National Institute for Health and Care Excellence

APG Pneumonia (hospital-acquired): draft for consultation

# Pneumonia (hospital-acquired): antimicrobial prescribing guideline

## Evidence review

*February 2019*

*Draft for consultation*

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ISBN:

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# 1 Context

## 1.1 Background

Pneumonia is an infection of the lung tissue. It affects the air sacs (alveoli) of the lungs, which fill with microorganisms, fluid and inflammatory cells, impacting their normal function (NICE guideline on pneumonia in adults: diagnosis and management [2014]).

Pneumonia is a common condition, affecting 8 in 1,000 people each year in the UK (NHS - pneumonia). It can affect people of any age but can be more serious for the very young or the elderly. Pneumonia is most commonly caused by a bacterial infection with *Streptococcus pneumoniae* (pneumococcal infection); other bacterial causes include *Haemophilus influenzae* and *Staphylococcus aureus* (NHS - pneumonia). Pneumonia is less commonly caused by viral or fungal infections.

Hospital-acquired pneumonia (HAP) is pneumonia that is acquired after at least 48 hours of hospital admission, but not incubating at the time of admission. Hospital-acquired pneumonia affects 0.5% to 1.0% of hospitalised patients and is the most common healthcare-associated infection contributing to death (Masterton et al 2008). A cohort study conducted using a national dataset in the USA showed the overall incidence of non-ventilator hospital-acquired pneumonia is 1.6% (Giulianio et al. 2018). Hospital-acquired pneumonia is usually caused by a bacterial infection rather than a virus. Early-onset hospital-acquired pneumonia (occurring within 4 days of hospital admission) is usually caused by *Streptococcus pneumonia* and late-onset hospital-acquired pneumonia is usually caused by microorganisms that are acquired from the hospital environment. Methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* and other non-pseudomonal Gram-negative bacteria are the most common causes (NICE guideline on pneumonia [2014]: final scope).

Clinical signs of pneumonia used in diagnosis include cough with at least one of sputum, wheeze, dyspnoea or pleuritic pain; the presence of focal chest signs such as dullness to percussion, course crepitation or vocal fremitus and at least one systemic feature present with or without temperature above 38°C, including sweat, fever or myalgia (CKS – chest infections, 2015).Hospital-acquired pneumonia is estimated to increase hospital stay by about 8 days and has a reported morality rate that ranges from 30 to 70%. Variations in clinical management and outcome occur across the UK (NICE guideline on pneumonia in adults: diagnosis and management [2014]) These figures include hospital-acquired pneumonia that develops in people who are intubated in an intensive care unit, known as ventilator-associated pneumonia (VAP) and is clinically distinct from hospital-acquired pneumonia in non-intubated people. Pneumonia that develops in hospital after intubation (ventilator-associated pneumonia) is not included in this guideline.

## 1.2 Managing infections that require antibiotics

Hospital-acquired pneumonia is a lower respiratory tract infection needing treatment with an antibiotic. Antibiotics should be started within 4 hours after diagnosis (NICE guideline on pneumonia in adults: diagnosis and management, 2014).

In line with the Public Health England guidance (Start Smart Then Focus) and the NICE guideline on antimicrobial stewardship consider reviewing intravenous antibiotic prescriptions at 48 to 72 hours, documenting response to treatment and any available microbiology results to determine if the antibiotic should be continued or switched to a narrower spectrum or an oral antibiotic.

### 1.2.1 Antibiotic prescribing strategies

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) provides recommendations for prescribing antimicrobials. The recommendations guide prescribers in decisions about antimicrobial prescribing and include recommending that prescribers follow local and national guidelines, use the shortest effective course length and record their decisions, particularly when these decisions are not in line with guidelines. The recommendations also advise that prescribers take into account the benefits and harms for a person when prescribing an antimicrobial, such as possible interactions, co-morbidities, drug allergies and the risks of healthcare associated infections.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that resources and advice should be available for people who are prescribed antimicrobials to ensure they are taken as instructed at the correct dose, via the correct route, for the time specified. Verbal advice and written information that people can take away about how to use antimicrobials correctly should be given, including not sharing prescription-only antimicrobials with anyone other than the person they were prescribed or supplied for, not keeping them for use another time and returning unused antimicrobials to the pharmacy for safe disposal and not flushing them down toilets or sinks.

## 1.3 Safety information

### 1.3.1 Safety netting

Hospital-acquired pneumonia requires immediate antibiotic treatment once the diagnosis is confirmed. The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that safety netting advice should be given to everyone who has an infection (regardless of whether or not they are prescribed or supplied with antimicrobials). This should include:

- How long symptoms are likely to last with and without antimicrobials
- What to do if symptoms get worse
- What to do if they experience adverse effects from the treatment
- When they should ask again for medical advice

Urgent medical attention should be given to people experiencing severe symptoms such as rapid breathing, chest pain or confusion (NHS – pneumonia).

People with a severe systemic infection should be assessed and managed as outlined in the NICE guideline on sepsis: recognition, diagnosis and early management (2016).

Children aged under 5 who present with fever should be assessed and managed as outlined in the NICE guideline on fever in under 5s: assessment and initial management (2013).

### 1.3.2 Medicines safety

Antibiotic-associated diarrhoea is estimated to occur in 2 to 25% of people taking antibiotics, depending on the antibiotic used (NICE clinical knowledge summary [CKS]: diarrhoea – antibiotic associated).

About 10% of the general population claim to have a penicillin allergy; this is often because of a skin rash that occurred while taking a course of penicillin as a child. Fewer than 10% of people who think they are allergic to penicillin are truly allergic. See the NICE guideline on

drug allergy: diagnosis and management (2014) for more information. People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics (BNF, December 2018).

Quinolones, including ciprofloxacin, cause arthropathy in the weight-bearing joints of immature animals and are generally not recommended in children or young people who are growing (BNF, December 2018).

Tendon damage (including rupture) has been reported rarely in people receiving fluoroquinolones (BNF, December 2018), and the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (press release October 2018) has recommended restricting the use of these antibiotics following a review of disabling and potentially long-lasting side effects mainly involving muscles, tendons and bones and the nervous system.

Fluoroquinolones may be associated with a small increased risk of aortic aneurysm and dissection, particularly in older people (MHRA Drug Safety Update, November 2018).

Loading and maintenance doses of vancomycin are calculated on the basis of the person's weight and renal function, with adjustments made according to serum-vancomycin concentrations.

## 1.4 Antimicrobial resistance

The consumption of antimicrobials is a major driver for the development of antibiotic resistance in bacteria, and the 3 major goals of antimicrobial stewardship are to:

- optimise therapy for individual patients
- prevent overuse, misuse and abuse, and
- minimise development of resistance at patient and community levels.

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) recommends that the risk of antimicrobial resistance for individual patients and the population as a whole should be taken into account when deciding whether or not to prescribe an antimicrobial.

When antimicrobials are necessary to treat an infection that is not life-threatening, a narrow-spectrum antibiotic should generally be first choice. Indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant even to these 'last-line' broad-spectrum agents, and also kills normal commensal flora leaving people susceptible to antibiotic-resistant harmful bacteria such as *C. difficile*. For infections that are not life-threatening, broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) need to be reserved for second-choice treatment when narrow-spectrum antibiotics are ineffective (CMO report 2011).

The ESPAUR report 2018 reported that antimicrobial prescribing declined significantly between 2013 and 2017, with the total consumption of antibiotics in primary and secondary care declining by 4.5%. This reflected a 13.2% decrease in primary care and a 7.7% increase in secondary care. The peak of antibiotic consumption over the last 20 years occurred in 2014, with levels falling since then. The most commonly used antibiotics in England remained stable between 2013 and 2017 and were: penicillins (44.6% in 2017), tetracyclines (22.2% in 2017) and macrolides (14.7% in 2017).

Over the 5-year period, significant declining trends of use were seen for penicillins (inhibitor combinations only), first and second-generation cephalosporins, sulfonamides and

trimethoprim, and anti-*C. difficile* agents. In contrast, use of third, fourth and fifth-generation cephalosporins and other antibacterials (including nitrofurantoin) have significantly increased.

In the 5-year period from 2013 to 2017, primary care use of penicillins declined by 10.9%, with use of penicillins in the dental setting remaining largely the same. In the hospital setting, prescribing of penicillins was higher in 2017 for both inpatients (2.4%) and outpatients (14.7%) compared to 2013. Prescribing of co-amoxiclav and amoxicillin between 2013 and 2017 decreased by 11.3% and 7.4%, respectively.

Overall use of tetracyclines was unchanged between 2013 and 2017, with doxycycline (49.7% in 2017) and lymecycline (36.3% in 2017) most commonly used. Macrolide use declined by 5.8% from 2013 to 2017. Azithromycin use continued to increase in 2017, with overall use rising by 31.3% since 2013. In contrast, erythromycin use has declined over the same period by 40.7%.

Pneumonia is often caused by bacterial infection, and in bacterial hospital-acquired pneumonia, the most common causative pathogens are *Streptococcus aureus*, *Pseudomonas aeruginosa, Klebsiella pneumoniae and Escherichia coli.* Data from the ESPAUR report 2018 found that the proportion of *Staphylococcus aureus* that were methicillin-resistant *S. aureus* (MRSA) continued to decline from 9.5% in 2012/13 to 6.6% in 2017/18.

## 1.5 Other considerations

### 1.5.1 Medicines adherence

Medicines adherence may be a problem for some people with medicines that require frequent dosing (for example, some antibiotics) (NICE guideline on medicines adherence [2009]). Longer treatment durations (for example, antibiotics) may also cause problems with medicines adherence for some people.

### 1.5.2 Resource impact

#### Antibiotics for hospital-acquired pneumonia

In England 1.5% of hospital inpatients have a hospital-acquired respiratory infection. Of these people, more than half (at least 7,000) have hospital-acquired pneumonia. Hospital-acquired pneumonia is estimated to increase hospital stay be about 8 days and has a reported mortality rate more than 30% (NICE guideline on pneumonia, cost statement).

Recommended antibiotics (except ceftazidime with avibactam) are available as generic formulations, see Drug Tariff for costs.

### 1.5.3 Regulatory status

Linezolid is not licensed in children and young people under 18 years, and is recommended for children with suspected or confirmed methicillin-resistant *Staphylococcus aureus* when vancomycin cannot be used. Use in children and young people would be off label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

# 2 Evidence selection

A range of evidence sources are used to develop antimicrobial prescribing guidelines. These fall into 2 broad categories:

- Evidence identified from the literature search (see section 2.1 below)
- Evidence identified from other information sources. Examples of other information sources used are shown in the interim process guide (2017).

See appendix A: evidence sources for full details of evidence sources used.

## 2.1 Literature search

A literature search was developed to identify evidence for the effectiveness and safety of antibiotics for managing pneumonia (including community-acquired pneumonia; see appendix C: literature search strategy for full details). Pneumonia that develops in hospital after intubation (ventilator-associated pneumonia) is not included in this guideline.

The literature search identified 15, 691 references. These references were screened using their titles and abstracts and 72 full text references for hospital–acquired pneumonia were obtained and assessed for relevance. Studies excluded at title and abstract screening included studies of community-acquired pneumonia.

No systematic reviews met the inclusion criteria for the review. Nine randomised controlled trials (RCTs) and 1 post-hoc analysis of a RCT were assessed as relevant to the guideline review question (see appendix B: review protocol). Ten percent of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%.

The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide. Nine included references were prioritised by the committee as the best available evidence and were included in this evidence review (see appendix F: included studies and appendix E: evidence prioritisation).

The remaining 62 references were excluded. These are listed in appendix J: excluded studies with reasons for their exclusion.

No systematic reviews or RCTs which fit the review protocol were identified in children. When making recommendations on antibiotic choice in children, the committee agreed that it was more appropriate to extrapolate from higher quality evidence in adults than search for lower quality observational studies in children.

See also appendix D: study flow diagram.

## 2.2 Summary of included studies

A summary of the included studies is shown in table 1. Details of the study citation can be found in appendix F: included studies. An overview of the quality assessment of each included study is shown in appendix G: quality assessment of included studies.

**Table 1: Summary of included studies: antimicrobials**

| Study | Number of participants | Population | Intervention | Comparison | Primary outcome |
|---|---|---|---|---|---|
| Antibiotic prescribing strategies | | | | | |
| Herer et al. (2009), France, open-label RCT, follow-up at up to 28 days after enrolment | n=68 | People with onset of pneumonia symptoms after 72 hours of hospitalisation | Immediate bronchoscopy with culture; choice of antibiotic treatment based on culture results | Immediate empirical antibiotic treatment | Clinical cure |
| Antibiotics versus other antibiotics | | | | | |
| Schmitt et al. (2006), 3 European countries, double-blind RCT, follow-up at up to 21 days after treatment | n=221 | People aged 18 years or older with a clinical and radiological diagnosis of pneumonia after at least 48 hours of hospitalisation | Piperacillin/tazobactam IV for 5 to 21 days | Imipenem/cilastatin IV for 5 to 21 days | Clinical response (cure/improved or treatment failure); bacteriological response; adverse events |
| Freire et al. (2010), multiple countries, double-blind RCT, follow-up at up to 21 days after treatment | n=945 | People aged 18 years or older with onset of pneumonia symptoms after at least 48 hours of hospitalisation | Tigecycline IV for 10 days (median) | Imipenem/cilastatin for 10 days (median) | Clinical response (cure; failure) |
| Ramirez et al. (2013), multiple countries, double-blind RCT, follow-up at up to 21 days after treatment | n=108 | Adults with the onset of pneumonia symptoms after at least 48 hours of hospitalisation | Tigecycline IV (2 dosage regimens) for 8 days (average) | Imipenem/cilastatin IV for 8 days (average) | Clinical response |
| Hoffken et al. (2007), multiple countries, open-label RCT, | n=161 | People aged 18 years or older with a clinical diagnosis of pneumonia after at | Moxifloxacin IV then oral for 7 to 14 days | Ceftriaxone IV then cefuroxime oral for 7 to 14 days | Clinical response (resolution; clinical failure); |

| Study | Number of participants | Population | Intervention | Comparison | Primary outcome |
|---|---|---|---|---|---|
| follow-up at up to 31 days after treatment | | least 48 hours of hospitalisation | | | Bacteriological response;<br>Adverse events; |
| Awad et al. (2014), multiple countries, double-blind RCT, follow-up at up to 35 days after treatment | n=781 | People aged 18 years or older with a clinical diagnosis of pneumonia after at least 72 hours of hospitalisation | Ceftobiprole IV plus placebo for 7 to 14 days | Ceftazidime IV plus linezolid IV for 7 to 14 days | Clinical cure;<br>Microbiological eradication;<br>Adverse events |
| Torres et al. (2017), multiple countries, double-blind non-inferiority RCT, follow-up at up to 25 days after randomisation | n=829 | People aged between 18 and 90 years in hospital with pneumonia after at least 48 hours of hospitalisation | Ceftazidime/avibactam IV for 7 to 14 days | Meropenem IV for 7 to 14 days | Clinical cure;<br>Adverse events |
| Rubinstein et al. (2014), Israel and USA, non-inferior double-blind RCT, follow-up at up to 14 days after treatment | n=1,076 | People aged 18 years or older with non-ventilator associated pneumonia acquired after at least 48 hours of hospitalisation | Telavancin IV for 7 to 21 days | Vancomycin IV for 7 to 21 days | Clinical cure;<br>Adverse events |
| Kim et al. (2012), South Korea, open-label RCT, follow-up at up to 28 days | n=109 | People aged 18 years or older with pneumonia acquired more than 48 hours after admission to hospital intensive care unit | Imipenem/cilastatin IV plus vancomycin IV with subsequent de-escalation (mean total duration 12.5 days) | Empirical antibiotics (except carbapenem or vancomycin) without de-escalation (mean total duration 14.1 days) | Antimicrobial adequacy;<br>Mortality rate;<br>Duration of intensive care unit stay |
| Abbreviations: IV, intravenous; RCT, Randomised controlled trial | | | | | |

# 3 Evidence summary

Full details of the evidence are shown in appendix H: GRADE profiles.

