1992[11]					Clinical cure: absence of signs and symptoms of infection at the time treatment was stopped @ At least 7 days Numbers 'improved': 37/137 and 45/134									
	137	134	NR	NR	80/137	63/134	NR	NR	NR	NR	NR	NR	NR	NR
Oh 1996[82]					Clinical cure: resolution of clinical symptoms and signs @ 7-28 days Note: 2 in cephalosporin group said to have empyema and lung abscess (unclear whether pneumonia was		Discontinuation due to adverse events @ 7-28 days Urticarial rash in one patient and vomiting in the other							

					also present)									
	24	24	NR	NR	20/24	18/24	0/24	2/24	NR	NR	NR	NR	NR	NR
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**		**Withdrawal due to adverse events @ End of follow-up**									
Brambilla 1992[11]			Maintaining cure/improvement: signs and symptoms resolved or subsided @ 7-28 days post-treatment											
	137	134	101/117	94/108	NR	NR								
Oh 1996[82]														
			NR	NR	NR	NR								
Stratum: High severity (hospital setting). Comparison: Cephalosporin vs narrow spectrum beta-lactam (class 2)														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	
Leuenberger 1983[62]					Cure: disappearance of all signs and symptoms of primary infection @ 8 days									
	16	18	NR	NR	15/16	16/18	NR	NR	NR	NR	NR	NR	NR	NR
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**		**Withdrawal due to adverse events @ End of follow-up**									
Leuenberger 1983[62]														
			NR	NR	NR	NR								

Stratum: High severity (hospital setting). Comparison: non-respiratory fluoroquinolone vs tetracycline																
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	
Harazim 1987[46]					Cure: resolution of cough and sputum production @ 10 days Numbers 'improved': 26/62 vs. 23/69									
	62	69	NR	NR	34/62	39/69	NR	NR	NR	NR	NR	NR	NR	NR
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**		**Withdrawal due to adverse events @ End of follow-up**									
Harazim 1987[46]														
			NR	NR	NR	NR								
Stratum: High severity (hospital setting). Comparison: Macrolide vs beta-lactamase stable penicillin																
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	
Genne 1997[43]			Mortality @ 2-3 weeks after the end of treatment Clarithromycin patient died		Overall therapeutic success @ 10 days		Treatment discontinuation due to adverse events @ 10 days							

			following bronchoaspiration in conjunction with existing neoplasm; co-amoxiclav patient died of ARDS with pneumococcal septic shock. A third patient died of acute anterior MI but the group was not stated.											
	56	56	1/56	1/56	48/56	47/56	1/56	3/56	NR	NR	NR	NR	NR	NR
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**		**Withdrawal due to adverse events @ End of follow-up**									
Genne 1997[43]														
			NR	NR	NR	NR								
Stratum: Low-severity (hospital setting). Comparison: Macrolide vs narrow spectrum beta-lactam (class 1)														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	
Bohte 1995-1[7]					Cure: disappearance of all signs and symptoms of pneumonia @ Discharge or 12-15 days Therapy was									

					switched in 6 azithromycin and 10 benzylpenicillin patients									
	36	30	NR	NR	24/35	14/29	NR	NR	NR	NR	NR	NR	NR	NR
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**		**Withdrawal due to adverse events @ End of follow-up**									
Bohte 1995-1[7]			Cure: disappearance of all signs and symptoms of pneumonia @ up to 21 days after discharge		Withdrawal or switching treatment due to adverse events @ up to 21 days after discharge 1 *E. coli* septicaemia, 1 GI side effects									
	36	30	29/35	19/29	2/35	0/29								

General

Stratum: Low-severity (hospital setting). Comparison: Macrolide vs beta-lactamase stable penicillin				
Protocol outcomes -->	**Numbers Randomised**		**Withdrawal due to adverse events @ End of treatment**	**Length of hospital stay @ End of follow-up**
Genne 1997[43]			Treatment discontinuation due to adverse events @ 10 days	Length of hospital stay @ Unclear Numerical results not reported
	56	56	Reported on dichotomous	Other Length of stay did not differ between the two groups

Review question	Single vs single – indirect comparison
Study	Moola 1999[77]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 504)
Countries and setting	Conducted in Australia, Canada, Czech Republic, Germany, Israel, Italy, New Zealand, Poland, South Africa, Spain, Sweden; Setting: 58 centres in 11 countries: in- and out-patients
Line of therapy	1st line
Duration of study	Intervention + follow up: 10 days treatment and 28-35 days post-treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical signs and symptoms and CXR confirmation
Stratum	Low severity (formal assessment): <7% PSI group III+
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with chest radiographs taken within 2 days of the start of study medication confirming pulmonary infiltration or consolidation likely to be caused by pneumonia, and patients presenting with one or more of the clinical signs and symptoms consistent with CAP—pleuritic chest pain, cough, fever (≥38°C), and auscultatory findings such as rales and/or evidence of consolidation. Patients could be treated in the community or could be admitted to the hospital, depending on the standard medical practice in different countries
Exclusion criteria	Nosocomial pneumonia; required immediate IV antibiotic therapy; received antibiotic therapy within 3 days before study entry; or had bronchial carcinoma, empyema, lung abscess, uncontrolled asthma, pulmonary tuberculosis, or cystic fibrosis. As well as other standard exclusion criteria for clinical trials, patients with an immunocompromised status, malabsorption syndromes, hepatic or renal impairment, and history of seizure disorders were excluded, as were those with known sensitivity to any quinolone or macrolide antibiotic. Administration of additional antimicrobials was not permitted for the duration of the study, and a record was kept of any medication taken concomitantly
Recruitment/selection of patients	Prospective
Age, gender and ethnicity	Age - Mean (SD): 48.5 (18.0). Gender (M:F): 40.5/59.5. Ethnicity: 79.4% white, 16.1% black, 2.2% Asian
Further population details	1. Age: All adults 2. Comorbidities: Not stated or unclear (62% had pre-existing medical condition on entry to the study, most commonly cardiovascular (23%) or respiratory (17%)). 3. Predominant disease aetiology (including resistance profiles): *Mycoplasma pneumoniae* (Of 153 isolated pathogens from 131 patients, 28% were *M. pneumoniae*, 24% *S. pneumoniae* and 18% *H. influenzae*).
Extra comments	The majority of patients, 73%, were > 35 years, with 23% being > 65 years old
Indirectness of population	No indirectness

Review question	Single vs single – indirect comparison
Interventions	(n = 251) Intervention 1: Antibiotic plus placebo - Respiratory fluoroquinolone (new) + placebo. Grepafloxacin, 600 mg qd orally. Duration 10 days. Concurrent medication/care: Additional antimicrobials not permitted Further details: 1. Antibiotic dose: BNF/SPC concordant (Highest marketed dose). 2. Duration of treatment: 7 days or more (n = 253) Intervention 2: Antibiotic plus placebo - Macrolide + placebo. Clarithromycin 500 mg bid orally. Duration 10 days. Concurrent medication/care: Additional antimicrobials not permitted Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Funding	Study funded by industry (Glaxo Wellcome)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RESPIRATORY FLUOROQUINOLONE (NEW; GREPAFLOXACIN) + PLACEBO versus MACROLIDE (CLARITHROMYCIN) + PLACEBO Protocol outcome 1: Mortality at 30 days - Actual outcome for Low severity (formal assessment): Mortality at up to 35 days post-treatment; Group 1: 2/251, Group 2: 0/253; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Withdrawal due to adverse events at End of treatment - Actual outcome for Low severity (formal assessment): Discontinuation of study drug due to adverse events at 10 days; Group 1: 16/251, Group 2: 18/253; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Clinical cure at End of follow-up - Actual outcome for Low severity (formal assessment): Cure or improvement: of clinical signs and symptoms inclusing radiographic evidence at 28-35 days post treatment; Group 1: 188/251, Group 2: 192/253; Risk of bias: High; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Clinical cure at End of treatment; Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; *C. difficile*-associated diarrhoea at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	O'Doherty 1997[80]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 264)

Review question	Single vs single – indirect comparison
Countries and setting	Conducted in Irish Republic, United Kingdom; Setting: 43 centres in UK and Ireland
Line of therapy	1st line
Duration of study	Intervention + follow up: 7-10 days plus 28-42 days post-treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical signs and symptoms plus CXR confirmation
Stratum	Low severity (community setting): Treated on an out-patient basis
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 18-80 years, with an established diagnosis (radiographic and consistent signs and symptoms) of suspected bacterial CAP suitable for treatment with an oral antibiotic on an outpatient basis. Clinical signs and symptoms must have included at least three of the following: cough, pyrexia, dyspnoea, decreased air entry and/or localized crackles. All patients had a CXR showing signs and symptoms consistent with a diagnosis in the 24 h prior to the study or in the following 24 h.
Exclusion criteria	Allergy to quinolone or penicillin antibiotics; pregnancy or lactation; women of childbearing potential not using acceptable contraception; evidence of a lung tumour, active tuberculosis or cystic fibrosis; current history or clinical signs of hepatic or renal impairment; current history of seizure disorders; malabsorption syndromes; respiratory tract infection requiring parenteral antimicrobial therapy; concomitant treatment with antimicrobial therapy other than topical or antifungal agents; treatment with other oral antibiotics within 3 days or with a longacting injectable antibiotic within 1 week before starting the study, unless the organism was resistant to the antibiotic used and the patient was a clinical treatment failure; previous participation in this or any other clinical trial with grepafloxacin; treatment with an investigational drug or device before 4 weeks of study entry; concomitant treatment with theophylline; chronic treatment with fenbufen, warfarin or probenecid; required inhalation of, or increase in dose of, systemic steroids for the treatment of respiratory tract infections; or terminal illness or immunocompromised status
Recruitment/selection of patients	September 1992 to November 1993
Age, gender and ethnicity	Age - Other: Mean: 55.3 years. Gender (M:F): Grepafloxacin group: 58.3/41.2%; amoxicillin group: 65.0/35.0%. Ethnicity: 99% white
Further population details	1. Age: All adults 2. Comorbidities: Not stated or unclear (49.6% and 54.7% alcohol consumption at least monthly). 3. Predominant disease aetiology (including resistance profiles): Haemophilus influenzae (Of 81 patients with isolated pathogens 50.6% had H. influenzae, 35.8% S. pneumoniae, and 7.4% M. catarrhalis).
Extra comments	Note that those who required inhalation of, or increase in dose of, systemic steroids for the treatment of respiratory tract infections were excluded
Indirectness of population	No indirectness

Review question	Single vs single – indirect comparison
Interventions	(n = 127) Intervention 1: Antibiotic alone - Respiratory fluoroquinolone - new. Grepafloxacin 600 mg daily. Duration 7-10 days. Concurrent medication/care: Theophylline, fenbufen, warfarin or systmeic steroids not permitted Further details: 1. Antibiotic dose: BNF/SPC concordant (Highest marketed dose). 2. Duration of treatment: 7 days or more Comments: After 7 days of treatment the investigator decided whether to stop medication (7 days of therapy) or to continue for an additional 3 days (10 days of therapy) (n = 137) Intervention 2: Antibiotic alone - Narrow spectrum beta-lactam (class 2). Amoxicillin, 500 mg tds. Duration 7-10 days. Concurrent medication/care: Theophylline, fenbufen, warfarin or systmeic steroids not permitted Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: After 7 days of treatment the investigator decided whether to stop medication (7 days of therapy) or to continue for an additional 3 days (10 days of therapy)
Funding	Study funded by industry (Otsuka America Pharmaceutical Inc)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RESPIRATORY FLUOROQUINOLONE - NEW (GREPAFLOXACIN) versus NARROW SPECTRUM BETA-LACTAM (CLASS 2; AMOXICLLIN) Protocol outcome 1: Mortality at 30 days - Actual outcome for Low severity (community setting): Mortality at up to 40 days post-treatment; Group 1: 2/127, Group 2: 0/137; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Withdrawal due to adverse events at End of treatment - Actual outcome for Low severity (community setting): Discontinuation of study treatment due to adverse events at 7-10 days; Group 1: 8/127, Group 2: 3/137; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Clinical cure at End of follow-up - Actual outcome for Low severity (community setting): Resolution or reduction in signs and symptoms that established CAP diagnosis at 28-42 days post-treatment; Group 1: 87/114, Group 2: 85/111; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Clinical cure at End of treatment; Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Hospital admission at End of follow-up; C. difficile-associated diarrhoea at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up

1.4.2.2 Single- antibiotic compared with dual-antibiotic therapy for low-severity CAP

Review question	Single- compared with dual-antibiotic therapy for low-severity CAP
Study	Rovira 1999[88]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 90)
Countries and setting	Conducted in Spain; Setting: Ambulatory patients from single hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 14 days plus follow-up to resolution
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical signs and radiographic evidence
Stratum	Low severity (formal assessment): Managed outside hospital with oral therapy based on not having complicated pneumonia on ATS criteria
Subgroup analysis within study	Not applicable
Inclusion criteria	>15 years of age, presenting at emergency department; CAP as diagnosed by acute onset of fever (>38°C) with pulmonary opacity on CXR; living in the community with no hospitalisation during the week before diagnosis
Exclusion criteria	Life-threatening diseases or a complicated course of pneumonia according to the ATS criteria, including HIV infection; pre-treatment with other antibiotics for >24h
Recruitment/selection of patients	Of 210 consecutive CAP patients screened, 101 were treated on an ambulatory basis and 90 met the inclusion criteria and consented to participate
Age, gender and ethnicity	Age - Mean (SD): 38 (15). Gender (M:F): 59/41%. Ethnicity: Not reported
Further population details	1. Age: 75 years or less (Majority were young). 2. Comorbidities: Minority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (Asthma, COPD, diabetes, high alcohol intake (>20g/day) and bronchiectasis all present in <10%;). 3. Predominant disease aetiology (including resistance profiles): No dominant pathogen (Of 25 cases (27.7%) in which aetiology was determined, 7 had *L. pneumophila*; 4 had *S. pneumoniae*; 4 had *M. pneumoniae*; 3 had influenza virus B).
Extra comments	A previous antibiotic treatment (at least one dose and less than 24-hour duration) had been administered in 31 patients (34%). The antibiotics were: amoxicillin (16%), amoxicillin + clavulanate (8%), cephalosporins (6%), erythromycin (2%), and ciprofloxacin (2%). Symptom duration before treatment was 5.2 ± 2.4 days, and fever duration was 3.9 ± 2.4 days.
Indirectness of population	No indirectness: Included patients over 15 years

Review question	Single- compared with dual-antibiotic therapy for low-severity CAP
Interventions	(n = 45) Intervention 1: Antibiotic plus antibiotic - Macrolide + broad spectrum beta-lactam. Clarithromycin 500 mg b.i.d. orally plus cefuroxime 500 mg b.i.d. orally. Duration 7 days. Concurrent medication/care: Not stated Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more (Note: shorter duration than with monotherapy). Comments: Note: duration of treatment differs between study arms. (n = 45) Intervention 2: Antibiotic alone - Macrolide. Clarithromycin 500 mg b.i.d. orally. Duration 14 days. Concurrent medication/care: Not stated Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more (Note: longer duration than with dual therapy). Comments: Note: Duration of treatment differs between study arms
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MACROLIDE (CLARITHROMYCIN) versus MACROLIDE (CLARITHROMYCIN) + CEPHALOSPORIN (CEFUROXIME) Protocol outcome 1: Mortality at 30 days - Actual outcome for Low severity (formal assessment): CAP-related mortality at Unclear; Group 1: 0/45, Group 2: 0/45; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Clinical cure at End of treatment - Actual outcome for Low severity (formal assessment): Treatment failure at 7-14 days; Group 1: 0/45, Group 2: 2/45; Risk of bias: Very high; Indirectness of outcome: Serious indirectness Protocol outcome 3: Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up - Actual outcome for Low severity (formal assessment): Pleural effusion at Unclear; Group 1: 1/45, Group 2: 0/45; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Hospital admission at End of follow-up - Actual outcome for Low severity (formal assessment): Hospital admission at Unclear; Group 1: 0/45, Group 2: 2/45; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Withdrawal due to adverse events at End of treatment; C. difficile-associated diarrhoea at End of follow-up; Clinical cure at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up

Review question	Single- compared with dual-antibiotic therapy for low-severity CAP
Study	Lee 2012[58]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n = 40)
Countries and setting	Conducted in South Korea; Setting: Single tertiary referral hospital
Line of therapy	Mixed line
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical and radiological criteria
Stratum	High severity (hospital setting): Managed in hospital based on PSI score >70 or PSI score <70 but either no improvement or worsening following prior treatment, multilobar pneumonia, lung comorbidity or an uncontrolled high fever
Subgroup analysis within study	Not applicable
Inclusion criteria	Radiological evidence of pneumonia on a chest x-ray and the presence of at least one of the following: oral temperature > 38°C or < 35.5°C, leukocytosis or >10% branded neutrophils and ability to produce sputum
Exclusion criteria	Suspected infection other than the respiratory system; suspected intolerance to study drugs; allergy or severe side effects from azithromycin, ceftriaxone, quinolones, macrolides or beta-lactams; recent hospital admission > 2 weeks before study entry; receipt of intravenous anti-bacterials within 24 h before enrollment; creatinine clearance < 20 ml/min; empyema requiring chest drainage; chronic lung disease with impaired lung function; clinical suspicion of TB; aspiration pneumonia; HIV or immunosuppression; long-term use of antiepileptic; comorbidity likely to confound clinical evaluation; receipt of any drug for other clinical experiments within 30 days; pregnancy or breastfeeding
Recruitment/selection of patients	2010 to 2011
Age, gender and ethnicity	Age - Mean (SD): Levofloxacin: 54 (20); ceftriaxone + azithromycin: 53 (16). Gender (M:F): 44/56. Ethnicity: Unclear
Further population details	1. Age: All adults 2. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (33% CVD, 28% alcohol consumers, 22% pulmonary disorders, 17% diabetes). 3. Predominant disease aetiology (including resistance profiles): *Streptococcus pneumoniae* (Of 11 identified pathogens, 6 (54.5%) were S. *pneumoniae*).
Extra comments	PSI class 1-2: levofloxacin - 71%; ceftriaxone + azithromycin - 53%; bilateral or multifocal consolidation: levofloxacin - 59%; ceftriaxone + azithromycin - 32%
Indirectness of population	Serious indirectness: Limited to those able to produce sputum
Interventions	(n=20) Intervention 1: Antibiotic alone - Respiratory fluoroquinolone - new. Levofloxacin 750 mg intravenously once daily,

Review question	Single- compared with dual-antibiotic therapy for low-severity CAP
	followed by the same dose orally at discharge when clinically improved. Duration Mean 11.8 days. Concurrent medication/care: Unclear - not stated Further details: 1. Antibiotic dose: High 2. Duration of treatment: 7 days or more (n=20) Intervention 2: Antibiotic plus antibiotic - Azithromycin + cephalosporin. Ceftriaxone 2.0 g intravenously once daily plus oral azithromycin 500 mg for 3 consecutive days, followed by oral cefpodoxime 200 mg per day at discharge after clinical improvement. Duration Mean 12.0 days. Concurrent medication/care: Unclear - not stated Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Funding	Study funded by industry (Daiichi Sankyo Korea Co. Ltd)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RESPIRATORY FLUOROQUINOLONE - NEW versus AZITHROMYCIN + CEPHALOSPORIN

Protocol outcome 1: Clinical cure at End of treatment
- Actual outcome for High severity (hospital setting): Clinical cure: no further antibacterials required; no remaining symptoms at Mean 12 days; Group 1: 16/17, Group 2: 16/19; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Withdrawal due to adverse events at End of treatment
- Actual outcome for High severity (hospital setting): Withdrawal or treatment discontinuation due to adverse events at Mean 12 days; Group 1: 3/20, Group 2: 1/20; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up
- Actual outcome for High severity (hospital setting): Pleural effusion at Mean 12 days; Group 1: 0/20, Group 2: 1/20; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at 30 days; Hospital admission at End of follow-up; *C. difficile*-associated diarrhoea at End of follow-up; Clinical cure at End of follow-up; Length of hospital stay at End of follow-up; Withdrawal due to adverse events at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up

1.4.3 Moderate – to high-severity CAP

1.4.3.1 Single- compared with other single- antibiotic therapy for moderate- to high-severity CAP

1.4.3.1.1 Patient characteristics, interventions and study design

Review question	Single compared with single antibiotic therapy for moderate- to high-severity CAP
Study	Nicolle 1996[79]
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Hoffman-La Roche Canada Inc)
Number of studies (number of participants)	1 (N = 37)
Countries and setting	Conducted in Canada; Setting: Geriatric wards of 2 acute care geriatric hospitals and 2 long-term care facilities in Manitoba
Line of therapy	1st line
Duration of study	Intervention + follow up: Up to 15 days after therapy
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinical and radiological confirmation
Stratum	Moderate to high severity (formal assessment): 'Moderate-to-severe'
Subgroup analysis within study	Not applicable
Inclusion criteria	Long-term care facility residents with radiologically documented moderate-to-severe pneumonia and required parenteral therapy based on clinical assessment of degree of illness (e.g. fever, leucocytosis, functional deterioration, potential inability to cooperate with oral medication regimen); age ≥ 65 years and at least one of: new or increased cough, altered functional state, new or worsened confusional state, fever > 37.2°C orally or 37.5°C rectally, hypothermia with rectal temperature < 36°C, increased quantity or change in colour of sputum, chills, localised pulmonary findings on physical examination; apical heart rate > 100 beats/min, or new or increased number of falls.
Exclusion criteria	Receipt of effective antibiotic within 72 hours of study admission, allergy to study drugs, requiring concomitant antimicrobial therapy, serum creatinine > 200 µg/l, pre-treatment bilirubin or aspartate aminotransferase levels 3-times normal, enrolment in study within prior 6 months, or survival for 72 h considered unlikely
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): Ampicillin: 83.2 (7.6); ceftriaxone: 81.6 (7.8). Gender (M:F): 50/50%. Ethnicity: Unclear
Further population details	1. Age: Over 75 years (All over 65 years). 2. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease

	[including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (COPD (32%), congestive heart disease (32%), cerebrovascular disease (29%), ischaemic heart disease (22%), hypertension (19%), arrhythmia (19%), chronic renal failure (19%)). 3. Predominant disease aetiology (including resistance profiles): No dominant pathogen (Only 8 patients had identified pathogens).
Extra comments	All from long-term care facilities; 50% of those screened not included
Interventions	Intervention 1: Antibiotic plus placebo ~ Cephalosporin + placebo. Ceftriaxone 1g IV daily, plus two daily infusions of saline. After 4 days an assessment was made to determine whether to intensify, maintain or modify to oral therapy. Duration 7 days or more (mean: 8.1 days). Concurrent medication/care: Concomitant antimicrobials not permitted (N = 17) Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Note: 2-4 g daily is recommended for severe infections Intervention 2: Antibiotic alone ~ Narrow spectrum beta-lactam (class 2). Ampicillin 1 g IV every 8 hours. After 4 days an assessment was made to determine whether to intensify, maintain or modify to oral therapy (could be switched to oral amoxicillin if considered appropriate). Duration Mean: 10.2 days. Concurrent medication/care: Concomitant antimicrobials not permitted(N = 20) Further details: 1. Antibiotic dose: High (Single 1 g dose). 2. Duration of treatment: 7 days or more Comments: Not licenced dosing regimen - should be 500 mg every 4-6 hours
Study	Roson 2001[87]
Study type	RCT (Patient randomised; Parallel)
Funding	Academic or government funding
Number of studies (number of participants)	1 (N = 378)
Countries and setting	Conducted in Spain; Setting: University hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: up to 1 month after discharge

Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Signs and symptoms plus chest x-ray
Stratum	Moderate to high severity (formal assessment)
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults hospitalised with moderate to severe CAP, defined as an acute respiratory illness associated with one or more of the following: fever or hypothermia, cough, sputum production, pleuritic chest pain, dyspnoea, altered breath sounds on auscultation; plus the presence of a new infiltrate on a chest radiograph. CAP considered moderate-to-severe when one or more of the following criteria were met: age ≥ 70 years; PaO_2 < 60 mmHg or PaO_2/FiO_2 < 300; multilobar radiological involvement; hypotension or shock; and underlying disease such as alcoholism, COPD, congestive heart failure, renal failure, splenectomy and diabetes mellitus
Exclusion criteria	Unwillingness to enter the study, age ≥ 16 years, hypersensitivity to beta-lactam antibiotics, pregnancy or breast-feeding, immunosuppression (AIDS, end-stage neoplasia, cytotoxic therapy, absolute neutropenia or transplantation)
Recruitment/selection of patients	Prospective recruitment Feb 1995 - May 1997
Age, gender and ethnicity	Age - Mean (SD): Co-amoxiclav: 66; ceftriaxone: 67 years. Gender (M:F): Co-amoxiclav: 66.8/33.2%; ceftriaxone: 74.2/25.8%. Ethnicity: Not stated
Further population details	1. Age: All adults (from age 16 years). 2. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (70.7% and 75.8% had underlying disease in each group (type not specified, but included cancer, COPD, chronic heart disease and diabetes)). 3. Predominant disease aetiology (including resistance profiles): *S. pneumoniae* (Of 154 identified pathogens, 116 (75%) were *S. pneumoniae*; 28 (18%) were *H. influenzae*. Approximately 89% of isolated pathogens were susceptible to the study drugs).
Extra comments	Excluded those suspected of having Legionella or atypical pneumonia; prior antibiotic therapy had been received in 18%; 59% were PSI class IV or V; 5.6% had empyema and 12.2% bacteraemia
Interventions	Intervention 1: Antibiotic alone ~ Beta-lactamase stable penicillin. Co-amoxiclav IV 2 g/200 mg every 8 hours for at least 72 hours, followed by oral co-amoxiclav 1 g/125 mg every 8 hours (after significant clinical improvement was achieved). Duration Mean: 10.9 days. Concurrent medication/care: Erythromycin IV was received as combination therapy in 9.2% of patients. No other antibiotics were allowed(N = 184) Further details: 1. Antibiotic dose: High (Double the recommended dose of the amoxicillin component, but would expect recommended doses to achieve similar results based on likely pathogens and their MICs). 2. Duration of treatment: 7 days or more

	Intervention 2: Antibiotic alone ~ Cephalosporin. Ceftriaxone IV 1 g every 24 hours for at least 72 hour followed by IM ceftriaxone 1 g every 24 hours. Duration Mean 10.1 days. Concurrent medication/care: Erythromycin IV was received as combination therapy in 12.9% of patients. No other antibiotics were allowed(N = 194) Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more

1.4.3.1.2 Results

Dichotomous

Roson 2001[87]			All-cause mortality @ within 30 days of hospitalisation For group with proven pneumococcal pneumonia: ceftriaxone - 7/63 (11.1%); amoxicillin-clavulanate - 5/53 (9.4%)		Cure: clinical signs disappeared and radiological improvement @ 24-48 h after completion of therapy For group with proven pneumococcal pneumonia: ceftriaxone - 56/63; amoxicillin-clavulanate - 48/53		Treatment discontinuation due to adverse events @ unclear		Empyema @ up to 1 month after discharge		ICU admission @ unclear			
	194	184	17/194	19/184	157/194	146/184	Reported as general data	Reported as general data	11/194	10/184	14/194	14/184	NR	NR
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**		**Withdrawal due to adverse events @ End of follow-up**									
Roson 2001[87]			Cure: clinical and radiological resolution @ up to 1 month after discharge											
	194	184	144/194	136/184	NR	NR								
Stratum: High severity (formal assessment) CAP. Comparison: Cephalosporin + placebo vs narrow spectrum beta-lactam (class 2)														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion,**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of**	

								abscess, metastatic infection) @ End of follow-up				**follow-up**	
Nicolle 1996[79]			Mortality @ up to 15 days post-treatment Ceftriaxone: one died of renal failure and pneumonia within 4 days. Ampicillin: one died within 4 days despite showing initial improvement; one died of congestive heart failure after relapse of pneumonia.										*C. difficile* infection @ up to 15 days post-treatment	
	17	20	1/17	2/20	NR	NR	NR	NR	NR	NR	NR	NR	2/17	1/20
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**		**Withdrawal due to adverse events @ End of follow-up**									
Nicolle 1996[79]			Cure: resolution of initial infection with no recurrence during follow-up @ 10-15 days post-treatment Ceftriaxone: 1 early (96 h) failure; ampicillin: 4 early (96 h) failures and 2 post-therapy relapses											

	17	20	16/17	14/20	NR	NR								
Stratum: High severity (hospital setting). Comparison: Cephalosporin vs beta-lactamase stable penicillin														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	

Continuous

Study	**Exp**	**Ctrl**	**Exp**	**Ctrl**
Stratum: Moderate to high severity (formal assessment). Comparison: Cephalosporin vs beta-lactamase stable penicillin				
Protocol outcomes -->	**Numbers Randomised**		**Length of hospital stay @ End of follow-up**	
Roson 2001[87]			Length of hospital stay @ until discharge For group with proven pneumococcal pneumonia: ceftriaxone - 12.7 ± 13.0 days; amoxicillin-clavulanate - 9.5 ± 5.0 days	
	194	184	11.3 (SD not stated); n = 194	10.7 (SD not stated); n = 184

General

Study	**Exp**	**Ctrl**	**Exp vs Ctrl**	**Exp vs Ctrl**
Stratum: Moderate to high severity (formal assessment). Comparison: Cephalosporin vs beta-lactamase stable penicillin				
Protocol outcomes -->	**Numbers Randomised**		**Withdrawal due to adverse events @ End of treatment**	**Length of hospital stay @ End of follow-up**
Roson 2001[87]			Treatment discontinuation due to adverse events @ unclear	Length of hospital stay @ until discharge For group with proven pneumococcal pneumonia: ceftriaxone - 12.7 ± 13.0 days; amoxicillin-clavulanate - 9.5 ± 5.0 days
	194	184	Proportion Overall 2 patients stopped treatment due to adverse	Reported on continuous

			events but the group was unclear	

1.4.3.2 Single- compared with dual- antibiotic therapy

1.4.3.2.1 Patient characteristics, interventions and study design

Review question	**Single- compared with dual-antibiotic therapy for CAP**
Study	Fogarty 2004[40]
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Ortho-McNeil Pharmaceutical)
Number of studies (number of participants)	1 (N = 269)
Countries and setting	Conducted in USA; Setting: 33 centres
Line of therapy	Unclear
Duration of study	Intervention + follow up: 7-14 days treatment plus 1 month post-treatment
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis ~ Signs and symptoms of CAP (radiological evidence not required at baseline)
Inclusion criteria	Adult patients with signs and symptoms of CAP who met ≥ 3 American Thoracic Society criteria for inpatient treatment. Either required mechanical ventilation, or had ≥ 2 of the following: fever (oral temperature, ≥ 39°C) or hypothermia (oral temperature, ≤ 35.5°C), a respiratory rate of 130 breaths/min, systolic hypotension (systolic blood pressure, < 90 mm Hg), a pulse rate of ≥ 130 beats/min, and/or altered mental status.
Exclusion criteria	Immunosuppression, hospitalized within 14 days of inclusion in the study, infection with a known or suspected resistant organism, either had or were at high risk for Pseudomonas infection, or had known or suspected meningitis
Recruitment/selection of patients	December 1997-March2000
Age, gender and ethnicity	Age - Mean (SD): 60.7 (17.37). Gender (M:F): 68/32%. Ethnicity: 66.5% white, 29.0% black, 1.9% Asian, 2.6% other
Further population details	1. Age: All adults 2. Comorbidities: Not stated or unclear 3. Predominant disease aetiology (including resistance profiles): Streptococcus pneumoniae
Extra comments	Mean APACHE II score at baseline: 15.9 (6.33). Nursing home patients were eligible for participation. 2 patients randomised to levofloxacin received combination therapy and were analysed in that group

Review question	Single- compared with dual-antibiotic therapy for CAP
Intervention 1	Antibiotic plus antibiotic ~ Macrolide + broad spectrum beta-lactam. Ceftriaxone sodium, 1–2 g iv or IM q24h, with erythromycin, 500–1000 mg iv q6h, and then switched to amoxicillin-clavulanate, 875 mg PO b.i.d., with clarithromycin, 500 mg PO b.i.d. Duration 7-14 days. Concurrent medication/care: Not stated (N = 135)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Comments	The switch from IV to oral therapy and hospital discharge were at the investigators discretion on the basis of signs of clinical improvement
Intervention 2	Antibiotic alone ~ Respiratory fluoroquinolone - new. Levofloxacin, 500 mg iv, followed by oral administration, q24h. Duration 7–14 days. Concurrent medication/care: Not stated (N = 134)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Comments	The switch from IV to oral therapy and hospital discharge were at the investigators discretion on the basis of signs of clinical improvement
Study	Frank 2002[41]
Study type	RCT (Patient randomised; Parallel)
Funding	Principal author funded by industry (Ortho-McNeil Pharmaceuticals)
Number of studies (number of participants)	1 (N = 236)
Countries and setting	Conducted in USA; Setting: Multicentre; hospitals
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 days treatment plus 2-7 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinical signs plus CXR; HAP excluded
Inclusion criteria	Patients aged ≥ 18 years; diagnosis of moderate to severe pneumonia acquired in the community or in a nursing home. The diagnostic criteria included (1) characteristic clinical signs, including ~1 of the following-fever (oral temperature > 38°C), hypothermia (oral temperature < 35.5°C), leukocytosis (> 10,000 white blood cells/mm3), or bands > 10%; (2) radiologic evidence of pneumonia (an acute infiltrate consistent with pneumonia on chest radiography); (3) collection of a mucopurulent sputum

Review question	Single- compared with dual-antibiotic therapy for CAP
	specimen for culture and Gram's staining within 24 hours before study drug administration; and (4) a Fine risk score of 71 to 130 (indicative of moderate to severe disease and associated need for hospitalization) at study inclusion. Patients who had received previous antimicrobial therapy for any infection were allowed to participate if the total duration of previous therapy was ≤ 24 hours or the patient had received > 72 hours of therapy but was classified as a treatment failure.
Exclusion criteria	Infection caused by a pathogen known or suspected to be resistant to any of the study drugs before their admission to the study; prior allergic reaction or serious adverse reaction to levofloxacin, azithromycin, ceftriaxone, or any other member of the quinolone, macrolide, or beta-lactam class of antimicrobial agents; hospitalized within 2 weeks before study entry (or within 1 month before study entry if antimicrobial therapy had been administered during this time), or life expectancy was ~72 hours; creatinine clearance < 20 mL/min; empyema or the presence of pleural fluid requiring an indwelling chest tube; pneumonia due to aspiration of gastric contents; HIV infection, with a CD4 cell count < 200/cm^3; presence of any seizure disorder or a psychiatric condition requiring chronic use of tranquilizers; or presence of any disease or disorder that could interfere with evaluation of the study treatments; receipt of any experimental drug within 30 days before study entry
Recruitment/selection of patients	Pneumonia acquired in the community or in a nursing home requiring hospital treatment
Age, gender and ethnicity	Age - Mean (SD): 67.6 (13.1). Gender (M:F): Levofloxacin: 66/34%; Comparator: 77/23%. Ethnicity: Majority white
Further population details	1. Age: All adults 2. Comorbidities: Not stated or unclear (29% current smokers). 3. Predominant disease aetiology (including resistance profiles): *Streptococcus pneumoniae* (Of 68 microbiologically evaluable patients, *S. pneumoniae* was isolated in 29 patients and *H. influenzae* in 22).
Extra comments	Duration of illness at baseline 7.3 days; Fine risk score 91.3 (range: 61-136) and 95.8 (range: 62-149) in mono and dual arms, respectively
Intervention 1	Antibiotic plus antibiotic ~ Macrolide + broad spectrum beta-lactam. Azithromycin 500 mg IV q24h for 2 days plus ceftriaxone 1 g IV q24h for ≥ 2 days, followed by an optional transition to azithromycin 500 mg PO q24h at the investigator's discretion. Duration 10 days. Concurrent medication/care: Systemic glucocorticosteroids not permitted unless already instituted for an unrelated condition (N = 121)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Comments	Duration of IV treatment: mean = 3.83 days (plus 2.36 days ceftriaxone)
Intervention 2	Antibiotic alone ~ Respiratory fluoroquinolone - new. Levofloxacin 500mg PO or IV q24h. Duration 10 days. Concurrent medication/care: Systemic corticosteroids not permitted unless already instituted for an unrelated condition (N = 115)

Review question	Single- compared with dual-antibiotic therapy for CAP
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Comments	Duration of IV treatment: mean = 3.67 days
Study	Leroy 2005[61]
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Unclear statement that the sponsor was involved in study design)
Number of studies (number of participants)	1 (N = 398)
Countries and setting	Conducted in France, South Africa, Tunisia; Setting: ICUs
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 10 to 14 days treatment (or up to 21 days in cases due to *Legionella* or associated with purulent pleurisy); plus follow-up of 21-45 days post-treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Pulmonary infiltrate (at presentation or within 48 h of admission) plus clinical signs
Inclusion criteria	Adults (i.e. age > 18 years) with severe CAP requiring ICU admission. CAP was defined by the presence of a new radiographic pulmonary infiltrate seen at the initial presentation or occurring within 48 h following hospitalization, and associated with a total leukocyte count of > 10,000 cells/µL or < 4,500 cells/µL and fever (oral or axillary or inguinal temperature of > 38°C, or rectal or aural temperature of > 38.5°C), plus at least one of the following clinical signs: cough of recent onset or recently exacerbated; purulent sputum of recent appearance; dyspnoea; chest pain; crackling rales; and/or signs of consolidation on pulmonary auscultation. The severity of CAP, justifying admission to the ICU, was confirmed by the presence either of a major criterion or two minor criteria. A major criterion was a PaO_2/fraction of inspired oxygen (FiO_2) ratio of < 250 mm Hg requiring invasive or non-invasive ventilation. Minor criteria were a respiratory rate of > 30 breaths/min, PaO_2 of < 60 mm Hg, or $PaCO_2$ of > 50 mm Hg at an FiO_2 of 0.21, a chest radiographic involvement of more than a single lobe, and altered mental status.
Exclusion criteria	Hospitalisation during the previous month, admitted from a nursing home, developed pneumonia > 48 h after hospital admission, or previously received antibiotic therapy for this CAP episode, presence of a CAP-causative pathogen known to be resistant to the antibiotics used in the study, infectious disease requiring concomitant antimicrobial treatment, septic shock prior to study inclusion, life expectancy of < 2 days, underlying terminal malignancy, cystic fibrosis, or suspected active tuberculosis, CD4 cell count of < 50 cells/µL secondary to HIV infection, immunosuppression (i.e. leukocyte count, < 1,000 cells/µL or on-going radiation treatment), hypersensitivity, or contraindications to any study medication. Patients who were unlikely to comply with the protocol requirements, having participated in another study or having taken another investigational drug in the month prior to study inclusion, or those not meeting the legal requirements for participation in an investigational study were also excluded

Review question	Single- compared with dual-antibiotic therapy for CAP
Recruitment/selection of patients	Prospective, multicentre, multinational study
Age, gender and ethnicity	Age - Mean (SD): Mono group: 59.8 ± 17.4; dual group: 59.5 ± 16. 2. Gender (M:F): Mono group: 70.5/29.5%; dual group: 66.0/34.0%. Ethnicity: Unclear
Further population details	1. Age: All adults (45.8% > 65 years). 2. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (Cardiac failure: 10.1%; Chronic respiratory failure: 35.1%; Diabetes mellitus: 16.6%; Neoplasm: 4.9%). 3. Predominant disease aetiology (including resistance profiles): *Streptococcus pneumoniae* (Of 55% who had organism identified, 40% had *S. pneumoniae*).
Extra comments	Duration of symptoms before enrolment was 4.1 days. Out-patients who had been treated for > 48h with antibiotics and admitted to ICU due to lack of response were included (17.5% had failed a prior antibiotic). In the mono group, there were four cases of nosocomial pneumonia, for which the causative organisms were methicillin-resistant *S. aureus* (n = 2) and *Pseudomonas aeruginosa* (n = 2). In the dual group, six patients exhibited nosocomial pneumonia due to methicillin-resistant *S. aureus* (n = 2) and *P. aeruginosa* (n = 4).
Intervention 1	Antibiotic plus antibiotic ~ Respiratory fluoroquinolone (old) + broad spectrum beta-lactam. 1 g cefotaxime by IV infusion over 20 to 60 min tid and 200 mg ofloxacin by IV infusion over 60 min bid. Oral ofloxacin was administered as a 200-mg tablet bid. A switch to monotherapy was possible when the identified causal organism was either *S pneumoniae* (ofloxacin therapy could be stopped) or *Legionella* sp (cefotaxime therapy could be stopped). Duration 10-14 days (up to 21 days if Legionella or purulent pleurisy). Concurrent medication/care: None stated (N = 202)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Comments	Switch to oral therapy was allowed once deemed possible for ofloxacin
Intervention 2	Antibiotic alone ~ Respiratory fluoroquinolone - new. 500 mg levofloxacin by IV infusion over 60 min bid. Thereafter, levofloxacin could be given as a 500-mg tablet bid. Duration 10-14 days (up to 21 days if Legionella or purulent pleurisy). Concurrent medication/care: None stated (N = 196)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Comments	Switch to oral therapy was allowed once deemed possible

Review question	Single- compared with dual-antibiotic therapy for CAP
Study	Lin 2007[64]
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Daiichi Pharmaceutical Co. Ltd.)
Number of studies (number of participants)	1 (N = 50)
Countries and setting	Conducted in Taiwan; Setting: 3000 bed tertiary teaching hospital in Taiwan
Line of therapy	1st line (< 24 hour prior antibiotics)
Duration of study	Intervention + follow up: 7 to 14 days intervention plus 1 month post-therapy
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinical signs and chest X-ray
Inclusion criteria	Aged ≥ 18 years with a diagnosis of pneumonia acquired in the community and had admitted to hospital. Diagnostic criteria were: (1) characteristic clinical signs, including ≥ 1 of the following: (a) fever (oral temperature ≥ 38°C) or hypothermia (≤ 35°C), (b) leukocytosis (> 10,000 white blood cells/mm3) or bands > 10%; (2) acute infiltrate consistent with pneumonia on chest radiography; (3) at least one respiratory symptom: (a) cough or increasing cough severity, (b) purulent sputum/acute change in the quality of sputum, (c) dyspnoea.
Exclusion criteria	(1) Previous allergic or serious adverse reaction to levofloxacin, clarithromycin, amoxicillin/clavulanate or any members of the fluoroquinolone, beta-lactam or macrolide classes of antimicrobials; (2) severe renal failure (creatinine clearance < 20 ml/min); (3) neutropenia (< 500 polymorphonuclear cells (PMNs)/mm^3); (4) unstable psychiatric conditions; (5) pregnancy or nursing; (6) use of study drugs within 30 days prior to entry into the study; (7) previous antimicrobial therapy, other than study drug, taken for more than 24 hours; (8) anticipated requirement for the initiation of systemic corticosteroids, unless such therapy was already being prescribed for an unrelated medical condition. Further exclusions included: those with healthcare-associated pneumonia (HCAP), including any patient who was hospitalized in an acute care hospital for two or more days within 90 days of the infection; anyone residing in a nursing home or long-term care facility; anyone receiving intravenous antibiotic therapy, chemotherapy or wound care within the past 30 days of the current infection; anyone attending a haemodialysis clinic.

Review question	Single- compared with dual-antibiotic therapy for CAP
Recruitment/selection of patients	Analysis performed before calculated sample size reached
Age, gender and ethnicity	Age - Mean (SD): Mono: 65.3 ± 13.2; dual: 71.0 ± 11.4. Gender (M:F): Mono: 65.2/34.8%; dual: 81.8/18.2%. Ethnicity: Unclear
Further population details	1. Age: All adults (Nearly 70% > 65 years). 2. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (91% had at least 1 comorbidity. Chronic pulmonary disease (56.5 / 36.4%); renal insufficiency 8.7 / 10.0%; liver disease (17.4 / 9.1%); CVD (13.0 / 9.1 %); diabetes (17.4 / 45.5%); malignancy (4.3 / 22.7%); alcoholism (13.0 / 0.0%); smoker or ex-smoker (60.9 / 59.1%)). 3. Predominant disease aetiology (including resistance profiles): No dominant pathogen (Microbiological success rate 60.0% in mono and 35.3% in dual; of the 33 microbiologically evaluable patients 15% (N = 5) had *S. pneumoniae*, 15% *Klebsiella pneumoniae* and 15% *Pseudomonas*. Other pathogens present in > 1 case included *E. coli, H. parainfluenzae, A. baumanniiq, S. aureus* and *H. influenzae*.).
Intervention 1	Antibiotic plus antibiotic ~ Macrolide + broad-spectrum beta-lactam. Amoxicillin/clavulanate 500 mg/100 mg IV q8h with oral clarithromycin 500 mg q12h and then switched to oral amoxicillin/clavulanate 250 mg/125 mg q8h with oral clarithromycin 500 mg q12h. Duration 7 to 14 days. Concurrent medication/care: Not stated - see exclusion criteria (N = 24)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Comments	General guidelines for switching to the oral regimen of the study medication include: (1) cough and respiratory distress are improving; (2) patient has been afebrile for a minimum of 8 hours; (3) the white blood cell count is returning to normal; (4) there is no evidence of abnormal gastrointestinal absorption
Intervention 2	Antibiotic alone ~ Respiratory fluoroquinolone - new. Levofloxacin 500 mg IV q24h transitioning to oral levofloxacin 500 mg q24h when the patients' condition was compatible. Duration 7 to 14 days. Concurrent medication/care: Not stated - see exclusion criteria (N = 26)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Comments	General guidelines for switching to the oral regimen of the study medication include:

Review question	Single- compared with dual-antibiotic therapy for CAP
	(1) cough and respiratory distress are improving; (2) patient has been afebrile for a minimum of 8 hours; (3) the white blood cell count is returning to normal; (4) there is no evidence of abnormal gastrointestinal absorption
Study	Torres 2008[100]
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Bayer HealthCare AG)
Number of studies (number of participants)	1 (N = 738)
Countries and setting	Conducted in Unknown multicentre; Setting: Hospital
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 7 to 14 days treatment plus 21 to 28 days post-treatment follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Radiological evidence and clinical signs and symptoms
Inclusion criteria	Radiological confirmation of the presence of infiltrates consistent with bacterial pneumonia. All of the following signs and symptoms of pneumonia: Fever (core, rectal, or tympanic temperature, ≥ 38.5°C; or axillary, oral, or cutaneous temperature, ≥ 38.0°C) or hypothermia (core, rectal, or tympanic temperature, ≤ 35.5°C; or axillary, oral, cutaneous temperature, ≤ 35.0°C). WBC count, > 10,000 cells/µL; ≥ 15% immature neutrophils (bands, regardless of WBC count); or WBC count, < 4500 cells/µL. Two or more of the following signs and symptoms: cough, purulent sputum production, dyspnoea or tachypnoea (respiratory rate, > 20 breaths/min), rigors and chills, chest pain, auscultatory findings on pulmonary examination of rales/crackles, and/or evidence of pulmonary consolidation.
Exclusion criteria	Patient pregnant or lactating; Hospitalization for > 48 h before development of pneumonia or discharge from hospital < 30 days before enrolment; Receipt of systemic antibacterial therapy for ≥ 24 h within 7 days before enrolment, unless treatment failure was deemed to have occurred after receiving an antibacterial regimen that did not contain a fluoroquinolone or a third-generation cephalosporin for ≥ 48 h; Need for concomitant systemic antibacterial agents; Tuberculosis or endemic fungal infection; Rapidly fatal underlying disease (death expected within 6 months); Structural lung disease (e.g., cystic fibrosis, bronchiectasis, lung cancer, or other conditions predisposing to nosocomial infection) or lung abscess; Plural empyema and risk factors for aspiration pneumonia (e.g., recent stroke, head injury, or dementia); Neutropenia (absolute neutrophil count, < 1000 cells/µL) due to receipt of immunosuppressive therapy or malignancy; AIDS (CD4 count, < 200 cells/µL, or HIV seropositivity in patients receiving HAART); Severe hepatic impairment (Child Pugh classification C); Renal failure (creatinine clearance, < 10 mL/min) or need for renal dialysis; History of epilepsy; Glucose-6-phosphate deficiency; Uncorrected hypokalaemia; Known

Review question	Single- compared with dual-antibiotic therapy for CAP
	congenital or acquired QTc prolongation; Concomitant use of drugs known to increase the QTc interval; Known hypersensitivity to study medications; Clinically relevant bradycardia; Clinically relevant heart failure with reduced ventricular ejection fraction; Previous history of symptomatic arrhythmias
Recruitment/selection of patients	Prospective; 7 were nursing home residents
Age, gender and ethnicity	Age - Mean (SD): Mono: 66.0 ± 16.2; dual 64.8 ± 16.7. Gender (M:F): Mono: 65.6/34.4%; dual: 59.0/41.0%. Ethnicity: Europe, Latin America and South Africa
Further population details	1. Age: All adults (60% ≥ 65 years; 34% ≥ 75 years). 2. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (31.5% cardiac disorders; 34.5% respiratory disorders; 19.0% diabetes; 7.9% renal failure/impairment). 3. Predominant disease aetiology (including resistance profiles): *S. pneumoniae* (Of 44% with identified pathogen; 30.8% had *S. pneumoniae*).
Extra comments	92 of those randomised were later found to violate the inclusion/exclusion criteria (but were included in the ITT analysis). Baseline characteristics (mono vs dual). Duration of symptoms prior to study entry: Mean (SD) 5.0 (3.5) vs 4.6 (2.8); Previous systemic antimicrobial treatment: 114 (39.2) 110 (39.6); Failure of previous systemic antimicrobial treatment: 39 (13.4) 40 (14.4); Pneumonia Severity Index score III: 122 (41.9) 111 (39.9); IV: 138 (47.4) 134 (48.2); V: 31 (10.7) 33 (11.9); IV/V: 169 (58.1) 167 (60.1); ICU admission: 25 (8.6) 30 (10.8)
Intervention 1	Antibiotic plus antibiotic ~ Respiratory fluoroquinolone + broad spectrum beta-lactam. Intravenous ceftriaxone (2 g once per day) plus sequential intravenous and oral levofloxacin (500 mg twice per day). The levofloxacin dosage was adjusted in patients with renal impairment, as recommended by the product prescribing information by the hospital pharmacist. After 3 days of intravenous therapy with levofloxacin, patients could be switched to oral therapy at the discretion of the investigator if the prescribed improvement criteria (reduction in severity and/or number of signs and symptoms of infection) had been fulfilled. Duration 7-14 days. Concurrent medication/care: No concomitant systemic antimicrobial therapy allowed (N = 367)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Comments	Median duration of IV therapy 6 days
Intervention 2	Antibiotic plus placebo ~ Respiratory fluoroquinolone (new) + placebo. Sequential intravenous and oral moxifloxacin (400 mg once per day). After 3 days of intravenous therapy patients could be switched to oral therapy at the discretion of the investigator if the prescribed improvement criteria (reduction in severity and/or number of signs and symptoms of infection) had been fulfilled No dosage adjustments made. Duration 7-14 days. Concurrent medication/care: No concomitant systemic antimicrobial therapy

Review question	Single- compared with dual-antibiotic therapy for CAP
	allowed (N = 371)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Comments	Median duration of IV therapy 5 days
Study	Vergis 2000[105]
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Part funded by Pfizer)
Number of studies (number of participants)	1 (N = 169)
Countries and setting	Conducted in USA; Setting: Four medical centres
Line of therapy	Unclear
Duration of study	Intervention + follow up: 7-10 days treatment plus up to 5 weeks post-treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Chest radiograph plus signs and symptoms
Inclusion criteria	Adults (aged ≥ 18 years) hospitalized with a primary diagnosis of community-acquired pneumonia. Community-acquired pneumonia was defined as (1) a new pulmonary infiltrate compatible with pneumonia by chest radiograph and confirmed by a radiologist; and (2) 1 or more signs and symptoms consistent with a lower respiratory tract infection, including temperature greater than 38°C, new or increased cough, production of purulent sputum, crackles, rhonchi, or pleuritic chest pain or dyspnoea; or (3) an elevated white blood cell count (> 10 × 109/L) or greater than 0.15 band forms.
Exclusion criteria	Known hypersensitivity to β-lactam or macrolide antibiotics, presence of gastrectomy or other condition affecting drug absorption, receipt of chemotherapy or other immunosuppressive therapy at time of pneumonia onset, known acquired immunodeficiency syndrome, severe renal impairment (creatinine clearance < 0.42 mL/s [< 25 mL/min]), neutropenia (< 0.5 × 109/L), hospitalization within the preceding 14 days, or nursing home residence; also if received treatment with an antibiotic other than the study drugs within 24 hours before enrolment.
Recruitment/selection of patients	Prospective; 1994-1996
Age, gender and ethnicity	Age - Mean (SD): Not stated. Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	1. Age: All adults (Stratified before randomisation to those aged less than 65 years and those 65 years or more).

Review question	Single- compared with dual-antibiotic therapy for CAP
	2. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (Azithromycin group: cigarette smoking in 51% (34/67), chronic obstructive lung disease in 37% (25/67), coronary artery disease in 22% (15/67), type 2 diabetes mellitus in 18% (12/67), chronic alcoholism in 16% (11/67), and ulcer disease in 15% (10/67). Cefuroxime-erythromycin group: cigarette smoking in 56% (44/78), chronic obstructive lung disease in 35% (27/78), coronary artery disease in 36% (28/78), type 2 diabetes mellitus in 15% (12/78), chronic alcoholism in 14% (11/78), and ulcer disease in 17% (13/78).). 3. Predominant disease aetiology (including resistance profiles): *S. pneumoniae* (Of 59% with pathogen(s) identified, the most common were *S. pneumoniae* found in 28 (33%), *L. pneumophila* in 20 (24%), *H. influenzae* in 19 (22%), *C. pneumoniae* in 15 (18%) and *M. pneumoniae* in 13 (15%)).
Intervention 1	Antibiotic plus antibiotic ~ Macrolide + broad spectrum beta-lactam. Cefuroxime combined with erythromycin. Cefuroxime was administered intravenously at a dosage of 750 mg every 8 hours for 2 to 7 days, followed by cefuroxime axetil at a dosage of 500 mg orally twice daily to complete a total of 7 to 10 days of therapy. In addition, erythromycin lactobionate or erythromycin base at a dosage of 500 to 1000 mg was given intravenously or orally every 6 hours and continued for up to 21 days. The decision to switch to oral therapy was made on the basis of improvement in cough, diminution in purulent sputum production, defervescence, and reduction in leukocytosis. Duration 7 to 10 days. Concurrent medication/care: None stated (N = 86)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Comments	Average duration was 10 days
Intervention 2	Antibiotic alone ~ Macrolide. Azithromycin dihydrate administered intravenously as a 1-hour infusion at a dosage of 500 mg once daily for 2 to 5 days, followed by 500 mg orally to complete a total of 7 to 10 days of therapy. The decision to switch to oral therapy was made on the basis of improvement in cough, diminution in purulent sputum production, defervescence, and reduction in leukocytosis. Duration 7-10 days. Concurrent medication/care: None stated (N = 83)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Comments	Average duration was 8 days
Study	Vetter 1997[106]
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Abbott Laboratories)
Number of studies (number of	1

Review question	Single- compared with dual-antibiotic therapy for CAP
participants)	(N = 235)
Countries and setting	Conducted in Austria, Canada, Irish Republic, Netherlands, Spain, Switzerland, United Kingdom; Setting: Hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 days + 4-6 weeks post-treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Radiological evidence plus clinical signs and symptoms
Inclusion criteria	Aged 18 years or older, requiring hospital admission and IV treatment, diagnosis of CAP based on radiological evidence plus clinical signs and symptoms consistent with CAP, including at least 2 of the following: cough, sputum colour or consistency indicative of an acute bacterial infection, pyrexia, development of or increase in chest discomfort/congestion, dyspnoea, crackles, wheeze or cyanosis
Exclusion criteria	Active TB; immunocompromised; infection requiring concomitant antibacterial; history of hypersensitivity to macrolide or cephalosporin; treatment with study drug within 4 weeks of study; history of severe renal or hepatic impairment or disease; pregnancy, risk of pregnancy or lactation; any condition that would interfere with completion if the study; treatment with a long-acting injectable antibiotic within 6 weeks prior to study drug administration; treatment with > 1 dose of other IV antibiotic within 24h of study drug
Recruitment/selection of patients	Prospective
Age, gender and ethnicity	Age - Other: Not stated. Gender (M:F): Note stated. Ethnicity: Not reported
Further population details	1. Age: All adults (Approximately half aged 60 years or more). 2. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (Experimental/control: Pulmonary disease: 42 vs. 32%; CVD: 40 vs. 28%; GI disease: 19 vs. 22%; LRTI infections in previous 12 months: 30%). 3. Predominant disease aetiology (including resistance profiles): *S. pneumoniae* (Of 47 bacteriologically evaluable patients 66% had *S. pneumoniae* and 38% *H. influenzae*).
Extra comments	Concomitant digoxin, carbamazepine, warfarin, theophylline or terfenadine not permitted
Intervention 1	Antibiotic plus antibiotic ~ Macrolide + broad spectrum beta-lactam. Erythromycin, IV 1 g three-times daily plus cefuroxime sodium 1.5 g three-times daily for 2-5 days following by oral erythromycin base 500 mg four times daily and cefuroxime axetil 500 mg twice daily. Duration 10 days in total (2-5 days IV). Concurrent medication/care: Concomitant antimicrobials were not permitted (N = 117)
Further details	1. Antibiotic dose: BNF/SPC concordant

Review question	Single- compared with dual-antibiotic therapy for CAP
	2. Duration of treatment: 7 days or more
Comments	Patients requiring > 5 days IV therapy were withdrawn from the study and classed as treatment failures; mean duration of IV therapy 3.2 days; mean total duration 9.5 days
Intervention 2	Antibiotic alone ~ Macrolide. Clarithromycin, IV 500 mg twice daily for 2-5 days followed by oral clarithromycin 500 mg twice daily. Duration 10 days in total (2-5 days IV). Concurrent medication/care: Concomitant antimicrobials were not permitted (N = 118)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Comments	Patients requiring > 5 days IV therapy were withdrawn from the study and classed as treatment failures; mean duration of IV therapy 3.2 days; mean total duration 9.8 days
Study	Zervos 2004[110]
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Sponsored by Pfizer)
Number of studies (number of participants)	1 (N = 212)
Countries and setting	Conducted in Canada, Unknown multicentre, USA; Setting: Hospital
Line of therapy	1st line (< 24h prior antibiotics)
Duration of study	Intervention + follow up: 7 to 14 days therapy plus follow-up at 35 to 49 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Radiological and clinical signs
Inclusion criteria	Inpatients aged 18 years or over, with radiological and clinical evidence consistent with CAP requiring initial IV therapy. New infiltrate on CXR plus at least one of: cough or increased coughing; acute changes in quality of sputum; body temp > 38°C or < 36.1°C or documented fever or hypothermia within last 24 h; auscultatory findings e.g. rales or pulmonary consolidation; dyspnoea, tachypnoea or hypoxemia; and/or leucocytosis
Exclusion criteria	Known or suspected hypersensitivity to any fluoroquinolone, penicillin, cephalosporin or macrolide antibiotic; treatment with a systemic antibiotic for ≥ 24 hours within 72 hours prior to baseline visit, or for > 7 days within past month; clinically significant renal or hepatic dysfunction or CVD; admitted from a skilled nursing facility; evidence of recent drug or alcohol abuse/dependence; pregnancy or breast feeding; known AIDS or suspected *P. carinii* pneumonia; neutropenia, immunosuppressive therapy; cavitatory lung disease, lung cancer, aspiration pneumonia, empyema or TB; CF; significant GI or other conditions that may affect drug absorption; history of epilepsy or seizure; bronchiectasis

Review question	Single- compared with dual-antibiotic therapy for CAP
Recruitment/selection of patients	40 centres across US, Canada and Europe. Clinical and radiological assessment prior to enrolment
Age, gender and ethnicity	Age - Mean (SD): Combi: male 69.5 (14.4)/ female 72.2 (12.4); mono: male 73.6 (10.3)/ female 71.8 (17.3). Gender (M:F): 56/44%. Ethnicity: North America and Europe; 85.8% white
Further population details	1. Age: All adults (Mean age 71.7 years). 2. Comorbidities: Not stated or unclear (Most common comorbidities were arthropathies, peripheral vascular disease, chronic airway obstruction, diabetes, hypertension, ischaemic heart disease, constipation, osteoporosis and chronic heart disease = prevalence not given). 3. Predominant disease aetiology (including resistance profiles): *S. pneumoniae* (Of 44 bacteriologically evaluable patients, 19 had *S. pneumoniae*, 9 *H. influenzae* and 7 each *S. aureus* and *P. aeruginosa*).
Extra comments	Mean PSI score: dual 97.7 (23.1) vs mono 97.8 (21.1); PSI I/II = 3.7%, III = 36.8%; IV = 50%; V = 9.4%
Intervention 1	Antibiotic plus antibiotic ~ Macrolide + broad spectrum beta-lactam. Azithromycin IV 500 mg once daily plus ceftriaxone IV 1 g daily for 2-5 days, followed by oral azithromycin 500 mg once daily. Considered eligible for oral switch if: temperature of 37.8 C for at least 8 h; improvement in coughing and shortness of breath; adequate oral intake and GI uptake; and WBC normalising. Duration 7 to 10 days. Concurrent medication/care: Use of other systemic medications limited to those necessary for well-being (N = 110)
Further details	1. Antibiotic dose: High (Not licenced for IV use). 2. Duration of treatment: 7 days or more
Comments	Permitted treatment with cefuroxime axetil concurrently with oral azithromycin if macrolide-resistant *S. pneumoniae* was documented (n = 8); mean duration of IV therapy 3.2 days + 6.1 days oral therapy
Intervention 2	Antibiotic plus antibiotic ~ Respiratory fluoroquinolone. Levofloxacin IV 500 mg/day for 2 to 5 days followed by oral levofloxacin 500 mg/day. Considered eligible for oral switch if: temperature of 37.8 C for at least 8 hours; improvement in coughing and shortness of breath; adequate oral intake and GI uptake; and WBC normalising. Duration 7 to 14 days. Concurrent medication/care: Use of other systemic medications limited to those necessary for well-being (N = 102)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more
Comments	Mean duration of IV therapy 3.2 days + 8.0 days oral therapy

1.4.3.2.2 *Results*

Dichotomous

Key: NR = outcome not reported for this study; TTE = results reported as time to event data and shown in that table; similarly 'dich' for dichotomous, 'con' for continuous and 'gen' for a general method of reporting outcomes.