The main results are summarised below for adults with hospital-acquired pneumonia. For the purpose of this review, studies in people with pneumonia that developed in hospital after intubation, known as ventilator-associated pneumonia, were not included. When studies included a mixed population (hospital-acquired pneumonia and ventilator-associated pneumonia), stratified results for people with hospital-acquired pneumonia were included when available. If the results could not be stratified, the quality of the evidence was downgraded due to indirectness. No evidence from systematic reviews of randomised controlled trials (RCTs) or RCTs was identified in children.

See the summaries of product characteristics, British National Formulary (BNF) and BNF for children (BNF-C) for information on contraindications, cautions and adverse effects of individual medicines, and for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding.

Although many studies included in the review were non-inferiority trials, the committee considered that the reasons for the choice of non- inferiority margin were poorly reported in the studies. Therefore the committee decided to treat non-inferiority trials as superior head to head trials. Clinical effectiveness was assessed using a minimal important difference of 1.0 and imprecision was assessed using the standard GRADE minimal important difference of a relative risk (RR) of 0.75 and 1.25 for all outcomes except mortality, for which a RR of 1.0 was used to assess both effectiveness and imprecision.

## 3.1 Antimicrobials in adults

### 3.1.1 Antibiotic prescribing strategies

The evidence review for antibiotic prescribing strategies in adults with hospital-acquired pneumonia is based on 2 randomised controlled trials (RCTs); Herer et al. 2009 and Kim et al. 2012).

**Bronchoscopy-guided prescribing versus empirical antibiotics**

Herer et al. 2009 compared clinical outcomes and costs of 2 prescribing strategies:

- antibiotic prescribing guided by the result of immediate bronchoscopy with culture of a protected specimen brush sample, which was carried out within 24 hours after clinical diagnosis of hospital-acquired pneumonia; gram stain results were available 4 to 6 hours after bronchoscopy and were used to modify treatment;
- immediate empirical antibiotic prescribing.

The study included a total of 68 people (mean age 66 years) with recent and persistent infiltration on chest radiograph and the onset of pneumonia symptoms after 72 hours of hospitalisation. None of these people were ventilated at the time of study enrolment. People were randomised to receive either bronchoscopy-guided antibiotic treatment or immediate empirical antibiotics. Ten people in each group received antibiotic treatment before inclusion, because of fever or suspected sepsis. All people (100%, n=34) in the immediate empirical antibiotic group received

antibiotics compared with 76.5% (n=34) in the bronchoscopy-guided antibiotic treatment group. Antibiotics used in the study included: third generation cephalosporins, quinolones, streptogramins, vancomycin, and beta-lactams as single therapy or combined therapy. All people in the bronchoscopy-guided antibiotic group had immediate bronchoscopy (100%, n=34); and 26.5% (n=9) people who received immediate empirical antibiotics and failed to respond to treatment had subsequent bronchoscopy.

Bronchoscopy-guided antibiotic treatment had no significant effect compared with immediate empirical antibiotic treatment on clinical response including clinical failure at day 3 (1 RCT, n=68, 8.8% versus 26.5%, RR 0.33, 95% confidence interval [CI] 0.10 to 1.13; low quality evidence) and clinical cure at day 28 (1 RCT, n=68, 73.5% versus 79.4%, RR 0.93, 95% CI 0.71 to 1.21; NICE analysis; low quality evidence).

There was no significant difference between bronchoscopy-guided antibiotic treatment and immediate empirical antibiotic treatment for mortality (day 3, n=68, 8.8% versus 2.9%, RR 3.00, 95% CI 0.33 to 27.42, NICE analysis, very low quality evidence; day 14, n=63, 15.6% versus 6.5%, RR 2.24, 95% CI 0.51 to 11.57, NICE analysis, very low quality evidence; day 28, n=62, 21.9% versus 10.0%, RR 2.19, 95% CI 0.62 to 7.69, NICE analysis; low quality evidence).

There was no significant difference between bronchoscopy-guided antibiotic treatment and immediate antibiotic treatment in the daily and total cost of antibiotics (daily antibiotic cost, n=68, MD=€4.9 lower, NICE analysis 95% CI €15.3 lower to €5.5 higher; low quality evidence; total antibiotic cost, n=68, MD=€106.2 lower, NICE analysis[1] 95% CI €270.1 lower to €57.7 higher; low quality evidence). The cost of bronchoscopy was significantly higher in bronchoscopy-guided antibiotic treatment than in immediate empirical antibiotic treatment (n=68, MD=€126.80 more [p<0.001], NICE analysis 95% CI €100.85 to €152.75 more; low quality evidence). There was no significant difference between bronchoscopy-guided antibiotic treatment and immediate empirical antibiotic treatment for total cost (total cost including bronchoscopy-related and antibiotic costs, n=68, MD €20.6 higher, NICE analysis 95% CI €150.1 lower to €191.3 higher; low quality evidence).

See GRADE profile: table 5.

**Broad spectrum antibiotics with de-escalation versus empirical antibiotics**

Kim et al. (2012) compared the effects of early treatment with broad-spectrum antibiotics followed by subsequent de-escalation with conventional antibiotic regimens in people aged 18 years or older (mean age 64 years) with pneumonia and a new infiltrate on chest x-ray occurring 48 hours or more after hospitalisation. The study included a total of 109 people, including 100 with hospital-acquired pneumonia (91.7%) and 9 with ventilator-associated pneumonia (8.3%).

Participants were randomly allocated to the broad spectrum group (where they initially received imipenem/cilastatin 0.5 g every 6 hours plus vancomycin 15 mg/kg every 12 hours, and after 3 to 5 days this was de-escalated individually based on culture results and clinical status) or the empirical group (where they received empirical antibiotic treatment with piperacillin/tazobactam, cephalosporins, quinolones, oxazolidinones, monobactams or aminoglycosides and their initial treatment was not de-escalated). The route of administration was not reported.

The number of people who received adequate initial antimicrobials was significantly higher in the broad spectrum group than the empirical group (n=54, 75.9% versus 48.0%, RR 1.58, 95% CI 1.00 to 2.50; NICE analysis; very low quality

evidence).Therefore, the early use of broad spectrum antimicrobials followed by subsequent de-escalation was more effective than conventional therapy in giving adequate antibiotic coverage in initial treatment. In the broad spectrum group, 30 people had vancomycin discontinued and 28 people had imipenem/cilastatin discontinued; of these, 17 switched to piperacillin/tazobactam with or without ciprofloxacin; 5 switched to ceftriaxone, 3 to ceftazidime, 3 to ampicillin/sulbactam and 2 to cefazolin. In the empirical group, 18 people had their initial empirical antibiotic changed to either carbapenem alone (n=10) or carbapenem plus vancomycin (n=8).

There was no significant difference between the broad spectrum group and the empirical group in mortality (all-cause mortality on day 28, n=109, 39.6% versus 25.5%, RR 1.56, 95% CI 0.89 to 2.73; NICE analysis; very low quality evidence), duration of antibiotic use (n=109, 12.5 days [SD 5.8] versus 14.1 days [SD 7.3], mean difference 1.6 days less, 95% CI 4.1 days less to 1.0 day more; very low quality evidence) and intensive care stay length (n=109, 21.1 days [IQR 6-35] versus 14.1 days [IQR 6-19], p=0.464; very low quality evidence).

Broad spectrum antibiotics with de-escalation was significantly worse than empirical antibiotics in overall incidence of emergence of multidrug resistant organisms, when only considering people who did not have multidrug resistant organism infection initially (n=71, 37.9% versus 16.7%, RR 2.28, 95% CI 1.00 to 5.17; NICE analysis; low quality evidence). However, there was no significant difference in any other resistance outcomes which were reported, including time to development of multidrug resistant organisms (n=71, 19.4 days [IQR 11 to 30] versus 22.7 days [IQR 9 to 30]); p=0.108; very low quality evidence), or emergence of any of the following pathogens: methicillin-resistant *Staphylococcus aureus*, gram-negative non-Enterobacteriaceae, *Stenotrophomonas maltophilia*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* or extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* (very low quality evidence).

See GRADE profile: table 6.

### 3.1.2 Choice of antibiotic

The evidence review for choice of antibiotic treatment is based on 6 RCTs and 1 post-hoc analysis of a RCT. The following comparisons of antibiotics were included:

- Penicillin with beta-lactamase inhibitor versus carbapenem (piperacillin/tazobactam versus imipenem/cilastatin: Schmitt et al. 2006)
- Tetracycline versus carbapenem (tigecycline versus imipenem/cilastatin: Freire et al. 2010; tigecycline versus imipenem/cilastatin: Ramirez et al.2013)
- Quinolone versus cephalosporin (moxifloxacin versus ceftriaxone followed by cefuroxime: Hoffken et al. 2007)
- Cephalosporin versus cephalosporin plus oxazolidinone (ceftobiprole versus ceftazidime plus linezolid: Awad et al. 2014)
- Cephalosporin with beta-lactamase inhibitor versus carbapenem (ceftazidime/avibactam versus meropenem: Torres et al. 2017)
- Glycopeptide versus glycopeptide (telavancin versus vancomycin: Rubinstein et al. 2014)

Overall, 6 included studies were non-inferiority trials, which compared a novel antibiotic with standard or existing antibiotic treatment for hospital-acquired pneumonia. Most of the included studies (n=4) had a mixed population including

people with hospital-acquired pneumonia and people with ventilator-associated pneumonia, and all of these studies conducted a subgroup analysis of people with non-ventilator-associated hospital-acquired pneumonia.

**Penicillin with beta-lactamase inhibitor versus carbapenem**

Schmitt et al. (2006) assessed the efficacy and safety of piperacillin/tazobactam compared with imipenem/cilastatin in people aged 18 years or over (mean age 67 years) who were severely ill with clinical and radiological evidence of pneumonia acquired 48 hours or later after hospitalisation. A total of 51 (23.1%) people required mechanical ventilation at baseline, but the study did not specify whether their pneumonia was developed after being on the ventilator. Participants randomly received either piperacillin/tazobactam 4 g/500 mg or imipenem/cilastatin 1 g/1 g intravenously (IV) every 8 hours for between 5 and 21 days. If *P. aeruginosa* was present, additional aminoglycoside therapy was mandatory. At baseline, 28.0% (n=30) of people who received piperacillin/tazobactam and 19.1% (n=21) of people who received imipenem/cilastatin required mechanical ventilation.

The study was terminated prematurely because of recruitment difficulties. At the first follow-up (up to 4 days after treatment), there was no significant difference between piperacillin/tazobactam and imipenem/cilastatin on clinical cure or improvement in people who received at least 6 doses of treatment (n=217, 66.4% versus 70.0%; RR 0.95, 95% CI 0.79 to 1.14; low quality evidence). Also, there was no significant difference in clinical cure or improvement at the second follow-up (up to 18 days after treatment; n=217, 59.8% versus 66.4%; RR 0.90, 95% CI 0.73 to 1.11; very low quality evidence).

Overall 74.5% and 64.9% of people who received piperacillin/tazobactam and imipenem/cilastatin, respectively, reported adverse events. The number of adverse events considered to be related to treatment was similar in both groups (n=217, 30.0% versus 25.2%; RR 1.19, 95% CI 0.77 to 1.83; NICE analysis; very low quality evidence). The most common treatment-related adverse events were diarrhoea and fever in the piperacillin/tazobactam group and increased alkaline phosphatase, nausea and vomiting in the imipenem/cilastatin group.

There was no significant difference between piperacillin/tazobactam and imipenem/cilastatin for mortality. There were 17 deaths in the piperacillin/tazobactam group and 11 deaths in the imipenem/cilastatin group. Two deaths in the piperacillin/tazobactam group were assessed as possibly related to the medication, the number of deaths related to medication in the imipenem/cilastatin group was not reported. Pneumonia was involved in the death of 1 patient in the piperacillin/tazobactam group and 2 in the imipenem/cilastatin group (n=221, 0.9% versus 1.8%; RR 0.50, 95% CI 0.05 to 5.48; NICE analysis; very low quality evidence).

See GRADE profile: table 7

**Tetracycline versus carbapenem**

Freire et al. (2010) assessed the non-inferiority of tigecycline to imipenem/cilastatin in terms of clinical efficacy in the treatment of people aged 18 years or over (mean age 58 years) with pneumonia symptoms starting at least 48 hours after hospital admission, and a new or evolving infiltrate on chest x-ray. The study included people with and without ventilator-associated pneumonia. Of those who received study treatment, 27.1% (n=253) were diagnosed with ventilator-associated pneumonia and 72.9% (n=681) were diagnosed with non-ventilator-associated pneumonia.