Study	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl
Stratum: High severity (formal assessment). Comparison: Respiratory fluoroquinolone - vs macrolide + broad-spectrum beta-lactam														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	
Fogarty 2004[40]			Mortality @ up to 30 days after end of treatment None of the deaths were considered to be related to study therapy		Clinical success at test-of-cure visit (cure or improvement with no further requirement for antimicrobial therapy for CAP) @ 3-12 days after end of treatment In the clinically evaluable population: 85/95 and 74/89 achieved clinical success. For the subgroup of the clinically evaluable population who required		Withdrawal due to adverse events @ 7-14 days							

					mechanical ventilation: 16/19 (12 'cured') and 12/19 (7 'cured') achieved clinical success. For the subgroup of the clinically evaluable population who required vasopressor support: 11/16 (7 'cured') and 7/14 (3 'cured') achieved clinical success.									
	134	135	15/132	9/137	96/132	88/137	3/132	12/137	NR	NR	NR	NR	NR	NR
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**											
Fogarty 2004[40]														
			NR	NR										
Stratum: High severity (formal assessment). Comparison: Respiratory fluoroquinolone - vs non-respiratory fluoroquinolone + broad-spectrum beta-lactam														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	
Leroy 2005[61]			Mortality @ 28 days In subgroup of mechanically ventilated patients 17/76 and 18/82 in mono and dual		Disappearance of acute signs and symptoms, and the improvement of radiographic abnormalities,		Adverse event requiring treatment discontinuation @ 7-21 days The adverse							

			groups died. Overall mortality rate also reported (at end of follow-up)		both related to CAP, with no requirement for further antimicrobial therapy @ TOC visit (1 day after end of therapy; 8-11 days) For subgroup of mechanically ventilated patients, 46/76 vs 58/82 in mono and dual groups respectively achieved clinical cure		events requiring discontinuation of treatment were cytolytic liver injury (n = 1), allergic rash (n = 1), leukopenia (n = 1), tendon rupture (n = 1), and agitation and persecutory delusion (n = 1) in the monotherapy group and allergic rash (n = 3) and thrombocytopenia (n = 1) in the dual therapy group.						
	196	202	18/149	20/159	112/149	123/159	5/194	4/201	NR	NR	NR	NR	NR	NR
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**											
Leroy 2005[61]			Disappearance of acute signs and symptoms, and the improvement of radiographic abnormalities, both related to CAP, with no requirement for further antimicrobial therapy @ 21-45 days post-treatment											
	196	202	88/149	99/159										
Stratum: High severity (formal assessment). Comparison: Respiratory fluoroquinolone + placebo vs respiratory fluoroquinolone + broad-spectrum beta-lactam														

Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	
Torres 2008[100]			Mortality @ 30 days PSI classes IV-V		Test of cure visit (4-14 days post-therapy) @ Test of cure visit (4-14 days post-therapy) PP analysis									
	371	367	17/214	10/215	143/169	145/167	NR	NR	NR	NR	NR	NR	NR	NR
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**											
Torres 2008[100]														
			NR	NR										
Stratum: High severity (hospital setting). Comparison: Macrolide vs macrolide + broad spectrum beta-lactam														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	
Vetter 1997[106]			All-cause mortality @ Up to 6 weeks post-treatment Causes of death: mono group - progressive respiratory insufficiency,		Clinical cure: signs/symptoms resolved @ 11-14 days Clinically evaluable population - PPA: 62/88 vs 54/81. Clinical 'success'		Study drug discontinuation due to adverse events @ 11-14 days This included 3 deaths during treatment (2 in						Diarrhoea @ up to 6 weeks post-treatment Unclear if *C. difficile*-associated	

			respiratory failure, bronchopneumonia, oliguria, abdominal complications, heart failure; dual group - MI and other CVD events, lung carcinoma, cardiac arrest (considered remotely related to the study drug), pulmonary embolus.		also reported (cure or improvement): 86/118 vs 79/117.		mono and 1 on dual group)							
	118	117	5/118	4/117	66/118	58/117	8/118	16/117	NR	NR	NR	NR	4/118	16/117
Vergis 2000[105]			In-hospital mortality @ Unclear Data based on ITT analysis (assumptions not clear); based on PPA 2/67 vs 1/78		Clinical cure: receipt of a minimum of 3 days of therapy with resolution of symptoms and signs at conclusion of therapy @ 7-10 days Data based on ITT analysis (assumptions not clear); based on PPA 61/67 vs 71/78						ICU admission @ Up to 6 weeks post-treatment			
	83	86	3/83	1/86	62/83	71/86	NR	NR	NR	NR	5/83	8/86	NR	NR
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**											
Vetter 1997[106]			Clinical cure: signs/symptoms											

			resolved @ 4-6 weeks post-treatment (or 11-14 days if no follow-up data) Clinically evaluable population - PPA: 69/88 vs 60/81. Clinical 'success' also reported (cure or improvement): 84/118 vs 77/117.											
	118	117	73/118	66/117										
Vergis 2000[105]														
			NR	NR										
Stratum: High severity (hospital setting). Comparison: Respiratory fluoroquinolone - vs macrolide + broad spectrum beta-lactam														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	
Lin 2007[64]					Clinical cure (resolution of abnormal pre-treatment clinical signs and symptoms, and no further antimicrobial therapy for CAP required) or clinical improvement (clinical findings									

			subsiding significantly but with incomplete resolution of clinical evidence of infection at the follow-up evaluation in a subject who requires no further antimicrobial therapy for CAP) @ Day 7 Available case analysis (clinically evaluable patients only). Post hoc subgroup analysis of low (Fine Risk Score < 71) and high (Fine Risk Score ≥ 71) severity: in low severity group 8/8 in levofloxacin group and 4/5 in combination group achieved clinical success; in high severity group 10/15 in levofloxacin group and 13/17 in combination group achieved clinical success. The				

					clinical response was not statistically significant in subgroups of patients with FRS below or above 71									
	26	24	NR	NR	18/23	17/22	NR	NR	NR	NR	NR	NR	NR	NR
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**											
Lin 2007[64]			Clinical cure (resolution of abnormal pre-treatment clinical signs and symptoms, and no further antimicrobial therapy for CAP required) or clinical improvement (clinical findings subsiding significantly but with incomplete resolution of clinical evidence of infection at the follow-up evaluation in a subject who requires no further antimicrobial therapy for CAP) @ 1 month post-treatment											

			Only assessed clinically successful population											
	26	24	16/18	15/17										
Stratum: Low severity (formal assessment). Comparison: Macrolide vs macrolide + broad spectrum beta-lactam														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	
Rovira 1999[88]			CAP-related mortality @ Unclear		Treatment failure @ 7-14 days				Pleural effusion @ Unclear		Hospital admission @ Unclear These were the same patients as those who were reported as treatment failures			
	45	45	0/45	0/45	0/45	2/45	NR	NR	1/45	0/45	0/45	2/45	NR	NR
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**											
Rovira 1999[88]														
			NR	NR										
Stratum: Moderate severity (formal assessment). Comparison: Respiratory fluoroquinolone + placebo vs respiratory fluoroquinolone + broad spectrum beta-lactam														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	

Torres 2008[100]			Mortality @ 30 days		Cure: complete resolution of acute signs and symptoms related to the infection or sufficient improvement such that additional or alternative antimicrobial therapy was not required @ Test of cure visit (4-14 days post-therapy)									
	371	367	1/150	2/142	110/122	105/111	NR	NR	NR	NR	NR	NR	NR	NR
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**											
Torres 2008[100]														
			NR	NR										
Stratum: Moderate to high severity (formal assessment). Comparison: Respiratory fluoroquinolone - vs macrolide + broad spectrum beta-lactam														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	
Zervos 2004[110]			All-cause mortality @ up to 35 days Deaths not attributable to study drugs and not classified as clinical failures		Clinical cure (resolution of symptoms to baseline level prior to pneumonia) @ 12-16 days Figures based on mITT analysis. Also		Treatment discontinued due to adverse events @ 12-16 days Reasons for discontinuation: mono group = lack of clinical efficacy						Diarrhoea @ up to 35 days Unclear if *C-difficile*-related. Also counted in withdrawal due to adverse event outcome	

					presented clinically evaluable cases (PPA); 36/75 vs 53/82 for mono vs dual. Clinical improvement also reported in an additional 27/97 vs 39/93 (i.e. 'success' in 85/97 vs 83/93).		(3); dual group: treatment-related phlebitis (1), diarrhoea (1), liver enzyme elevations (4), lack of clinical efficacy (4)							
	102	110	5/102	3/110	44/93	58/97	3/102	10/110	NR	NR	NR	NR	0/102	1/110
Frank 2002[41]					Clinical success (cure or improvement) not requiring further treatment @ 2-7 days post-treatment (or at early withdrawal) ITT population		Withdrawal due to adverse events @ 10 days ACA						Diarrhoea @ Up to 2-7 days post-treatment ACA	
	115	121	NR	NR	100/115	97/121	5/110	5/114	NR	NR	NR	NR	0/113	5/118
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**											
Zervos 2004[110]			Clinical cure (resolution of symptoms to baseline level prior to pneumonia and improvement or lack of progression of acute lung infiltrates) @ 28-35 days Figures based on mITT analysis. Also presented clinically											

			evaluable cases (PPA); 63/74 vs 66/74 for mono vs dual. Clinical improvement also reported.											
	102	110	77/92	81/94										
Frank 2002[41]														
			NR	NR										
Stratum: Moderate to high severity (formal assessment). Comparison: Respiratory fluoroquinolone + placebo vs respiratory fluoroquinolone + broad spectrum beta-lactam														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**		**Hospital admission @ End of follow-up**		***C. difficile*-associated diarrhoea @ End of follow-up**	
Torres 2008[100]			Mortality @ 30 days		Cure: complete resolution of acute signs and symptoms related to the infection or sufficient improvement such that additional or alternative antimicrobial therapy was not required @ Test of cure visit (4-14 days post-therapy) ITT population. Improvement reported in								*C. difficile*-associated diarrhoea @ Unclear Stool cultures for *C. difficile* were not performed routinely	

					evaluable population: 267/291 (91.8%) and 260/278 (93.5%); with cure rates of 253/291 (86.9%) and 250/278 (89.9%)									
	371	367	18/364	12/357	293/368	306/365	NR	NR	NR	NR	NR	NR	0/368	1/365
Protocol outcomes continued -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**											
Torres 2008[100]			Maintaining cure @ End of follow-up (21-28 days post-therapy) Among those with clinical success at TOC visit (PP analysis)											
	371	367	243/253	243/250										

Continuous

Study	Exp	Ctrl	Exp	Ctrl
Stratum: High severity (formal assessment). Comparison: Respiratory fluoroquinolone - vs non-respiratory fluoroquinolone + broad spectrum beta-lactam				
Protocol outcomes -->	**Numbers Randomised**		**Length of hospital stay @ End of follow-up**	
Leroy 2005[61]			Mean length of ICU stay (for survivors) @ Up to 45 days	
	196	202	11.9(SD 9.4); n=149	12(SD 9.7); n=159
Stratum: High severity (hospital setting). Comparison: Respiratory fluoroquinolone - vs macrolide + broad spectrum beta-lactam				
Protocol outcomes -->	**Numbers Randomised**		**Length of hospital stay @ End of follow-up**	
Lin 2007[64]			Mean length of hospital stay in clinically successful population @ up to 1 month post-treatment	
	26	24	7.4(SD 3.1); n=18	6.8(SD 2.1); n=17
Stratum: Moderate to high severity (formal assessment). Comparison: Respiratory fluoroquinolone - vs macrolide + broad spectrum beta-lactam				
Protocol outcomes -->	**Numbers Randomised**		**Length of hospital stay @ End of follow-up**	
Zervos 2004[110]			Length of hospital stay (evaluable patients) @ Unclear Post-hoc subgroup analysis for PSI IV/V mean length of stay was 9.0 vs 7.4 days (mono vs dual)	
	102	110	8.4(SD 6.9); n=75	7.7(SD 4.7); n=82

1.4.3.3 Dual- compared with other dual-antibiotic therapy

1.4.3.3.1 Clinical evidence tables – patient characteristics, interventions and study design

Review question	Dual- compared with dual-antibiotic therapy for moderate- to high-severity CAP
Study (subsidiary papers)	Gaillat 1994[42]
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	1 (N = 117)
Countries and setting	Conducted in France; Setting: 17 centres including departments of pneumology, infectious diseases and ICUs
Line of therapy	Unclear
Duration of study	Intervention + follow up: 10 days treatment and follow-up to 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinical and radiologic evidence
Stratum	High severity (formal assessment): Severely ill: PaO_2 < 60 mmHg and/or SAPS ≥ 10 and/or SAPS ≥ 7 associated with pre-existing illness or host factors such as alcoholism, chronic obstructive lung disease with either resting hypoxemia or dyspnoea, congestive cardiac failure, renal failure or haemodialysis, end-stage neoplastic disease or drug-induced immunosuppression
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults (over 18 years) severely ill with CAP fulfilling one or more of the following: PaO_2 < 60 mmHg or SAPS ≥ 10 or SAPS ≥ 7 associated with pre-existing illness or host factors such as alcoholism, chronic obstructive lung disease with either resting hypoxemia or dyspnoea, congestive cardiac failure, renal failure or haemodialysis, end-stage neoplastic disease or drug-induced immunosuppression
Exclusion criteria	Previous adverse reaction to study drugs; neutrophil count ≤ 500/mm^3; $CD4^+$ cell count ≤ 400/mm^3 in patients with HIV; lung cancer; prior treatment with any of the protocol drugs within 48 h prior to admission; nosocomial pneumonia
Recruitment/selection of patients	October 1990 to September 1991
Age, gender and ethnicity	Age - Mean (SD): Penicillin/ofloxacin: 61.6 (18.4); amoxiclav/erythromycin: 64.0 (15.9) years. Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	1. Age: All adults 2. Comorbidities: Not stated or unclear 3. Predominant disease aetiology (including resistance profiles): *S. pneumoniae* (Of 64 identified pathogens, 35 (54.7%) were *S. pneumoniae*, 9 (14.1%) were *S. aureus* and 6 (9.4%) were *H. influenzae*. One *S. pneumonia* strain was

Review question	Dual- compared with dual-antibiotic therapy for moderate- to high-severity CAP
	resistant to penicillin, six resistant to ofloxacin and 5 resistant to erythromycin.).
Extra comments	Number mechanically ventilated - Penicillin/ofloxacin: 14 (27%); co-amoxiclav/erythromycin: 11 (22%). Mean SAPS (SD): Penicillin/ofloxacin: 10.3 (4.4); co-amoxiclav/erythromycin: 10.9 (4.4).
Interventions	**Intervention 1**: Antibiotic plus antibiotic ~ Fluoroquinolone (old) + class 1 narrow spectrum beta-lactam. Penicillin G 3 x 10^6 U/6 h plus ofloxacin 200 mg twice daily IV, followed by oral amoxicillin 1 g/8 h plus ofloxacin 200 mg/12 h. Duration At least 10 days. Concurrent medication/care: Unclear, additional therapy for haemodynamic and respiratory failure may have been permitted (N = 58) Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more Comments: Treatment with a single antibiotic from the assigned regimen was allowed after 72 h, provided the micro-organism isolated was sensitive to the drug **Intervention 2**: Antibiotic plus antibiotic ~ Macrolide + beta-lactamase stable penicillin. Amoxiclav 1 g/6 h plus erythromycin 1 g/8 h IV, followed by oral amoxiclav 500 mg/8 h plus erythromycin 1 g/12 h. Duration At least 10 days. Concurrent medication/care: Unclear, additional therapy for haemodynamic and respiratory failure may have been permitted (N = 59) Further details: 1. Antibiotic dose: High (Dose IV co-amoxiclav unclear, but it is likely that the 1g relates to the amoxicillin content of the dose – by convention this would mean a 1.2 g dose of co-amoxiclav but more frequently than recommended. If a lower dose is being given, it is being given more frequently so more or less an equivalent dose is being given). 2. Duration of treatment: 7 days or more Comments: Treatment with a single antibiotic from the assigned regimen was allowed after 72 h, provided the micro-organism isolated was sensitive to the drug
Study	Tamm 2007[99]
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Pfizer)
Number of studies (number of participants)	1 (N = 278)
Countries and setting	Conducted in Austria, Belgium, Finland, France, Germany, Israel, Italy, Netherlands, Portugal, South Africa, Spain, Switzerland, Turkey; Setting: Hospital
Line of therapy	Mixed line

Review question	Dual- compared with dual-antibiotic therapy for moderate- to high-severity CAP
Duration of study	Intervention + follow up: 7 to-14 days treatment plus follow-up to day 28 to 35
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinical and radiological findings
Stratum	Moderate to high severity (formal assessment): Minimum APACHE II score of 8; 51.8% PSI IV or V, 26.6% PSI III; 21.6% PSI I or II
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults aged ≥ 18 years with clinical and radiological findings consistent with CAP requiring hospitalisation and initial intravenous antibiotic therapy. Radiographic appearance of new pulmonary infiltrate and at least 2 of the following: cough or increasing severity of coughing, acute changes in sputum quality, oral body temperature or equivalent > 38°C or < 36.1°C, or documented fever or hypothermia within the past 24 h, auscultatory findings such as rales or evidence of pulmonary consolidation, dyspnoea or tachypnoea, and leukocytosis (WBC count > 10,000/mm^3 or > 15% immature neutrophils/bands), minimum APACHE II score of 8
Exclusion criteria	Pregnant or lactating women or of childbearing age and not using adequate contraception; treatment with any systemic antibiotic for ≥ 24 hours within 72 hours of baseline visit or treatment for >7 days within past month unless documented evidence of clinical or bacteriological failure; life expectancy ≤ 48 hours; AIDS or suspected *Pneumocystis carinii* pneumonia; significant neutropenia; radiological evidence of cavitary lung disease, primary or metastatic lung cancer, aspiration pneumonia, empyema or tuberculosis; cystic fibrosis; progressive neoplastic disease; history of epilepsy or seizure; bronchiectasis, bronchial obstruction or history of post-obstructive pneumonia; patients already hospitalised or who had resided in a long-term care facility for > 14 days before onset of symptoms.
Recruitment/selection of patients	Prospective: April 2002 - March 2003
Age, gender and ethnicity	Age - Mean (SD): Azithromycin group: 64.2 (17.1); clarithromycin group: 62.4 (18.7). Proportion over 65 years: 63% and 57%. Gender (M:F): 68.7/31.3%. Ethnicity: Not stated
Further population details	1. Age: All adults 2. Comorbidities: Not stated or unclear 3. Predominant disease aetiology (including resistance profiles): *S. pneumoniae* (Of 87 patients with pathogens isolated, *S. pneumoniae* was isolated in 44% and 57% in the two groups; *H. influenzae* in 25% and 18%, and *S. aureus* from 13% and 4%).
Extra comments	Mean PSI score: 91.8 (27.2), 92.2 (26.0)
Interventions	**Intervention 1**: Antibiotic plus antibiotic ~ Macrolide + cephalosporin. Ceftriaxone 1-2 g once daily IV, plus either clarithromycin 500 mg twice daily IV or erythromycin 1 g three times a day for 2 to 5 days followed by step-down to either oral clarithromycin 500 mg twice daily or erythromycin 1 g three-times a day for a total of 7 to 14 days. Duration 7 to 14 days. Concurrent medication/care: Unclear (N = 143)

Review question	Dual- compared with dual-antibiotic therapy for moderate- to high-severity CAP
	Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more (Mean: 10.5 days (mean duration IV: 4.7 days)). Comments: Rationalised to macrolide monotherapy when transitioned to oral therapy. The switch to oral could be made on day three if: oral temperature or equivalent < 38°C for > 8 hours; cough and shortness of breath improvement; adequate oral intake and GI absorption; and white blood cell count normalising. Erythromycin was substituted for clarithromycin in countries where IV clarithromycin is not approved. **Intervention 2**: Antibiotic plus antibiotic ~ Azithromycin + cephalosporin. Ceftriaxone 1-2 g once daily IV, plus azithromycin 500 mg once-daily IV for 2 to 5 days followed by step-down to oral azithromycin 500 mg once-daily for a total of 7 to 10 days. Duration 7 to 10 days. Concurrent medication/care: Unclear (N = 135) Further details: 1. Antibiotic dose: BNF/SPC concordant. 2. Duration of treatment: 7 days or more (Mean: 9.5 days (mean duration IV: 5.0 days)). Comments: Rationalised to azithromycin monotherapy when transitioned to oral therapy. The switch to oral could be made on day three if: oral temperature or equivalent < 38°C for > 8 hours; cough and shortness of breath improvement; adequate oral intake and GI absorption; and white blood cell count normalising.

1.4.3.3.2 *Results*

Results – dichotomous

Study	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl
Stratum: High-severity (formal assessment) CAP. Comparison: Non-respiratory fluoroquinolone (old) + class 1 narrow spectrum beta-lactam vs macrolide + beta-lactamase stable penicillin										
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**	
Gaillat 1994[42]			Mortality @ Unclear - during treatment		Therapeutic success: apyrexia, and signs, symptoms and pulmonary infiltrates disappeared @ At least 10 days (mean: 14 days)				Superinfection @ 30 days Superinfection with *Acinetobacter baumanii*	
	58	59	6/52	6/50	40/52	38/50	NR	NR	1/32	0/36
Stratum: Moderate to high severity (formal assessment). Comparison: Azithromycin + cephalosporin vs macrolide + cephalosporin										
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**	
Tamm 2007[99]			Mortality @ 28-35 days None of the deaths were considered to be treatment-related		Clinical response: resolution of signs and symptoms of pneumonia or resolution of fever but incomplete resolution of other signs and symptoms without requirement for additional antibiotic therapy @ 12-16 days		Treatment discontinuation due to adverse events @ 12-16 days In azithromycin discontinuation was due to elevated hepatic enzyme levels; in the clarithromycin group			

					Response stratified by PSI category. Class III: 27/35 vs 28/35; class IV: 46/53 vs 46/52; class V: 7/9 vs 6/7		one had cutaneous erythematous eruption, one anorexia, emesis, urticaria and taste perversion, one emesis and hearing loss on left side, and one phlebitis of left had at infusion site.			
	135	143	7/135	5/143	102/121	104/126	1/135	4/143	NR	NR

Results – continuous

Study	Exp	Ctrl	Exp	Ctrl
Stratum: Moderate to high severity (formal assessment). Comparison: Azithromycin + cephalosporin compared with macrolide + cephalosporin				
Protocol outcomes -->	**Numbers Randomised**		**Length of hospital stay @ End of follow-up**	
Tamm 2007[99]			Length of hospital stay @ 28-35 days Numbers analysed not stated	
	135	143	10.7(SD 6.8); n=135	12.6(SD 10.8); n=143

Results – general

Study	Exp	Ctrl	Exp vs Ctrl
Stratum: Moderate to high severity (formal assessment). Comparison: Azithromycin + cephalosporin compared with macrolide + cephalosporin			
Protocol outcomes -->	**Numbers Randomised**		**Clinical cure @ End of follow-up**
Tamm 2007[99]			Clinical cure: resolution of signs and symptoms of pneumonia @ 28-35 days Numbers analysed not stated
	135	143	Proportion 81.7% for ceftriaxone plus azithromycin; 75.0% for ceftriaxone plus clarithromycin/erythromycin

1.4.4 Duration of antibiotic therapy

Review question	Duration of antibiotic therapy
Study	Leophonte 2002[60]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n = 244)
Countries and setting	Conducted in France; Setting: Multicentre study involving 50 French wards of Pneumology, Internal Medicine and Infectious Diseases between 1994 to1996.
Line of therapy	1st line
Duration of study	Follow up (post intervention): 45 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Presented with fever (≥ 38C), and at least two clinical signs for CAP (purulent expectoration, chest pain, dyspnoea, chills, focal signs on auscultation, cough, and with radiological confirmation (recent alveolar opacity, parenchymatous infiltration), if the patient requires hospitalisation for at least 5 days or if there are at least one of the severity risk factors.
Stratum	Overall: Community Acquired Pneumonia (CAP)
Subgroup analysis within study	Not applicable
Inclusion criteria	Presented with fever (≥ 38C), and at least two clinical signs for CAP (purulent expectoration, chest pain, dyspnoea, chills, focal signs on auscultation, cough, and with radiological confirmation (recent alveolar opacity, parenchymatous infiltration), if the patient requires hospitalisation for at least 5 days or if there are at least one of the severity risk factors (age ≥ 65 years, tobacco addiction (≥ 10 packs per year), chronic alcoholism (≥ 50g per day for male, and ≥ 30 g per day for females), and non-decompensated underlying disease, malnutrition or obesity (BMI < 17 or > 25). The patient could have been given antibiotic per OS previously for the same indication as long as this initial treatment had been followed adequately for 48 hours but less than 4 days without noted decrease of pyrexia or improvement of clinical signs.
Exclusion criteria	Patients presenting with nosocomial pneumonia, hospitalised for over 72 h, presenting initial severity signs such as decompensated underlying disease threatening for the vital prognostic or acute vital distress (PaO2 <60 mmHg) systolic pressure > 90 mmHg, heart beat rate > 140 beats/min, respiratory rate > 30ml/min and confusion. Received antibiotic of the same "spectre" for this indication (3rd generation cephalosporins, beta lactams combined with a beta lactam inhibitors, and an imipenem/cilastatin combination). Pregnancy. Absence of contraception for women of reproductive age. Documented allergy to beta-lactams and/or local anaesthetics, any blood disease or non-pulmonary cancer under therapy, any terminal-phase disease, purulent pleurisy requiring evacuation, some bronchopulmonary diseases (bronchiectasis, cystic fibrosis, documented bronchopulmonary cancer). Immunodepression (glucocorticosteroid therapy, neutropenia, immunosupressive treatment), AIDS, psychiatric

Review question	Duration of antibiotic therapy
	disorders or impairment of intellectual performance.
Recruitment/selection of patients	Patients were randomly selected for 2 groups
Age, gender and ethnicity	Age - Range of means: Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. Age: 2. Comorbid condition: Not applicable / Not stated / Unclear
Indirectness of population	Patient could have received previous antibiotic orally, 21/125 (16.8%) in the 5D group, 17 /119 (14.3%) in the 10 D group.
Interventions	(n = 119) Intervention 1: Longer or standard duration - Cephalosporin. ceftriaxone 1 g od 10/7, 5 days IV, 5 days IM. Duration 10 days. Concurrent medication/care: Not described Further details: 1. Antibiotic dose: BNF/SPC concordant (Standard dose). 2. Duration of treatment: Not applicable / Not stated/unclear 3. Route of administration: IV (1 g/24 hours, 5 days by IV, 5 days by IM). (n = 125) Intervention 2: Shorter duration - Cephalosporins. Dose/quantity, brand name, extra details. Duration 5 days. Concurrent medication/care: ceftriaxone 1 g OD 5/7 IV, plus placebo 5/7 IM Further details: 1. Antibiotic dose: BNF/SPC concordant (Standard dose). 2. Duration of treatment: Not applicable (No specification of minimum duration of treatment). 3. Route of administration: IV (1 gram per day, 5 days IV). Comments: Ceftriaxone
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEPHALOSPORIN versus CEPHALOSPORINS Protocol outcome 1: Mortality at 30 days - Actual outcome: Death at 44 days; Group 1: 4/125, Group 2: 7/119; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Clinical cure at End of treatment - Actual outcome: Clinical cure, defined as apyrexia(less or equal to 37.5C) at D10. at 10 days; Group 1: 77/94, Group 2: 76/92; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Clinical cure, defined as absence of clinical signs at D10. at 10 days; Group 1: 82/119, Group 2: 81/125; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Withdrawal due to adverse events at End of treatment - Actual outcome: Withdrawal due to AE not reported. at 44 days; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: C. difficile-associated diarrhoea at end of follow-up	

Review question	Duration of antibiotic therapy
- Actual outcome: Death due to C diff related diarrhoea at 44 days; Group 1: 0/125, Group 2: 1/119; Risk of bias: ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up; Length of hospital stay at End of follow-up; Clinical cure at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up
Study	Siegel 1999[95]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n = 56)
Countries and setting	Conducted in USA; Setting: Inpatient ward, US.
Line of therapy	1st line
Duration of study	Follow up (post intervention): 42 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Chest X-ray and clinical history
Stratum	Overall: Uncomplicated CAP
Subgroup analysis within study	Not applicable
Inclusion criteria	New pulmonary infiltrate on chest radiograph, AND, either 1) clinical history consistent with pneumonia (e.g. fever, chills, cough, sputum, or chest pain), 2) physical findings suggestive of pneumonia (localised crackles or bronchial breath sound).
Exclusion criteria	Excluded if they have empyema, septic shock, or respiratory failure; had an allergy or hypersensitivity to cephalosporins; had received systemic antibiotics in the past 72 hours, or had been admitted to the study in the past.
Recruitment/selection of patients	Patients admitted to an inpatient ward, immediately after the treating emergency department or clinic physician determined the patient should be admitted for the treatment of CAP.
Age, gender and ethnicity	Age - Gender (M:F): Define. Ethnicity: 54% African American, 27% Hispanic, 17% White, 2% Asian
Further population details	1. Age: All adults 2. Comorbid condition: Not applicable / Not stated / Unclear
Extra comments	Patients with CAP diagnosed by x-ray and clinical characteristics, hospitalised and admitted through the emergency department.
Indirectness of population	No indirectness
Interventions	(n = 24) Intervention 1: Shorter duration - Cephalosporins. Cefuroxime 7 days (2 days 750mg 8 hour IV, 5 days 500mg 12-hourly orally, 3 days placebo). Duration 7 days. Concurrent medication/care: no other pharmacotherapy for pneumonia listed Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more 3. Route of administration: Mixed

Review question	Duration of antibiotic therapy
	(n=22) Intervention 2: Longer or standard duration - Cephalosporin. Cefuroxime 10 days (2 days 750mg 8 hour IV, 8 days 500mg 12 hourly orally). Duration 10 days. Concurrent medication/care: No other pharmacotherapy for pneumonia stated Further details: 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more 3. Route of administration: Mixed
Funding	Study funded by industry (Supported by grant from Glaxo)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEPHALOSPORINS versus CEPHALOSPORIN Protocol outcome 1: Mortality at 30 days - Actual outcome: Treatment failures during treatment; Group 1: 1/24, Group 2: 2/22; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Not predefined. Reported as part of treatment failure. at up to 44 days; Group 1: 1/24, Group 2: 0/22; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Withdrawal due to adverse events at end of treatment - Actual outcome: "patient was unable to tolerate medication" during treatment; Group 1: 0/24, Group 2: 0/22; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Complications (composite of empyema, effusion, abscess, metastatic infection) at End of follow-up - Actual outcome: Therapeutic cure. Resolution of fever and leukocytosis, "substantial improvement" chest x ray by day 42 at 42 days; Group 1: 21/24, Group 2: 20/22; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Clinical cure at End of treatment; Length of hospital stay at End of follow-up; C. difficile-associated diarrhoea at end of follow-up; Clinical cure at End of follow-up; Quality of life - EQ5D or SF-36 at End of follow-up

Review question	Duration of antibiotic treatment
Study	Dunbar2003[31]
Study type	RCT (randomised; Parallel)
Funding	Study funded by industry (Ortho McNeil)
Number of studies (number of participants)	(N = 530)
Countries and setting	Conducted in USA; Setting: Inpatient and community - patient who have PSI ≤ 70 could be treated as in patient or outpatient. Patients with PSI > 70 treated as in patients for at least 24 hours. Multicentre (70 sites)
Line of therapy	1st line
Duration of study	Follow-up (post-intervention): 7 to 14 post therapy
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Chest x-ray and clinical history
Inclusion criteria	Adult men and women (age, ⩾18 years) with a diagnosis of mild-to-severe CAP based on clinical signs and symptoms of a lower respiratory tract infection and radiographic evidence of acute pneumonia. Presence of ≥ 1 of the following: fever (oral temperature ≥ 38C) hypothermia (oral temperature ≤ 35C, leucocytosis (WBC > 10,000 cells/mm3) or > 10% bands.
Exclusion criteria	Infection due to organisms known to be resistant to levofloxacin. Previously allergic or serious reaction to any quinolone. Previous treatment failure, with any quinolone, life expectancy < 72 hours, pneumonia acquired in a hospital, at high risk of infection with P. aeruginosa, neutropenia, empyema or presence of pleural fluid requiring a chest tube, pneumonia known to be due to aspiration of gastric contents, documented HIV infection with a CD4 cell count of ≤ 200 cells/mm3, known or suspected meningitis, pregnancy, nursing. Calculated creatinine clearance of < 50 mL/min
Recruitment/selection of patients	Recruited from patients from 70 centres in the US.
Age, gender and ethnicity	Age: 54.2 ± 17.9. Gender (M:F): 310: 218. Ethnicity: White 68.8% , African American, 21.8% Hispanic, 7.6%
Further population details	1. Age: All adults 2. Weight: 79.5 ± 19.5 for the short duration group, 76.7 ± 21.1 for the longer duration group 3. Comorbidities: Not reported.
Intervention 1	Shorter duration ~ Levofloxacin 750 mg once daily for 5 days plus placebo one daily for 5 days, either by IV or oral according to investigator discretion. Duration 5 days. Concurrent medication/care: no other pharmacotherapy for pneumonia listed.
Further details	1. Antibiotic dose: BNF/SPC concordant. 2. Duration of treatment: less than 7 days
Intervention 2	Longer or standard duration ~ Levofloxacin 500 mg once daily for 10 days, either by IV or oral according to investigator discretion. Duration 5 days. Concurrent medication/care: no other pharmacotherapy for pneumonia listed.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Levofloxacin 750 mg once daily (5 days, IV or oral) versus Levofloxacin 500 mg once daily (10 days, IV or oral)	