Participants randomly received either tigecycline 100 mg IV followed by 50 mg every 12 hours or imipenem/cilastatin 500 mg to 1 g IV every 8 hours for between 7 and 14 days. Optional adjunctive ceftazidime could be added in the tigecycline group for *P. aeruginosa* coverage; and optional adjunctive vancomycin could be added in the imipenem/cilastatin for MRSA coverage. Both groups could also receive an aminoglycoside for double coverage of *P. aeruginosa*. In the tigecycline group, 40.9% received adjunctive vancomycin or its placebo and 39.6% received adjunctive ceftazidime or its placebo; in the imipenem/cilastatin group, respectively 47.1% and 47.1% received adjunctive vancomycin and ceftazidime or their placebos; and aminoglycosides were administered to 14.3% of both groups.

In the subgroup of people without ventilator-associated pneumonia who met study inclusion criteria and received at least 1 dose of study treatment (clinically modified intention-to-treat population), the clinical cure rates at the test-of-cure visit (10 to 21 days after completion of treatment) were 69.3% in the tigecycline group and 71.2% in the imipenem/cilastatin group. The difference for clinical cure between groups was not significant (n=626, 69.3% versus 71.2%, RR 0.97, 95% CI 0.88 to 1.08; absolute difference 1.9% fewer, 95% CI 9.4% fewer to 5.6% more; NICE analysis; moderate quality evidence). Similar results were reported in the analysis based on participants whose response to antibiotic treatment could be measured and determined (clinically evaluable population) (n=371, 75.4% versus 81.3%, RR 0.93, 95% CI 0.83 to 1.03; absolute difference 5.9% fewer, 95% CI 14.5% fewer to 3.0% more; NICE analysis; moderate quality evidence).

In the subgroup analysis of people without ventilator-associated pneumonia, 12.2% (n=41) of people in the tigecycline group and 12.5% (n=43) of the imipenem/cilastatin group died during the study (RR 0.98, 95% CI 0.66 to 1.46; NICE analysis; low quality evidence). Shock and respiratory failure were the most reported reasons for death. Three deaths were considered to be related to the study drug (1 death from pneumonia in the tigecycline group and 2 in the imipenem/cilastatin group; low quality evidence).

Overall, there was no difference between tigecycline and imipenem/cilastatin for adverse events which included nausea, vomiting and diarrhoea, in the full study population, which included ventilator-associated and non-ventilator associated pneumonia. However, tigecycline significantly increased the number of people who discontinued treatment due to adverse events which included pneumonia and respiratory failure compared with imipenem/cilastatin (n=934, 10.9% versus 6.6%, RR 1.65, 95% CI 1.07 to 2.52; NNH 23, 95% CI 12 to 150; NICE analysis; very low quality evidence).

Ramirez et al. (2013) assessed the non-inferiority of tigecycline to imipenem/cilastatin for clinical cure in the treatment of adults (mean age 62 years) with pneumonia symptoms starting 48 hours or more after hospital. The study included people with and without ventilator-associated pneumonia. Of people who received study treatment, 39.0% (n=41) of people were diagnosed with ventilator-associated pneumonia and 61.0%% (n=54) with non-ventilator-associated pneumonia.

People were randomised into 1 of 3 arms: an initial 150mg dose of tigecycline, followed by tigecycline 75 mg IV every 12 hours; an initial 200mg dose of tigecycline followed by tigecycline 100 mg IV every 12 hours; or, imipenem/cilastatin 1 g IV every 8 hours. The average duration of antibiotic treatment was 8 days. People randomised to tigecycline also received adjunctive ceftazidime and tobramycin or amikacin at the start of therapy unless there was no concern about *P. aeruginosa* or

MRSA infection; and people randomised to imipenem/cilastatin were given adjunctive vancomycin and tobramycin or amikacin. Approximately 58% of people in the tigecycline groups received adjunctive ceftazidime and 65% of people in the imipenem/cilastatin group received adjunctive vancomycin. Aminoglycosides were given to approximately 46% of the tigecycline group and 29% of the imipenem/cilastatin group.

The study was terminated early due to small sample size. In the subgroup of people without ventilator-associated pneumonia whose response to antibiotics could be measured and determined (clinically evaluable population), the clinical cure rates at the test of cure visit (10 to 21 days after completion of treatment) were higher with tigecycline 100mg (84.6%) compared with tigecycline 75mg (68.8%) and imipenem/cilastatin (73.3%). However, there was no significant difference between either dose of tigecycline and imipenem/cilastatin (tigecycline 75 mg, n=31, 68.8% versus 73.3%, RR 0.94, 95% CI 0.60 to 1.47; absolute difference 4.4% fewer, 95% CI 29.3% fewer to 34.5% more; NICE analysis; very low quality evidence; tigecycline 100 mg, n=28, 84.6% versus 73.3%, RR 1.15, 95% CI 0.79 to 1.69; absolute difference 11.0% more, 95% CI 15.4% fewer to 50.6% more; NICE analysis; low quality evidence). There was no significant difference between the 2 doses of tigecycline for clinical cure in people without ventilator-associated pneumonia (n=29, 68.8% versus 84.6%, RR 0.81, 95% CI 0.54 to 1.22; NICE analysis; low quality evidence).

There was also no significant difference between tigecycline and imipenem/cilastatin for mortality and adverse events (diarrhoea, nausea, vomiting) in the full study population which included both people with and without ventilator-associated pneumonia. Although the incidence of diarrhoea, nausea and vomiting were highest in the higher dose tigecycline group.

See GRADE profile: tables 8 and 9

**Quinolone versus cephalosporin**

Hoffken et al. (2007) assessed the non-inferiority of moxifloxacin to a cephalosporin (ceftriaxone followed by cefuroxime) for clinical cure at the test of cure visit (4 to 15 days after completion of treatment) in people aged 18 years or older (mean age 66 years) who had new onset pneumonia at least 48 hours after hospitalisation, and a new infiltrate on chest x-ray. Fourteen people (8.8%) required mechanical ventilation but the study excluded people who had been on mechanical ventilation for more than 5 days at enrolment (therefore only people with non-ventilator-associated hospital-acquired pneumonia were likely to be included in this study). The average time between hospitalisation and diagnosis of hospital-acquired pneumonia was 7 days, which ranged from 0 to 107 days; therefore, there is an unknown percentage of participants who acquired pneumonia before hospitalisation and are likely to have community-acquired pneumonia. Participants randomly received either moxifloxacin 400 mg once daily IV followed by oral moxifloxacin 400 mg once daily or ceftriaxone 2 g once daily IV followed by oral cefuroxime 500 mg twice daily for 7 to 14 days. Participants could be switched from IV to oral antibiotics from day 4 onwards, at the discretion of the investigator. Forty people (52%) in the moxifloxacin group and 42 (51%) people who were treated with a cephalosporin used antibiotics prior to the study.

This study terminated prematurely because of low recruitment rate. Up to 15 days after treatment, the clinical cure rate for moxifloxacin was similar to a cephalosporin with no significant difference between treatment groups (n=159, 72.7% versus

68.3%, RR 1.06, 95% CI 0.87 to 1.30; absolute difference 4.4% more, 95% CI 10.1% fewer to 18.4% more; NICE analysis; very low quality evidence). Similar results were reported in the analysis based on participants whose response to antibiotic treatment could be measured and determined (clinically evaluable population) (n=120, 86.7% versus 83.3%, RR 1.04, 95% CI 0.89 to 1.21; absolute difference 3.3% more, 95% CI 9.8% fewer to 16.0% more; NICE analysis; low quality evidence).

Overall, there was no difference between moxifloxacin and a cephalosporin for serious adverse events. However, moxifloxacin increased the number of people who reported drug-related adverse events compared with a cephalosporin (n=159, 29.9% versus 15.9%, RR 1.88, 95% CI 1.03 to 3.45; NNH 7, 95% CI 3 to 84; NICE analysis; very low quality evidence). There was no significant difference between moxifloxacin and a cephalosporin for mortality, with none of the deaths considered to be related to study medication.

See GRADE profile: table 10.

**Cephalosporin versus cephalosporin plus oxazolidinone**

Awad et al. (2014) assessed the non-inferiority of ceftobiprole to ceftazidime plus linezolid for clinical cure in people aged 18 years or older with a clinical diagnosis of pneumonia after at least 72 hours of hospitalisation. The study included 73.1% (n=571) of people with non-ventilator-associated hospital-acquired pneumonia and 26.9% (n=210) of people with ventilator-associated pneumonia. A large proportion of participants (44.8%) were characterised as severely ill.

Participants randomly received either ceftobiprole 500 mg IV every 8 hours plus placebo IV every 12 hours, or ceftazidime 2 g IV every 8 hours plus linezolid 600 mg IV every 12 hours for 7 to14 days. Additional open-label treatment with a quinolone or an aminoglycoside was allowed for people who were at risk of pseudomonal infection in both groups. Ten percent and 11% of people in the ceftobiprole and ceftazidime plus linezolid groups, respectively, had pseudomonas; and 59% and 62% had received prior antibiotics within 24 hours of study enrolment.

In the subgroup of people with non-ventilator-associated hospital-acquired pneumonia, the clinical cure rates at the test-of-cure visit (7 to 14 days after completion of study treatment) were similar in people treated with ceftobiprole or ceftazidime plus linezolid, and the difference between treatment groups was not significant (n=571, 59.6% versus 58.8%, RR 1.01, 95% CI 0.88 to 1.16; intention-to-treat population; absolute difference 0.8% more, 95% CI 7.3% fewer to 8.8% more; NICE analysis; high quality evidence). Similar results were reported in the analysis based on participants whose response to antibiotic treatment could be measured and determined (clinically evaluable population; n=383, 77.8% versus 76.2%, RR 1.02, 95% CI 0.91 to 1.14; absolute difference 1.6% more, 95% CI 6.9% fewer to 10.0% more; NICE analysis; moderate quality evidence).

There was no significant difference between ceftobiprole and ceftazidime plus linezolid in the subgroup of people with non-ventilator-associated hospital-acquired pneumonia for all-cause mortality at 30 days (n=571, 16.7% versus 18.0%, RR 0.93, 95% CI 0.65 to 1.33; NICE analysis; moderate quality evidence) or pneumonia-specific mortality (n=571, 5.9% versus 5.6%, RR 1.05, 95% CI 0.54 to 2.04; NICE analysis; moderate quality evidence). Treatment-related adverse events were similar in the full study population, which included people with non-ventilator-associated hospital-acquired pneumonia and those with ventilator-associated pneumonia (n=772, 24.9% versus 25.4%, RR 0.98, 95% CI 0.77 to 1.25; NICE analysis; low quality evidence).

See GRADE profile: table 11.

**Cephalosporin with beta-lactamase inhibitor versus carbapenem**

Torres et al. (2017) assessed the non-inferiority of ceftazidime/avibactam to meropenem in terms of efficacy and safety in people aged between 18 and 90 years (mean age 62 years) with an onset of pneumonia at least 48 hours after hospital admission. A total of 480 (66.1%) people without ventilator-associated pneumonia and 246 (33.9%) people with ventilator-associated pneumonia were included and received study treatment. Participants randomly received either ceftazidime/avibactam 2000/500 mg IV every 8 hours or meropenem 1000 mg IV every 8 hours for between 7 and 14 days. Sixty-six percent (n=234) and 68% (n=253) of people in the ceftazidime/avibactam group and the meropenem group used antibiotics prior to the study. In the study, open-label linezolid or vancomycin was given to people whose infections were caused by gram-positive pathogens, and open-label amikacin (or another aminoglycoside) was given to people whose infections were caused by gram-negative pathogens. The study reported that 80% (n=284) and 82% (n=302) of people receiving ceftazidime/avibactam and meropenem received a concomitant aminoglycoside.

In the subgroup of people without ventilator-associated pneumonia who met inclusion criteria and received study treatment (clinically modified intention-to-treat population), the clinical cure rates at the test-of-cure visit (21 to 25 days after randomisation) were similar for people treated with ceftazidime/avibactam or meropenem. There was no significant difference between treatment groups (n=480, 68.3% versus 72.3%, RR 0.94, 95% CI 0.84 to 1.06; absolute difference 4.3% fewer, 95% CI 11.6% fewer to 4.3% more; NICE analysis; high quality evidence). Similar results were reported in the analysis based on participants whose response to antibiotic treatment could be measured and determined (clinically evaluable population; n=364, 77.4% versus 79.1%, RR 0.98, 95% CI 0.88 to 1.09; absolute difference 1.6% fewer, 95% CI 9.5% fewer to 7.1% more; NICE analysis; high quality evidence).

The safety profile of ceftazidime/avibactam was similar to that of meropenem in the full study population. There was no significant difference between ceftazidime/avibactam and meropenem in the number of people reporting at least 1 adverse event (n=808, 74.6% versus 74.2%, RR 1.01, 95% CI 0.93 to 1.09; NICE analysis; moderate quality evidence) or the number of people reporting adverse events that were related to treatment (n=808, 16.3% versus 13.4%, RR 1.45, 95% CI 0.68 to 3.08; NICE analysis; low quality evidence). Few adverse events resulted in discontinuation of the study treatment; 4.0% (n=16) and 2.7% (n=13) of people in the ceftazidime/avibactam and meropenem groups, respectively. There was also no significant difference between ceftazidime/avibactam and meropenem for all-cause mortality (n=808, 9.4% versus 7.4%, RR 1.26, 95% CI 0.80 to 1.99; NICE analysis; low quality evidence) or mortality related to disease progression (n=808, 3.2% versus 2.0%, RR 0.68, 95% CI 0.68 to 3.86; NICE analysis; low quality evidence).

See GRADE profile: table 12.

**Glycopeptide (telavancin) versus glycopeptide (vancomycin)**

Rubinstein et al. (2014) extracted data from 2 RCTs (Rubinstein et al. 2011) which assessed the non-inferiority of telavancin to vancomycin in terms of clinical efficacy for treating people aged 18 years or over (mean age 64.5 years) who had pneumonia acquired after 48 hours of hospitalisation. This post-hoc analysis specifically included data from a subgroup of people with non-ventilator-associated pneumonia (which included people who were ventilated but developed their pneumonia prior to being

ventilated). Participants randomly received either telavancin 10 mg/kg IV every 24 hours or vancomycin 1 g IV every 12 hours for 7 to 21 days.

Up to 14 days after study treatment, of people whose response to antibiotics could be measured and determined (clinically evaluable population), the clinical cure rates were similar for people treated with telavancin or vancomycin and there was no significant difference between groups (n=519, 83.1% versus 84.1%, RR 0.99, 95% CI 0.91 to 1.07; absolute difference 0.8% fewer, 95% CI 7.6% fewer to 5.9% more; NICE analysis; moderate quality evidence). The incidence of adverse events was also similar between telavancin and vancomycin; common adverse events reported in both groups were gastrointestinal events including constipation, diarrhoea and nausea. The incidence of any renal events was higher with vancomycin (11.8%) than with telavancin (8.4%); 7.1% and 5.0% of people receiving telavancin or vancomycin discontinued their treatment due to adverse events.

See GRADE profile: table 13.

### 3.1.3 Antibiotic dosage, duration and route of administration

No systematic reviews or RCTs met the inclusion criteria.

# 4 Terms used in the guideline

### 4.1.1 Hospital-acquired pneumonia

Pneumonia that develops 48 hours or more after hospital admission and that was not incubating at hospital admission (NICE guideline on pneumonia [2014]). When managed in hospital the diagnosis is usually confirmed by chest X-ray. For the purpose of this guideline, pneumonia that develops in hospital after intubation (ventilator-associated pneumonia) is excluded from this definition.

### 4.1.2 Ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is a hospital-acquired infection. Although there is no consensus definition, it is often defined as pneumonia that occurs in patients who have had intubation with an endotracheal or tracheostomy tube to help or control respiratory function continuously for at least 48 hours before the onset of the pneumonia (American Thoracic Society and Infectious Diseases Society of America, 2005).

# Appendices

# Appendix A: Evidence sources

| Key area | Key question(s) | Evidence sources |
|---|---|---|
| Background | • What is the natural history of the infection?<br>• What is the expected duration and severity of symptoms with or without antimicrobial treatment?<br>• What are the most likely causative organisms?<br>• What are the usual symptoms and signs of the infection?<br>• What are the known complication rates of the infection, with and without antimicrobial treatment?<br>• Are there any diagnostic or prognostic factors to identify people who may or may not benefit from an antimicrobial? | • NICE guideline on pneumonia in adults: diagnosis and management (2014)<br>• NHS – pneumonia<br>• Masterson et al. 2008<br>• Giulianio et al. 2018<br>• British Lung Foundation – pneumonia<br>• Start Smart Then Focus – Public Health England<br>• NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial use (2015)<br>• NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) |
| Safety information | • What safety netting advice is needed for managing the infection?<br>• What symptoms and signs suggest a more serious illness or condition (red flags)? | • NHS – pneumonia<br>• NICE guideline on sepsis: recognition, diagnosis and early management (2016; updated 2017)<br>• NICE guideline on fever in under 5s: assessment and initial management (2013; updated 2017)<br>• NICE clinical knowledge summary: diarrhoea-antibiotic associated (2014)<br>• NICE guideline on drug allergy: diagnosis and management |

| Key area | Key question(s) | Evidence sources |
|---|---|---|
| | | • British National Formulary (BNF), December 2018<br>• Committee experience |
| Antimicrobial resistance | • What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection<br>• What is the need for broad or narrow spectrum antimicrobials?<br>• What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials? | • NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015)<br>• Chief medical officer (CMO) report (2011)<br>• ESPAUR report (2018) |
| Medicines adherence | • What are the problems with medicines adherence (such as when longer courses of treatment are used)? | • NICE guideline on medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009) |
| Resource impact | • What is the resource impact of interventions (such as escalation or de-escalation of treatment)? | • NHSBSA Drug Tariff<br>• NICE guideline on pneumonia in adults: diagnosis and management (2014) |
| Regulatory status | • What is the regulatory status of interventions for managing the infection or symptoms? | • Summary of product characteristics |
| Antimicrobial prescribing strategies | • What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms? | • Evidence review – see appendix F for included studies |
| Antimicrobials | • What is the clinical effectiveness and safety of antimicrobials for managing the infection or symptoms? | • Evidence review – see appendix F for included studies<br>• NICE clinical knowledge summary: diarrhoea – antibiotic associated.<br>• NICE guideline on drug allergy: diagnosis and management (2014)<br>• British National Formulary (BNF) December 2018 |

| Key area | Key question(s) | Evidence sources |
|---|---|---|
| | • Which people are most likely to benefit from an antimicrobial? | • Evidence review – see appendix F for included studies |
| | • Which antimicrobial should be prescribed if one is indicated (first, second and third line treatment, including people with drug allergy)? | • Evidence review – see appendix F for included studies |
| | • What is the optimal dose, duration and route of administration of antimicrobials? | • Evidence review – see appendix F for included studies<br>• British National Formulary (BNF) December 2018<br>• Summary of product characteristics |

# Appendix B: Review protocol

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| I | Review question | What antimicrobial interventions are effective in managing hospital-acquired pneumonia? | • antimicrobials include antibiotics<br>• search will include terms for lower respiratory tract infection, pneumonia and chest infection |
| II | Types of review question | Intervention questions will primarily be addressed through the search. | These will, for example, also identify natural history in placebo groups and causative organisms in studies that use laboratory diagnosis, and relative risks of differing management options. |
| III | Objective of the review | To determine the effectiveness of prescribing and other interventions in managing hospital-acquired pneumonia in line with the major goals of antimicrobial stewardship. This includes interventions that lead prescribers to:<br>• optimise outcomes for individuals<br>• reduce overuse, misuse or abuse of antimicrobials | The secondary objectives of the review of studies will include:<br>• indications for prescribing an antimicrobial (individual patient factors [including adverse events] and illness severity)<br>• indications for no or delayed antimicrobials |

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| | | All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making. | • antimicrobial choice, optimal dose, duration and route for specified antimicrobial(s)<br>• the natural history of the infection |
| IV | Eligibility criteria – population/ disease/ condition/ issue/domain | Population: Adults and children (aged 72 hours and older) with hospital-acquired pneumonia<br><br>Studies with a mixed population of hospital-acquired pneumonia and community-acquired pneumonia will be excluded unless ≥75% are a hospital-acquired pneumonia population.<br><br>Studies with a mixed population of ventilator and non-ventilator associated pneumonia, where data cannot be extracted for non-ventilator associated pneumonia only, will be excluded.<br><br>Studies that use for example symptoms or signs (prognosis), clinical diagnosis, chest x-ray, imaging, microbiological methods, or laboratory testing of blood for diagnosing the condition. | Subgroups of interest, those:<br>• with protected characteristics under the Equality Act 2010.<br>• with chronic conditions (such as high blood pressure, diabetes or heart disease).<br>• at high risk of serious complications because of pre-existing comorbidity[1]<br>• with symptoms and signs suggestive of serious illness and/or complications[2]<br>• <18 years (children) including those with fever and additional intermediate or high risk factors[3]<br>• people older than 65 years and older than 80 years[4]<br>• with asthma. |
| V | Eligibility criteria – intervention(s)/ exposure(s)/ | The review will include studies which include:<br>• Antimicrobial interventions[5].<br><br>For the treatment of hospital acquired pneumonia as outlined above, in primary, secondary or other care settings (for | Limited to those interventions commonly in use (as agreed by the committee) |

[1]significant heart, lung, renal, liver or neuromuscular disease, immunosuppression and young children who were born prematurely
[2] Including heart, lung, kidney, liver or neuromuscular disease, or immunosuppression
[3] Outlined in more detail in CG160 Fever in under 5s: assessment and initial management
[4] hospitalisation in previous year; type 1 or type 2 diabetes, history of congestive heart failure, current use of oral glucocorticoids.
[5] Antimicrobial pharmacological interventions include:, narrow or broad spectrum, single, dual or triple therapy, escalation or de-escalation of treatment.

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| | prognostic factor(s) | example walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example patient group direction). | |
| VI | Eligibility criteria – comparator(s)/ control or reference (gold) standard | Any other plausible strategy or comparator, including:<br>• Placebo<br>• Non-pharmacological interventions.<br>• Non-antimicrobial pharmacological interventions<br>• Other antimicrobial pharmacological interventions. | |
| VII | Outcomes and prioritisation | a) Clinical outcomes such as:<br>• mortality<br>• infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment)<br>• time to clinical cure (mean or median time to resolution of illness)<br>• reduction in symptoms (duration or severity)<br>• rate of complications with or without treatment<br>• safety, tolerability, and adverse effects.<br>b) Changes in antimicrobial resistance patterns, trends and levels as a result of treatment.<br>c) Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction.<br>d) Ability to carry out activities of daily living.<br>e) Service user experience. | The committee have agreed that the following outcomes are critical:<br>• reduction in symptoms (duration or severity) for example difference in time to substantial improvement<br>• time to clinical cure (mean or median time to resolution of illness)<br>• rate of complications[6] (including mortality) with or without treatment, including escalation of treatment<br>• health and social care utilisation (including length of stay, ITU stays, planned and unplanned contacts).<br><br>The committee have agreed that the following outcomes are important: |

[6] These would include but are not limited to more common complications e.g. pleural effusion and empyema, lung abscess, and septicaemia

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| | | f) Health and social care related quality of life, including long-term harm or disability.<br>g) Health and social care utilisation (including length of stay, planned and unplanned contacts).<br><br>The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the Committee were asked to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness). | • patient-reported outcomes, such as medicines adherence, patient experience, sickness absence<br>• changes in antimicrobial resistance patterns, trends and levels as a result of treatment |
| VIII | Eligibility criteria – study design | The search will look for:<br>• Systematic review of randomised controlled trials (RCTs)<br>• RCTs<br>If insufficient evidence is available progress to:<br>• Controlled trials<br>• Systematic reviews of non-randomised controlled trials<br>• Non-randomised controlled trials<br>• Observational and cohort studies<br>• Pre and post intervention studies (before and after)<br>• Time series studies | Committee to advise the NICE project team on the inclusion of information from other condition specific guidance and on whether to progress due to insufficient evidence. |
| IX | Other inclusion exclusion criteria | The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: | |

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| | | • non-English language papers, studies that are only available as abstracts<br>• community-acquired pneumonia<br>• ventilator-associated pneumonia<br>• a lower respiratory tract infection without a confirmed diagnosis of pneumonia i.e. acute or chronic bronchitis<br>• pneumonia associated with<br>  ○ exacerbations of chronic obstructive pulmonary disease<br>  ○ cystic fibrosis<br>  ○ bronchiectasis<br>• non-antimicrobial interventions<br>• non-pharmacological interventions | |
| X | Proposed sensitivity/ sub-group analysis, or meta-regression | The search may identify studies in population subgroups (for example adults, older adults, children (those aged under 18 years of age), and people with co-morbidities or characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment). These will be analysed within these categories to enable the production of management recommendations. | |
| XI | Selection process – duplicate screening/ selection/ analysis | All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above.<br>A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will be screened by one reviewer only. Disagreement will be resolved through discussion. | |

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| | | Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved.<br>If large numbers of papers are identified and included at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes. | |
| XII | Data management (software) | Data management will be undertaken using EPPI-reviewer software. GRADEpro will be used to assess the quality of evidence for each outcome. | |
| XIII | Information sources – databases and dates | The following sources will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley<br>• Cochrane Database of Systematic Reviews (CDSR) via Wiley<br>• Database of Abstracts of Effectiveness (DARE) via Wiley – legacy, last updated April 2015<br>• Embase via Ovid<br>• Health Technology Assessment (HTA) via Wiley<br>• MEDLINE via Ovid<br>• MEDLINE-in-Process via Ovid<br><br>The search strategy will be developed in MEDLINE and then adapted or translated as appropriate for the other sources, taking into account their size, search functionality and subject coverage.<br><br>Database functionality will be used, where available, to exclude: | |

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| | | • non-English language papers<br>• animal studies<br>• editorials, letters, news items, case reports and commentaries<br>• conference abstracts and posters<br>• theses and dissertations<br>• duplicates.<br><br>Date limits will be applied to restrict the search results to:<br>• studies published from 2006 to the present day<br><br>The results will be downloaded in the following mutually exclusive sets:<br>• Systematic reviews and meta-analysis<br>• Randomised controlled trials<br>• Observational and comparative studies<br>• Other results<br><br>See appendix B for further details on the search strategy.<br><br>Duplicates will be removed using automated and manual processes. The de-duplicated file will be uploaded into EPPI-Reviewer for data screening. | |
| XV | Author contacts | Web: https://www.nice.org.uk/guidance/indevelopment/gid-ng10050/consultation/html-content<br>Email: infections@nice.org.uk | |

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| XVI | Highlight if amendment to previous protocol | For details please see the interim process guide (2017). | |
| XVII | Search strategy – for one database | For details see appendix C. | |
| XVIII | Data collection process – forms/duplicate | GRADE profiles will be used, for details see appendix H. | |
| XIX | Data items – define all variables to be collected | GRADE profiles will be used, for details see appendix H. | |
| XX | Methods for assessing bias at outcome/ study level | Standard study checklists were used to critically appraise individual studies. For details please see the interim process guide (2017). The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ | |
| XXI | Criteria for quantitative synthesis (where suitable) | For details please see the interim process guide (2017). | |
| XXII | Methods for analysis – | For details please see the interim process guide (2017). | |

| | | | |
|---|---|---|---|
| | combining studies and exploring (in)consistency | | |
| XXIII | Meta-bias assessment – publication bias, selective reporting bias | For details please see the interim process guide (2017). | |
| XXIV | Assessment of confidence in cumulative evidence | For details please see the interim process guide (2017). | |
| XXV | Rationale/ context – Current management | For details please see the interim process guide (2017). | |
| XXVI | Describe contributions of authors and guarantor | A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with the interim process guide (2017). Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline. | |
| XXVII | Sources of funding/support | Developed and funded by NICE. | |

| | | | |
|---|---|---|---|
| XXVIII | Name of sponsor | Developed and funded by NICE. | |
| XXIX | Roles of sponsor | NICE funds and develops guidelines for those working in the NHS, public health, and social care in England. | |

1

# Appendix C: Literature search strategy

The main search strategy will take the following format:

(Lower respiratory tract infections OR Acute cough OR Bronchitis OR Pneumonia)

AND (Named Antibiotics OR Classes of Antibiotics OR Pharma interventions OR Honey OR Herbal Medicines OR Drinking Fluids OR Prescribing Strategies OR Self Care)

AND (Systematic Reviews OR Randomised Controlled Trials OR Observational Studies)

AND Limits

The strategy includes a top up search for the following terms:

(Lower respiratory tract infections OR Acute cough OR Bronchitis OR Pneumonia)

AND General term “Antibiotics”

AND Systematic Reviews

| Main concepts | Concept | Proposed search terms |
|---|---|---|
| Lower respiratory tract infections (cough) | Acute cough | Cough/<br>cough*.ti,ab<br>((postnasal* or post nasal*) adj3 drip*).ti,ab. |
| | Bronchitis | Bronchitis/<br>(bronchit* or tracheobronchit*).ti,ab<br>(bronchial adj2 infect*).ti,ab |
| | Lower respiratory tract infection | Respiratory Tract Infections/<br>Respiratory Syncytial Virus Infections/<br>((pulmonary or lung* or airway* or airflow* or bronch* or respirat*) adj3 syncytial virus*).ti,ab<br>Pneumovirus*.ti,ab<br>(("respiratory tract*" or "acute respiratory" or "lower respiratory" or chest) adj3 (infect* or cough*)).ti,ab.<br>LRTI.ti,ab |
| | Pneumonia | exp Pneumonia/<br>(pneumon* or bronchopneumon* or pleuropneumon*).ti,ab |

| | | |
|---|---|---|
| Named Antibiotics | Amoxicillin | Amoxicillin/<br>(Amoxicillin* or Amoxycillin* or Amoxil*).ti,ab. |
| | Amoxicillin and a macrolide dual therapy | - |
| | Ampicillin | Ampicillin/<br>Ampicillin*.ti,ab |
| | Azithromycin | Azithromycin/<br>(Azithromycin* or Azithromicin* or Zithromax*).ti,ab |
| | Aztreonam | Aztreonam/<br>(Aztreonam* or Azactam*).ti,ab |
| | Benzylpenicillin sodium | Penicillin G/<br>(Benzylpenicillin* or "Penicillin G").ti,ab |
| | Beta-lactamase stable beta-lactam | - |
| | Cefaclor | Cefaclor/<br>(Cefaclor* or Distaclor* or Keftid*).ti,ab |
| | Cefixime | Cefixime/<br>(Cefixime* or Suprax*).ti,ab |
| | Cefotaxime | Cefotaxime/<br>Cefotaxime*.ti,ab. |

| | | |
|---|---|---|
| | Ceftaroline fosamil | (Ceftaroline* or Zinforo*).ti,ab |
| | Ceftazidime | Ceftazidime/<br>(Ceftazidime* or Fortum* or Tazidime*).ti,ab |
| | Ceftobiprole<br>No Mesh | (Ceftobiprole* or Zevtera*).ti,ab |
| | Ceftolozane-tazobactam | (Ceftolozane* or Tazobactam* or Zerbaxa*).ti,ab |
| | Ceftriaxone | Ceftriaxone/<br>(Ceftriaxone* or Rocephin* or Rocefin*).ti,ab |
| | Cefuroxime | Cefuroxime/<br>(Cefuroxime* or Cephuroxime* or Zinacef* or Zinnat* or Aprokam*).ti,ab |
| | Chloramphenicol | Chloramphenicol/<br>(Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab |
| | Ciprofloxacin | Ciprofloxacin/<br>(Ciprofloxacin* or Ciproxin*).ti,ab |
| | Clarithromycin | Clarithromycin/<br>(Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab |
| | Clindamycin | Clindamycin/<br>(Clindamycin* or Dalacin* or Zindaclin*).ti,ab |
| | Co-amoxiclav | Amoxicillin-Potassium Clavulanate Combination/ |

| | | |
|---|---|---|
| | | (Co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab |
| | Co-trimoxazole | Trimethoprim, Sulfamethoxazole Drug Combination/<br><br>(Septrin* or Co-trimoxazole* or Cotrimoxazole* or Sulfamethoxazole Trimethoprim Comb* or Trimethoprim Sulfamethoxazole Comb*).ti,ab |
| | Colistin | Colistin/<br><br>(Colistin* or Colistimethate* or Colimycin* or Coly-Mycin* or Colymycin* or Colomycin* or Promixin*).ti,ab. |
| | Doxycycline | Doxycycline/<br><br>(Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab |
| | Ertapenem | (Ertapenem* or Invanz*).ti,ab |
| | Erythromycin | Erythromycin/<br><br>Erythromycin Estolate/<br><br>Erythromycin Ethylsuccinate/<br><br>(Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab |
| | Fosfomycin | Fosfomycin/<br><br>(Fosfomycin* or Phosphomycin* or Fosfocina* or Monuril* or Monurol* or Fomicyt*).ti,ab |
| | Flucloxacillin | Floxacillin/<br><br>(Floxacillin* or Flucloxacillin*).ti,ab. |
| | Fluoroquinolone | - |
| | Gentamicin | Gentamicins/ |

| | | |
|---|---|---|
| | | (Gentamicin* or Gentamycin* or Cidomycin*).ti,ab |
| | Imipenem | Imipenem/<br>(Imipenem* or Primaxin*).ti,ab |
| | Levofloxacin | Levofloxacin/<br>(Levofloxacin* or Evoxil* or Tavanic*).ti,ab. |
| | Linezolid | Linezolid/<br>(Linezolid* or Zyvox*).ti,ab |
| | Meropenem | (Meropenem*).ti,ab |
| | Moxifloxacin | (Moxifloxacin* or Avelox*).ti,ab |
| | Ofloxacin | Ofloxacin/<br>(Ofloxacin* or Tarivid*).ti,ab |
| | Piperacillin with Tazobactam | Piperacillin/<br>(Piperacillin* or Tazobactam* or Tazocin*).ti,ab |
| | Rifampicin | Rifampin/<br>(Rifampicin* or Rifampin* or Rifadin* or Rimactane*).ti,ab |
| | Teicoplanin | Teicoplanin/<br>(Teicoplanin* or Targocid*).ti,ab |
| | Telavancin | (Telavancin* or Vibativ*).ti,ab |
| | Temocillin | (Temocillin* or Negaban*).ti,ab |
| | Tigecycline | (Tigecycline* or Tygacil*).ti,ab |

| | | |
|---|---|---|
| | Vancomycin | Vancomycin/<br>(Vancomycin* or Vancomicin* or Vancocin*).ti,ab |
| Classes of Antibiotics | Aminoglycoside | exp Aminoglycosides/<br>Aminoglycoside*.ti,ab |
| | Antipseudomonal penicillin | exp Penicillins/<br>Penicillin*.ti,ab |
| | Beta-lactamase | exp beta-Lactamases/<br>(“beta Lactamase*” or betaLactamase* or “beta-Lactamase*”).ti,ab<br><br>exp beta-Lactamase inhibitors/<br>((“beta Lactamase*” or betaLactamase*) adj3 (inhibitor* or antagonist*)).ti,ab |
| | Beta-lactam (stable) | beta-Lactams/<br>(“beta-Lactam” or betaLactam or “beta Lactam” or “beta-Lactams” or betaLactams or “beta Lactams”).ti,ab |
| | Carbapenems | exp Carbapenems/<br>Carbapenem*.ti,ab |
| | Cephalosporin | exp Cephalosporins/<br>Cephalosporin*.ti,ab |
| | Fluoroquinolone | exp Fluoroquinolones/<br>Fluoroquinolone*.ti,ab |

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|---|---|---|
| | Macrolides | exp Macrolides/<br>macrolide*.ti,ab |
| | Polymyxins | Polymyxins/<br>Polymyxin*.ti,ab |
| | Quinolones | exp Quinolones/<br>Quinolone*.ti,ab |
| | Tetracycline | exp Tetracyclines/<br>Tetracycline*.ti,ab |
| Pharma interventions | Analgesics | analgesics/<br>exp analgesics, non-narcotic/<br>analgesics, short-acting/<br>antipyretics/<br>(analgesic* or antipyretic*).ti,ab |
| | Paracetamol | Acetaminophen/<br>(paracetamol* or acetaminophen* or Panadol* or perfalgan* or calpol*).ti,ab |
| | Anticholinergics | Cholinergic antagonists/<br>(Anticholinergic* or "Anti-cholinergic*" or "Anti cholinergic*" or Antimuscarinic* or Anti muscarinic* or Anti-muscarinic*).ti,ab<br>((cholinergic* or acetylcholine* or cholinolytic* or muscarinic*) adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab |
| | Beta-2 agonists | Adrenergic beta-2 Receptor Agonists/ |

| | | |
|---|---|---|
| | | (("adrenergic beta" or "beta adrenergic" or beta2 or "beta 2") adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.<br><br>Albuterol/<br><br>(Salbutamol* or Albuterol* or Salbulin* or Ventolin* or Salamol*).ti,ab |
| | Bronchodilators | Bronchodilator Agents/<br><br>(Bronchodilator* or broncholytic* or bronchial dilat* or bronchodilating* or bronchodilatant*).ti,ab |
| | Codeine and Pholcodine | exp Codeine/<br><br>(Codeine* or Pholcodine* or Covonia* or Galenphol* or Pavacol* or Galcodine*).ti,ab. |
| | Corticosteroids | Adrenal Cortex Hormones/<br><br>(Corticosteroid* or corticoid* or Adrenal Cortex Hormone*).ti,ab |
| | Cough mixtures<br><br>Non-prescription drugs<br><br>Antitussive agents<br><br>Anti-histamines<br><br>Demulcents<br><br>Glycerol<br><br>Menthol<br><br>Honey and Lemon | Nonprescription Drugs/<br><br>(non prescription* or nonprescription* or otc or “over the counter*” or “over-the-counter*”).ti,ab<br><br>Antitussive Agents/<br><br>(Antitussive*).ti,ab<br><br>(cough* adj3 (suppressant* or mixture* or syrup* or medicine* or medicinal* or product or products or remedies* or remedy*)).ti,ab<br><br>exp Histamine Antagonists/<br><br>Antazoline/ |

| | | |
|---|---|---|
| | | Brompheniramine/<br>Chlorpheniramine/<br>Cinnarizine/<br>Cyproheptadine/<br>Diphenhydramine/<br>Doxylamine/<br>Ergotamine/<br>Hydroxyzine/<br>Ketotifen/<br>Pizotyline/<br>Promethazine/<br>Trimeprazine/<br>Triprolidine/<br>(histamin* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab<br>(antihistamin* or anti-histamin* or Alimemazine* or Trimeprazine* or Antazoline* or Brompheniramine* or Chlorpheniramine* or Chlorphenamine* or Cinnarizine* or Stugeron* or Cyproheptadine* or Periactin* or Diphenhydramine* or Doxylamine* or Ergotamine* or Migril* or Hydroxyzine* or Atarax* or Ketotifen* or Zaditen* or Promethazine* or Phenergan* or Sominex* or Pizotifen* or Pizotyline* or Triprolidine* or Acrivastine*).ti,ab<br><br>Demulcents/<br>(demulcent* or mucoprotective* or muco protective* or Linctus*).ti,ab |

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|---|---|---|
| | | Glycerol/<br>(Glycerol* or Glycerine*).ti,ab<br><br>Menthol/<br>(menthol*).ti,ab<br><br>Honey/<br>Apitherapy/<br>(honey* or lemon*).ti,ab |
| | Dextromethorphan | Dextromethorphan/<br>(Dextromethorphan*).ti,ab |
| | Prednisolone | exp Prednisolone/<br>(Prednisolone* or Fluprednisolone* or Methylprednisolone* or Deltacortril* or Dilacort* or Pevanti* or Deltastab* or Predsol*).ti,ab |
| | Non-steroidal anti-inflammatory drugs | Anti-Inflammatory Agents, Non-Steroidal/<br>(nsaid*).ti,ab<br>((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).ti,ab |
| | Ibuprofen | Ibuprofen/<br>(ibuprofen* or arthrofen* or ebufac* or rimafen* or brufen* or calprofen* or feverfen* or nurofen* or orbifen*).ti,ab |

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|---|---|---|
| | Leukotriene receptor antagonists | Leukotriene Antagonists/<br>(leukotriene* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.<br>(Montelukast*).ti,ab<br>(Zafirlukast* or Accolate*).ti,ab |
| | Mucolytics | exp Expectorants/<br>exp Guaifenesin/<br>Ipecac/<br>(expectorant* or mucolytic* or guaifenesin* or ipecac* or ipecacuanha*).ti,ab<br><br>Mannitol/<br>(Mannitol* or Osmohale* or Bronchitol*).ti,ab<br>(Dornase alfa* or Dornase alpha* or Pulmozyme*).ti,ab. |
| Herbal remedies | Herbal medicines<br>Pelargonium (kaloba)<br>Echinacea<br>Japonica<br>Thyme<br>Eucalyptus<br>Forsythiae | Drugs, Chinese Herbal/<br>Plants, Medicinal/<br>exp Geraniaceae/<br>Echinacea/<br>Fallopia Japonica/<br>Thymus Plant/<br>Eucalyptus/<br>Forsythia/ |

| | | |
|---|---|---|
| | Liquorice<br>Andrographis | exp Glycyrrhiza/<br>Andrographis/<br>(herb* or Geraniaceae* or Pelargonium* or Geranium* or Kaloba* or Echinacea* or Coneflower* or Japonica* or Knotweed* or Thyme* or Thymus* or Eucalyptus* or Forsythia* or Forsythiae* or Goldenbell* or Lian Qiao* or Glycyrrhiza* or Licorice* or Liquorice* or Andrographis*).ti,ab<br>((medicine* or medical* or medicinal* or product or products or remedies* or remedy*) adj3 (plant* or plants or root or roots or flower or flowers or bark or barks or seed or seeds or shrub or shrubs or botanic*)).ti,ab |
| Drinking Fluids | Fluid therapy | Drinking/<br>Drinking Behavior/<br>Fluid therapy/ |
| | Drinking water, beverages, fluids or liquids | exp Beverages/<br>((water* or fluid* or liquid* or beverage* or drinks) adj3 (consumption* or consume* or consuming* or intake* or drink* or hydrat* or rehydrat* or therap*)).ti,ab |
| Prescribing Strategies | Active surveillance<br>No intervention<br>Watchful waiting | watchful waiting/<br>"no intervention*".ti,ab<br>(watchful* adj2 wait*).ti,ab.<br>(wait adj2 see).ti,ab<br>(expectant* adj2 manage*).ti,ab<br>(active* adj2 surveillance*).ti,ab |
| | Prescribing times<br>Delayed treatment | ((prescription* or prescrib*) adj4 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv*)).ti,ab |

| | | |
|---|---|---|
| | | ((misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*) adj4 (bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*")).ti,ab<br><br>((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab.<br><br>anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/<br><br>(antibacter* or anti-bacter* or antibiot* or anti-biot* or antimicrobial* or anti-microbial*).ti,ab.<br><br>(delay* or defer* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or (prescribing adj strateg*) or "red flag*").ti,ab<br><br>Inappropriate prescribing/ |
| Self Care | Self management | Self Care/<br><br>Self medication/<br><br>((self or selves or themsel*) adj4 (care or manag*)).ti,ab |
| Systematic Reviews | Meta analysis<br><br>Systematic Reviews<br><br>Reviews | Standard search filter |
| Randomised Controlled Trials | Controlled Clinical Trials<br><br>Cross over studies | Standard search filter |

| | | |
|---|---|---|
| | Randomised controlled trials (rcts) | |
| Observational Studies | Case-Control Studies<br>Cohort Studies<br>Controlled Before-After Studies<br>Cross-Sectional Studies<br>Epidemiologic Studies<br>Observational Study | Standard search filter |
| Limits | Exclude Animal studies<br>Exclude letters, editorials and letters<br>Limit date to 2006-Current | Standard search limits |

| | No. of hits in MEDLINE | Position in the strategy |
|---|---|---|
| Search with limits and Systematic Reviews | 5376 | Line 247 |
| Search with limits and RCTs (not SRs) | 3431 | Line 266 |

| | | |
|---|---|---|
| Search with limits and Observational Studies (not SRs or RCTs) | 5648 | Line 289 |
| Search with limits (without SRs, RCTs, Observational) | 10093 | Line 290 |
| Total for screening | 24548 | |