Review question	Duration of antibiotic treatment
Protocol outcome 1: All-cause mortality: Group 1: 5/256, Group 2: 9/265; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Clinical cure (measured as resolution of pre-treatment syndrome) or improvement at end of treatment (by severity) at 7 to 14 days after therapy: - All patients: Group 1: 183/198, Group 2: 175/192; Risk of bias: High; Indirectness of outcome: No indirectness - Low severity patients: Group 1: 114/122, Group 2: 102/106; Risk of bias: High; Indirectness of outcome: No indirectness - Moderate-to-high severity patients: Group 1: 69/76, Group 2: 73/86; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Withdrawal due to adverse events: Group 1: 18/256, Group 2: 22/265; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Hospital re-admission, length of hospital stay, health-related quality of life, complications, relapse rate, C. difficile-associated diarrhoea
Study	Elmoussaoui2006[32]
Study type	RCT (randomised; parallel)
Funding	Study funded by health insurance company
Number of studies (number of participants)	(N = 121)
Countries and setting	Conducted in Netherlands, between 2000 and 2003. Setting: Multicentre (9 sites)
Line of therapy	1st line
Duration of study	Follow-up (post-intervention): Up to Day 28
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Chest x-ray and clinical history
Inclusion criteria	Patients who had substantially improved after three days' treatment with intravenous amoxicillin, improvement assessed at 72 hours based on 4 symptoms (dyspnoea, cough, coughing up sputum, colour of sputum) and general improvement on a 5 point scale ranging from -2 for worsening to 3 for completely recovered. Adult men and women (age ≥ 18 years) with a diagnosis of mild-to-moderate (PSI score of ≤ 110) CAP based on clinical signs and symptoms of a lower respiratory tract infection and radiographic evidence of new infiltrate consistent with pneumonia. Fever (body temperature > 38C), but elderly with temperature < 38C are eligible clinical signs are evident of pneumonia and abnormalities shown in chest x-ray.
Exclusion criteria	Pregnant women and patients with a history of allergy to amoxicillin; neutropenia (< 1.0 x 109/l); HIV infection with an indication for prophylaxis against pneumocystis pneumonia; agammaglobulinaemia; asplenia; life expectancy less than one month; treatment with an effective antimicrobial agent for more than 24 hours before admission; any other infection necessitating treatment with systemic antibiotics; recent admittance to a hospital or nursing home; serious respiratory

Review question	Duration of antibiotic treatment
	insufficiency (arterial partial pressure of oxygen < 6.67 kPa); admittance to an intensive care unit; empyema; and suspicion of aspiration, atypical, Klebsiella, or staphylococcal pneumonia.
Recruitment/selection of patients	Recruited from patients from 9 centres in the Netherlands. 121 out of 186 patients enrolled and treated for pneumonia met inclusion criteria (38 did not improve significantly)
Age, gender and ethnicity	Age: Median 60 (IQR 40-74). Gender (M:F): 71: 48. Ethnicity: Not reported
Further population details	1. Age: All adults 2. Weight: Not reported 3. Comorbidities: Shorter duration group: Underlying disease: 39 (70%); Chronic obstructive pulmonary disease: 14 (25%); Frequent pneumonia 8 (14%) Other lung disease: 6 (11%); Diabetes mellitus: 9 (16%); Cardiovascular disease: 11 (20%); Smoker 31 (55%); Longer duration group: Underlying disease: 40 (64%); Chronic obstructive pulmonary disease: 16 (25%); Frequent pneumonia: 11(18%); Other lung disease: 6 (10%); Diabetes mellitus: 7 (11%); Cardiovascular disease: 13 (21%)
Intervention 1	Shorter duration. Amoxicillin IV (dose not stated) for 3 days, followed by placebo for 5 days. Duration 3 days. Concurrent medication/care: no other pharmacotherapy for pneumonia listed.
Further details	1. Antibiotic dose: BNF/SPC concordant. 2. Duration of treatment: less than 7 days
Intervention 2	Longer duration. Amoxicillin IV (dose not stated) for 3 days, followed by amoxicillin 750 mg per oral 3 times daily for 5 days. Duration 8 days. Concurrent medication/care: no other pharmacotherapy for pneumonia listed.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Amoxicillin 3 days IV versus Amoxicillin 8 days Protocol outcome 1: All-cause mortality: Group 1: 1/56, Group 2: 1/63; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Clinical cure (measured as continued resolution or improvement of symptoms) at 28 days after therapy: Group 1: 47/56, Group 2: 49/63; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Withdrawal due to adverse events: 0 in both groups; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Complications (worsening infections, abscess, metastatic infection, MODS). Group 1: 2/57, Group 2: 3/63; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol details not reported by the study	Hospital re-admission, length of hospital stay, health-related quality of life, relapse rate

1.5 Glucocorticosteroid treatment

1.5.1.1.1 Patient characteristics, interventions and study design

Review question	**Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital**
Study	**Confalonieri 2005[27]**
Study type	RCT (Patient randomised; Parallel)
Funding	Academic or government funding (Assisi Foundation of Memphis - part funded)
Number of studies (number of participants)	1 (N = 48)
Countries and setting	Conducted in Italy; Setting: ICU
Line of therapy	1st line
Duration of study	Intervention + follow-up: up to 60 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinical and radiographic evidence of pneumonia
Inclusion criteria	Severe CAP as defined by meeting two minor or one major 1993 ATS criterion for severe pneumonia. Minor criteria included respiratory rate greater than 30 breaths per minute at admission; ratios of PaO_2 to fraction of inspired oxygen less than 250; chest radiograph showing bilateral involvement or multilobar involvement; systolic blood pressure less than 90 mm Hg; or diastolic blood pressure less than 60 mm Hg. Major criteria included requirement of mechanical ventilation; increase in the size of opacities on chest radiograph of 50% or more at 48 hours; requirement of vasopressors for more than 4 hours; or serum creatinine 2 or more mg/dl.
Exclusion criteria	Nosocomial pneumonia; severe immunosuppression; acute burn injury; a pre-existing medical condition with a life expectancy less than 3 months; pregnancy; a major gastrointestinal bleed within 3 months of the current hospitalization; or a condition requiring more than 0.5 mg/kg/day of prednisone equivalent (i.e. acute asthma or chronic obstructive pulmonary disease [COPD]).
Recruitment/selection of patients	After an interim analysis enrolment was suspended because a significant difference was identified for improvement of $Pa0_2$:FIO_2 and mortality.
Age, gender and ethnicity	Age - Mean (SD): Glucocorticosteroid group: 60.4 (17.3); placebo group: 66.6 (14.7). Gender (M:F): 70/30%. Ethnicity: NA
Further population details	1. Age: All adults 2. Comorbidities: Minority with relevant comorbidities 3. Predominant disease aetiology: No dominant pathogen (*S. pneumoniae*. and Legionella spp.).

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
Extra comments	At entry 34 patients needed mechanical ventilation and 33 had comorbidities (hypertension, IHD, DM, alcohol abuse, chronic liver disease, COPD, chronic renal insufficiency)
Intervention 1	Antibiotic plus glucocorticosteroid ~ Antibiotic (according to guidelines) + hydrocortisone. Hydrocortisone IV as 200 mg loading bolus followed by an infusion (hydrocortisone 240 mg in 500 cc 0.9% saline) at a rate of 10 mg/hour. Initial antibiotic therapy followed the 1993 American Thoracic Society guidelines for the initial management of adults with CAP. **Antibiotics included:** Macrolide (20) Third or fourth generation cephalosporin (10) Fluoroquinolone (5) Anti-pseudomonal penicillin (8) Aminoglycoside (3) Glycopeptide (1) Duration glucocorticosteroid for 7 days; antibiotic variable. Concurrent medication/care: Not stated **(N = 24)**
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Class of antibiotic: Mixed 3. Duration of treatment: BNF/SPC concordant 4. Route of administration of antibiotic: IV 5. Route of administration of glucocorticosteroid: IV 6. Glucocorticosteroid dose: BNF/SPC concordant 7. Type of glucocorticosteroid: Hydrocortisone
Intervention 2	Antibiotic plus placebo ~ Antibiotic (not specified or mixed; according to local/national guidelines) + placebo. Placebo (saline) IV in same volume as glucocorticosteroid Initial antibiotic therapy followed the 1993 American Thoracic Society guidelines for the initial management of adults with CAP. **Antibiotics included:** Macrolide (20) Third or fourth generation cephalosporin (9) Fluoroquinolone (9) Anti-pseudomonal penicillin (5)

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
	Aminoglycoside (5) Glycopeptide (1) Duration Placebo for 7 days; antibiotic variable. Concurrent medication/care: None stated **(N = 24)**
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Class of antibiotic: Mixed 3. Duration of treatment: BNF/SPC concordant 4. Route of administration of antibiotic: IV 5. Route of administration of glucocorticosteroid: Not applicable / Not stated / Unclear 6. Glucocorticosteroid dose: Not applicable / Not stated / Unclear 7. Type of glucocorticosteroid: Not applicable / Not stated / Unclear
Study	**Fernandez-Serrano 2011[37]**
Study type	RCT (Patient randomised; Parallel)
Funding	Academic or government funding
Number of studies (number of participants)	1 (N =n45)
Countries and setting	Conducted in Spain; Setting: Hospital Universitari de Bellvitge
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 9 day intervention and 1 month follow-up after discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Pneumonia was diagnosed on the basis of a lung radiographic opacity and at least two of the following conditions: fever (> 38.5°C), purulent expectoration, pleuritic chest pain, or leukocytosis (white blood cell count of > 10,000/mm³). HAP was excluded based on a definition of pneumonia that developed within 8 days of hospital discharge.
Inclusion criteria	Extensive radiological consolidations (completely affecting at least two lobes); and respiratory failure ($pO_2/FiO_2 < 300$)
Exclusion criteria	Age < 18 years and > 75 years; no written informed consent available; known hypersensitivity to glucocorticosteroids; glucocorticosteroid treatment in the previous 48 h; need for glucocorticosteroid treatment for any reason (asthma, chronic obstructive pulmonary disease (COPD), and so on); uncontrolled diabetes mellitus; active peptic ulcer; active mycobacterial or fungal infection; reported severe immunosuppression; hospital admission during the previous eight days; empyema; extrapulmonary septic manifestations; presence of shock; pre-mortem status; aspiration pneumonia; and need for mechanical ventilation (MV) prior to inclusion in the study.

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
Recruitment/selection of patients	Prospective from all admitted to the hospital with CAP
Age, gender and ethnicity	Age - Median (IQR): Placebo: 61 (48 - 66); glucocorticosteroid: 66 (49 - 70). Gender (M:F): Placebo: 64/36%; glucocorticosteroid: 70/30%. Ethnicity: Unclear
Further population details	1. Age: 75 years or less (18 to 75 years). 2. Comorbidities: Minority with relevant comorbidities (13% with COPD, CVD or diabetes). 3. Predominant disease aetiology*: S. pneumoniae* (Also high proportion *L. pneumophila* (26.7%)).
Extra comments	**Previous antibiotic treatment** had been received in 17% in the steroid group and 23% in the placebo group **Comorbid conditions**: COPD - placebo 2, glucocorticosteroid 4; CVD - placebo 2, glucocorticosteroid 4; diabetes - placebo 4, glucocorticosteroid 2. **Fine score** I n = 0, II n = 4; III n = 13; IV n = 25; V n = 2.
Intervention 1	Antibiotic plus glucocorticosteroid ~ Cephalosporin plus quinolone + methylprednisolone. Empirical antibiotic treatment with IV 1g/day ceftriaxone and 500 mg/day levofloxacin Bolus of 200 mg methylprednisolone 30 minutes before starting antibiotic treatment followed by a maintenance, titrated IV dose of 20 mg every 6 hours for 3 days, then 20 mg per 12 hours for 3 days then 20 mg/day for 3 days. Duration 9 days (cef. IV for full 9 days; quin. IV for 5 days then oral for at least 20 days). Concurrent medication/care: Omeprazole to minimise glucocorticosteroid side effects Insulin to control blood glucose levels if necessary (N = 28)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Class of antibiotic: Mixed 3. Duration of treatment: BNF/SPC concordant 4. Route of administration of antibiotic: IV 5. Route of administration of glucocorticosteroid: IV 6. Glucocorticosteroid dose: BNF/SPC concordant (At top of licensed range). 7. Type of glucocorticosteroid: Methylprednisolone
Intervention 2	Antibiotic plus placebo ~ Cephalosporin plus fluoroquinolone + placebo. Empirical antibiotic treatment with IV 1g/day ceftriaxone and 500 mg/day levofloxacin. Bolus of 200 mg placebo 30 minutes before starting antibiotic treatment followed by a maintenance titrated IV dose of 20 mg every 6

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
	hours for 3 days, then 20 mg per 12 hours for 3 days then 20 mg/day for 3 days. Placebo formulation provided by Sanofi-Aventis. Duration 9 days (cef. IV for full 9 days; quin. IV for 5 days then oral for at least 20 days). Concurrent medication/care: Omeprazole to minimise glucocorticosteroid side effects Insulin to control blood glucose levels if necessary **(N = 28)**
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Class of antibiotic: Mixed (Cephalosporin + quinolone). 3. Duration of treatment: BNF/SPC concordant 4. Route of administration of antibiotic: IV 5. Route of administration of glucocorticosteroid: Not applicable / Not stated / Unclear 6. Glucocorticosteroid dose: Not applicable / Not stated / Unclear 7. Type of glucocorticosteroid: Not applicable / Not stated / Unclear
Study	**Marik 1993[67]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	1 (N = 30)
Countries and setting	Conducted in South Africa; Setting: ICU of teaching hospital
Line of therapy	1st line
Duration of study	Intervention + follow-up: Followed to ICU discharge or death
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis ~ Criteria for diagnosis included radiological confirmation but this was not a requirement; unclear how CAP differentiated from HAP
Inclusion criteria	CAP admitted to the medical admissions ward with three or more of the following criteria (BTS criteria of severe pneumonia): 1) respiratory rate > 30/mm; (2) diastolic BP < 60 mm Hg; (3) confusion;(4) $Pa0_2$ < 55 mm Hg (on room air); (5) WBC count < 4 or > 30 x 10'@/L;(6) serum urea > 7 mmol/l; (7) platelet count < 140 x 10'/L; and (8) radiographic evidence of multilobar involvement.
Exclusion criteria	Allergy to beta-lactam antibiotics, malignancy or receiving immunosuppressive therapy, active TB, HIV, and age < 18 or > 70 years

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
Recruitment/selection of patients	Consecutive patients admitted to the medical admissions ward
Age, gender and ethnicity	Age - Mean (SD): glucocorticosteroid: 31.7 (12.8); placebo: 40.6 (14.7). Gender (M:F): Not reported. Ethnicity: NA
Further population details	1. Age: 75 years or less 2. Comorbidities: Not applicable / Not stated / Unclear 3. Predominant disease aetiology: Not applicable / Not stated / Unclear
Extra comments	Average duration of symptoms on admission: 3.3 (1.8) days; mean APACHE II score: glucocorticosteroid group - 11.2, placebo group - 14.2. Patients in the placebo group generally had a worse clinical condition
Intervention 1	Antibiotic plus glucocorticosteroid ~ Antibiotic (according to guidelines) + hydrocortisone. All initially received ceftriaxone 1 g IV every 6 hours. The first dose was given 30 minutes after hydrocortisone. Additional antibiotics were added according to microbiological results - amikacin, cloxacillin or erythromycin. Hydrocortisone was given as a single 10 mg/kg bolus. Duration Unclear. Concurrent medication/care: Appropriate supportive treatment, including mechanical ventilation and ionotropic support as indicated. (N = 14)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Class of antibiotic: Beta-lactam 3. Duration of treatment: Not applicable / Not stated / Unclear 4. Route of administration of antibiotic: IV 5. Route of administration of glucocorticosteroid: IV 6. Glucocorticosteroid dose: Low 7. Type of glucocorticosteroid: Hydrocortisone
Intervention 2	Antibiotic plus placebo ~ Antibiotic (not specified or mixed; according to local/national guidelines) + placebo. All initially received ceftriaxone 1 g IV every 6 hours. The first dose was given 30 minutes after placebo. Additional antibiotics were added according to microbiological results - amikacin, cloxacillin or erythromycin. Placebo was saline solution given as a single bolus. Duration Unclear. Concurrent medication/care: Appropriate supportive treatment, including mechanical ventilation and ionotropic support as indicated. (N = 16)
Further details	1. Antibiotic dose: Not applicable / Not stated / Unclear 2. Class of antibiotic: Beta-lactam

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
	3. Duration of treatment: Not applicable / Not stated / Unclear 4. Route of administration of antibiotic: Oral 5. Route of administration of glucocorticosteroid: Not applicable / Not stated / Unclear 6. Glucocorticosteroid dose: Not applicable / Not stated / Unclear 7. Type of glucocorticosteroid: Not applicable / Not stated / Unclear
Study	**McHardy 1972[69]**
Study type	RCT (Hospital/practice cluster randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	1 (N = 126)
Countries and setting	Conducted in United Kingdom (Scotland); Setting: Respiratory wards
Line of therapy	Mixed line
Duration of study	Not clear
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis ~ Chest radiograph or clinical evidence if not radiograph was available, but those with only clinical evidence on entry subsequently excluded if no radiological evidence found
Inclusion criteria	Admitted as emergencies to the respiratory wards with a diagnosis of pneumonia (radiological evidence of pneumonia or clinical evidence of pneumonia)
Exclusion criteria	Classed as “desperately ill” and judged to be at risk of dying within 24 hours, if they were known to be hypersensitive to penicillin or ampicillin.
Recruitment/selection of patients	Patients with diabetes mellitus or symptoms of recent peptic ulceration were excluded from the random allocation of prednisolone All patients were randomised at the individual level to either 1 g or 2 g of ampicillin and in some wards patients were randomly allocated to receive adjunctive prednisolone. 'Chemotherapy' before admission had been received in 40% on ampicillin alone (both doses) and 50% and 65% in the steroid groups (1 g and 2 g antibiotic respectively)
Age, gender and ethnicity	Age - Mean (SD): Antibiotic alone: 59; antibiotic plus glucocorticosteroid: 62 years. Gender (M:F): 48.4/51.6%. Ethnicity: Not stated
Further population details	1. Age: All adults (Aged over 12 years). 2. Comorbidities: Not applicable / Not stated / Unclear

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
	3. Predominant disease aetiology: *S. pneumoniae*
Extra comments	71% had no previous pneumonia episodes; 52% were current smokers and 15% ex-smokers; 26% were admitted within 3 days of onset; 20% had mild disease; 64% moderate; and 16% severe as judged by the clinician.
Intervention 1	Antibiotic plus glucocorticosteroid ~ Beta-lactam + prednisolone. Ampicillin 1 g (in 4 divided doses) plus prednisolone 20 mg daily (in 4 divided doses). Both interventions administered orally. Duration 7 days maximum for prednisolone; 7 days minimum for ampicillin, plus an additional 7 days if satisfactory response not achieved. Further treatment beyond 14 days was at the physician's discretion. Concurrent medication/care: Unclear (N = 20)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Class of antibiotic: Beta-lactam (Ampicillin). 3. Duration of treatment: BNF/SPC concordant 4. Route of administration of antibiotic: Oral 5. Route of administration of glucocorticosteroid: Oral 6. Steroid dose: BNF/SPC concordant (20 mg/day). 7. Type of glucocorticosteroid: Prednisolone
Comments	Diabetic patients were excluded from randomisation to this arm
Intervention 2	Antibiotic plus steroid ~ Beta-lactam + prednisolone. Ampicillin 2 g (in 4 divided doses) plus prednisolone 20 mg daily (in 4 divided doses) Both interventions administered orally. Duration 7 days maximum for prednisolone; 7 days minimum for ampicillin, plus an additional 7 days if satisfactory response not achieved. Further treatment beyond 14 days was at the physician's discretion.. Concurrent medication/care: Unclear (N=20)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Class of antibiotic: Beta-lactam (Ampicillin). 3. Duration of treatment: BNF/SPC concordant 4. Route of administration of antibiotic: Oral 5. Route of administration of glucocorticosteroid: Oral 6. Glucocorticosteroid dose: BNF/SPC concordant (20 mg/day). 7. Type of glucocorticosteroid: Prednisolone
Comments	Diabetic patients were excluded from randomisation to this arm
Intervention 3	Antibiotic ~ Beta-lactam. Ampicillin 1 g (in 4 divided doses) plus prednisolone 20 mg daily (in 4 divided doses). Duration 7 days

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
	minimum, plus an additional 7 days if satisfactory response not achieved. Further treatment beyond 14 days was at the physician's discretion. Concurrent medication/care: Unclear (N = 43)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Class of antibiotic: Beta-lactam (Ampicillin). 3. Duration of treatment: BNF/SPC concordant 4. Route of administration of antibiotic: Oral 5. Route of administration of glucocorticosteroid: Not applicable / Not stated / Unclear 6. Glucocorticosteroid dose: Not applicable / Not stated / Unclear 7. Type of glucocorticosteroid: Not applicable / Not stated / Unclear
Intervention 4	Antibiotic ~ Beta-lactam. Ampicillin 2 g (in 4 divided doses) plus prednisolone 20 mg daily (in 4 divided doses). Duration 7 days minimum, plus an additional 7 days if satisfactory response not achieved. Further treatment beyond 14 days was at the physician's discretion. Concurrent medication/care: Unclear (N = 43)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Class of antibiotic: Beta-lactam (Ampicillin). 3. Duration of treatment: BNF/SPC concordant 4. Route of administration of antibiotic: Oral 5. Route of administration of glucocorticosteroid: Not applicable / Not stated / Unclear 6. Glucocorticosteroid dose: Not applicable / Not stated / Unclear 7. Type of glucocorticosteroid: Not applicable / Not stated / Unclear

Study	Meijvis 2011[71]
Study type	RCT (Patient randomised; Parallel)
Funding	No funding
Number of studies (number of participants)	1 (N = 304)
Countries and setting	Conducted in Netherlands; Setting: Two teaching hospitals
Line of therapy	Mixed line
Duration of study	Intervention + follow-up: Treatment (4 days of glucocorticosteroid; antibiotic course as appropriate); control visit at 30 days (convalescent period)

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ New pulmonary infiltrate on chest radiograph plus at least two of the following: cough, sputum production, temperature more than 38°C or lower than 35°C, auscultatory findings consistent with pneumonia, C-reactive protein concentration > 15 mg/l, white blood cell count > 10 x 10(9) cells/L or < 4 x 10(9) cells/l, or > 10% of rods in leucocyte differentiation. CAP defined by exuding those diagnosed > 24 hours after admission.
Inclusion criteria	Age 18 years or over and confirmed CAP
Exclusion criteria	Known congenital or acquired immunodeficiency, or haematological malignant disease; receipt of chemotherapy, oral glucocorticosteroid or immunosuppressive medication in previous six weeks; requiring immediate admission to ICU; pregnant or breastfeeding women.
Recruitment/selection of patients	Prospective enrolment. Antibiotic treatment before admission in 28% in glucocorticosteroid group and 25% in placebo group.
Age, gender and ethnicity	Age - Mean (SD): 63.6. Gender (M:F): 56/44. Ethnicity: 99% white
Further population details	1. Age: All adults (Included both over and under 75s). 2. Comorbidities: Minority with relevant comorbidities (Some had relevant comorbidities but no more than 16%). 3. Predominant disease aetiology: *S. pneumoniae* (Mixed - majority unidentified or *S. pneumoniae*).
Extra comments	Pneumonia severity index risk class (Dexamethasone group / Placebo group); Class 1: 12% / 14%; Class 2: 20% / 22%; Class 3: 16% / 22%; Class 4: 36% / 28%; Class 5: 17% / 14%. Comorbidities at baseline (Dexamethasone group/Placebo group); Neuroplastic disease (6%/7%); Liver disease (1%/0); Congenital heart failure (16%/16%); renal disease (13%/7%); Diabetes (15%/14%); COPD (13%/9%).
Intervention 1	Antibiotic plus glucocorticosteroid ~ Antibiotic (according to guidelines) + dexamethasone. All received dexamethasone (5 mg) intravenously once daily for 4 days; antibiotic choice, duration and administration were at the discretion of the medical team and in accordance with national guidelines. All patients received antibiotics within 4 hours of hospital admission; antibiotic treatment modified based on outcome of microbiological tests. Mean time to switching to oral antibiotics = 5.0 days (SD 4.2). 87% completed the 4-day course of study treatment. **Antibiotics used:** Amoxicillin in 61 (40.4%) Amoxicillin plus macrolide in 14 (9.3%) Amoxicillin plus fluoroquinolone in 12 (7.9%) Cephalosporin in 43 (28.5%)

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
	Cephalosporin combinations with macrolide/fluoroquinolone in 14 (9.3%) Other 7 (4.7%) Amoxicillin/clavulanic acid in 4 (3.8%). Duration 4 days for glucocorticosteroid; variable for antibiotics. Concurrent medication/care: None stated (N = 151)
Further details	1. Antibiotic dose: BNF/SPC concordant (According to national guidance). 2. Class of antibiotic: Mixed 3. Duration of treatment: BNF/SPC concordant (4 days for glucocorticosteroid; according to national guidance for antibiotics). 4. Route of administration of antibiotic: Mixed 5. Route of administration of glucocorticosteroid: IV 6. Glucocorticosteroid dose: BNF/SPC concordant (5 mg/day). 7. Type of glucocorticosteroid: Dexamethasone
Comments	Glucocorticosteroid given within a maximum of 12 hours of admission; all patients received antibiotics before the glucocorticosteroid was given.
Intervention 2	Antibiotic plus placebo ~ Antibiotic (not specified or mixed; according to local/national guidelines) + placebo. All patients received antibiotics within 4 hours of hospital admission. Mean time to switching to oral antibiotics = 5.1 days (SD 3.5). 88% completed the 4-day course of study treatment. **Antibiotics used:** Amoxicillin in 74 (48.4%) Amoxicillin plus macrolide in 10 (6.5%) Amoxicillin plus fluoroquinolone in 9 (5.9%) Cephalosporin in 40 (26.1%) Cephalosporin combinations with macrolide/fluoroquinolone in 8 (5.3%) Other 12 (8%). Duration 4 days for placebo; variable for antibiotics. Concurrent medication/care: None stated (N = 153)
Further details	1. Antibiotic dose: Not applicable / Not stated / Unclear 2. Class of antibiotic: Not applicable / Not stated / Unclear

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
	3. Duration of treatment: Not applicable / Not stated / Unclear 4. Route of administration of antibiotic: Not applicable / Not stated / Unclear 5. Route of administration of glucocorticosteroid: Not applicable / Not stated / Unclear 6. Glucocorticosteroid dose: Not applicable / Not stated / Unclear 7. Type of glucocorticosteroid: Not applicable / Not stated / Unclear
Comments	Placebo given within a maximum of 12 hours of admission; all patients received antibiotics before the placebo was given.

Study	Mikami 2007[76]
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	1 (N = 31)
Countries and setting	Conducted in Japan; Setting: Kanto Central Hospital
Line of therapy	1st line
Duration of study	Intervention + follow-up: Unclear duration of follow-up
Method of assessment of guideline condition	Unclear method of assessment/diagnosis ~ Diagnosis of CAP was based on clinical signs and symptoms of LRTI. Radiographic abnormalities consistent with infection were neither pre-existing nor caused by any other previous conditions (unclear if all had new consolidations on X-ray). None had been transferred from nursing facilities or admitted to hospital during 3 months prior to study entry
Inclusion criteria	Patients hospitalised for CAP
Exclusion criteria	HIV infection, impaired immune systems, collagen vascular disease, interstitial pneumonia, COPD, asthma requiring 10 mg prednisolone at least daily, cerebrovascular disease or other neurologic disorder that significantly impairs daily activity, active malignant neoplasm, CHF, liver cirrhosis, HAP, sepsis, mechanical ventilation or non-invasive positive pressure ventilation on day of admission, and severe CAP that required ICU admission according to ATS criteria.
Recruitment/selection of patients	Of 60 eligible patients from prospective recruitment only 31 were randomised; 6 declined to participate but 23 (38%) were not invited to participate for undisclosed 'logistical' reasons
Age, gender and ethnicity	Age - Mean (SD): Glucocorticosteroid group: 75.9 (16.0); placebo group: 68.4 (22.8). Gender (M:F): 74/26%. Ethnicity: NA
Further population details	1. Age: All adults (High mean age). 2. Comorbidities: Minority with relevant comorbidities (COPD excluded).