Key to search operators

| | |
|---|---|
| / | Medical Subject Heading (MeSH) term |
| Exp | Explodes the MeSH terms to retrieve narrower terms in the hierarchy |
| .ti | Searches the title field |
| .ab | Searches the abstract field |
| * | Truncation symbol (searches all word endings after the stem) |
| adj*n* | Adjacency operator to retrieve records containing the terms within a specified number (*n*) of words of each other |

Database(s): **Ovid MEDLINE(R)** 1946 to October Week 1 2017**, Ovid MEDLINE(R) Epub Ahead of Print** October 16, 2017**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations** October 16, 2017**, Ovid MEDLINE(R) Daily Update** October 16, 2017

Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | Cough/ | 15165 |

| | | |
|---|---|---|
| 2 | cough*.ti,ab. | 45432 |
| 3 | ((postnasal* or post nasal*) adj3 drip*).ti,ab. | 589 |
| 4 | Bronchitis/ | 21093 |
| 5 | (bronchit* or tracheobronchit*).ti,ab. | 22136 |
| 6 | (bronchial adj2 infect*).ti,ab. | 782 |
| 7 | Respiratory Tract Infections/ | 37036 |
| 8 | Respiratory Syncytial Virus Infections/ | 6243 |
| 9 | ((pulmonary or lung* or airway* or airflow* or bronch* or respirat*) adj3 syncytial virus*).ti,ab. | 12118 |
| 10 | Pneumovirus*.ti,ab. | 343 |
| 11 | (("respiratory tract*" or "acute respiratory" or "lower respiratory" or chest) adj3 (infect* or cough*)).ti,ab. | 30623 |
| 12 | LRTI.ti,ab. | 980 |
| 13 | exp Pneumonia/ | 88843 |
| 14 | (pneumon* or bronchopneumon* or pleuropneumon* or tracheobronchit*).ti,ab. | 176553 |
| 15 | or/1-14 | 323542 |

| | | |
|---|---|---|
| 16 | limit 15 to yr="2006 -Current" | 133940 |
| 17 | limit 16 to english language | 120589 |
| 18 | Animals/ not (Animals/ and Humans/) | 4643829 |
| 19 | 17 not 18 | 108249 |
| 20 | limit 19 to (letter or historical article or comment or editorial or news or case reports) | 18545 |
| 21 | 19 not 20 | 89704 |
| 22 | anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/ | 908739 |
| 23 | (antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*").ti,ab. | 433955 |
| 24 | or/22-23 | 1095907 |
| 25 | Amoxicillin/ | 9361 |
| 26 | (Amoxicillin* or Amoxycillin* or Amoxil*).ti,ab. | 16425 |
| 27 | Ampicillin/ | 13807 |
| 28 | Ampicillin*.ti,ab. | 22039 |
| 29 | Azithromycin/ | 4771 |

| | | |
|---|---|---|
| 30 | (Azithromycin* or Azithromicin* or Zithromax*).ti,ab. | 7221 |
| 31 | Aztreonam/ | 1437 |
| 32 | (Aztreonam* or Azactam*).ti,ab. | 2951 |
| 33 | Penicillin G/ | 9348 |
| 34 | (Benzylpenicillin* or "Penicillin G").ti,ab. | 8206 |
| 35 | Cefaclor/ | 881 |
| 36 | (Cefaclor* or Distaclor* or Keftid*).ti,ab. | 1741 |
| 37 | Cefixime/ | 772 |
| 38 | (Cefixime* or Suprax*).ti,ab. | 1569 |
| 39 | Cefotaxime/ | 5575 |
| 40 | Cefotaxime*.ti,ab. | 8120 |
| 41 | (Ceftaroline* or Zinforo*).ti,ab. | 583 |
| 42 | Ceftazidime/ | 3797 |
| 43 | (Ceftazidime* or Fortum* or Tazidime*).ti,ab. | 8387 |

| | | |
|---|---|---|
| 44 | (Ceftobiprole* or Zevtera*).ti,ab. | 262 |
| 45 | (Ceftolozane* or Tazobactam* or Zerbaxa*).ti,ab. | 3869 |
| 46 | Ceftriaxone/ | 5707 |
| 47 | (Ceftriaxone* or Rocephin* or Rocefin*).ti,ab. | 9632 |
| 48 | Cefuroxime/ | 2190 |
| 49 | (Cefuroxime* or Cephuroxime* or Zinacef* or Zinnat* or Aprokam*).ti,ab. | 4248 |
| 50 | Chloramphenicol/ | 20280 |
| 51 | (Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab. | 26700 |
| 52 | Ciprofloxacin/ | 12735 |
| 53 | (Ciprofloxacin* or Ciproxin*).ti,ab. | 23629 |
| 54 | Clarithromycin/ | 6001 |
| 55 | (Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab. | 8465 |
| 56 | Clindamycin/ | 5646 |
| 57 | (Clindamycin* or Dalacin* or Zindaclin*).ti,ab. | 9899 |

| | | |
|---|---|---|
| 58 | Amoxicillin-Potassium Clavulanate Combination/ | 2501 |
| 59 | (Co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab. | 14738 |
| 60 | Trimethoprim, Sulfamethoxazole Drug Combination/ | 6860 |
| 61 | (Septrin* or Co-trimoxazole* or Cotrimoxazole* or Sulfamethoxazole Trimethoprim Comb* or Trimethoprim Sulfamethoxazole Comb*).ti,ab. | 6035 |
| 62 | Colistin/ | 3468 |
| 63 | (Colistin* or Colistimethate* or Colimycin* or Coly-Mycin* or Colymycin* or Colomycin* or Promixin*).ti,ab. | 4884 |
| 64 | Doxycycline/ | 9238 |
| 65 | (Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab. | 12343 |
| 66 | (Ertapenem* or Invanz*).ti,ab. | 1256 |
| 67 | Erythromycin/ | 14229 |
| 68 | Erythromycin Estolate/ | 154 |
| 69 | Erythromycin Ethylsuccinate/ | 522 |
| 70 | (Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab. | 20574 |

| | | |
|---|---|---|
| 71 | Fosfomycin/ | 1839 |
| 72 | (Fosfomycin* or Phosphomycin* or Fosfocina* or Monuril* or Monurol* or Fomicyt*).ti,ab. | 2623 |
| 73 | Floxacillin/ | 739 |
| 74 | (Floxacillin* or Flucloxacillin*).ti,ab. | 842 |
| 75 | Gentamicins/ | 18583 |
| 76 | (Gentamicin* or Gentamycin* or Cidomycin*).ti,ab. | 25954 |
| 77 | Imipenem/ | 4016 |
| 78 | (Imipenem* or Primaxin*).ti,ab. | 9709 |
| 79 | Levofloxacin/ | 2965 |
| 80 | (Levofloxacin* or Evoxil* or Tavanic*).ti,ab. | 6626 |
| 81 | Linezolid/ | 2599 |
| 82 | (Linezolid* or Zyvox*).ti,ab. | 4911 |
| 83 | Meropenem*.ti,ab. | 5187 |
| 84 | (Moxifloxacin* or Avelox*).ti,ab. | 4045 |

| | | |
|---|---|---|
| 85 | Ofloxacin/ | 6224 |
| 86 | (Ofloxacin* or Tarivid*).ti,ab. | 6844 |
| 87 | Piperacillin/ | 2713 |
| 88 | (Piperacillin* or Tazobactam* or Tazocin*).ti,ab. | 6818 |
| 89 | Rifampin/ | 17357 |
| 90 | (Rifampicin* or Rifampin* or Rifadin* or Rimactane*).ti,ab. | 22688 |
| 91 | Teicoplanin/ | 2234 |
| 92 | (Teicoplanin* or Targocid*).ti,ab. | 3467 |
| 93 | (Telavancin* or Vibativ*).ti,ab. | 369 |
| 94 | (Temocillin* or Negaban*).ti,ab. | 302 |
| 95 | (Tigecycline* or Tygacil*).ti,ab. | 2562 |
| 96 | Vancomycin/ | 12899 |
| 97 | (Vancomycin* or Vancomicin* or Vancocin*).ti,ab. | 24386 |
| 98 | or/25-97 | 276644 |

| | | |
|---|---|---|
| 99 | exp Aminoglycosides/ | 154042 |
| 100 | Aminoglycoside*.ti,ab. | 18162 |
| 101 | exp Penicillins/ | 81338 |
| 102 | Penicillin*.ti,ab. | 54151 |
| 103 | exp beta-Lactamase inhibitors/ | 7519 |
| 104 | (("beta Lactamase*" or betaLactamase*) adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab. | 2897 |
| 105 | beta-Lactams/ | 6140 |
| 106 | ("beta-Lactam" or betaLactam or "beta Lactam " or "beta-Lactams" or betaLactams or "beta Lactams").ti,ab. | 19809 |
| 107 | exp Carbapenems/ | 9627 |
| 108 | Carbapenem*.ti,ab. | 10899 |
| 109 | exp Cephalosporins/ | 42255 |
| 110 | Cephalosporin*.ti,ab. | 21163 |
| 111 | exp Fluoroquinolones/ | 31349 |
| 112 | Fluoroquinolone*.ti,ab. | 14729 |

| | |
|---|---|
| 113 exp Macrolides/ | 105782 |
| 114 Macrolide*.ti,ab. | 14603 |
| 115 exp Polymyxins/ | 8638 |
| 116 Polymyxin*.ti,ab. | 6747 |
| 117 exp Quinolones/ | 45007 |
| 118 Quinolone*.ti,ab. | 13119 |
| 119 exp Tetracyclines/ | 47435 |
| 120 Tetracycline*.ti,ab. | 34131 |
| 121 or/99-120 | 497907 |
| 122 Bronchodilator Agents/ | 19033 |
| 123 (Bronchodilator* or broncholytic* or bronchial dilat* or bronchodilating* or bronchodilatant*).ti,ab. | 14064 |
| 124 analgesics/ | 46460 |
| 125 exp analgesics, non-narcotic/ | 322666 |
| 126 analgesics, short-acting/ | 8 |

| | | |
|---|---|---|
| 127 | antipyretics/ | 2591 |
| 128 | (analgesic* or antipyretic*).ti,ab. | 77553 |
| 129 | Acetaminophen/ | 17280 |
| 130 | (paracetamol* or acetaminophen* or Panadol* or perfalgan* or calpol*).ti,ab. | 22807 |
| 131 | Cholinergic antagonists/ | 4933 |
| 132 | (Anticholinergic* or "Anti-cholinergic*" or "Anti cholinergic*" or Antimuscarinic* or Anti muscarinic* or Anti-muscarinic*).ti,ab. | 14963 |
| 133 | (("adrenergic beta" or "beta adrenergic" or beta2 or "beta 2") adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab. | 23087 |
| 134 | Adrenergic beta-2 Receptor Agonists/ | 2581 |
| 135 | (("adrenergic beta" or "beta adrenergic" or beta2 or "beta 2") adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab. | 23087 |
| 136 | Albuterol/ | 9858 |
| 137 | (Salbutamol* or Albuterol* or Salbulin* or Ventolin* or Salamol*).ti,ab. | 9742 |
| 138 | exp Codeine/ | 6616 |
| 139 | (Codeine* or Pholcodine* or Covonia* or Galenphol* or Pavacol* or Galcodine*).ti,ab. | 4854 |
| 140 | Adrenal Cortex Hormones/ | 63302 |

| | | |
|---|---|---|
| 141 | (Corticosteroid* or corticoid* or Adrenal Cortex Hormone*).ti,ab. | 102411 |
| 142 | Nonprescription Drugs/ | 5876 |
| 143 | (non prescription* or nonprescription* or otc or "over the counter*" or "over-the-counter*").ti,ab. | 12255 |
| 144 | Antitussive Agents/ | 2841 |
| 145 | Antitussive*.ti,ab. | 1887 |
| 146 | (cough* adj3 (suppressant* or mixture* or syrup* or medicine* or medicinal* or remedy* or remedies* or product or products)).ti,ab. | 915 |
| 147 | exp Histamine Antagonists/ | 63352 |
| 148 | Antazoline/ | 212 |
| 149 | Brompheniramine/ | 351 |
| 150 | Chlorpheniramine/ | 1989 |
| 151 | Cinnarizine/ | 805 |
| 152 | Cyproheptadine/ | 2322 |
| 153 | Diphenhydramine/ | 4027 |
| 154 | Doxylamine/ | 384 |

| | | |
|---|---|---|
| 155 | Ergotamine/ | 2436 |
| 156 | Hydroxyzine/ | 1451 |
| 157 | Ketotifen/ | 1175 |
| 158 | Pizotyline/ | 283 |
| 159 | Promethazine/ | 3130 |
| 160 | Trimeprazine/ | 327 |
| 161 | Triprolidine/ | 309 |
| 162 | (histamin* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab. | 9260 |
| 163 | (antihistamin* or anti-histamin* or Alimemazine* or Trimeprazine* or Antazoline* or Brompheniramine* or Chlorpheniramine* or Chlorphenamine* or Cinnarizine* or Stugeron* or Cyproheptadine* or Periactin* or Diphenhydramine* or Doxylamine* or Ergotamine* or Migril* or Hydroxyzine* or Atarax* or Ketotifen* or Zaditen* or Promethazine* or Phenergan* or Sominex* or Pizotifen* or Pizotyline* or Triprolidine* or Acrivastine*).ti,ab. | 28590 |
| 164 | Demulcents/ | 4 |
| 165 | (demulcent* or mucoprotective* or muco protective* or Linctus*).ti,ab. | 227 |
| 166 | Glycerol/ | 25266 |

| | | |
|---|---|---|
| 167 | (Glycerol* or Glycerine*).ti,ab. | 48554 |
| 168 | Menthol/ | 1800 |
| 169 | menthol*.ti,ab. | 2448 |
| 170 | exp Prednisolone/ | 51015 |
| 171 | (Prednisolone* or Fluprednisolone* or Methylprednisolone* or Deltacortril* or Dilacort* or Pevanti* or Deltastab* or Predsol*).ti,ab. | 38273 |
| 172 | exp Anti-Inflammatory Agents, Non-Steroidal/ | 193330 |
| 173 | nsaid*.ti,ab. | 23343 |
| 174 | ((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).ti,ab. | 37248 |
| 175 | Ibuprofen/ | 8334 |
| 176 | (ibuprofen* or arthrofen* or ebufac* or rimafen* or brufen* or calprofen* or feverfen* or nurofen* or orbifen*).ti,ab. | 12307 |
| 177 | Dextromethorphan/ | 1806 |
| 178 | Dextromethorphan*.ti,ab. | 2510 |
| 179 | Leukotriene Antagonists/ | 3063 |
| 180 | (leukotriene* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab. | 3798 |