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
	3. Predominant disease aetiology: No dominant pathogen (Only 39% of sputum cultures were positive).
Extra comments	**PORT risk classes**: I n = 3; II n = 2; III n = 9; IV n = 14; V n = 3. **Mean PSI:** 94.8 ± 29.9 in glucocorticosteroid group and 85.9 ± 31.6 in control group. Very strict exclusion criteria.
Intervention 1	Antibiotic plus glucocorticosteroid ~ Antibiotic (according to guidelines) + prednisolone. Antibiotics (IV) within 8 hours of hospital arrival and modified based on culture results. Selection and duration of antibiotics was decided by the treating physician. Prednisolone 40 mg in 100 ml saline IV. Duration 3 days for glucocorticosteroid; variable for antibiotics. Concurrent medication/care: Not stated (N = 15)
Further details	1. Antibiotic dose: Not applicable / Not stated / Unclear 2. Class of antibiotic: Mixed (Generally ampicillin/sulbactam or carbapenem; macrolides in 42%.). 3. Duration of treatment: Not applicable / Not stated / Unclear 4. Route of administration of antibiotic: IV 5. Route of administration of glucocorticosteroid: IV 6. Glucocorticosteroid dose: BNF/SPC concordant 7. Type of glucocorticosteroid: Prednisolone
Comments	Antibiotic choice not based on a protocol but generally ampicillin/sulbactam or carbapenem, although macrolides were used in 42%.
Intervention 2	Antibiotic ~ Antibiotic (not specified or mixed; according to local/national guidance). Antibiotics (IV) within 8 hours of hospital arrival and modified based on culture results. Selection and duration of antibiotics was decided by the treating physician. Duration Variable. Concurrent medication/care: Not stated (N = 16)
Further details	1. Antibiotic dose: Not applicable / Not stated / Unclear 2. Class of antibiotic: Mixed 3. Duration of treatment: Not applicable / Not stated / Unclear 4. Route of administration of antibiotic: IV 5. Route of administration of glucocorticosteroid: Not applicable / Not stated / Unclear 6. Glucocorticosteroid dose: Not applicable / Not stated / Unclear 7. Type of glucocorticosteroid: Not applicable / Not stated / Unclear
Comments	Antibiotic choice not based on a protocol but generally ampicillin/sulbactam or carbapenem, although macrolides were used in 42%.
Study	**Sabry 2011[90]**

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
Study type	RCT (Patient randomised; Parallel)
Funding	No funding
Number of studies (number of participants)	1 (N = 80)
Countries and setting	Conducted in Egypt; Setting: ITU/critical care unit
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 8 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinical factors and radiographic evidence
Inclusion criteria	Presence of CAP, including two minor or one major 1998 American Thoracic Society (ATS) criterion for severe pneumonia which is modified in 2007. Minor criteria included: Respiratory rate > 30 bpm on admission; Ratio of PaO2 to fraction of inspired oxygen (PaO_2:FIO_2) < 250; Chest radiograph showing bilateral involvement or multilobar involvement; Systolic blood pressure < 90 mm Hg; or diastolic blood pressure < 60 mm Hg. Major criteria included: requirement of MV; Increase in the size of opacities on chest radiograph of ≥ 50% at 48 hours; Requirement of vasopressors > 4 hours; or serum creatinine ≥ 2 mg/dl or more.
Exclusion criteria	Children; Aspiration or hospital acquired pneumonia; Discharge from hospital within the previous 14 days; Transferred from another hospital; Immunosuppressed patients; Chronic chest disease; TB, obstructive pneumonia; cystic fibrosis, bronchiectasis; Concomitant infections (e.g., sinusitis, urinary tract infections); Congestive heart failure (CHF); Chronic renal or hepatic disease; Acute burn injury; Malignancy; Pregnancy; and Major gastrointestinal bleed within 3 months of the current hospitalization.
Recruitment/selection of patients	Consecutive patients between July 2010 and January 2011 at 2 hospitals in Egypt
Age, gender and ethnicity	Age - Mean (SD): glucocorticosteroid group: 61.95 (6.97); placebo group: 62.5 (4.26). Gender (M:F): 72.5/27.5%. Ethnicity: Egyptian
Further population details	1. Age: All adults 2. Comorbidities: Not applicable / Not stated / Unclear 3. Predominant disease aetiology: *S. pneumoniae*
Intervention 1	Antibiotic plus steroid ~ Antibiotic (according to guidelines) + hydrocortisone. Maximal conventional therapy plus intravenous hydrocortisone (loading dose of 200 mg over 30 minutes, followed by 300 mg in 500 ml 0.9% saline at a rate of 12.5 mg/hr). Standard therapy was continued after day 7. Duration 7 days. Concurrent medication/care: Not stated (N = 40)
Further details	1. Antibiotic dose: Low 2. Class of antibiotic: Mixed 3. Duration of treatment: BNF/SPC concordant 4. Route of administration of antibiotic: IV

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
	5. Route of administration of glucocorticosteroid: IV 6. Glucocorticosteroid dose: Low 7. Type of glucocorticosteroid: Hydrocortisone
Intervention 2	Antibiotic plus placebo ~ Antibiotic (not specified or mixed; according to local/national guidelines) + placebo. Maximal conventional therapy plus equal volume of intravenous normal saline solution as placebo. Standard therapy was continued after day 7. Duration 7 days. Concurrent medication/care: Not stated (N = 40)
Further details	1. Antibiotic dose: Low 2. Class of antibiotic: Mixed 3. Duration of treatment: BNF/SPC concordant 4. Route of administration of antibiotic: IV 5. Route of administration of glucocorticosteroid: IV 6. Glucocorticosteroid dose: Low 7. Type of glucocorticosteroid: Hydrocortisone
Comments	Almost all patients initially treated empirically with IV antibiotics

Study	Snijders 2010[97]
Study type	RCT (Patient randomised; Parallel)
Funding	Other author(s) funded by industry
Number of studies (number of participants)	1 (N = 213)
Countries and setting	Conducted in Netherlands; Setting: Teaching hospital
Line of therapy	Mixed line
Duration of study	Intervention + follow-up: 7 days treatment plus follow-up to 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ New consolidations on chest radiograph plus clinical symptoms suggestive of CAP. HAP was excluded based on a definition of pneumonia that developed within 8 days of hospital discharge.
Inclusion criteria	Written informed consent obtained; clinical symptoms suggestive of CAP (cough with or without sputum, fever > 38.5°C, pleuritic chest pain, or dyspnoea; new consolidations on chest radiograph; age 18 years or over.
Exclusion criteria	Presence of severe immunosuppression (HIV, immunosuppressant use); malignancy; pregnancy or breast feeding; use of macrolides for >24 hours; use of prednisolone ≥ 15mg for > 24 hours; any condition requiring glucocorticosteroids;

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
	any likely infection other than CAP; obstructive pneumonia; pneumonia that developed within 8 days of hospital discharge.
Recruitment/selection of patients	Prospective enrolment. 25% in the glucocorticosteroid group and 22% in the placebo group received antibiotics before admission
Age, gender and ethnicity	Age - Mean (SD): 63.5 (18.2). Gender (M:F): 57.9/42.1%. Ethnicity: NA
Further population details	1. Age: All adults (Included both over and under 75s). 2. Comorbidities: Minority with relevant comorbidities (Some had relevant comorbidities but no more than 23% with any one condition). 3. Predominant disease aetiology: S*. pneumoniae* (Mixed - majority unidentified or *S. pneumoniae*).
Extra comments	Baseline characteristics (prednisolone group n = 104/placebo group n = 109). Age (years): 63.0 (17.9)/64.0 (18.7); Male: 52.9%/63.3%; CURB65 ≥ 3: 28/26; PSI IV-V: 48/45. COPD 18.4/22.0%; asthma 7.9/9.5%; diabetes 9.6/11.0%; neurological disease 6.8/10.1%; chronic heart disease 9.7/22.2% 33.3-47.8% in Category 1 (mild pneumonia), likely to have received initial oral therapy
Intervention 1	Antibiotic plus glucocorticosteroid ~ Antibiotic (according to guidelines) + prednisolone. 40 mg prednisolone once daily by the same mode of administration as the antibiotics, which was at the discretion of the medical team (IV or oral); antibiotic choice was according to national guidance; when patients were switched from IV to oral antibiotics the study drug was also switched. **Antibiotics used:** Amoxicillin in 58 (55.8%) Moxifloxacin in 42 (40.4%) Amoxicillin/clavulanic acid in 4 (3.8%). Duration 7 days for glucocorticosteroid; variable for antibiotic. Concurrent medication/care: None stated (N = 104)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Class of antibiotic: Mixed (Penicillins, fluoroquinolones and combinations). 3. Duration of treatment: BNF/SPC concordant 4. Route of administration of antibiotic: Mixed 5. Route of administration of glucocorticosteroid: Mixed (Same route as antibiotic).

Review question	Glucocorticosteroid plus antibiotic compared with antibiotic alone in hospital
	6. Glucocorticosteroid dose: BNF/SPC concordant 7. Type of glucocorticosteroid: Prednisolone
Intervention 2	Antibiotic plus placebo ~ Antibiotic (not specified or mixed; according to local/national guidelines) + placebo. Placebo once daily by the same mode of administration as the antibiotics, which was at the discretion of the medical team (IV or oral); antibiotic choice was according to national guidance; when patients were switched from IV to oral antibiotics the study drug was also switched. **Antibiotics used:** Amoxicillin in 64 (58.7%) Moxifloxacin in 38 (34.9%) Amoxicillin/clavulanic acid in 5 (4.6%) Amoxicillin and acyclovir in 1 (0.9%) Ciprofloxacin and cefuroxime in 1 (0.9%). Duration 7 days for placebo; variable for antibiotic. Concurrent medication/care: None stated (N = 109)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Class of antibiotic: Mixed 3. Duration of treatment: BNF/SPC concordant 4. Route of administration of antibiotic: Mixed (IV and oral). 5. Route of administration of glucocorticosteroid: Not applicable / Not stated / Unclear 6. Glucocorticosteroid dose: Not applicable / Not stated / Unclear 7. Type of glucocorticosteroid: Not applicable / Not stated / Unclear

1.5.1.1.2 *Results – dichotomous*

Key: NR = outcome not reported for this study; TTE = results reported as time to event data and shown in that table; similarly 'dich' for dichotomous, 'con' for continuous and 'gen' for a general method of reporting outcomes.

Study	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl
Stratum: Community-acquired pneumonia. Comparison: Antibiotic (according to guidelines) + dexamethasone compared with antibiotic (not specified or mixed; according to local/national guidelines) + placebo														
Protocol outcomes -->	**Numbers randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Ventilatory or ionotropic support @ End of follow-up**		**Hyperglycaemia @ End of follow-up**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**	
Meijvis 2011[71]			Mortality @ 30 days		NR		NR		Hyperglycaemia (non-fasting glucose > 11 mmol/l(17)) @ up to 30 days		NR		Superinfection, empyema or pleural effusion @ up to 30 days Glucocorticosteroid group: 7 empyema or pleural effusion, 7 superinfection; placebo group: 5 empyema or pleural effusion, 5 superinfection	
	151	153	9/151	11/153	NR	NR	NR	NR	67/151	35/153	NR	NR	14/151	10/153
Stratum: Community-acquired pneumonia. Comparison: Antibiotic (according to guidelines) + hydrocortisone compared with antibiotic (not specified or mixed;														

Study	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl
according to local/national guidelines) + placebo														
Protocol outcomes -->	**Numbers randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Ventilatory or ionotropic support @ End of follow-up**		**Hyperglycaemia @ End of follow-up**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**	
Sabry 2011[90]			ICU mortality @ 8 days				Mechanical ventilation @ 8 days At study day 1 the numbers on mechanical ventilation were: steroid group 26/40; control group 34/40						Complications (MODS and lung abscess) @ 8 days 12/40 and 26/40 had MODS; 0/40 and 2/40 had lung abscess	
	40	40	2/40	6/40	NR	NR	10/40	26/40	NR	NR	NR	NR	12/40	28/40
Confalonieri 2005[27]			Mortality @ 60 days All deaths occurred before study day 28. Causes were: septic shock (4), ARDS (1), hypoxemic respiratory failure (1), MODS (1) and recurrent		NR		Mechanical ventilation @ 8 days		NR		NR		MODS @ 8 days	

Study	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl
			pneumonia (1).											
	24	24	0/23	8/23	NR	NR	6/23	15/23	NR	NR	NR	NR	8/23	16/23
			Mortality @ 8 days											
	24	24	0/23	2/23										
Marik 1993[67]			Mortality @ Up to death or discharge from ICU		NR		Ventilatory support @ Until discharge or death		NR		NR		NR	
	14	16	1/14	3/16	NR	NR	2/14	4/16	NR	NR	NR	NR	NR	NR
Stratum: Community-acquired pneumonia. Comparison: Antibiotic (according to guidelines) + prednisolone compared with antibiotic (not specified or mixed; according to local/national guidelines) + placebo														
Protocol outcomes -->	**Numbers randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Ventilatory or ionotropic support @ End of follow-up**		**Hyperglycaemia @ End of follow-up**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**	
Snijders 2010[97]			Mortality @ 30 days		Resolution or improvement of symptoms and clinical signs related to pneumonia without the need for additional or alternative therapy @ Day 7		NR		Hyperglycaemia with need for additional therapy @ Unclear		Withdrawal due to adverse events (end of treatment) @ Day 7 or 30 (unclear) ACA - self-calculated		Superinfection, pleural effusion or empyema @ Unclear In glucocorticosteroid group 6 with pleural effusion or empyema and 10 with	

Study	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl
					Don't double count with time-to-event outcome								superinfection; in control group 1 with pleural effusion and 4 with superinfection	
	104	109	6/104	6/109	84/104	93/109	NR	NR	5/104	2/109	3/100	4/106	16/104	5/109
					Resolution or improvement of symptoms and clinical signs related to pneumonia without the need for additional or alternative therapy @ Day 30 Don't double count with time-to-event outcome									
	104	109			69/104	84/109								
Stratum: Community-acquired pneumonia. Comparison: Cephalosporin plus quinolone + methylprednisolone compared with cephalosporin plus fluoroquinolone + placebo														
Protocol outcomes -->	**Numbers randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Ventilatory or ionotropic support @ End of follow-up**		**Hyperglycaemia @ End of follow-up**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**	

Study	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl
Fernandez-Serrano 2011[37]			Mortality @ up to 30 days post-discharge		Median time to resolution of morbidity (calculated using a semi-quantitative score - days between randomization & first day when all of the following occurred: improvement or stability of all abnormalities on chest radiograph by comparison with previous serial films, respiratory rate ≤ 24 breaths/min for 24 hours, oral temperature ≤ 37.97°C for 24 hours, and normalized oxygenation, defined as $PaO_2/FiO_2 \geq 285$ or ≥ 90% O_2 saturation on room air). @ Unclear		Requiring mechanical ventilation		NR		NR		NR	
	28	28	1/28	1/28	Gen.	Gen	1/28	5/28	NR	NR	NR	NR	NR	NR

Study	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl
Stratum: Community-acquired pneumonia. Comparison: Oral beta-lactam + prednisolone compared with Beta-lactam														
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Ventilatory or ionotropic support @ End of follow-up**		**Hyperglycaemia @ End of follow-up**		**Withdrawal due to adverse events @ End of treatment**		**Complications (composite of empyema, effusion, abscess, metastatic infection) @ End of follow-up**	
McHardy 1972[69]			Mortality - 1g ampicillin @ Unclear In the steroid group the patient had a cerebrovascular accident. In the ampicillin alone group 6 died due to pneumonia-related causes and one from bronchogenic carcinoma.		NR		NR		NR		NR		NR	
	20	43	1/20	7/43	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
McHardy 1972[69]			Mortality - 2g ampicillin @ Unclear In the glucocorticosteroid group the		NR		NR		NR		NR		NR	

Study	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl
			patient had a cerebrovascular accident. In the ampicillin alone group 6 died due to pneumonia-related causes and one from bronchogenic carcinoma.											
	20	43	2/20	2/43	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

1.5.1.2.1 *Results – continuous*

Study	Exp	Ctrl	Exp	Ctrl
Stratum: Community-acquired pneumonia. Comparison: Antibiotic (according to guidelines) + prednisolone compared with antibiotic (not specified or mixed; according to local/national guidelines) + placebo				
Protocol outcomes -->	**Numbers randomised**		**Clinical cure @ End of treatment**	
Snijders 2010[97]			Mean time to clinical stability @ up to 90 days	
	104	109	4.9(SD 6.8); n = 104	4.9(SD 5.2); n = 109

1.5.1.2.2 *Results – time to event*

Study	Exp	Ctrl	Exp vs Ctrl	Exp vs Ctrl
Stratum: Community-acquired pneumonia. Comparison: Antibiotic (according to guidelines) + dexamethasone compared with antibiotic (not specified or mixed; according to local/national guidelines) + placebo				
Protocol outcomes -->	**Numbers randomised**		**Length of hospital stay @ End of follow-up**	**Clinical cure @ End of treatment**
Meijvis 2011[71]			Days to hospital discharge or death @ 30 days HR calculation based on discharge figures; general rule for hospital discharge was that patients were clinically stable and in a condition to leave hospital	NR
	151	153	HR 1.46 (95%CI 1.13 to 1.89) Reported	NR
Stratum: Community-acquired pneumonia. Comparison: Antibiotic (according to guidelines) + prednisolone compared with antibiotic (not specified or mixed; according to local/national guidelines) + placebo				
Protocol outcomes -->	**Numbers randomised**		**Length of hospital stay @ End of follow-up**	**Clinical cure @ End of treatment**
Snijders 2010[97]			Time to discharge @ up to 90 days	Time to clinical stability (clinical stability defined as meeting all four of the following criteria: improvement of cough and shortness of breath, temperature less than 37.8°C for at least 8 hours, declining serum CRP levels, and adequate oral intake and gastrointestinal absorption). @ up to 40 days
	104	109	HR 1.15 (95%CI 0.81 to 1.55) Reported	HR 1.14 (95%CI 0.82 to 1.59) Reported

1.5.1.2.3 *Results – general*

Study	Exp	Ctrl	Exp vs Ctrl	Exp vs Ctrl	Exp vs Ctrl
Stratum: Community-acquired pneumonia. Comparison: Antibiotic (according to guidelines) + dexamethasone compared with antibiotic (not specified or mixed; according to local/national guidelines) + placebo					
Protocol outcomes -->	**Numbers randomised**		**Quality-of-life @ End of follow-up**	**Length of hospital stay @ End of follow-up**	**Clinical cure @ End of treatment**
Meijvis 2011[71]			Quality-of-life: SF-36 @ 30 days	Days to hospital discharge or death @ 30 days	NR
	151	153	Mean p = 0.0091 for social functioning scale at 30 days; no significant differences at 3 days	(Median (IQR) glucocorticosteroid group: 6.5 (5.0 - 6.0); placebo group: 7.5 (5.3 - 11.5))	NR
Stratum: Community-acquired pneumonia. Comparison: Antibiotic (according to guidelines) + hydrocortisone compared with antibiotic (not specified or mixed; according to local/national guidelines) + placebo					
Protocol outcomes -->	**Numbers randomised**		**Quality-of-life @ End of follow-up**	**Length of hospital stay @ End of follow-up**	**Clinical cure @ End of treatment**
Confalonieri 2005[27]			NR	Median length of hospital stay @ 60 days	NR
	24	24	NR	(Median (range) glucocorticosteroid: 13 (10 - 53); placebo: 21 (3 - 72))	NR
Stratum: Community-acquired pneumonia. Comparison: Cephalosporin plus quinolone + methylprednisolone compared with cephalosporin plus fluoroquinolone + placebo					
Protocol outcomes -->	**Numbers randomised**		**Quality-of-life @ End of follow-up**	**Length of hospital stay @ End of follow-up**	**Clinical cure @ End of treatment**
Fernandez-Serrano 2011[37]				Median total hospital stay @ Unclear	Median time to resolution of morbidity (calculated using a semi-quantitative score - days between randomization & first day when all of the following occurred:

Study	Exp	Ctrl	Exp vs Ctrl	Exp vs Ctrl	Exp vs Ctrl
					improvement or stability of all abnormalities on chest radiograph by comparison with previous serial films, respiratory rate ≤ 24 breaths/min for 24 hours, oral temperature ≤ 37.97°C for 24 hours, and normalized oxygenation, defined as PaO_2/FiO_2 ≥ 285 or ≥ 90% O_2 saturation on room air). @ Unclear
	28	28	NR	(Median (IQR) Glucocorticosteroid: 10 (9 - 13); Placebo: 12 (9 - 18))	(Median (IQR) glucocorticosteroid: 5 (2 - 6); Placebo: 7 (3 - 10))

1.6 Gas exchange

1.6.1 CPAP compared with standard care (Cosentini 2010[28])

Reference	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Comments
Cosentini 2010[28] **Study type:** Multicentre, prospective, open-label, controlled trial in parallel groups **Selection / patient setting:** Patients with moderate hypoxemic ARF due to CAP treated in four ED in Italy between January 2006 and February 2008 Patients were randomised using a computer-generated randomisation list unique for each centre. Sequentially numbered, opaque sealed envelopes were used for allocation concealment. The block size was known only to the study statistician	**Total N:** 47 **N (CPAP):** 20 **N (Standard therapy):** 27 **Inclusion criteria:** Age ≥18 years, diagnosis of CAP as the only cause of ARF, respiratory rate ≤ 35 breaths/min, and PaO_2/FIO_2 ratio ≥ 200 and ≤ 300 evaluated during oxygen therapy **Exclusion criteria:** HAP, immunosuppression, acute cardiogenic pulmonary oedema, unstable angina	**Pneumonia definition:** CAP was defined as the presence of new pulmonary infiltrate on CXR with at least one of the following: new or increased cough, abnormal temperature, leucocytosis or leukopenia, **Age, mean (SD):** **-CPAP:** 65 (17) -**Control:** 72 (13) **Gender: female, n (%):** **-CPAP:** 6 (30) -**Control:** 11 (41) **Comorbidities > 10%, n (%):** **-CPAP:** Cardiovascular disease: 10 (50) COPD: 5 (25) Liver disease: 2 (10)	**CPAP** delivered through a high-flow generator (90 to 140 L/min) using a helmet as interface with a PEEP valve. CPAP was applied with an initial PEEP of 10 cm H_2O and with a FiO_2 set to maintain a pulse oximetry 92%. PEEP value was maintained at 10 cm H_2O until CPAP removal	**Standard oxygen therapy** supplied through a Venturi mask with an FiO_2 delivered to maintain a pulse oximetry 92%	48 hours	**Outcome 1: Median time to reach $PaO_2/FiO_2 \geq 315$:** -CPAP: 1.5 h -Control: 48 h P < 0.001 **Outcome 2: Proportion of patients who reached PaO2/FiO2 ≥ 315:** -CPAP: 95% (95%CI 85%-100%) -Control: 30% (95%CI 12%-47%) P < 0.001 [Participants who did not reach this threshold level before the last planned arterial blood gas (ABG) measurement at 48 hours were considered as failures] **Outcome 3: PaO_2/FiO_2 (SD) at baseline and 1 hour** -CPAP: Baseline: 249 (25) 1 hour: 349 (69)	**Funding:** NR **Limitations:** Based on 80% power to detect a significant difference with α error ≤ 0.05 two-tailed, 120 patients were required for each study arm. However, the study was prematurely interrupted after recruiting 47 patients because patients randomised to CPAP reached the endpoint more quickly than anticipated in the protocol Outcome was a surrogate of clinical improvement, and the follow up period was very short (48 hours) **Notes:** Population was treated outside the ICU and included patients with

Reference	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Comments
Addressing missing data/non reliability of data: Only 2 participants (4.3%) lost to follow-up. Missing values of PaO_2/FiO_2 ratio were replaced with the LOCF. In the CPAP group, ¼ of patients missed the re-evaluation after 1 hour of treatment **Statistical analysis (including confounders adjusted for):** ITT univariate and repeated measures of variance, COX survival analysis	or acute myocardial infarction, respiratory acidosis, failure of three or more organs, systolic BP < 90 mmHg despite fluid resuscitation or vasopressors, severe arrhythmias, contraindications to CPAP treatment, or pregnancy	Diabetes: 3 (15) **-Control:** Cardiovascular disease: 15 (58) COPD: 5 (19) Liver disease: 1 (3.7) Diabetes: 5 (19) All patients had one single organ failure **Disease severity-SAPSII score (SD):** - CPAP: 21 (7.4) - Control: 21 (5.7) **PaO_2/FiO_2 (SD):** - CPAP:249 (25) - Control: 256 (20)				-Control: Baseline: 246 (20) 1 hour: 244 (51) P < 0.001 **Outcome 4: Cox analysis – adjusted for centre, age, and baseline PaO_2/FiO_2 ratio:** CPAP was the only predictor for reaching the endpoint: HR 11.3 (95% CI 3.51-36.32) No patients were intubated No patients died	CAP and early, moderate and hypoxemic ARF No centre effect was found

1.6.2 CPAP compared with standard care (Confalonieri 1999[26])

Reference	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size	Comments
Confalonieri 1999[26] **Study type:** Multicentre, prospective, randomised controlled trial **Selection / patient setting:** Consecutive patients with severe CAP admitted to three ITU in Italy Patients were randomised using computer-generated random assignments. Sealed envelopes were used to ensure allocation concealment. No information was provided regarding blinding.	**Total N:** 56 **N (CPAP):** 28 **N (Standard therapy):** 28 **Inclusion criteria:** Participants with severe CAP and acute respiratory failure (ARF) **Exclusion criteria:** Requirement for emergency intubation for cardiopulmonary resuscitation, respiratory arrest, severe haemodynamic instability, encephalopathy, severe neurologic disease, concomitant severe disease with an expectation of life less than 4 months (for example,	**Pneumonia definition:** criteria for severe CAP were 1 or more of the American Thoracic Society (ATS) non-respiratory criteria and the criteria for severe ARF were 2 or more of the following criteria: 1) acute respiratory distress including severe dyspnoea at rest and a respiratory rate (RR) > 35 breaths/min and/or active contraction of the accessory muscles of respiration or paradoxical abdominal motion 2) PaO_2 < 68 mmHg while receiving a fraction of inspired oxygen (FiO_2) ≥ 0.4, or a ratio of the partial pressure of	**CPAP** delivered through a full face mask and standard oxygen supplementation through a Venturi mask	**Standard therapy** consisted of medical management and oxygen supplementation, and included initial antibiotics following the ATS guidelines. Medical management was similar in the 2 groups	2 months	**Outcome 1: Hospital mortality** **CPAP, n (%)** / **Standard, n (%)** **All patients (n = 56)**: 7 (25) / 6 (21.4) **With COPD (n = 23)**: 1 (8.3) / 2 (18.2) **Without COPD (n = 33)**: 6 (37.5) / 4 (23.5) **Outcome 2: Need for intubation** **CPAP, n (%)** / **Standard, n (%)** **All patients (n = 56)**: 6 (21) / 17 (61) **With COPD (n = 23)**: 0 / 6 (54.6) **Without COPD (n = 33)**: 6 (37.5) / 8 (47.1) **Outcome 3: Duration of intubation** **CPAP, days (SD)** / **Standard, days (SD)** **All**: 7 (3) / 10 (3)	**Funding:** NR **Limitations:** Microbiological diagnosis of CAP was not confirmed in half of the patients, as they were receiving antibiotic treatment at the time of ITU admission **Notes:**

Reference	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size			Comments
Addressing missing data/non reliability of data: No participants lost to follow-up **Statistical analysis (including confounders adjusted for):** t tests, Mann-Whitney U tests, Chi square tests, ANOVA, multiple logistic regression analysis	advanced cancer), long-term oxygen therapy or home mechanical ventilation, contraindications for using masks (tracheostomy or facial deformities), or inability to expectorate	arterial oxygen to the fraction of inspired oxygen (PaO_2: FiO_2) < 250, while receiving a FiO_2 > 0.5 3) hypercapnoea (PaCO2 > 50 mmHg) with respiratory acidosis (pH < 7.33) **Age, mean (SD):** **All patients-** -CPAP: 66 (14) -Control: 61 (21) **With COPD-** - CPAP: 68 (4.8) - Control: 73 (5.1) **Without COPD-** - CPAP: 64.2 (4.2) - Control: 53.3 (4.1) **Gender: female, n (%):** **-CPAP:** 5 (17.8) -**Control:** 11 (39.3) **Comorbidities > 10%, n (%):** **-CPAP:** COPD: 12 (42.8) **-Control:**				**patients (n = 56)**			
						With COPD (n = 23)	0 (0.1)	12.3 (3.9)	
						Without COPD (n = 33)	6.8 (4.2)	8.0 (3.4)	
						Outcome 4: Duration of hospital stay			
							CPAP, days (SD)	**Standard, days (SD)**	
						All patients (n = 56)	17 (2)	18 (2)	
						With COPD (n = 23)	14.9 (3.4)	22.5 (3.5)	
						Without COPD (n = 33)	17.9 (2.9)	15.1 (2.8)	
						Outcome 5: Duration of ITU stay			
							CPAP, days (SD)	**Standard, days (SD)**	
						All patients (n = 56)	1.8 (0.7)	6 (2)	
						With COPD (n = 23)	0.25 (2.1)	7.6 (2.2)	

Reference	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures and effect size			Comments
		COPD: 11 (39.3) **Disease severity-APACHE II (SD):** **- CPAP:** 20 (5) **- Control:** 18 (5) **PaO_2/FiO_2 (SD):** **All patients-** - CPAP:183 (36) - Control: 167 (47) **With COPD-** - CPAP:194 (31) - Control: 170 (42) **Without COPD-** - CPAP: 165 (30) - Control: 164 (52)				**Without COPD (n = 33)**	2.9 (1.8)	4.8 (1.7)	

1.7 Monitoring

1.7.1 Randomised data

Reference	Patient Characteristics	Experimental group	Control group	Outcome measures	Effect sizes			Comments
Author and year: Schuetz 2012[92,93] **Study type**: Systematic review and individual patient data meta-analysis **Selection / patient setting:** Any trials in any setting meeting the protocol **Addressing missing data/non reliability of data:** Non-event imputation (with sensitivity analysis for opposite assumption) **Statistical analysis:** All patients were analysed in the study group to which they were randomized. Multivariable hierarchical logistic regression with the following variables: use of PCT algorithm, plus important prognostic factors such as patient age and ARI diagnosis as additional fixed effects. Trial included as a random effect. Sensitivity analyses: quality	**Diagnosis:** initial suspicion of ARI (independent of final diagnosis) **Inclusion criteria:** Patients in eligible randomized or quasi-randomized trials had to be adults with a clinical diagnosis of either upper or lower ARI. **Exclusion criteria:** Trials were excluded if they exclusively focused on paediatric patients or if they used PCT for a purpose other than to guide initiation and duration of antibiotic treatment. Not: no exclusions based on language or publication status of reports **All patients,** N: 14 trials with 4551 patients Exclusions due to: incorrect population (sepsis not related to ARI; n = 340) **Included N:** 4211 **Age, mean:** PCT group – 59.4	**N = 2085 (999 with CAP)** PCT-guided antibiotics (physicians could deviate from algorithm if needed) Similar PCT algorithms used But, one trial in primary care and one in ED used only a single PCT measurement on admission to guide initiation of antibiotics (total of 90 patients with CAP across both groups; approximately 4.4% of total sample),	**N = 2126 (1028 with CAP)** No PCT		**Exp (PCT)**	**Control (no PCT)**	**Adjusted OR or difference***	**Funding:** BRAHMS/Thermo Fisher scientific **Limitations:** unclear if IPD obtained for all trials; different PCT algorithms used between trials but not differentiated in the analysis (~4.4% did not have PCT used for monitoring) and all used PCT for initiation as well as monitoring; publication bias unclear; majority initially seen in ED (unclear how many admitted to hospital ward) **Additional outcomes:** Initiation of
				Multivariable results for those with confirmed CAP				
				Mortality	92/999 (9.2%)	111/1028 (10.8%)	0.89 (0.64-1.23)	
				Treatment failure	190/999 (19.0%)	240/1028 (23.4%)	0.77 (0.62-0.96)	
				Median (IQR) duration of antibiotics	7 (5 - 10)	10 (8 - 14)	-3.34 (-3.79 to -2.88)	
				Total exposure to antibiotics in days, median (IQR)	6 (4 - 10)	10 (8 - 14)	-3.98 (-4.44 to -3.52)	
				*Multivariable hierarchical regression with outcome as dependent variable; PCT group, age, and ARI diagnosis as independent variables; and trial as a random effect.				

Reference	Patient Characteristics	Experimental group	Control group	Outcome measures	Effect sizes	Comments
indicators, alternate definition of treatment failure, excluding trials with low adherence to PCT algorithms (< 70%), excluding all ICU trials. Pre-specified analyses stratified by clinical setting and ARI diagnosis and formally tested for potential subgroup effects by adding the clinical setting and ARI diagnosis in turn to the regression model together with the corresponding interaction term with PCT group as fixed effects. Meta-analyses with aggregate data performed to investigate inconsistency and heterogeneity of effects	(20.1); control group – 60.1 (19.4) **Gender (male/female):** 54.2/45.8% **Comorbidities:** N/A **Clinical setting** Primary care: 24% (2 studies) Emergency department: 62% (7 studies) ICU: 14% (5 studies) **Primary diagnosis** Total upper ARI: 13% Total lower ARI: 87% (majority confirmed CAP)	whereas the most trials used repeated measurements for guiding the duration of treatment				antibiotics **Notes:** -

Reference	Patient Characteristics	Experimental group	Control group	Outcome measures	Effect sizes			Comments
Author and year: Christ-Crain 2006[24] **Study type**: RCT (unblinded) **Selection / patient setting:** Patients with CAP admitted to the emergency department from 2003 to 2005 **Addressing missing data/non reliability of data:** ITT analysis **Statistical analysis:** Chi^2 test and Mann-Whitney U test. Time to discontinuation was compared using the log-rank test. Rate of antibiotic treatment discontinuation was assessed using Cox proportional hazards regression analysis adjusting for PSI Power calculation = sample size gave the study a power of 74% to detect a 10% increase in the	**Diagnosis:** CAP **Inclusion criteria:** Patients aged > 18 years, diagnosis of CAP, defined as new infiltrate on CXR, and the presence of ≥ 1 acute respiratory signs or symptoms (cough, sputum, dyspnoea, temperature > 38 C, abnormal auscultatory findings, abnormal leukocyte count) **Exclusion criteria:** Patients with cystic fibrosis, active pulmonary tuberculosis, HAP, or severely immunocompromised **All patients,** N: 404 Exclusions due to: reasons above, death before inclusion, no informed consent **Included N:** 302 PCT: 151 Control: 151 **Age, mean:** PCT group – 70 (17); control group – 70 (17) **Gender (male %):** 62 **Comorbidities > 10% in both groups – PCT/ control (%):** Coronary heart disease: 33/32 Hypertension: 28/24 Renal: 24/30 Diabetes: 21/19 COPD: 29/21 Neoplastic disease: 17/15	**N = 151** PCT-guided antibiotics • PCT < 0.1 µg/L: antibiotics strongly discouraged • PCT 0.1 to 0.25 µg/L: antibiotics discouraged • PCT 0.25 to 0.5 µg/L: antibiotic initiation or continuation encouraged • PCT > 0.5 µg/L: antibiotics strongly encouraged PCT levels were reassessed at day 4, 6, and 8	**N = 151** Antibiotics were chosen following usual practice guidelines, the physician was unaware of baseline PCT levels.		**PCT**	**Control**	**Difference**	**Funding:** Brahms, Pfizer, and Mepha, and University Hospital Basel **Limitations:** • Open intervention trial • Cohort of mainly elderly patients with a high rate of comorbidities • Limited power to prove the safety of PCT to guide clinical care and assess optimal duration of antibiotics for different types of bacteria, especially atypical pathogens • Mean duration of antibiotics in the control group of 13% appears very long, apart from guideline-recommendations
				Antibiotics withheld at baseline	15%	1%	<0.001	
				Antibiotic discontinuation HR adjusted for PSI (95% CI)	HR in PCT group compared with control: 3.2 (2.5 – 4.2)			
				Antibiotic duration – days mean (SD)	5.8 (5.3)	12.9 (6.5)	<0.001	
				Antibiotics appropriateness, n (%)	124 (97)	144 (97)	0.83	
				Length of hospital stay, days (SD)	12.0 (9.1)	13.0 (6.5)	<0.001	
				Need for ICU stay, n (%)	20 (13)	21 (14)	0.87	
				Pneumonia-related mortality, n (%)	10 (56)	10 (50)	0.73	
				Quality-of-life (higher scores indicates worse quality-of-life)	10 (10)	11 (10)	0.14	
				Clinical cure at follow-up (4 to 6 weeks), n (%)	108 (85)	105 (85)		

Reference	Patient Characteristics	Experimental group	Control group	Outcome measures	Effect sizes			Comments
combined treatment failure and complication rate (10% to 20%)	**Severity (%) – PCT/Control:** PSI < IV (mild to moderate) – 81/85% PSI ≥ IV (severe) – 19/15% **Primary diagnosis** Total upper ARI: 13% Total lower ARI: 87% (majority confirmed CAP) **PCT (µg/L) at baseline:** PCT group, median (IQ range): 0.57 (0.2 – 2.5) Control group, median (IQ range): 0.44 (0.2 – 1.9) **CRP (mg/L) at baseline:** PCT group, median (IQ range): 111 (57 – 204) Control group, median (IQ range): 152 (72 – 212)			**Treatment failure (including deaths and those lost to follow-up), n (%)**	24 (16)	27 (18)	0.65	**Additional outcomes:** Initial antibiotic prescription, pneumonia recurrence, laboratory outcomes, functional status (VAS) **Notes:** Quality-of-life questionnaire for patients with respiratory illnesses, scale not reported
				Clinical and radiologic recurrence, n (%)	4 (3)	4 (3)	1.0	

1.7.2 Observational studies – HR/OR

1.7.2.1 CRP change

Reference	Patient Characteristics	Monitoring procedures performed (including thresholds used, frequency and timing)	Outcomes measures	Effect sizes			Comments
Author and year: Bruns 2008[13] **Study type:** Retrospective analysis based on data from prospective RCT **Selection / patient setting:** Multicentre (5 teaching hospitals and 2 University Medical Centres in the Netherlands) **Addressing missing data/non reliability of data:** not stated **Statistical analysis (including confounders adjusted for):** Calculated adjusted OR, corrected for patient characteristics (age, sex and comorbid illnesses), Pneumonia	**Diagnosis:** CAP **Inclusion criteria:** Adults (> 18 years) admitted due to CAP (defined as at least two symptoms of acute LRTI with onset before hospital admission and a new or progressive pulmonary infiltrate on chest radiograph). **Exclusion criteria:** interstitial pneumonia, cystic fibrosis, history of colonisation with Gram-negative bacteria due to structural damage to the respiratory tract, a life expectancy of < 1 month because of an underling disease, severe neutropenia or HIV infection with a CD4 count < 200 cells/mm^3, infections other than pneumonia necessitating treatment with intravenous antibiotics, and patients admitted directly to ICU **Included N: 289** CRP measurements available from 264 (91.3%) on day 3 and 210 (72.6%) on day 7	CRP measured on admission to ED and days 3 and 7 of hospitalisation Serum concentrations of CRP were measured by monoclonal immunoassay using a VITROS analyser (Ortho-Clinical Diagnostics, Johnson and Johnson, Amersham, UK) The normal reference range for this assay is < 10 mg/l **Appropriate antibiotic treatment** was defined as at least one antibiotic covering all of the causative pathogens identified **Early treatment failure** was defined as clinical instability (respiratory rate > 25 breaths/min; oxygen saturation < 90%; PaO_2 < 7.3 kPa (< 55 mmHg); haemodynamic instability or acute alterations in mental state), ITU admission or mortality in the first 3 days of admission	**Mean decline in CRP**				**Funding:** not stated **Limitations:** restricted population to more severe CAP limits generalisability **Additional outcomes**: - **Notes: -**
				Appropriate treatment (n = 112)	Inappropriate treatment (n = 25)	Mean % difference (95% CI)	
			Day 0 - 3	44.5 ± 30.5	25.2 ± 24.4	19.3 (6.1 - 32.5)	
			Day 0 - 7	75.5 ± 24.7	60.4 ± 32.3	15.1 (1.8 - 28.5)	
			Received inappropriate antibiotic treatment: multivariable analysis				
			Day 0 - 3 decline < 60%	AOR: 6.98 (1.56 - 31.33)			
			Day 0 - 7 decline < 90%	AOR: 3.74 (1.12 - 13.77)			
			28 day mortality: multivariable analysis				
			Day 0 - 3 decline < 60%	AOR: 1.09 (0.32 – 3.73)			
			Day 0 - 7 decline < 90%	AOR: 1.23 (0.45 – 2.99)			
			Early (within 3 days) treatment failure: multivariable analysis				
			Day 0 - 3 decline < 60%	AOR: 1.57 (0.85 – 2.92)			

Reference	Patient Characteristics	Monitoring procedures performed (including thresholds used, frequency and timing)	Outcomes measures	Effect sizes	Comments
Severity Index score, symptoms and signs of pneumonia (cough, sputum production, sore throat, dyspnoea, chest pain, haemoptisis, confusion, blood pressure, respiratory rate, pulse and oxygen saturation) by multivariate assessment. A p-value of < 0.10 in univariable analysis or any clinically relevant parameter was used as an entry criterion for multivariate analysis. A p-value of < 0.05 was considered statistically significant.	**Age, mean:** 69.7 (13.8) years **Gender (male/female):** 65.7/34.3% **Nursing home patients:** not reported **Comorbidities:** 62.3% Congestive heart failure 12.5% Neoplasm 22.5% Liver disease 1.0% Cerebrovascular disease 8.7% Chronic renal disease 9.3% COPD 30.4% **Pneumonia severity:** PSI class IV – 198 (68.5%) V – 52 (18.0%)	**Late treatment failure** was defined as clinical deterioration or complications including mortality, the need for mechanical ventilation, re-administration of intravenous antibiotics after a switch to oral therapy, re-admission for pulmonary infection after discharge, or an increase in body temperature after initial improvement in the follow-up period. **Delayed normalisation** of CRP was defined as a decline of < 60% in CRP levels in 3 days and a decline of < 90% in CRP levels in 7 days.	**Late (within 28 days) treatment failure: multivariable analysis**		
			Day 0 - 3 decline < 60%	AOR: 1.29 (0.62 – 2.68)	
			Day 0 - 7 decline < 90%	AOR: 0.87 (0.39 – 1.94)	
			Overall death rate		
				20/289 (6.9%)	

1.7.2.2 CRP on day 1 or day 3

Reference	Patient Characteristics	Monitoring procedures performed (including thresholds used, frequency and timing)	Outcomes measures	Effect sizes		Comments
Author and year: Menendez 2008[72] **Study type:** Prospective **Selection / patient setting:** Consecutive patients admitted to 2 hospitals **Addressing missing data/non reliability of data:** not stated **Statistical analysis (including confounders adjusted for):** Calculated adjusted OR by multivariate logistic regression analyses to predict any, early and late treatment failure (dependent variables). For early failure prediction, patients with late failure were excluded, and vice versa. Independent variables were initial severity, comorbid condition, cytokine levels and markers. CRP and PCT levels were dichotomised using the values of the 75th percentile for each marker in the non-treatment failure group as the cut-off. Comorbid conditions	**Diagnosis:** CAP **Inclusion criteria:** presence of a new radiographic infiltrate and at least two compatible clinical symptoms **Exclusion criteria:** admission in the previous 15 days, immunosuppressive treatment and/or corticosteroids (> 15 mg/day of prednisone or its equivalent), leukopenia < 1000/mm or neutropenia < 500/mm (except if attributable to CAP) and HIV positive with a CD4 count < 100. **Included N: 453** **Age, mean:** 67.3 (17.1) years **Gender (male/female):** 62/38% **Nursing home patients:** 5.3% **Comorbidities:** Smoking: 21.9% Cardiac failure: 16.8% Renal failure: 5.5% Diabetes: 20.1%	Blood samples were obtained on the first day and after 72 h of treatment An immunoluminometric technique was used to measure PCT (Liaison Brahms PCT; DiaSorin, Saluggia, Italy) with a detection limit of 0.3 ng/ml. CRP was measured with an immunoturbidimetric method using a commercially available test (Bayer Diagnostics, Leverkusen, Germany) **Adequate empiric antibiotic treatment** was defined as active against causal micro-organism identified **Early treatment failure** was defined as clinical deterioration within 72 h of treatment, as indicated by the need for mechanical ventilation and/or shock or death. **Late treatment failure** was defined as persistence or reappearance of fever (> 37.8°C), radiographic	**Multivariable analyses using threshold of 75th percentile**			**Funding:** academic/government (CIBRES) **Limitations:** non-significant results not reported; did not adjust for key confounders; thresholds chosen based on study results **Additional outcomes**: sensitivity, specificity, NPV and PPV of markers on day 1 **Notes: -**
				AOR (95% CI)	**p-value**	
			Overall treatment failure			
			CRP day 1	2.6 (1.5 - 4.6)	0.001	
			PCT day 1	-	-	
			CRP day 3	3.4 (1.7 - 6.7)	0.001	
			PCT day 3	-	-	
			Early treatment failure			
			CRP day 1	2.6 (1.2 - 5.5)	0.01	
			PCT day 1	2.7 (1.3 - 5.8)	0.01	
			Late treatment failure			
			CRP day 1	2.6 (1.3 - 5.3)	0.009	
			PCT day 1	-	-	
			CRP day 3	4.8 (2.1 - 11.2)	0.0001	
			PCT day 3	-	-	

Reference	Patient Characteristics	Monitoring procedures performed (including thresholds used, frequency and timing)	Outcomes measures	Effect sizes	Comments
(COPD, cardiac, liver, renal and CNS diseases) were included in the model and dichotomised into ''yes'' or ''no''. Initial severity was categorised as high (Fine risk classes IV–V) or low (classes I–III). In analysis of day 3 values, day 1 values were also included in the model.	Liver disease: 2.6% COPD: 17.4% **Pneumonia severity:** PSI class by group (failure vs no failure) I – 8% vs 11% II – 11% vs 17% III – 13% vs 23% IV – 36% vs 37% V – 32% vs 12%	progression (> 50% increase), including pleural effusion and/or empyema, nosocomial infection, impairment of respiratory failure (defined as PO_2/FiO_2 < 250 with respiratory rate ≥ 30/min) and need for mechanical ventilation or shock after 72 hours.			

1.7.2.3 CRP change by day 4

Reference	Patient Characteristics	Monitoring procedures performed (including thresholds used, frequency and timing)	Outcomes measures	Effect sizes		Comments
Author and year: Chalmers 2008A[22] **Study type:** Prospective **Selection / patient setting:** Consecutive patients **Addressing missing data/non reliability of data:** unclear **Statistical analysis (including confounders adjusted for):** Multiple logistic regression. Covariates included age, sex, pneumonia severity (using CURB65 score), co-morbidity (chronic cardiac failure, stroke, chronic renal failure, diabetes mellitus), and smoking status. Age was entered into the model as a continuous variable, other variables coded as binary data.	**Diagnosis:** CAP **Inclusion criteria:** adult patients admitted between February 2005 and February 2007 with a primary diagnosis of community-acquired pneumonia: history consistent with pneumonia (1 or more of the following: new-onset shortness of breath, cough, sputum production, haemoptysis, chest pain, new-onset confusion, or pyrexia) and new infiltrates on the chest radiograph. **Exclusion criteria:** Hospital-acquired pneumonia (development of symptoms > 48 hours after admission to hospital or discharge from an acute care facility within 14 days of admission); active thoracic or extrathoracic malignancy; conditions likely to cause diagnostic confusion or where chest radiograph changes are equivocal (e.g. pulmonary fibrosis, allergic bronchopulmonary aspergillosis); chronic lung disease (chronic obstructive pulmonary	CRP measured on admission in all patients and repeated routinely at day 4. CRP was repeated at other times as clinically indicated. Measured by fluorescence polarization immunoassay using an Abbott TDX analyzer and Abbott reagents (Abbott Laboratories, Abbott Park, Ill).	**Change in CRP by day 4**			**Funding:** not stated **Limitations:** high rate of attrition; low ratio of events: covariates **Additional outcomes**: sensitivity, specificity, NPV and PPV of CRP on admission **Notes: -**
				CRP decreased ≥ 50% (n = 175)	**CRP increased or decreased < 50% (n = 93)**	
			30-day mortality	0.5%	18.3%	
			Invasive ventilation/ ionotropic support	1.7%	22.6%	
			Complicated pneumonia*	2.3%	19.4%	
			Multivariable AOR: failure of CRP to fall by 50% at day 4			
			Outcome	**AOR (95% CI)**	**p-value**	
			30-day Mortality	24.5 (6.4 - 93.4)	< 0.0001	
			Need for invasive ventilation or ionotropic support	7.1 (2.8 - 17.8)	< 0.0001	
			Complicated pneumonia*	15.4 (6.32 - 37.6)	< 0.0001	
			*Lung abscess, empyema or complicated			

Reference	Patient Characteristics	Monitoring procedures performed (including thresholds used, frequency and timing)	Outcomes measures	Effect sizes		Comments
	disease, bronchiectasis, chronic asthma); immunosuppression; solid organ transplant; haematological disorders including haematological malignancy; chronic liver disease or cirrhosis; other acute co-morbid illnesses leading to physiological or metabolic derangement such that pneumonia severity assessment would be inappropriate (e.g. acute pulmonary embolism); patients for whom active treatment is not considered appropriate (e.g. palliative care) **Included N: 570** from 936 screened (common exclusion reasons included chronic lung disease, active malignancy, persistent shadowing on chest x-ray at follow-up, lung cancer, HAP and immunosuppression) **NOTE**: only 358 (63%) had repeat measurement at day 4 (but baseline characteristics similar to full sample); majority of those not available had been discharged before 4 days, 26 died or were admitted to ICU and data were		parapneumonic effusion)			
			Hospital re-admission within 7 days among those discharged before day 4 (n = 223; CRP available in 208)			
			Discharge CRP < 100 mg/l	1/162		
			Discharge CRP ≥ 100 mg/l	4/46	p-value = 0.009	

Reference	Patient Characteristics	Monitoring procedures performed (including thresholds used, frequency and timing)	Outcomes measures	Effect sizes	Comments
	missing in 53 **Age, median:** 62 (IQR: 44 - 76) years **Gender (male/female):** 49/51% **Comorbidities:** Chronic cardiac disease: 13.2% Cerebrovascular disease: 8.9% Chronic renal failure: 4.4% Diabetes mellitus: 6.6% Current smokers: 36% **Pneumonia severity:** PSI class I – 14% II – 23% III – 19% IV – 28% V – 16%				

1.7.2.4 CRP on day 3

Reference	Patient Characteristics	Monitoring procedures performed (including thresholds used, frequency and timing)	Outcomes measures	Effect sizes	Comments
Author and year: Menendez 2009B[73] **Study type:** Prospective **Selection / patient setting:** Consecutive patients admitted to 2 hospitals **Addressing missing data/non reliability of data:** not stated **Statistical analysis (including confounders adjusted for):** Multivariable logistic regression analyses were performed to predict the absence of severe complications after day 3 (dependent variable). Independent variables were clinical stability within the first 72 h of treatment, levels of CRP on day 3 and levels of PCT on day 3. In order to calculate the predictive value of markers (CRP and PCT) together with clinical criteria of stability, the area under the ROC curve (AUC) was calculated from the	**Diagnosis:** CAP **Inclusion criteria:** new radiographic infiltrate compatible with the presence of acute pneumonia and at least two signs or symptoms of CAP (e.g. temperature > 38°C, productive cough, chest pain, shortness of breath, crackles on auscultation). **Exclusion criteria:** admission in the previous 15 days, nursing home patients, immunosuppressive treatment and/or glucocorticosteroids (> 15 mg/day of prednisone or its equivalent), leukopenia < 1000/mm^3 or neutropenia < 500/mm^3 (except if attributable to CAP). **Included N:** 394 **Age, mean:** 66.5 (17.2) years **Gender (male/female):** 62/38% **Nursing home patients:** excluded **Comorbidities:**	Blood samples were obtained on the first day and day 3 An immunoluminometric technique was used to measure **PCT** (Liaison Brahms PCT, DiaSorin, Saluggia, Italy) with a detection limit of 0.3 ng/ml. **CRP** was measured with an immunoturbidimetric method using a commercially available test (Bayer Diagnostics) with an Advia 2400 (detection limit 1.5 mg/dl). **Clinical stability** was defined using a modification of Halm's criteria as achieving the following threshold values for all parameters: temperature ≤ 37.2 °C, heart rate ≤ 100 beats/min, respiratory rate ≤ 24 breaths/min, systolic blood pressure ≥ 90 mm Hg and oxygen saturation ≥ 90% or arterial oxygen tension ≥ 60 mm Hg when the patient was not receiving supplemental	**Multivariable analyses for predicting severe complications after 72 h** **Factor** / **AOR (95% CI)** Clinical stability: 0.78 (0.71 - 0.86) CRP < 3 mg/dl day 3: 0.86 (0.77 - 0.97) PCT < 0.25 ng/ml day 3: 1.17 (0.78 - 1.76) **Number of complications** CRP < 3 mg/dl day 3: 3/105 CRP ≥ 3 mg/dl day 3: 24/214 PCT < 0.25 ng/ml day 3: 5/103 PCT ≥ 0.25 ng/ml day 3: 22/213		**Funding:** academic/government (CIBRES) **Limitations:** did not adjust for key confounders; thresholds chosen based on study results **Additional outcomes**: sensitivity, specificity, LRs, NPV and PPV of markers on day 3 **Notes: -**

Reference	Patient Characteristics	Monitoring procedures performed (including thresholds used, frequency and timing)	Outcomes measures	Effect sizes	Comments
multivariate logistic regression analyses performed with several combinations. For each regression logistic model the AUC was calculated for absence of severe complications.	Cardiac insufficiency: 16.5% Renal insufficiency: 5.1% Diabetes: 19.8% Liver disease: 2.8% COPD: 17.8% **Pneumonia severity:** PSI class I – 11.9% II – 17.8% III – 22.3% IV – 36.0% V – 11.9%	oxygen. In patients on home oxygen therapy, stability was considered to be achieved when their oxygen needs were the same as those before admission. **Severe complications** after 72 h of treatment was defined as death after 72 h of treatment and within 30 days of admission; shock or need for mechanical ventilation (invasive or non-invasive); or admission to the ITU after 72 h of treatment			

1.7.2.5 CRP sequential ratio (ITU)

Reference	Patient Characteristics	Monitoring procedures performed (including thresholds used, frequency and timing)	Outcomes measures	Effect sizes	Comments
Author and year: Coelho 2012[25] **Study type:** Prospective cohort **Selection / patient setting:** Consecutive patients at medical-surgical ICUs at 2 hospitals **Addressing missing data/non reliability of data:** not stated **Statistical analysis (including confounders adjusted for):** Multivariable logistic regression analyses were performed to identify variables predicting outcomes. Age, sex, APACHE-II score, day 1 PaO_2/FiO_2 ratio, mechanical ventilation, ICU-acquired infection, septic shock, day 5 CRP ratio > 0.5 and day 1 SOFA included in initial model (only those with $p < 0.05$ required for inclusion in final model).	**Diagnosis:** severe CAP **Inclusion criteria:** Severe CAP requiring ICU admission **Exclusion criteria:** severe immunosuppression (e.g. solid organ or bone marrow transplant, HIV or immunosuppressive treatment), or tuberculosis **Included N:** 191 **Age, median (IQR):** 70 (54 - 81) years **Gender (male/female):** 53.4/46.6% **Comorbidities:** COPD: 21.4% Diabetes: 18.8% Asthma: 5.2% Cardiac failure: 4.7% Septic shock: 41.3% **Pneumonia severity:** Median (IQR) APACHE-II score: 15 (12-19) Median (IQR) CURB65 points: 3 (3-4)	CRP measured during first week of ITU stay on days 1, 3, 5 and 7. CRP ratio calculated in relation to day 1 concentration **Fast response**: Day 5 CRP ≤ 0.4 of day 1 CRP **Slow response**: Day 5 CRP > 0.4 of day 1 CRP **Non-response**: Day 7 CRP > 0.8 of day 1 CRP **Note:** patients were treated according to best standard ICU practice without reference to CRP levels	**Multivariable analyses for predicting ICU mortality**		**Funding:** none stated **Limitations:** non-significant AORs not reported**;** did not adjust for key confounders **Additional outcomes**: AUC, sensitivity, specificity, LRs of CRP on day 5 **Notes: -**
			Factor	**AOR (95% CI)**	
			Day 5 CRP ratio > 0.5	4.47 (1.64 - 12.20)	
			Note: AOR for day 3 and day 7 ratios not reported		
			ICU mortality by response rate		
			Fast response	4.6%	
			Slow response	17.3%	
			Non-response	36.4%	
				$p < 0.001$	
			Hospital mortality by response rate		
			Fast response	9.5%	
			Slow response	25.9%	
			Non-response	43.2%	
				$p = 0.001$	
			Follow-up until death or hospital discharge		

1.7.2.6 PCT change day 1-3 (ITU)

Reference	Patient Characteristics	Monitoring procedures performed (including thresholds used, frequency and timing)	Outcomes measures	Effect sizes		Comments
Author and year: Boussekey 2006[10] **Study type:** Prospective cohort **Selection / patient setting:** Consecutive patients at 1 hospital **Addressing missing data/non reliability of data:** not included in analysis **Statistical analysis (including confounders adjusted for):** logistic regression analysis. First, univariate analysis on significant parameters recovered in a previous study: age > 40 years, multilobar involvement, anticipated death within 5 years, septic shock on admission, no aspiration pneumonia, and invasive ventilation. 3 additional variables: increase of PCT, LOD score, and decrease of PaO_2/FiO_2 ratio between days 1 to 3. Secondly, multivariate	**Diagnosis:** severe CAP **Inclusion criteria:** CAP defined by the following criteria observed at initial presentation or within 48 hours following hospitalisation: admission from home, presence of a new radiographic pulmonary infiltrate, acute onset of at least one major (cough, sputum production, fever) or two minor (dyspnoea, pleuritic chest pain, altered mental status, pulmonary consolidation on physical examination, total leukocyte count > 12000/mm^3) clinical or biological findings suggestive of pneumonia. Criteria for ICU admission were according to ATS; presence of either two of three minor criteria (systolic blood pressure ≤ 90 mm Hg, multilobar disease, PaO_2/FIO_2 ratio < 250) or one of two major criteria (need for mechanical ventilation or septic shock) **Exclusion criteria:** hospitalisation within 30 days prior to developing pneumonia, radiographic abnormalities	PCT level measured with immunoluminometric assay (Lumitest PCT, Brahms Diagnostica, Berlin) with a 0.5 ng/ml sensitivity and 0.1 ng/ml precision.	**Overall death rate**			**Funding:** not stated **Limitations:** did not adjust for key confounders; definition of prognostic factor unclear **Additional outcomes**: sensitivity, specificity and PVs of PCT decrease day 1-3 for predicting mortality **Notes: -**
				30%		
			PCT levels			
			Time point	Survivor	Non-survivor	
			Day 1	4.5 (< 0.5 - 7.6)	6.4 (1.4 - 37)	
			Day 3	1.6 (< 0.5 - 7.6)	8.2 (2.9 - 53)	
			Multivariable analyses for predicting mortality			
			Factor	**AOR (95% CI)**		
			PCT increase day 1 to day 3	4.539 (1.31-15.75)		

Reference	Patient Characteristics	Monitoring procedures performed (including thresholds used, frequency and timing)	Outcomes measures	Effect sizes	Comments
analysis with parameters significant in univariate analysis.	attributed solely to pulmonary embolus, lung carcinoma or congestive heart failure **Included N:** 120 20 lost to follow-up: 8 left ITU, 8 died within 48 h, 4 failed to have PCT measured) 100 analysed **Age, mean (SD):** 62.9 (15.1) years **Gender (male/female):** 64/36% **Comorbidities:** not stated **Pneumonia severity:** Mean (SD) SAPS II: 45.8 (16.8)				

1.8 Safe discharge

Reference	Patient characteristics	Prognostic factors	Outcomes measured	Results	Comments
Author and year: Aliberti et al. 2013[2] **Study type:** Observational retrospective study **Selection/patient setting:** Consecutive patients with CAP admitted to the Veterans Administration Medical Center in Louisville, USA **Addressing missing data/non reliability of data:** **Statistical**	**Diagnosis:** CAP was defined as the presence of a new pulmonary infiltrate on CXR associated with at least one of the following – new or increased cough, abnormal temperature, or abnormal serum leukocyte count **Inclusion criteria:** Patients aged at least 18 years of age with a diagnosis of CAP **Exclusion criteria:** NR **All patients:** N: 487 Exclusion reasons: NR **Included:** N: 487 **Age, median (range):** 73 (61 - 79) **Gender: male, n (%):** 477 (97.9) **Nursing home patients, n (%):** 21 (4.3) **Comorbidities > 10%, n**	**Criteria for clinical stability** ATS 2001: • Improved symptoms of pneumonia (cough and shortness of breath) • Lack of fever for at least 8 h • Improving leucocytosis (decrease at least 10% from the previous day) ATS/IDSA 2007: • Temperature ≤ 37.8 C • Heart rate ≤ 100 beats/min • Respiratory rate ≤ 24 breaths/min • Systolic blood pressure ≥ 90 mmHg • Arterial oxygen	• 30-day mortality post-discharge • 30-day hospital re-admission post-discharge	Clinical outcomes in patients who reached clinical stability within from admission according to ATS 2001 and ATD/IDSA 2007 criteria: • Rehospitalisation within 30 days of discharge: - Outcome in patients achieving ATS 2001 clinical stability criteria (n/N): 62/429 - Outcome in patients achieving ATS/IDSA 2007 clinical stability criteria (n/N): 59/410 • Mortality 30 days after discharge: - Outcome in patients achieving ATS 2001 clinical stability criteria (n/N): 14/429 - Outcome in patients achieving ATS/IDSA 2007 clinical stability criteria (n/N): 14/410	**Funding:** NR **Limitations:** • Retrospective design • Population from a single hospital and mainly elderly people and males, with a high number of comorbidities **Additional outcomes:** **Notes:**

Reference	Patient characteristics	Prognostic factors	Outcomes measured	Results	Comments
analysis (including confounders adjusted for):	**(%):** • Essential hypertension – 339 (69.6) • Coronary artery disease – 206 (42.3) • Congestive heart failure – 123 (25.3) • COPD – 241 (49.5) • Cerebrovascular disease – 56 (11.5) • Diabetes – 177 (36.3) • Renal disease – 74 (15.2) • Immunocompromised – 83 (17.0) **Pneumonia severity, n (%):** CURB65 ≥ 3: 49 (10.1) PSI ≥ IV: 282 (57.9)	saturation ≥ 90% if a partial pressure of oxygen ≥ 60 mmHg on room air • Normal mental status			

<table>
<tr><th>Reference</th><th>Patient characteristics</th><th>Prognostic factors</th><th>Outcomes measured</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Author and year:
Akram et al. 2013[1]

Study type: Secondary analysis of a prospective, observational cohort study

Selection/patient setting: Consecutive patients with CAP admitted to NHS Lothian University Hospitals in Edinburgh, UK

Addressing missing data/non reliability of data:

Statistical</td>
<td>Diagnosis: Patients with a principal diagnosis of pneumonia based on the presence of signs and symptoms of pneumonia in combination with a new infiltrate on CXR

Inclusion criteria: Patients with CAP (see above)
Exclusion criteria: HAP, discharge from hospital within 24 h of admission/assessment, active thoracic malignancy, immunosuppression, pulmonary embolism on admission, and patients receiving palliative care

All patients:
N: 1079

Included:
N: 1079
Age, median (range): 68 (53-80)
Gender, male n (%): 537 (49.8)
Nursing home: NR</td>
<td>ATS 2001 criteria for clinical stability:
ATS 2001:
• Improved symptoms of pneumonia (cough and shortness of breath)
• Lack of fever for at least 8 hours
• Improving leucocytosis (decrease at least 10% from the previous day)
• Adequate oral intake

Halm criteria of clinical stability:
• Temperature ≤ 37.8 C
• Respiratory rate ≤ 24/min
• Heart rate ≤ 100/min
• Systolic blood pressure ≥ 90 mmHg
• Oxygen saturation ≥ 90%
• Normal mental status</td>
<td>• 30-day mortality
• Complicated pneumonia: defined as development of a complicated parapneumonic effusion, empyema or pulmonary abscess</td>
<td>AUC for each criteria, assessed on the first 7 days of hospitalisation (95% CI)
<table>
<tr><th>Criteria</th><th>30-day mortality</th><th>Complicated pneumonia</th></tr>
<tr><td>Halm’s criteria</td><td>0.95 (0.94-0.96)</td><td>0.92 (0.91-0.93)</td></tr>
<tr><td>ATS criteria</td><td>0.94 (0.93-0.95)</td><td>0.8 (0.86-0.88)</td></tr>
<tr><td>CURB</td><td>0.82 (0.81-0.84)</td><td>0.74 (0.72-0.75)</td></tr>
<tr><td></td><td></td><td></td></tr>
</table></td>
<td>Funding: NR
Limitations:
• Secondary analysis of a dataset from a prospective study

Additional outcomes:

Notes:</td>
</tr>
</table>

Reference	Patient characteristics	Prognostic factors	Outcomes measured	Results	Comments
analysis (including confounders adjusted for): ROC analysis	**Comorbidities > 10%, n (%):** • Congestive heart failure: 211 (19.6) • Cerebrovascular disease: 125 (11.6) • Diabetes: 109 (10.1) • COPD: 251 (23.3) **Pneumonia severity, n (%):** PSI median (range): 3 (2-4) CURB65 median (range): 2 (1-3)	• Normal oral intake **CURB severity tool:** • Confusion • Urea > 7 mm/L • Respiratory rate ≥ 30 breaths/min • Blood pressure – systolic < 90 mmHg or diastolic ≤ 60 mmHg			