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|---|---|
| 181 Montelukast*.ti,ab. | 1980 |
| 182 (Zafirlukast* or Accolate*).ti,ab. | 419 |
| 183 exp Expectorants/ | 16597 |
| 184 exp Guaifenesin/ | 776 |
| 185 Ipecac/ | 639 |
| 186 (expectorant* or mucolytic* or guaifenesin* or ipecac* or ipecacuanha*).ti,ab. | 3101 |
| 187 Mannitol/ | 12719 |
| 188 (Mannitol* or Osmohale* or Bronchitol*).ti,ab. | 17698 |
| 189 (Dornase alfa* or Dornase alpha* or Pulmozyme*).ti,ab. | 240 |
| 190 or/122-189 | 850363 |
| 191 Honey/ | 3396 |
| 192 Apitherapy/ | 114 |
| 193 (honey* or lemon*).ti,ab. | 22587 |
| 194 or/191-193 | 22919 |

| | | |
|---|---|---|
| 195 | Drugs, Chinese Herbal/ | 37457 |
| 196 | Plants, Medicinal/ | 58533 |
| 197 | exp Geraniaceae/ | 607 |
| 198 | Echinacea/ | 740 |
| 199 | Fallopia Japonica/ | 181 |
| 200 | Thymus Plant/ | 1219 |
| 201 | Eucalyptus/ | 2144 |
| 202 | Forsythia/ | 161 |
| 203 | exp Glycyrrhiza/ | 2539 |
| 204 | Andrographis/ | 392 |
| 205 | (herb* or Geraniaceae* or Pelargonium* or Geranium* or Kaloba* or Echinacea* or Coneflower* or Japonica* or Knotweed* or Thyme* or Thymus* or Eucalyptus* or Forsythia* or Forsythiae* or Goldenbell* or Lian Qiao* or Glycyrrhiza* or Licorice* or Liquorice* or Andrographis*).ti,ab. | 164139 |
| 206 | ((medicine* or medical* or medicinal* or product or products or remedies* or remedy*) adj3 (plant* or plants or root or roots or flower or flowers or bark or barks or seed or seeds or shrub or shrubs or botanic*)).ti,ab. | 22856 |

| | |
|---|---|
| 207 or/195-206 | 250647 |
| 208 Fluid therapy/ | 19132 |
| 209 Drinking/ | 14141 |
| 210 Drinking Behavior/ | 6828 |
| 211 exp Beverages/ | 124467 |
| 212 ((water* or fluid* or liquid* or beverage* or drinks) adj3 (consumption* or consume* or consuming* or intake* or drink* or hydrat* or rehydrat* or therap*)).ti,ab. | 93975 |
| 213 or/208-212 | 232893 |
| 214 watchful waiting/ | 2801 |
| 215 "no intervention*".ti,ab. | 6967 |
| 216 (watchful* adj2 wait*).ti,ab. | 2321 |
| 217 (wait adj2 see).ti,ab. | 1352 |
| 218 (active* adj2 surveillance*).ti,ab. | 6517 |
| 219 (expectant* adj2 manage*).ti,ab. | 3048 |
| 220 or/214-219 | 21495 |

| | | |
|---|---|---|
| 221 | Self Care/ | 31538 |
| 222 | Self medication/ | 4616 |
| 223 | ((self or selves or themsel*) adj4 (care or manag*)).ti,ab. | 37143 |
| 224 | or/221-223 | 59581 |
| 225 | Inappropriate prescribing/ | 2110 |
| 226 | ((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab. | 29049 |
| 227 | ((prescription* or prescrib*) adj3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*)).ti,ab. | 24600 |
| 228 | ((bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*") adj3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*)).ti,ab. | 103402 |
| 229 | or/225-228 | 154677 |
| 230 | 24 or 98 or 121 or 190 or 194 or 207 or 213 or 220 or 224 or 229 | 2645544 |
| 231 | 21 and 230 | 30468 |

| | | |
|---|---|---|
| 232 | Meta-Analysis.pt. | 91779 |
| 233 | Network Meta-Analysis/ | 220 |
| 234 | Meta-Analysis as Topic/ | 17154 |
| 235 | Review.pt. | 2443246 |
| 236 | exp Review Literature as Topic/ | 10197 |
| 237 | (metaanaly* or metanaly* or (meta adj3 analy*)).ti,ab. | 130880 |
| 238 | (review* or overview*).ti. | 435300 |
| 239 | (systematic* adj5 (review* or overview*)).ti,ab. | 130897 |
| 240 | ((quantitative* or qualitative*) adj5 (review* or overview*)).ti,ab. | 8451 |
| 241 | ((studies or trial*) adj2 (review* or overview*)).ti,ab. | 40696 |
| 242 | (integrat* adj3 (research or review* or literature)).ti,ab. | 9912 |
| 243 | (pool* adj2 (analy* or data)).ti,ab. | 25735 |
| 244 | (handsearch* or (hand adj3 search*)).ti,ab. | 8417 |
| 245 | (manual* adj3 search*).ti,ab. | 5300 |

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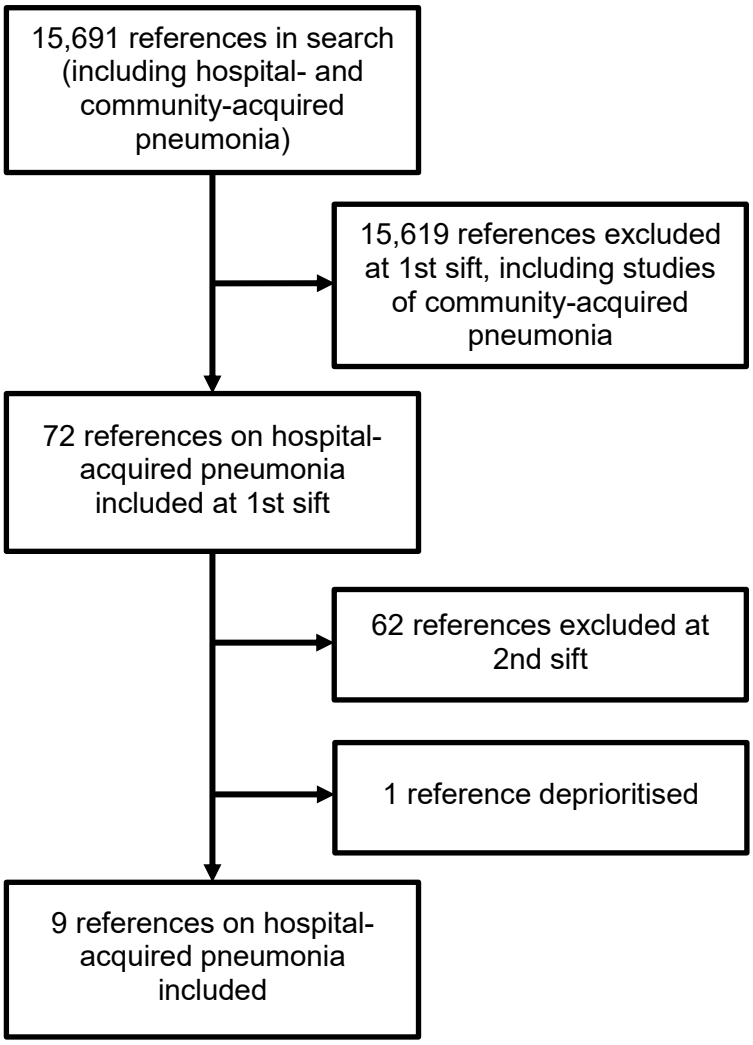
|---|---|
| 246 or/232-245 | 2725485 |
| 247 231 and 246 | 5376 |
| 248 98 or 121 or 190 or 194 or 207 or 213 or 220 or 224 or 229 | 2086858 |
| 249 21 and 248 | 23218 |
| 250 Randomized Controlled Trial.pt. | 497031 |
| 251 Controlled Clinical Trial.pt. | 99256 |
| 252 Clinical Trial.pt. | 548028 |
| 253 exp Clinical Trials as Topic/ | 332203 |
| 254 Placebos/ | 36433 |
| 255 Random Allocation/ | 99660 |
| 256 Double-Blind Method/ | 157533 |
| 257 Single-Blind Method/ | 26574 |
| 258 Cross-Over Studies/ | 45016 |
| 259 ((random* or control* or clinical*) adj3 (trial* or stud*)).ti,ab. | 1115406 |

| | | |
|---|---|---|
| 260 | (random* adj3 allocat*).ti,ab. | 31822 |
| 261 | placebo*.ti,ab. | 209215 |
| 262 | ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab. | 167858 |
| 263 | (crossover* or (cross adj over*)).ti,ab. | 82346 |
| 264 | or/250-263 | 1895644 |
| 265 | 249 and 264 | 4969 |
| 266 | 265 not 247 | 3431 |
| 267 | Observational Studies as Topic/ | 2818 |
| 268 | Observational Study/ | 46520 |
| 269 | Epidemiologic Studies/ | 7973 |
| 270 | exp Case-Control Studies/ | 948245 |
| 271 | exp Cohort Studies/ | 1823837 |
| 272 | Cross-Sectional Studies/ | 269121 |
| 273 | Controlled Before-After Studies/ | 297 |

| | | |
|---|---|---|
| 274 | Historically Controlled Study/ | 149 |
| 275 | Interrupted Time Series Analysis/ | 369 |
| 276 | Comparative Study.pt. | 1908513 |
| 277 | case control*.ti,ab. | 114928 |
| 278 | case series.ti,ab. | 59535 |
| 279 | (cohort adj (study or studies)).ti,ab. | 156605 |
| 280 | cohort analy*.ti,ab. | 6292 |
| 281 | (follow up adj (study or studies)).ti,ab. | 47161 |
| 282 | (observational adj (study or studies)).ti,ab. | 81605 |
| 283 | longitudinal.ti,ab. | 210546 |
| 284 | prospective.ti,ab. | 509033 |
| 285 | retrospective.ti,ab. | 431491 |
| 286 | cross sectional.ti,ab. | 278740 |
| 287 | or/267-286 | 4334061 |

| | |
|---|---|
| 288 249 and 287 | 7941 |
| 289 288 not (247 or 266) | 5648 |
| 290 249 not (247 or 266 or 289) | 10093 |

# Appendix D: Study flow diagram



# Appendix E: Evidence prioritisation

| Key questions | Included studies[1] | | Studies not prioritised[2] | |
|---|---|---|---|---|
| | Systematic reviews | RCTs | Systematic reviews | RCTs |
| **Which antibiotic prescribing strategies are effective?** | | | | |
| Antibiotics guided by bronchoscopy with culture versus immediate empirical antibiotic prescribing | - | Herer et al. 2009 | - | - |
| **Is an antibiotic effective?** | | | | |
| Antibiotics versus placebo | - | - | - | - |
| **Which antibiotic is most effective?** | | | | |
| Penicillin with beta-lactamase versus carbapenem | - | Schmitt et al. 2006 | - | Rea-Neto et al. 2008 |
| Tetracycline versus carbapenem | - | Freire et al. 2010; Ramirez et al.2013 | - | - |
| Quinolone versus cephalosporin | - | Hoffken et al. 2007 | - | - |
| Cephalosporin versus cephalosporin plus oxazolidinone | | Awad et al. 2014 | - | - |
| Carbapenem versus cephalosporin with beta-lactamase inhibitor | - | Torres et al. 2017 | - | - |
| Glycopeptide versus glycopeptide | - | Rubinstein et al. 2014 | - | - |
| Carbapenem plus glycopeptide versus other empirical antibiotics | - | Kim et al. 2012 | - | - |
| **What is the optimal dosage, duration and route of administration of antibiotic?** | | | | |
| Dose and/or frequency studies | - | - | - | - |
| Course length studies | - | - | - | - |
| Route of administration studies | - | - | - | - |

[1] See appendix F for full references of included studies

# Appendix F:Included studies

Awad Samir S, Rodriguez Alejandro H, Chuang Yin-Ching, et al (2014) A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 59(1), 51-61

Freire Antonio T, Melnyk Vasyl, Kim Min Ja, Datsenko Oleksiy, et al and Study Group (2010) Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. Diagnostic microbiology and infectious disease 68(2), 140-51

Herer B, Fuhrman C, Gazevic Z, Cabrit R, and Chouaid C (2009) Management of nosocomial pneumonia on a medical ward: a comparative study of outcomes and costs of invasive procedures. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases 15(2), 165-72