Reference	Patient characteristics	Prognostic factors	Outcomes measured	Results	Comments
Author and year: Capelastegui et al. 2008[20] **Study type:** Prospective, observational cohort study **Selection/patient setting:** Patients with CAP managed at Galdakao hospital in Spain **Addressing missing data/non reliability of data:** **Statistical analysis (including confounders adjusted for):** Multivariate	**Diagnosis:** Patients with a principal diagnosis of pneumonia based on clinician judgement in combination with a new infiltrate on CXR **Inclusion criteria:** Patients with CAP (see above) **Exclusion criteria:** HIV-positive, chronically immunosuppressed, or patients hospitalised in the previous 14 days **All patients:** N: 945 Exclusion reasons: death in hospital **Included:** N: 870 **Age, mean (SD):** 69.9 (16.1) **Age ≥ 65, n (%):** 618 (71) **Gender: female, n (%):** 309 (35.5) **Nursing home patients, n (%):** 64 (7.4) **Charlson comorbidity index, n (%):**	**Criteria for clinical instability** in the 24 hours prior to hospital discharge: • Temperature > 37.5 C • Respiratory rate > 24 breaths/min • Heart rate > 100 beats/min • Systolic blood pressure < 90 mmHg and/or diastolic BP < 60 mmHg • Oxygen saturation < 90% **A score of instability** at discharge was also calculated: Variables were grouped into major (temperature > 37.5°C, 2 points) and minor (systolic BP < 90 mm Hg and/or diastolic BP < 60 mm Hg, respiratory rate > 24 breaths/min, and oxygen saturation < 90%, 1 point respectively). The points assigned to each variable were totalled and a score	• 30-day mortality post-discharge • 30-day hospital re-admission post-discharge	After discharge: • 30-day mortality, n (%): 29 (3.3) • 30-day re-admission, n (%): 72 (8.3) **Multivariate analysis adjusted for each of the variables: HR (95% CI) for outcomes 30-days post-discharge** Temperature > 37.5 C: Mortality 30-days 4.5 (1–19.2); Re-admission at 30-days 0.9 (0.1–6.2) SBP < 90 mmHg and/or DBP > 60 mmHg: Mortality 30-days 2.6 (1.2–5.8); Re-admission at 30-days 0.7 (0.3–1.4) Respiratory rate > 24 breaths/min: Mortality 30-days 2.4 (1.1–5.2); Re-admission at 30-days 1.4 (0.8–2.4) Oxygen saturation < 90%: Mortality 30-days 2.4 (1.1–5.2); Re-admission at 30-days 1.8 (1.1–3.2) Heart rate > 100 beats/min: Mortality 30-days 0.9 (0.2–3.6); Re-admission at 30-days 0.3 (0.1–1.4) **Multivariate analysis adjusted for PSI and COPD history: HR (95% CI) for 30-day mortality** Instability score ≥ 2: 4.2 (2.0 - 9.0) Number of instability factors ≥ 1: 2.3 (1.0 - 4.9) **Multivariate analysis adjusted for CURB65, Katz index, Charlson comorbidity index, and length of**	**Funding:** NR **Limitations:** • Conducted in a single hospital • Cause of death was not obtained • Mental condition was not included as a stability criterion • The same data set was used to derive the prediction model and test it, therefore performance of the model may be overestimated **Additional outcomes:** sens, spec, PPV, NPV of definitions of the instability

Reference	Patient characteristics	Prognostic factors	Outcomes measured	Results		Comments
Cox proportional hazard regression analysis	• 0 – 281 (32.4) • 1-2 – 478 (55.1) • ≥ 3 – 108 (12.5) **Pneumonia severity, n (%):** PSI ≥ IV: 447 (51.4) CURB65 ≥3: 195 (22.4) All patients at discharge were able to eat and receive oral medication	was determined for each patient. Patients with a score ≥ 2 are considered unstable		**stay: HR (95% CI) for 30-day mortality**		score **Notes:** Authors conclude that instability on discharge is a marker of 30-day mortality but no correlation was found with re-admission
				Instability score ≥ 2	5.8 (2.5 - 13.1)	
				Number of instability factors ≥ 1	2.4 (1.0 - 5.9)	

Reference	Patient characteristics	Prognostic factors	Outcomes measured	Results	Comments
Author and year: Capelastegui et al. 2009[19] **Study type:** Prospective, observational cohort study **Selection/patient setting:** Patients with CAP managed at Galdakao hospital in Spain **Addressing missing data/non reliability of data:** **Statistical analysis (including confounders adjusted for):** Multivariate	**Diagnosis:** Patients with a principal diagnosis of pneumonia based on clinician symptoms in combination with a new infiltrate on CXR **Inclusion criteria:** Patients with CAP (see above) **Exclusion criteria:** HIV-positive, chronically immunosuppressed, patients hospitalised in the previous 14 days, nursing home residents **All patients:** N: 1189 Exclusion reasons: death in hospital **Included:** N: 1117 **Age, mean (SD):** 69.4 (16.6) **Age ≥ 65, n (%):** 785 (70.3) **Gender: female, n (%):** NR **Nursing home patients, n (%):** excluded	**Criteria for clinical stability** in the 24 h prior to hospital discharge: • Temperature < 37.2 C • Respiratory rate < 24 breaths/min • Heart rate > 100 beats/min • Systolic blood pressure > 90 mmHg • Oxygen saturation ≥ 90% or PO_2 ≥60 mmHg • Patient not receiving mechanical ventilation or supplemental oxygen by face mask or nasal prongs	• 30-day hospital re-admission post-discharge	After discharge: • 30-day mortality, n (%): 55 (4.9) • 30-day re-admission, n (%): 81 (7.3) **Multivariate Cox proportion al hazard regression model: HR (95% CI) for pneumonia-related 30-day hospital re-admission** Instability factors ≥ 1: 2.8 (1.3 - 6.2) (not reported what the model was adjusted for)	**Funding:** NR **Limitations:** • Conducted in a single hospital • Mental condition was not included as a stability criterion **Additional outcomes:** **Notes:**

Reference	Patient characteristics	Prognostic factors	Outcomes measured	Results	Comments
Cox proportional hazard regression analysis	**Charlson comorbidity index, n (%):** • 0 – 389 (34.9) • 1-2 – 581 (52.1) • ≥ 3 – 144 (12.9) **Pneumonia severity, n (%):** PSI ≥ IV: 543 (48.6) All patients at discharge were able to eat and receive oral medication				

Reference	Patient characteristics	Prognostic factors	Outcomes measured	Results			Comments
Author and year: Dagan et al. 2006[29] **Study type:** Prospective, observational study in one hospital **Selection/patient setting:** Patients with CAP discharged from a regional	**Diagnosis:** Patients with a principal diagnosis of pneumonia based on clinician symptoms in combination with a new infiltrate on CXR **Inclusion criteria:** Patients with CAP **Exclusion criteria:** NR **All patients:** N: 373 Exclusion reasons: NR **Included:** N: 373 **Age ≥ 60, n (%):** 231	**Number of clinical instabilities** (unstable factors) 24 h prior hospital discharge: • Temperature > 37.8 C • Respiratory rate > 24/min • Heart rate > 100/min • Systolic blood pressure ≤ 90 mmHg • Oxygen saturation <	• 30-day mortality post-discharge • 30-day hospital re-admission post-discharge	30 day mortality relative risk (unadjusted) of patients with > 1 instability compared with no instabilities: RR = 6.2 (95% CI 1.9 – 20.7)			**Funding:** NR **Limitations:** Performed at a single institution Functional status of the population was not assessed, which could influence the outcome of CAP **Additional**
					Death n (%)	Re-admission n (%)	
				≥ 1 instability (n = 82)	7 (8.5)	9 (11.0)	
				No instabilities (n = 291)	4 (1.4)	19 (19 (6.5)	

Reference	Patient characteristics	Prognostic factors	Outcomes measured	Results	Comments
hospital in Israel **Addressing missing data/non reliability of data:** **Statistical analysis (including confounders adjusted for):** t-test and Mann-Whitney test, Chi-square test	(61.9) **Gender: male, n (%):** 201 (53.9) **Nursing home patients, n (%):** 57 (15.3) **Comorbidities > 10%, n (%):** • Diabetes – 87 (23.3) • Renal insufficiency – 50 (13.4) **Pneumonia severity, n (%):** PSI I: 55 (14.7) PSI II: 53 (14.2) PSI III: 59 (15.8) PSI IV: 126 (33.8) PSI V: 80 (21.4)	90% • Altered mental status • Inability to maintain oral intake			**outcomes:** 60-day mortality and re-admission **Notes:**

<table>
<tr><th>Reference</th><th>Patient characteristics</th><th>Prognostic factors</th><th>Outcomes measured</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Author and year:
Halm et al.2002[45]
Study type:
Prospective, multicentre, observational study (PORT cohort study)

Selection/patient setting:
Patients with CAP enrolled in the PORT study from 1991 to 1994</td>
<td>Diagnosis: Patients with a principal diagnosis of pneumonia according to the ICD-9-CM

Inclusion criteria:
Patients aged at least 18 years of age, symptoms of acute pneumonia, and radiographic evidence of pneumonia
Exclusion criteria: HIV-positive, or patients hospitalised within 10 days

All patients:
N: 680
Exclusion reasons: NR
Included:
N: 680
Age ≥ 65, n (%): 299 (44)
Gender: female, n (%): 349 (51)</td>
<td>Number of clinical instabilities (unstable factors) 24 h prior hospital discharge:
• Temperature > 37.8 C
• Respiratory rate > 24/min
• Heart rate > 100/min
• Systolic blood pressure ≤ 90 mmHg
• Oxygen saturation < 90%
• Altered mental status
• Inability to maintain oral intake</td>
<td>• 30-day mortality post-discharge
• 30-day hospital re-admission post-discharge
• Failure to return to usual activities 30 days post-discharge</td>
<td>After discharge:
• 30-day mortality, n (%): 23 (3.4)
• 30-day re-admission, n (%): 67 (9.9)
• Failure to return to usual activities within 30 days of discharge (data for 641 patients only), n (%): 223 (32.8)
Multivariate analysis: adjusted odds ratios for 30-day outcomes (OR adjusted for PSI index, age, sex, nursing home residence, comorbidities, initial laboratory values, and vital signs)
<table>
<tr><th></th><th>Death (OR 95% CI)</th><th>Re-admission (OR 95% CI)</th><th>Failure to return to usual activities (OR 95% CI)</th></tr>
<tr><td>Any instability (≥ 1)</td><td>2.1 (0.8 4)</td><td>1.5 (0.8 - 2.7)</td><td>1.5 (1.0 - 2.4)</td></tr>
<tr><td>1 instability</td><td>1.1 (0.3 - 3.5)</td><td>1.3 (0.7 - 2.5)</td><td>1.5 (1.0 - 2.4)</td></tr>
<tr><td>≥ 2 instabilities</td><td>14.1 (3.1 - 69.0)</td><td>3.5 (1.0 - 12.4)</td><td>1.6 (0.4 - 6.1)</td></tr>
<tr><td colspan="4">*Control group: 0 instabilities</td></tr>
</table>
</td>
<td>Funding:
Grant from the Agency for Healthcare research and quality, grant from Pneumonia PORT

Limitations:
As this is an observational study, causality can't be inferred. We don't know what would have happened to patients identified as unstable had they stayed in hospital</td>
</tr>
</table>

Reference	Patient characteristics	Prognostic factors	Outcomes measured	Results	Comments
Addressing missing data/non reliability of data: **Statistical analysis (including confounders adjusted for):** Logistic regression analysis	**Nursing home patients, n (%):** 60 (9) **Comorbidities, n (%):** • COPD – 143 (21) • CAD – 133 (20) • Diabetes – 90 (13) • CHF – 78 (11) **Pneumonia severity, n (%):** PSI I: 148 (22) PSI II: 187 (28) PSI III: 151 (22) PSI IV: 138 (20) PSI V: 56 (8)				**Additional outcomes:** sens, spec, PPV, NPV of definitions of instability on discharge to detect the composite outcome of re-admission + death (major adverse events) **Notes:**

1.9 Patient information

Reference	Study type	Number of patients	Patient characteristics	Length of follow-up	Outcome measures Effect sizes	Source of funding	Comments
Brandenburg et al, 2000[12] Clinical Presentation, Processes and Outcomes of Care for Patients with Pneumococcal Pneumonia	Prospective cohort study as part of Pneumonia Patient Outcomes Research Team (PORT) multicentre, This cohort is linked to Metlay 1997 but patients here had *S. pneumoniae* as the presumed or definite diagnosis of pneumonia	N = 158	Study inclusion: aged > 18 years, acute onset of symptoms suggestive of pneumonia within 24 hours of presentation, and provision of informed consent by the participants or patient proxy. Exclusion: hospitalization within the last 10 days prior to initial presentation with CAP, HIV positive, previously enrolled to the cohort study Baseline characteristics: - 50% were over 65 years - 58.2% were men - 89.2% were treated as inpatients	30 days	1) Symptoms at 30 days: • cough: 50% • dyspnoea: 47.5% • sputum production:52% • pleuritic chest pain: 86.6% • fatigue: 37.1% 2) Return to daily household activities: 17 days 3) Return to usual activities for workers: 9 days 4) Return to work: 12 days	Grant from the Agency for Health Care Policy and Research (RO1-HS 06468)	The Authors aim was to compare the symptoms of the bacteraemic and non bacteraemic forms of pneumonia

Reference	Study type	Number of patients	Patient characteristics		Length of follow-up	Outcome measures Effect sizes	Source of funding	Comments
Bruns et al, 2010[14]; Pneumonia recovery; Discrepancies in Perspectives of the Radiologist, Physician and Patient	Prospective cohort study linked to study by El Moussaoui et al, 2006. Pneumonia related symptoms were scored by the CAP questionnaire on admission and at days 10 and 28.	N = 119	Mild to severe CAP (defined as PSI ≤ 110) patients with new pulmonary opacities admitted to hospital. All patients were initially treated with intravenous amoxicillin monotherapy.		28 days after the beginning of treatment (two follow ups- day 10 and day 28).	CAP validate questionnaire contains 8 items based on respiratory symptoms and well-being (low values indicate more severe symptoms). Normalization of the CAP score was defined as a CAP score equal to or greater than the initial pre-pneumonia score, and this was regarded as a proof of clinical cure according to patient's perspective. • At day 10: 33/103 (32%) of the patients had normalization of the CAP score • At day 28: 43/103 (41.7%) of the patients had normalization of the CAP score	By a health care insurance board grant, The Netherlands (OG99-038)	The purpose of the study was to compare the radiographic resolution of mild to moderately severe CAP to resolution of clinical symptoms as assessed by the physician or the patient
			Baseline characteristics	Sample (N = 119)				
			PSI score, mean (SD)	65.5 (22.1)				
			Age, mean (SD)	56.6 (17.8)				
			At least one comorbidity	66.4%				

Reference	Study type	Number of patients	Patient characteristics	Length of follow-up	Outcome measures Effect sizes	Source of funding	Comments
El Moussaoui et al, 2006[33]; Long-term Symptom Recovery and Health-Related Quality-of-Life in Patients With Mild-to-Moderate-Severe Community-Acquired Pneumonia	Follow up of the Duration Antibiotic Therapy Evaluation Study-Pneumonia RCT which compared two durations of treatment of CAP (El Moussaoui et al, 2006)	N = 102 (66%) returned the CAP and/or SF-36 questionnaire; 91 returned at least one CAP questionnaire beyond 28 days and 71 returned the SF at 18 months.	Inclusion criteria: temperature > 38C, clinical signs of pneumonia, radiologic evidence of new infiltrate consistent with pneumonia, and PSI ≤ 110. Exclusion criteria: pregnancy, history of allergy to amoxicillin, severe underlying disease, treatment with an effective antimicrobial agent for > 24 hours prior to hospital admission, any other infection necessitating the administration of concomitant systemic antibiotics, a concurrent disease considered likely to interfere with the clinical course of pneumonia, serious respiratory insufficiency or admission to ITU. All patients who met the criteria and consented were treated with IV amoxicillin. Baseline characteristics (N = 102) • Male: 60 (59%) • Median age in years(IQR): 65 (48 to 72) • Underlying disease: • COPD: 26 (27%) • Diabetes mellitus: 16 (17%) • Cardiovascular disease: 23 (24%) • PSI (mean, SD): 71 (23) • Length of hospital stay (median, range): 8 (5 to 11) days	18 months after the beginning of antibiotic treatment.	1) CAP score: was divided into respiratory (cough, sputum, dyspnoea) and well-being section (fitness, general state of health) - The respiratory section returned within 14 days to the pre-pneumonia level while the well-being score showed less improvement - At 28 days patients still had significantly lower scores than at the pre-pneumonia level - At 6 months, the well-being score had returned to the pre-pneumonia levels 2) SF-36: 18 months after the pneumonia episode, patients had significantly lower scores in two of the eight dimensions; physical functioning, general health (compared to reference population) 3) SF-36 was significantly better for patients who at 18 months had high CAP scores (indicating high recovery from pneumonia related symptoms) compared to those with low CAP scores (indicating low recovery from pneumonia-related symptoms) in all dimensions (except emotional functions and mental health).	Healthcare Insurance Board, the Netherlands (Grant OG99-038)	The authors also reported predictors of CAP and Quality of life score improvement.

Reference	Study type	Number of patients	Patient characteristics			Length of follow-up	Outcome measures Effect sizes				Source of funding	Comments
Fernandez et al 2010[35]; Predictors of health decline in older adults with pneumonia: findings from the Community Acquired Pneumonia Impact Study	Community based study (CAPIS) designed to identify the impact of CAP on the lives of older adults (60 years and older) and their family carers in Canada. The x ray technicians at each of the 8 radiology clinics in a city (Brant County) were recruiting potential candidates (aged > 60 years presenting with a confirmatory chest x-ray) over a period of 15 months.	N = 195 (192 had information on symptoms) Decline in health status was assessed based on a question of rating of overall health (SF-8) before and while they had CAP		Decline in health status		Telephone interviews were performed 4 weeks after x-ray was taken		Decline in health status			Part of a large study funded by the Canadian Institutes of Health Research	The authors do not give any information regarding the CAP severity of patients or the presence of comorbidities
				Yes (n = 161)	No (n = 31)		Symptoms 4 weeks after diagnosis	Yes (%)	No (%)	Unadjusted OR (95% CI)		
			Female gender	103 (88%)	14 (12%)		Sweats -yes	89 (46.4%)	11 (16.1%)	2.25 (1.01, 5.00)		
			Heart disease -yes	27 (69.2%)	12 (30.8%)		Shortness of breath -yes	111 (89.5%)	13 (10.5%)	3.07 (1.40, 6.76)		
							Sore throat -yes	69 (92%)	6 (8%)	3.13 (1.22, 8.03)		
							No energy -yes	127 (88.8%)	16 (11.2%)	3.50 (1.57, 7.79)		
							Headache -yes	56 (91.8%)	5 (8.2%)	2.77 (1.01, 7.62)		

Reference	Study type	Number of patients	Patient characteristics	Length of follow-up	Outcome measures Effect sizes	Source of funding	Comments
Fine et al, 1996[38]; Prognosis and outcomes of patients with Community-Acquired Pneumonia	Systematic review on the prognosis and outcomes of patients with CAP. Studies were included if they provided the number of deaths and the total number of patients studied.	127 studies included in the SR representing 33148 patients.	The majority of studies included were prospective (48.8%) or retrospective (43.3%). 56.6% of patients were male and the mean age was 61 years (SD 13). The three most prevalent comorbid conditions were cigarette smoking (48.6% reported by 38 studies), pulmonary disease (32.7%) and congestive heart failure (26.2%). Focus of included studies on patients: -Hospitalized: 84 (66.1%) -Specific etiologic agents: 84 (66.1%) -ITU patients: 43 (33.9%) -Bacteraemic patients: 13 (10.2%) -Elderly: 9 (7.1%) -Nursing home patients: 6 (4.7%) -Hospitalized and ambulatory patients: 6 (4.7%) -Other: 22 (17.3%)	Ranged within studies	Return to work: 5 out of 127 studies in the systematic review reported the outcome return to work or to usual activities; ranged from 78.2% of ambulatory and hospitalized patients returned to work within 1 month to 92.6% for military recruits. Return to usual activities: ranged from 45% for a study of hospitalized elderly at 6 weeks to 81.2% of a cohort of ambulatory and hospitalized adult patients at 8 weeks. Functional status: assessed by one study and showed that 43.3% of patients treated in the ICU and discharged from the hospital had returned to their baseline physical health study by 6 months after hospital admission	Part of the PORT project funded by the Agency for Health Care Policy and Research (Grant HS-06488)	No reference was made which studies have reported these outcomes and no quality assessment of studies has been performed.

Reference	Study type	Number of patients	Patient characteristics			Length of follow-up	Outcome measures Effect sizes	Source of funding	Comments
Labarere et al 2007[57]; Comparison of outcomes for Low-Risk Outpatients and Inpatients with Pneumonia	Follow up from a RCT (assessed the PSI to guide the selection of initial sites of treatment for patient with pneumonia, Yealy 2005) in 32 emergency departments in USA. Outpatient treatment was defined as discharge from the emergency department to any outpatient setting within 24 hours of presentation. Inpatient treatment was defined as hospital admission, transfer from an emergency department to an inpatient hospital or ED unit > 24 hours after initial	N = 1493 (944 (63%) were outpatient and 549 (37%) were inpatients)	Patients with low-risk CAP (PSI I to III) who did not have evidence of arterial oxygen desaturation at presentation, contraindications to outpatient treatment (clinical and psychological factors that may affect compliance with oral antibiotic therapy) frailty or severe neuromuscular disorder, serious concomitant illness, severe abnormalities in vital signs or laboratory values and suppurative infection. Inclusion criteria: ≥ 18 years old with a clinical diagnosis of pneumonia and new pulmonary infiltrates seen on a radiograph. Exclusion criteria: hospital-acquired pneumonia, pulmonary tuberculosis, immune suppression, positive serology for HIV, alcoholism with evidence of end-organ damage, illicit drug use within the past 30 days or social problems that were incompatible with outpatient treatment, study enrolment or follow up.			30 days from hospital presentation	• Return to work (days) Outpatients: 7 (4-14) In-patients: 14 (8-29+) Unadjusted OR (95% CI): 2.02 (1.63-2.50) Adjusted OR (95% CI): 2.01 (1.53-2.64) • Return to usual activities (days) for workers Outpatients: 13 (6 - 23) In-patients: 22 (11 - 29+) Unadjusted OR (95% CI): 1.89 (1.51 - 2.38) Adjusted OR (95% CI): 1.68 (1.27 - 2.22) • Return to usual activities (days) for non-workers Outpatients: 14 (6 - 28) In-patients: 20 (9 - 29+) Unadjusted OR (95% CI): 1.50 (1.24 - 1.82) Adjusted OR (95% CI): 1.44 (1.12 - 1.85) *Results were adjusted by patient, provider and department.	None mentioned	The authors also reported results on mortality and assess the effect of physician judgment.
				Outpatients (n = 944)	In-patients (n = 549)				
			Male gender	456 (48%)	242 (44%)				
			Age (years)	44 (35 - 59)	66 (48 - 77)				
			PSI -I -II	 511(54%) 318(34%)	 87(16%) 227(41%)				

Reference	Study type	Number of patients	Patient characteristics			Length of follow-up	Outcome measures Effect sizes	Source of funding	Comments
	presentation. Research nurses obtained follow up data regarding the outcomes by telephone interview.		-III	115(12%)	235(43%)				
			Comorbidities (> 5%)						
			-congestive heart failure	12 (1%)	33 (6%)				
			-coronary disease	67 (7%)	107 (19%)				
			-pulmonary disease	157 (17%)	142 (26%)				
			-diabetes	88 (9%)	101 (18%)				

Reference	Study type	Number patients	Patient characteristics		Length of follow-up	Outcome measures Effect sizes		Source of funding	Comments
Marrie et al, 2000[68]; Predictors of Symptom Resolution in Patients with Community Acquired Pneumonia	Cohort of patients in emergency departments in 19 hospitals who participate in a RCT (Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin (CAPITAL), Marrie 2000). The research nurse asked the question "during the past week, have you had absence of the following symptoms?" (fever, cough, shortness of breath, chest pain, sputum production, fatigue)	N = 535	Patients were eligible if they presented with ≥ 2 signs of symptoms of CAP and had chest radiograph that indicated acute pneumonia. Exclusion criteria: patients with evidence of immune deficiency or chronic liver failure who required direct admission to the intensive care unit, pregnant or nursing, or who had alcoholism.		Patients who were discharged from the emergency department completed symptom questionnaires at 2 and 6 weeks follow-up after cessation of antibiotic therapy.	Symptoms 2 weeks following treatment: - fatigue: 66.7% - cough: 55.5% - shortness of breath:58%* - sputum production: 46%* - chest pain on breathing: 18%* - fever: 9%* - any symptom: 86%* Symptoms 6 weeks following treatment: - fatigue: 45% - cough: 35.3% - shortness of breath:34%* - sputum production: 26%* - chest pain on breathing: 12%* - fever: 5%* - any symptom: 64.3% *Data are approximations as taken by a graph.		Janssen-Ortho, Inc, Toronto, Ontario, Canada. Medical Research Council 9807PT-39621-UI-D.	The authors also reported the results from a multivariate analysis; resolution of CAP symptoms at 6 weeks follow up was associated with absence of COPD, younger age, absence of asthma, and treatment with levofloxacin.
				Sample (N = 535)					
			Age, mean (SD)	61.6 (19.1)					
			Male %	52.3					
			Nursing home %	3.2					
			Admitted to hospital	53.8					
			Pleural effusion%	9.9					
			Mean PSI (SD)	76.2 (32.8)					
			-asthma -COPD	16.9 26.1					
			Comorbidity > 5% -congestive heart failure -cerebrovascular disease	 12 6.6					
			Antibiotic treatment - monotherapy -double therapy -triple therapy	 75.1 20.4 3.6					

Reference	Study type	Number of patients	Patient characteristics	Length of follow-up	Outcome measures Effect sizes	Source of funding	Comments
Metlay et al 1997[75]; Measuring symptomatic and functional recovery in patients with community-acquired pneumonia	Prospective multicentre study as part of the Pneumonia Patient Outcomes Research Team (PORT) study of medical outcomes in ambulatory and hospitalized patients with CAP in USA and Canada.	N = 576 (61.5%) (939 low risk patients enrolled in the study and 707 participated). Reasons for non-participation: patient or physician's request (25%), language barriers (13%), cognitive or physical impairment (12%).	Inclusion criteria: age of at least 18 years, acute onset of at least 1 of 18 clinical symptoms suggestive of acute illness, chest radiographic evidence of acute pneumonia within 24 hours of presentation, informed consent by the patient/patient proxy. Exclusion criteria: discharge from the hospital within the 10 days preceding presentation, HIV positive, or previously enrolled to the cohort study. The detailed study cohort included consecutive sample of patients with low severity illness (defined by PSI with risk of mortality < 4%) who completed questionnaire (self-administered or through interviews) at four points in time (day O, days 7, 30 and 90 from the radiographic diagnosis).	Up to 90 days from the radiographic diagnosis.	The questionnaire included five symptoms: cough, dyspnoea, sputum production, pleuritic chest pain, fatigue).	Gramt R01 HS06468 and NRSA grant 5T32PE11001-08	None.

	Study population (n = 576)
Age %	
< 40 years	46
40-59 years	32

% reporting symptoms	Day 7	Day 30	Day 90
Fatigue (moderate to severe)	80% (48%)	65% (28%)	51% (20%)
Cough (moderate to severe)	82% (51%)	53% (23%)	32% (13%)
Dyspnoea (moderate to severe)	50% (15%)	36% (7%)	28% (6%)
Sputum (moderate to severe)	59% (23%)	40% (12%)	27% (8%)
Pleuritic chest pain (moderate to severe)	22% (11%)	12% (5%)	8% (2%)

Mean scores SF-36 domains	Day 7	Day 30	Day 90

Reference	Study type	Number of patients	Patient characteristics		Length of follow-up	Outcome measures Effect sizes				Source of funding	Comments
			≥ 60 years	22							
			Female gender %	62		Physical function	59.5	75	81.2		
			Site of care (outpatient) %	65		Physical role function	25.2	63.2	77.5		
			Number of comorbidities 0 1 ≥ 2	 51% 32% 17%		Bodily pain	73.9	84.7	86.6		
			Age ≥ 60 years, female gender and site of care were significantly different between the study group and the remaining low risk group in the prospective study.			Vitality	38.3	56.2	63.2		
						Social function	53.3	80.1	86.8		
						Mental health	74.9	78.1	79.5		
						Emotional role function	71.6	80.5	86		
						General health perception	64.2	65.6	67.2		
						- Re-consultation (pneumonia related ambulatory visit) at day 30: 284 (49%) - Re-consultation (pneumonia related ambulatory visit) at day 90: 80 (13.9%)					

Reference	Study type	Number patients	Patient characteristics		Length of follow-up	Outcome measures Effect sizes		Source funding	Comments
Metlay 1998[74]; Time course of symptom resolution in patients with community-acquired pneumonia	Part of a prospective study of outcomes in patients with CAP managed under a new outpatient protocol in Boston (Atlas et al, 1998)	N = 166 Response rate: 76% (n = 126)	Inclusion criteria: all patients aged 18-84 presented to emergency department with CAP symptoms (cough, dyspnoea, change in sputum, pleuritic chest pain, myalgia or fatigue) and a new infiltrate on chest radiography. Only patients of low risk CAP (assessed by PSI) were included. Exclusion criteria: recent hospitalization within the preceding 10 days, nursing home residence, chronic immunosuppression (including HIV), pregnancy, severe psychosocial problems or homelessness, severe neuromuscular diseases, inability to take oral medications and chronic oxygen dependence or hypoxia at the time of presentation. Authors noted no difference in the characteristics between the study population and those who didn't consent to participate.		Up to 28 days from the time of diagnosis.	A five item self-administered daily symptom questionnaire was developed for this study (based on results of a prior study, Metlay 1997) and was distributed to the patients at the date of enrolment. The questionnaire rated the severity of cough, fatigue, dyspnoea, myalgia and fever on a six point scale (0 = absent, 5 = severe). -81% of the participants completed the questionnaire had no missing information. - Median resolution of symptoms: • fever: 3 days • myalgia: 5 days • dyspnoea: 6 days • cough, fatigue: 14 days • all symptoms: 21 days - Patients with unresolved symptoms by day 28: • fever:4% • fatigue: 26% • at least one unresolved symptoms: 35% - Median time to resolution of all 5 symptoms (symptomatic cure): 21 days (21-28)		NRSA grant 5T32PE11001-08	
				Sample (N = 126)					
			Age, mean	52.7					
			Female %	45.2					
			COPD %	11.1					
			Asthma %	12.7					
			Outpatient treatment %	55.6					
			PSI, mean	55.2					

Reference	Study type	Number of patients	Patient characteristics				Length of follow-up	Outcome measures Effect sizes	Source of funding	Comments
Sicras-Mainar et al 2012[94]; Retrospective epidemiological study for the characterization of community-acquired pneumonia and pneumococcal pneumonia in adults in a well-defined area of Barcelona	Retrospective multicentre study using electronic medical records of both outpatients and inpatients in six primary centres in Barcelona, Spain. Data were recorded over a 6-month period from the diagnosis.	N = 581		Total (N = 581)	In patients (n = 241)	Out patients (n = 340)	Not applicable as retrospective study over a 6-month period	1) change of initial treatment: 7.1% (mainly due to lack of response) 2) time to recovery in days (mean, SD): - whole sample: 29.9 (17.2) - outpatients: 27.3 (14.5) - inpatients: 33.8 (15.7)	None.	The authors also reported cost analysis of hospital admissions.

2 HAP

2.1 Severity assessment tools

No evidence identified.

2.2 Diagnostic tests

No evidence identified.

2.3 Microbiological tests

No evidence identified.

2.4 Antibiotic therapy

2.4.1 Single- compared with other single-antibiotic therapy

2.4.1.1 Patient characteristics, interventions and study design

Review question	**Single- compared with single-antibiotic therapy for HAP**
Study	**Hoffken 2007[49]**
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Bayer Vital GmbH)
Number of studies (number of participants)	1 (N = 161)
Countries and setting	Conducted in Australia, Austria, Canada, Finland, Germany, Greece, Israel, Lithuania, Mexico, Poland, Slovenia, Spain, Switzerland, Turkey; Setting: > 40 centres across Europe and Australia, Israel, Mexico and Turkey
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 7 to 14 days treatment, plus 21 to 31 days post-treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ New-onset HAP ≥ 48 hours after hospitalisation; new infiltrates on CXR

Inclusion criteria	Age ≥ 18 years with clinical picture of new-onset HAP ≥ 48 hours after hospitalisation. New infiltrations on CXR not attributed to another disease process and at least 2 of: cough or increased severity of coughing, purulent or mucopurulent sputum or change in character of sputum, body temperature > 38°C or < 36°C (oral temperature), auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation, dyspnoea, tachypnoea, or respiratory rate ≥ 30/min, hypoxemia with PO^2 < 60 mmHg or respiratory failure requiring mechanical ventilation, WBC > 10,000/mm^3 or leukopenia < 4,500 mm^3, APACHE II score ≤ 20 within 24 hours prior to enrolment
Exclusion criteria	Known hypersensitivity to study drugs, pregnancy or lactation, severe or life-threatening disease with life-expectancy < 2 months, active TB, aspiration pneumonia, chronic immunosuppressant therapy, neutropenia, AIDS or HIV-positive receiving HAART, end-stage liver cirrhosis, known QTc prolongation, or use of concomitant medication reported to increase the QTc interval, history of tendinopathy with quinolones, concomitant systemic antibacterial agents, pre-treatment with systemic antibacterial agent for > 24 hours prior to enrolment. Also excluded conditions known to be associated with an enhanced likelihood of infections with non-fermenters (i.e. severe HAP, sepsis with hypotension and/or end-organ dysfunction, shock, vasopressors required for > 4 hours, mechanical ventilation > 5 days, severe renal impairment requiring dialysis, and structural lung diseases such as bronchiectasis and cystic fibrosis)
Recruitment/selection of patients	Trial prematurely terminated due to low recruitment rate (open May 2000 - Feb 2002)
Age, gender and ethnicity	Age - Mean (SD): Moxifloxacin: 67.1 (17.1); cephalosporin: 64.8 (16.6). Gender (M:F): Moxifloxacin: 49/51%; cephalosporin: 57/43%. Ethnicity: Not stated
Further population details	1. Age: All adults 2. Comorbidities: Not stated or unclear 3. Predominant disease aetiology (including resistance profiles): *S. aureus* (Causative organisms were identified in 20% of cases, the most commonly isolated were *S. aureus*, *S. pneumoniae*, and *H. influenzae*).
Extra comments	8.8% on mechanical ventilation at baseline and 41% had received prior antibiotics. Time between hospitalisation and diagnosis of HAP; median (IQR): moxifloxacin, 7 (4 - 12); cephalosporin, 7 (4 - 11)
Intervention 1	Antibiotic alone ~ Respiratory fluoroquinolone - new. Moxifloxacin (Avelox®, Bayer HealthCare) 400 mg IV once daily followed by oral moxifloxacin 400 mg once daily. Duration 7 to 14 days. Concurrent medication/care: Unclear (N = 78)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more 3. Route of administration: Mixed
Comments	Switch to oral therapy could be made from day 4 onwards (after receiving the first 3 doses) at the investigator's discretion
Study	**Schmitt 2006[91]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	1 (N = 221)
Countries and setting	Conducted in Czech Republic, Germany, Hungary; Setting: 33 hospitals

Line of therapy	Unclear
Duration of study	Intervention + follow up: up to 21 days treatment plus 7 to 21 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinical and radiological evidence of pneumonia acquired 48 hours or later after hospitalisation
Inclusion criteria	Hospitalised patients with HAP, at least 18 years of age and clinical and radiological evidence of pneumonia acquired 48 h or later after hospitalisation and a new or evolving infiltrate on CXR associated with pneumonia. Plus at least 3 of: dyspnoea, purulent tracheal/bronchial sputum, body temperature ≥ 38°C or < 36.1°C, characteristic auscultation for pneumonia, leucocytosis, CRP > 3-times ULN, and identification of causative pathogen
Exclusion criteria	Participation in a clinical study within last 30 days, pregnancy or breast-feeding, infection with study-drug resistant pathogens, acute or chronic conditions likely to interfere with patient compliance, CF, pulmonary malignancy, obstructive pneumonia, pulmonary abscess, empyema, active TB, bronchiectasis, or *P. carinii* pneumonia, known or suspected concomitant viral, fungal or parasitic infection requiring systemic treatment or known/suspected bacterial infection in addition to pneumonia, received systemic antibacterial medication 24 hours prior to study start, unless a respiratory cultured showed that the pathogen was resistant to that agent, any clinically significant CNS diseases or cardiac disorders that would contraindicate the use of imipenem/cilastatin, concurrent haemodialysis, peritoneal dialysis or plasmapheresis, symptoms of shock within past 48 hours or SBP <90 mmHg for >2 hours, known or suspected hypersensitivity to study drugs and APACHE II score < 8 or > 25
Recruitment/selection of patients	Jan 1999 - Dec 2001
Age, gender and ethnicity	Age - Mean (SD): Piperacillin-tazobactam: 68.4 (13.7); imipenem/cilastatin: 65.7 (13.8) years. Gender (M:F): Piperacillin-tazobactam: 77/33%; imipenem/cilastatin: 64/47%. Ethnicity: Not stated
Further population details	1. Age: All adults 2. Comorbidities: Not stated or unclear 3. Predominant disease aetiology (including resistance profiles): (*Enterobacteriaceae* (n = 72) and *S. aureus* (n = 26)).
Extra comments	Mean (SD) APACHE II score: P/T = 13.5 (4.2); I/C = 13.3 (4.3)
Intervention 1	Antibiotic alone ~ Beta-lactamase stable penicillin. Piperacillin-tazobactam 4 g/0.5 g IV q8h. Duration 5 to 21 days. Concurrent medication/care: If P. aeruginosa was present additional aminoglycoside therapy was mandatory (N = 110)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more 3. Route of administration: IV
Comments	Total number with *P. aeruginosa* was 4%
Intervention 2	Antibiotic alone ~ Carbapenem. Imipenem-cilastatin 1 g/1 g IV q8h. Duration 5 to 21 days. Concurrent medication/care: If *P. aeruginosa* was present additional aminoglycoside therapy was mandatory (N = 111)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more 3. Route of administration: IV

2.4.1.2 Results

Dichotomous

Key: NR = outcome not reported for this study; TTE = results reported as time to event data and shown in that table; similarly 'dich' for dichotomous, 'con' for continuous and 'gen' for a general method of reporting outcomes.

Study	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl
Stratum: Overall. Comparison: Beta-lactamase stable penicillin vs carbapenem										
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Clinical cure @ End of follow-up**	
Schmitt 2006[91]			Mortality @ up to 21 days post-treatment 2 deaths in the piperacillin group were considered possibly treatment-related and pneumonia was thought to be related to the deaths of 1 patient in the piperacillin group and 2 in the imipenem group		Cure/improved (based on respiratory secretions, body temperature, need for MV/additional oxygen, and lung radiography) @ End of treatment (5 - 21 days)		Withdrawal due to adverse events @ Treatment discontinued due to adverse events		Cure/improved (based on respiratory secretions, body temperature, need for MV/additional oxygen, and lung radiography) @ End of follow-up (14 ± 4 days post-treatment)	
	110	111	17/110	11/111	76/107	85/110	13/110	9/111	64/107	73/110
Stratum: Overall. Comparison: Respiratory fluoroquinolone vs cephalosporin										
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**		**Clinical cure @ End of follow-up**	
Hoffken 2007[49]			Mortality @ 21 - 31 days post-treatment ITT				Premature discontinuation of therapy due to adverse events @ 7 - 14 days		Resolution @ Test-of-cure visit (7 - 10 days post-treatment) ITT	
	78	83	8/77	11/82	NR	NR	4/78	2/83	56/77	56/82

2.4.2 Single- compared with dual-antibiotic therapy

2.4.2.1 Patient characteristics, interventions and study design

Review question	Single- compared with dual-antibiotic therapy for HAP
Study	**Fernandez-Guerrero 1991[36]**
Study type	RCT (Patient randomised; Parallel)
Funding	Funding not stated
Number of studies (number of participants)	1 (N = 588)
Countries and setting	Conducted in Spain; Setting: 32 hospitals (not admitted to ITU)
Line of therapy	1st line
Duration of study	Intervention + follow-up: duration unclear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ a) fever above 38°C b) lung infiltrate documented by X-ray, and c) onset of symptoms more than 72 hours after hospital admission
Inclusion criteria	Diagnosis of HAP (hospital admission, fever above 38° C, lung infiltrate documented by X-ray, and onset of symptoms more than 72 hours after hospital admission)
Exclusion criteria	Known hypersensitivity to cephalosporins or penicillins, receiving antibiotic therapy in the 7 days before the onset of the disease, and hospitalisation in an intensive care unit/receiving mechanical ventilation
Recruitment/selection of patients	September 1988 to November 1989
Age, gender and ethnicity	Age - Median (range): Mono: 67 (18-94); dual: 65 (18-96). Gender (M:F): 69/41%. Ethnicity: Not stated
Further population details	1. Age: All adults 2. Comorbidities: Not stated or unclear 3. Predominant disease aetiology (including resistance profiles): Not stated or unclear
Extra comments	Most common diagnoses at admission: diseases of the cardiovascular system (21%), neoplasms (17%), diseases of the digestive system (16%), diseases of the respiratory system (12%), wounds, traumas and poisoning (11%)
Intervention 1	Antibiotic plus antibiotic ~ Broad-spectrum beta-lactam + aminoglycoside. Not randomised to a specific combination therapy but to the antibiotic combination routinely used in each centre. Combinations included: Cefotaxime + aminoglycosides, cefotaxime + other antibiotics, broad-spectrum penicillins + aminoglycosides, cephalosporins with

Review question	Single- compared with dual-antibiotic therapy for HAP
	action predominantly against gram-positive organisms + aminoglycosides, cephalosporins with action predominantly against gram-negative organisms + aminoglycosides, cephalosporins active against pseudomonas + aminoglycosides, cephalosporins active against anaerobes + aminoglycosides, clindamycin + aminoglycosides, narrow-spectrum penicillins active against gram-positive organisms + aminoglycosides, other antibiotics + aminoglycosides, other antibiotic combinations. Duration Continued until at least 3 days after clinical remission, X-ray normalisation and microbiological test negativity. Concurrent medication/care: Not stated (N = 308)
Further details	1. Antibiotic dose: Not stated or unclear 2. Duration of treatment: Not stated or unclear 3. Route of administration: Not applicable / Not stated / Unclear
Comments	Not randomised to a specific combination therapy but to the antibiotic combination routinely used in each centre
Intervention 2	Antibiotic alone ~ Cephalosporin. Cefotaxime (IV), starting with a dose of 2 g every 8 hours, reduced to 2 g every 12 hours after observing improvement in the clinical picture. Duration Continued until at least 3 days after clinical remission, X-ray normalisation and microbiological test negativity. Concurrent medication/care: Not stated (N = 2 80)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: Not stated or unclear 3. Route of administration: IV
Study	**Jaspers 1998[54]**
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Zeneca Pharmaceuticals)
Number of studies (number of participants)	1 (N = 79 in total (all serious nosocomial infections); 41 with pneumonia evaluable)
Countries and setting	Conducted in Netherlands; Setting: 5 hospitals in the Netherlands
Line of therapy	1st line (no prior antibiotic within 3 days)
Duration of study	Intervention + follow up: 5-10 days treatment (max 28 days) plus 2-4 weeks follow-up
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis ~ Signs and symptoms and/or auscultatory findings and radiographic or other laboratory evidence supporting the diagnosis. Definition of nosocomial based on CDC criteria (i.e. not incubating at admission; becomes evident > 48 hours after admission)

Review question	Single- compared with dual-antibiotic therapy for HAP
Inclusion criteria	≥ 65 years of age, able to provide informed consent, one or more (proven or suspected) of the following serious bacterial infections: sepsis syndrome, intra-abdominal infection, LRTI, complicated urinary tract infection, and/or bacteraemia.
Exclusion criteria	Known hypersensitivity to beta-lactam antibiotic, hepatic impairment (three times the upper reference limit of liver transaminases for each hospital), hepatic failure or hepatic coma, a granulocyte count of ≤ 500 cells/mm^3, cystic fibrosis, or a life expectancy of < 48 hours; previous participation in the trial or received another investigational drug or antibiotic within 30 days or 3 days prior to randomization, respectively (unless the organism was resistant)
Recruitment/selection of patients	11-month recruitment period
Age, gender and ethnicity	Age - Mean (range): 76 (65-91) in full group. Gender (M:F): Define. Ethnicity: Not stated
Further population details	1. Age: (≥ 65 years). 2. Comorbidities: Majority with relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) (Most common were CVD, GI disease, bronchopulmonary and GU disease). 3. Predominant disease aetiology (including resistance profiles): (*Enterobacteriaceae*).
Extra comments	Baseline characteristics not stratified for type of infection
Intervention 1	Antibiotic plus antibiotic ~ Broad-spectrum beta-lactam + aminoglycoside. Cefuroxime IV (Glaxo Wellcome, Zeist, The Netherlands) 1.5 g (dissolved in 100 ml of sterile isotonic saline) every 8 h, in cases of renal impairment, the dosages were as follows: for a creatinine clearance rate of 10 to 50 ml/min, 1.5 g BID and for a rate of <10 ml/min, 1.5 g once daily. Gentamicin (Schering-Plough, Amstelveen, The Netherlands) was administered at a dosage of 4 mg/kg of body weight (dissolved in 100 ml of sterile isotonic saline) once daily or in two or three divided doses; in cases of renal impairment, the dosages were as follows: for a creatinine clearance rate of 50 to 70 ml/min, 1.8 mg/kg once daily; for a rate of 10 to 50 ml/min, 1.5 mg/kg once daily; and for a rate of < 10 ml/min, 1.5 mg/kg every 2 days. Duration up to 28 days (mean 7.4 days; range 3-17). Concurrent medication/care: Not stated (N = 40)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more 3. Route of administration: IV
Comments	Number with pneumonia randomised to this group unclear but 21 with pneumonia were evaluable
Intervention 2	Antibiotic alone ~ Broad-spectrum beta-lactam. Meropenem IV (Zeneca Farma, Ridderkerk, The Netherlands) 1 g (dissolved in 20 ml of sterile water–80 ml of sterile isotonic saline) every 8 h; in cases of renal impairment, the dosages were as follows: for a creatinine clearance rate of 26 to 50 ml/min, 1 g twice a day (BID); for a rate of 10 to 25 ml/min,

Review question	Single- compared with dual-antibiotic therapy for HAP
	0.5 g BID; for a rate of < 10 ml/min, 0.5 g once daily. Duration up to 28 days (mean 7.5 days; range 3-21). Concurrent medication/care: Not stated (N = 39)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: 7 days or more 3. Route of administration: IV
Comments	Number with pneumonia randomised to this group unclear but 20 with pneumonia were evaluable
Study	**Rubinstein 1995[89]**
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Glaxo R&D)
Number of studies (number of participants)	1 (N = 580 (297 with pneumonia))
Countries and setting	Conducted in
Line of therapy	Mixed line
Duration of study	Intervention + follow-up: Up to 25 days treatment plus up to 14 days treatment follow-up after treatment
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Respiratory rate, blood pressure, temperature, WBC count and radiographic findings (onset > 48 hours after admission)
Inclusion criteria	Adults with nosocomial bacterial pneumonia, sepsis or severe upper urinary tract infection > 48 hours after hospitalisation
Exclusion criteria	None stated
Recruitment/selection of patients	January 1988 to January 1990
Age, gender and ethnicity	Age - Mean (SD): 56 (NA). Gender (M:F): 59/41%. Ethnicity: Mixed
Further population details	1. Age: All adults 2. Comorbidities: Not stated or unclear 3. Predominant disease aetiology (including resistance profiles): (*P. aeruginosa, Klebsiella, Acinetobacter, E. coli*).
Extra comments	Baseline characteristics only available for the full study population, no information for the subgroup with pneumonia only. Approximately 40% acquired the infection on ICU and of these 65% were mechanically ventilated
Intervention 1	Antibiotic plus antibiotic ~ Aminoglycoside + cephalosporin. Ceftriaxone IV, 2 g once daily plus tobramycin, loading dose 2 mg/kg then

Review question	Single- compared with dual-antibiotic therapy for HAP
	3-5 mg/kg daily IV or IM. Duration Mean 9 days (range: 0-25). Concurrent medication/care: Metronidazole 500 mg three-times daily could be added (N = 138)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: Not stated or unclear 3. Route of administration: Mixed (IV or IM).
Comments	7 patients received a higher and 22 a lower dose of ceftriaxone than specified in the protocol; 45 patients received a lower dose of tobramycin - these data are from the full group (number with pneumonia unclear). In full study group 39% had received prior antibiotics (unclear how many of these had pneumonia).
Intervention 2	Antibiotic alone ~ Cephalosporin. Ceftazidime IV, 2 g twice daily (infusion or short-bolus injection). Dose was modified for patients with renal impairment. Duration Mean 9 days (range: 0-25). Concurrent medication/care: Metronidazole 500 mg three-times daily could be added (N = 159)
Further details	1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: Not stated or unclear 3. Route of administration: IV
Comments	7 patients received a higher and 22 a lower dose than specified in the protocol in the full group (number with pneumonia unclear). In full study group 36% had received prior antibiotics (unclear how many of these had pneumonia)

Table 1: Diagnosis at admission from Fernandez-Guerrero 1991[36]

Diagnosis at admission	Number with diagnosis			
	Monotherapy	Combination therapy	Total	Percentage
Diseases of the cardiovascular system	61	60	121	20.6%
Neoplasms	39	60	99	16.8%
Diseases of the digestive system	57	37	94	16.0%
Diseases of the respiratory system	35	33	68	11.6%
Wounds, traumas and poisoning	20	45	65	11.1%
Infectious and parasitic diseases	11	16	27	4.6%
Endocrine, nutritional, metabolic and immune diseases	15	6	21	3.6%
Diseases of the locomotor system and connective tissue	6	14	20	3.4%
Ill-defined symptoms, signs and conditions	9	8	17	2.9%
Diseases of the genitourinary system	9	4	13	2.2%
Diseases of the nervous system and sensory organs	3	9	12	2.0%
Diseases of the blood and hematopoietic organs	5	4	9	1.5%
No information	3	6	9	1.5%
Mental disorders	1	5	6	1.0%
Complications of pregnancy, labour and confinement	5	0	5	0.9%
Diseases of the skin and subcutaneous tissue	1	1	2	0.3%

Table 2: Clinical cure data stratified by treatment regimen from Fernandez-Guerrero 1991[36]

Regimen	N	Cure	
		Number	%
Cefotaxime	275	217	79 (74-84)
Antibiotic combinations	273	194	71 (65-76)
Cefotaxime + aminoglycosides	78	60	77 (66-86)
Cefotaxime + other antibiotics	13	10	77 (46-95)
Broad-spectrum penicillins + aminoglycosides	31	23	74 (55-88)
Cephalosporins with action predominantly against gram-positive organisms + aminoglycosides	21	10	48 (26-70)
Cephalosporins with action predominantly against gram-negative organisms + aminoglycosides	24	16	67 (45-84)
Cephalosporins active against Pseudomonas + aminoglycosides	21	16	76 (53-92)
Cephalosporins active against anaerobes + aminoglycosides	18	11	61 (36-83)
Clindamycin + aminoglycosides	12	7	58 (2-55)
Narrow-spectrum penicillins active against gram-positive organisms + aminoglycosides	18	13	72 (46-90)
Other antibiotics + aminoglycosides	15	11	73 (45-92)
Other antibiotic combinations	22	16	73 (50-89)

2.4.2.2 Results

Dichotomous

Key: NR = outcome not reported for this study; TTE = results reported as time to event data and shown in that table; similarly 'dich' for dichotomous, 'con' for continuous and 'gen' for a general method of reporting outcomes.

Study	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl
Stratum: Overall. Comparison: Broad-spectrum beta-lactam vs broad-spectrum beta-lactam + aminoglycoside								
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**	
Jaspers 1998[54]					Satisfactory response (resolved or improved) at end of treatment and no new symptoms at post-treatment follow-up @ Up to 28 days Clinically evaluable population with HAP			
	39	40	NR	NR	17/20	16/21	NR	NR
Stratum: Overall. Comparison: Cephalosporin vs aminoglycoside + cephalosporin								
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**	
Rubinstein 1995[89]					Clinical cure - complete resolution of signs and symptoms @ End of treatment (mean 9 days; up to 25 days) Number achieving improvement: 24/159 and 26/138			
	159	138	NR	NR	92/159	64/138	NR	NR
Stratum: Overall. Comparison: Cephalosporin vs broad-spectrum beta-lactam + aminoglycoside								
Protocol outcomes -->	**Numbers Randomised**		**Mortality @ 30 days**		**Clinical cure @ End of treatment**		**Withdrawal due to adverse events @ End of treatment**	

Fernandez-Guerrero 1991[36]			Mortality @ Unclear Cause of death (mono vs dual): Respiratory failure 6 vs 18; No information 4 vs 7; Cardiorespiratory arrest 4 vs 6; Septicaemia 4 vs 4; Ictus 2 vs 4; Pulmonary embolism 4 vs 1; Hepatic failure 2 vs 2; Renal failure 2 vs 2; Diabetic ketoacidosis 2 vs 1; Gastrointestinal bleeding 1 vs 2; Coma 1 vs 2; Heart failure 1 vs 1; Mycotic superinfection 0 vs 1; Malnutrition 1 vs 0; Acute abdomen 1 vs 0; Acute lung oedema 0 vs 1; Sudden death 1 vs 0		Clinical cure @ Unclear Modified ITT (assumed all missing were failures and excluded protocol violators). See breakdown of response by treatment regimen.			
	280	308	36/280	52/308	217/275	194/273	NR	NR

2.4.3 Dual- compared with other dual-antibiotic therapy for HAP

2.4.3.1 Patient characteristics, interventions and study details

Review question	Dual- compared with other dual-antibiotic therapy for HAP
Study	Joshi 1999[56]
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Wyeth-Ayerst Research part funded)
Number of studies (number of participants)	1 (N = 300)
Countries and setting	Conducted in Canada, USA; Setting: 25 hospital centres
Line of therapy	Mixed line
Duration of study	Intervention + follow-up: Minimum 5 days treatment plus up to 30 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Clinically or bacteriologically confirmed diagnosis of hospital-acquired (developed > 72 hours after admission) LRTI - chest x-ray to differentiate pneumonia and bronchitis
Stratum	Overall
Subgroup analysis within study	Post-hoc subgroup analysis: Type of infection - pneumonia or bronchitis
Inclusion criteria	Male or female hospitalised patients, aged 16 y or over with a clinically or bacteriologically confirmed diagnosis of hospital-acquired LRTI caused by bacteria thought to be susceptible to piperacillin/ tazobactam and ceftazidime were eligible for entry into the study. A 'hospital-acquired infection' was defined as one that developed >72 h after admission to a hospital or other medical facility. Patients were randomly assigned to one of the two treatment groups based on a computer-generated randomization schedule. Patients must have had either acute bacterial pneumonia or acute purulent tracheobronchitis. Clinical criteria for enrolment included: the recent onset of, or significant increase in, purulent sputum; a temperature of > 38°C; and/or a peripheral white blood cell count of > 10 x 10^9/L with > 5% immature neutrophils. A pre-enrolment Gram's stain of respiratory secretions must have shown > 25 polymorphonuclear cells and < 10 squamous epithelial cells per field at 100 x magnification and a predominant pathogen. Female patients of childbearing potential must have had a negative pregnancy test within 48 h before enrolment into the study.
Exclusion criteria	Cases of: known or suspected hypersensitivity to penicillins, cephalosporins, other beta-lactam antibiotics, beta-lactamase inhibitors, or aminoglycosides; moderate to severe renal dysfunction (creatinine clearance < 40 mL/min or serum creatinine > 225 umol/L), haemodialysis, peritoneal dialysis, plasmapheresis or haemoperfusion; evidence of active liver disease (serum transaminases, alkaline phosphatase or bilirubin > 2x the ULN); peripheral granulocyte counts 1 x 10^9/L or platelet counts < 50 x 10^9/L; more than two doses of another non-study antibacterial agent within 72 hours before enrolment (unless this agent had proved to be clinically and bacteriologically ineffective); recovery of

Review question	Dual- compared with other dual-antibiotic therapy for HAP
	a pathogen resistant to piperacillin/tazobactam, ceftazidime or tobramycin; treatment with probenecid; presence of septic shock, cystic fibrosis, active or treated leukaemia, acquired immune deficiency syndrome or known seropositivity for HIV antigen or antibody, active tuberculosis, lung cancer or metastatic lung disease or bronchial obstruction; a history of pneumonia, lung abscess, empyema or pleural effusion > 500 mL; administration of another investigational drug within 1 month before enrolment; presence of concomitant infection other than hospital-acquired LRTI and associated bacteraemia; patients requiring positive end expiratory pressure ventilation > 5 cm H_2O, patients requiring FiO_2 > 60% to maintain arterial haemoglobin oxygen saturation > 90%; no bacterial pathogen in pre-treatment culture of sputum or other respiratory secretions within 72 hours before enrolment; any concomitant condition which could preclude evaluation of response or make it unlikely that the patient could complete the study.
Recruitment/selection of patients	1989-1992. 88% nosocomial acquisition and 13% nursing home acquisition. 85% moderate to severe infection
Age, gender and ethnicity	Age - Mean (range): 56.4 (16-96) years. Gender (M:F): 75/25%. Ethnicity: 78% Caucasian; 20% Black; 2% other
Further population details	1. Age: All adults (Note: included from age 16). 2. Comorbidities: Not stated or unclear (Stated not to be statistically significantly different in the evaluable groups - but unclear which were evaluated). 3. Predominant disease aetiology (including resistance profiles): *H. influenzae* (Of 217 pathogens identified 32 (14.7%) were *H. influenzae*; 31 (14.3%) *S. aureus*; 22 (10.1%) *P. aeruginosa*; 21 (9.7%) *S. pneumoniae*; 16 (7.4%) *E. coli* and 14 (6.5%) *K. pneumoniae*).
Extra comments	Mean APACHE II score in evaluable patients: piperacillin-tazobactam group = 11.9; ceftazidime group = 13.7. 36% of patients had received antibiotics in the 72 h immediately before initiation of study medication but in all cases the agent was ineffective or prophylactic perioperative doses were used for ≤ 48 hours and LRTI developed during or after treatment.
Interventions	**Intervention 1:** Antibiotic plus antibiotic ~ Broad-spectrum beta-lactam + aminoglycoside. Piperacillin-tazobactam (3 g/375 mg) every 4 hours, plus tobramycin IV 5 mg/kg/day given in divided doses every 8 hours. Each dose of study medication was to be given by iv infusion over 30 min. In those patients with *P. aeruginosa* isolated from sputum at baseline, tobramycin was to be continued for the duration of the study. When a baseline isolate of *P. aeruginosa* was resistant to tobramycin, amikacin at a dose of 15 mg/kg/day could be substituted. Tobramycin could be discontinued in other patients after the baseline culture results were known. Duration at least 5 days (mean 9 days). Concurrent medication/care: Patients who received concomitant antibacterial therapy were categorized as failures (N = 155) **Further details:** 1. Antibiotic dose: BNF/SPC concordant

Review question	Dual- compared with other dual-antibiotic therapy for HAP
	2. Duration of treatment: Not stated or unclear 3. Route of administration: IV **Comments:** 134 participants with pneumonia. Each patient was to be treated for a minimum of 5 days, although it was recommended that in patients with a satisfactory clinical response, treatment be continued for at least 48 hours after the resolution of signs and symptoms. **Intervention 2:** Antibiotic plus antibiotic ~ Aminoglycoside + cephalosporin. Ceftazidime (2 g) administered every 8 hours plus tobramycin IV 5 mg/kg/day given in divided doses every 8 hours. Each dose of study medication was to be given by IV infusion over 30 min. In those patients with *P. aeruginosa* isolated from sputum at baseline, tobramycin was to be continued for the duration of the study. When a baseline isolate of *P. aeruginosa* was resistant to tobramycin, amikacin at a dose of 15 mg/kg/day could be substituted. Tobramycin could be discontinued in other patients after the baseline culture results were known. Duration at least 5 days (mean 9 days). Concurrent medication/care: Patients who received concomitant antibacterial therapy were categorized as failures (N = 145) **Further details:** 1. Antibiotic dose: BNF/SPC concordant 2. Duration of treatment: Not stated or unclear 3. Route of administration: IV **Comments:** 103 with pneumonia. Each patient was to be treated for a minimum of 5 days, although it was recommended that in patients with a satisfactory clinical response, treatment be continued for at least 48 hours after the resolution of signs and symptoms.

2.4.3.2 Results

Dichotomous

Key: NR = outcome not reported for this study; TTE = results reported as time to event data and shown in that table; similarly 'dich' for dichotomous, 'con' for continuous and 'gen' for a general method of reporting outcomes.

Study	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl	Exp	Ctrl
Stratum: Overall. Comparison: Broad-spectrum beta-lactam + aminoglycoside compared with aminoglycoside + cephalosporin										
Protocol outcomes -->	Numbers Randomised		Mortality @ 30 days		Withdrawal due to adverse events @ End of treatment		*C. difficile*-associated diarrhoea @ End of follow-up		Clinical cure @ End of follow-up	
Joshi 1999[56]			Mortality @ up to 30 days post-treatment Seven of the 24 deaths in the ceftazidime treatment group appeared to be directly related to failure to control infection, while only one of the 12 deaths in the piperacillin/ tazobactam treatment group was due to progression of pneumonia and failure to control infection. Only one death, in a ceftazidime-treated patient, was judged probably drug-related by the investigator.		Withdrawal due to adverse events @ up to 14 days post-treatment Piperacillin/tazobactam: 1 pancreatitis, 2 fever and 1 diarrhoea. Two of these patients also had laboratory abnormalities: decreased platelet counts and elevated liver function tests. Ceftazidime: 1 respiratory arrest, 1 erythema multiforme, 1 cardiac arrest, 2 rash, 1 cerebral haemorrhage and elevated liver function tests.		*C. difficile*-associated diarrhoea @ up to 14 days post-treatment Of those with severe diarrhoea (3 in piperacillin-tazobactam group) none had C. diff.		Clinical success (cure or improvement) at end of follow-up @ 1-14 days after end of treatment In subgroup analysis of evaluable patients only (excluding those with no baseline pathogen identified or pathogen identified resistant to randomised drug, inadequate signs and symptoms, pre-study antibiotics, no validated evaluation, concomitant infection or incorrect diagnosis), in those with pneumonia 51/70 compared with 22/42 achieved clinical success (Note: only 52 and 41% of the total pneumonia populations included)	
	155	145	12/155	24/145	4/155	7/145	0/155	0/145	115/155	84/145

2.5 Glucocorticosteroid treatment

No evidence identified.

2.6 Gas exchange

No evidence identified.

2.7 Monitoring

No evidence identified.

2.8 Safe discharge

No evidence identified.

2.9 Patient information

No evidence identified.

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