Hoffken G, Barth J, Rubinstein E, Beckmann H, and group H A. P. study (2007) A randomized study of sequential intravenous/oral moxifloxacin in comparison to sequential intravenous ceftriaxone/oral cefuroxime axetil in patients with hospital-acquired pneumonia. Infection 35(6), 414-20

Kim Jong Wook, Chung Joowon, Choi Sang-Ho, Jang Hang Jea, et al (2012) Early use of imipenem/cilastatin and vancomycin followed by de-escalation versus conventional antimicrobials without de-escalation for patients with hospital-acquired pneumonia in a medical ICU: a randomized clinical trial. Critical care (London, and England) 16(1), R28

Ramirez Julio, Dartois Nathalie, Gandjini Hassan, Yan Jean Li, et al (2013) Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage tigecycline regimens versus imipenem-cilastatin for treatment of hospital-acquired pneumonia. Antimicrobial agents and chemotherapy 57(4), 1756-62

Rubinstein Ethan, Stryjewski Martin E, and Barriere Steven L (2014) Clinical utility of telavancin for treatment of hospital-acquired pneumonia: focus on non-ventilator-associated pneumonia. Infection and drug resistance 7, 129-35

Schmitt D V, Leitner E, Welte T, and Lode H (2006) Piperacillin/tazobactam vs imipenem/cilastatin in the treatment of nosocomial pneumonia--a double blind prospective multicentre study. Infection 34(3), 127-34

Torres A, Zhong N, Pachl J, Timsit J F et al (2017) Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): A randomised, double-blind, phase 3 non-inferiority trial. The Lancet Infectious Diseases

# Appendix G: Quality assessment of included studies

## G.1 Antibiotic prescribing strategies

**Table 2: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)**

| Study reference | Herer et al. (2009) |
|---|---|
| Did the trial address a clearly focused issue? | Yes |
| Was the assignment of patients to treatments randomised? | Yes |
| Were patients, health workers and study personnel blinded? | No[1] |
| Were the groups similar at the start of the trial? | Yes |
| Aside from the experimental intervention, were the groups treated equally? | Yes |
| Were all of the patients who entered the trial properly accounted for at its conclusion? | Yes |
| How large was the treatment effect? | See GRADE profiles |
| How precise was the estimate of the treatment effect? | See GRADE profiles |
| Can the results be applied in your context? (or to the local population) | Yes |
| Were all clinically important outcomes considered? | See GRADE profiles |
| Are the benefits worth the harms and costs? | See GRADE profiles |
| Footnote 1. Open label study | |

# G.2 Antibiotics

**Table 3: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)**

| Study reference | Schmitt et al. (2006) | Freire et al. (2010) | Ramirez et al. (2013) |
|---|---|---|---|
| Did the trial address a clearly focused issue? | Yes | Yes | Yes |
| Was the assignment of patients to treatments randomised? | Yes | Yes | Yes |
| Were patients, health workers and study personnel blinded? | Yes | Yes | Yes |
| Were the groups similar at the start of the trial? | No[1] | Yes | Yes |
| Aside from the experimental intervention, were the groups treated equally? | Yes | Yes | Yes |
| Were all of the patients who entered the trial properly accounted for at its conclusion? | Yes | Yes | Yes |
| How large was the treatment effect? | See GRADE profiles | See GRADE profiles | See GRADE profiles |
| How precise was the estimate of the treatment effect? | See GRADE profiles | See GRADE profiles | See GRADE profiles |
| Can the results be applied in your context? (or to the local population) | Yes | Yes | Yes |
| Were all clinically important outcomes considered? | See GRADE profiles | See GRADE profiles | See GRADE profiles |
| Are the benefits worth the harms and costs? | See GRADE profiles | See GRADE profiles | See GRADE profiles |
| Footnote 1. In-balance of the percentage of people who needed mechanical ventilation at baseline | | | |

**Table 4: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)**

| Study reference | Hoffken et al. (2007) | Awad et al. (2014) | Torres et al. (2017) | Kim et al. (2012) | Rubinstein et al (2014) |
|---|---|---|---|---|---|
| Did the trial address a clearly focused issue? | Yes | Yes | Yes | Yes | Yes |
| Was the assignment of patients to treatments randomised? | Yes | Yes | Yes | Yes | Yes |

| Study reference | Hoffken et al. (2007) | Awad et al. (2014) | Torres et al. (2017) | Kim et al. (2012) | Rubinstein et al (2014) |
|---|---|---|---|---|---|
| Were patients, health workers and study personnel blinded? | No[1] | Yes | Yes | No[1] | Yes |
| Were the groups similar at the start of the trial? | Yes | Yes | Yes | Yes | |
| Aside from the experimental intervention, were the groups treated equally? | Yes | Yes | Yes | Yes | Yes |
| Were all of the patients who entered the trial properly accounted for at its conclusion? | Yes | Yes | Yes | Yes | Unclear[2] |
| How large was the treatment effect? | See GRADE profiles | See GRADE profiles | See GRADE profiles | See GRADE profiles | See GRADE profiles |
| How precise was the estimate of the treatment effect? | See GRADE profiles | See GRADE profiles | See GRADE profiles | See GRADE profiles | See GRADE profiles |
| Can the results be applied in your context? (or to the local population) | Yes | Yes | Yes | Yes | Yes |
| Were all clinically important outcomes considered? | See GRADE profiles | See GRADE profiles | See GRADE profiles | See GRADE profiles | See GRADE profiles |
| Are the benefits worth the harms and costs? | See GRADE profiles | See GRADE profiles | See GRADE profiles | See GRADE profiles | See GRADE profiles |
| Footnote 1. Open label study; 2. A post-hoc analysis of RCTs (extracted data on people with non-ventilated hospital-acquired pneumonia | | | | | |

# Appendix H: GRADE profiles

## H.1 Antibiotic prescribing strategies

**Table 5: GRADE profile – bronchoscopy-guided prescribing versus empirical antibiotics**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Guided antibiotic prescribing[1] | Immediate antibiotic prescribing | Relative (95% CI) | Absolute | | |
| **Clinical failure at day 3** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | no serious indirectness | serious[4] | none | 3/34 (8.8%) | 9/34 (26.5%) | NICE analysis: RR 0.33 (0.1 to 1.13) | 177 fewer per 1000 (from 238 fewer to 34 more) | ⊕⊕OO LOW | CRITICAL |
| **Clinical cure, up to 28 days after study enrolment** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | no serious indirectness | serious[4] | none | 25/34 (73.5%) | 27/34 (79.4%) | NICE analysis: RR 0.93 (0.71 to 1.21) | 56 fewer per 1000 (from 230 fewer to 167 more) | ⊕⊕OO LOW | CRITICAL |
| **Mortality, up to 28 days after study enrolment** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | no serious indirectness | serious[5] | none | 15/98 (15.3%) | 6/95 (6.3%) | NICE analysis: RR 2.4 (0.98 to 5.87) | 88 more per 1000 (from 1 fewer to 308 more) | ⊕⊕OO LOW | CRITICAL |
| **Mortality at day 3** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | no serious indirectness | very serious[6] | none | 3/34 (8.8%) | 1/34 (2.9%) | NICE analysis: RR 3 (0.33 to 27.42) | 59 more per 1000 (from 20 fewer to 777 more) | ⊕OOO VERY LOW | CRITICAL |
| **Mortality at day 14** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | no serious indirectness | very serious[6] | none | 5/32 (15.6%) | 2/31 (6.5%) | NICE analysis: RR 2.42 (0.51 to 11.57) | 92 more per 1000 (from 32 fewer to 682 more) | ⊕OOO VERY LOW | CRITICAL |
| **Mortality at day 28** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | no serious indirectness | serious[5] | none | 7/32 (21.9%) | 3/30 (10%) | NICE analysis: RR 2.19 (0.62 to 7.69) | 119 more per 1000 (from 38 fewer to 669 more) | ⊕⊕OO LOW | CRITICAL |

**Abbreviations:** CI, confidence interval; RR, relative risk; SD, standard deviation

[1] Antibiotic prescribing guided by the result of immediate bronchoscopy with protected specimen brush sample culture which was carried out within 24 hours after clinical diagnosis of hospital-acquired pneumonia. Results of culture were available 4 to 6 hours after bronchoscopy and were used to modify the treatment

[2] Herer et al. 2009. Antibiotics that used in study included: 3rd generation cephalosporin, quinolone, streptogramins, vancomycin, beta-lactam as single therapy or combined therapy
[3] Downgraded 1 level: the study was conducted in one hospital.
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable benefit with guided antibiotic prescribing.
[5] Downgraded 1 level: at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm
[6] Downgraded 2 levels: at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm and wide confidence interval.

## Table 6: GRADE profile –broad spectrum antibiotics with de-escalation versus empirical antibiotics

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Broad spectrum with de-escalation** | **Empirical** | **Relative (95% CI)** | **Absolute** | | |
| **Number of people who received adequate initial empiric antimicrobials** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | serious[4] | none | 22/29 (75.9%) | 12/25 (48.0%) | NICE analysis: RR 1.58 (1.00 to 2.50) | 278 more per 1000 (from 0 more to 720 more) | ⊕OOO VERY LOW | IMPORTANT |
| **Mortality - At day 28** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | serious[5] | none | 21/53 (39.6%) | 14/55 (25.5%) | NICE analysis: RR 1.56 (0.89 to 2.73) | 143 more per 1000 (from 28 fewer to 440 more) | ⊕OOO VERY LOW | CRITICAL |
| **Mortality - hospital mortality** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | serious[5] | none | 23/53 (43.4%) | 18/55 (32.7%) | NICE analysis: RR 1.33 (0.81 to 2.16) | 108 more per 1000 (from 62 fewer to 380 more) | ⊕OOO VERY LOW | CRITICAL |
| **Duration of antibiotics, mean (Better indicated by lower values)** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | serious[6] | none | 12.5 days (SD 5.8) | 14.1 days (SD 7.3) | - | MD 1.6 lower (4.07 lower to 0.87 higher) | ⊕OOO VERY LOW | IMPORTANT |
| **Duration of ICU stay, mean (Better indicated by lower values)** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | serious[7] | none | 21.1 days (IQR 6-35) | 14.1 days (IQR 6-19) | - | Not estimated (study reported p=0.464) | ⊕OOO VERY LOW | IMPORTANT |
| **Emergence of multidrug resistant organisms** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | serious[8] | none | 11/29 (37.9%) | 7/42 (16.7%) | NICE analysis: RR 2.28 (1.00 to 5.17) | 213 more per 1000 (from 0 more to 695 more) | ⊕⊕OO LOW | IMPORTANT |
| **Time to development of multidrug resistant organisms, mean** | | | | | | | | | | | | |

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Broad spectrum with de-escalation | Empirical | Relative (95% CI) | Absolute | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | serious[7] | none | 19.4 days (IQR 11-30) | 22.7 days (IQR 9-30) | - | Not estimated (study reported p=0.108) | ⊕OOO VERY LOW | IMPORTANT |
| **Emergence of methicillin-resistant Staphylococcus aureus** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | serious[8] | none | 8/29 (27.6%) | 4/42 (9.5%) | NICE analysis: RR 2.9 (0.96 to 8.73) | 181 more per 1000 (from 4 fewer to 734 more) | ⊕OOO VERY LOW | IMPORTANT |
| **Emergence of Gram-negative non-Enterobacteriaceae** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | very serious[9] | none | 4/29 (13.8%) | 5/42 (11.9%) | NICE analysis: RR 1.16 (0.34 to 3.95) | 19 more per 1000 (from 79 fewer to 351 more) | ⊕OOO VERY LOW | IMPORTANT |
| **Emergence of Stenotrophomonas maltophilia** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | very serious[9] | none | 3/29 (10.3%) | 2/42 (4.8%) | NICE analysis: RR 0.29 (0.01 to 5.76) | 34 fewer per 1000 (from 47 fewer to 227 more) | ⊕OOO VERY LOW | IMPORTANT |
| **Emergence of imipenem-resistant Acinetobacter baumannii** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | very serious[9] | none | 0/29 (0%) | 2/42 (4.8%) | NICE analysis: RR 0.29 (0.01 to 5.76) | 34 fewer per 1000 (from 47 fewer to 228 more) | ⊕OOO VERY LOW | IMPORTANT |
| **Emergence of imipenem-resistant Pseudomonas aeruginosa** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | very serious[9] | none | 0/29 (0%) | 1/42 (2.4%) | NICE analysis: RR 0.48 (0.02 to 11.33) | 12 fewer per 1000 (from 23 fewer to 246 more) | ⊕OOO VERY LOW | IMPORTANT |
| **Emergence of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | very serious[9] | none | 1/29 (3.4%) | 0/42 (0%) | NICE analysis: RR 4.3 (0.18 to 102.01) | - | ⊕OOO VERY LOW | IMPORTANT |

**Abbreviations:** CI, confidence interval; RR, relative risk; MD, mean difference; ICU, intensive care unit; IQR, interquartile range

[1] Kim et al 2012
[2] Downgraded 1 level: the study was conducted in one hospital.
[3] Downgraded 1 level: both people with non-ventilator-associated pneumonia (VAP) and VAP were included in the study, 8.3% of population had VAP
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable benefit with broad spectrum antibiotics.
[5] Downgraded 1 level: at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm.
[6] Downgraded 1 level: at a default minimal important difference (MID) of 0.5 SD data are consistent with no meaningful difference or appreciable benefit with broad spectrum antibiotics.
[7] Downgraded 1 level: standard deviations were not reported in the study, and data were not normally distributed. P value was calculated using Kolmogorov-Smirno test, SDs and 95% CI of estimated effect cannot be calculated.

[8] Downgraded 1 level: at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with broad-spectrum antibiotics with de-escalation
[9] Downgraded 2 levels: at a default minimal important difference (MID) of 25% relative risk increase, effect estimate is consistent with appreciable benefit or appreciable harm.

# H.2 Antibiotics compared with other antibiotics

### Table 7: GRADE profile – piperacillin with beta-lactamase inhibitor versus carbapenem

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Piperacillin/tazobactam | Imipenem/cilastatin | Relative (95% CI) | Absolute | | |
| **Clinical response[1], intention-to-treat population, 3± 1 days after the end of treatment** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | no serious inconsistency | serious[4] | no serious imprecision | none | 71/107 (66.4%) | 77/110 (70%) | NICE analysis: RR 0.95 (0.79 to 1.14) | 35 fewer per 1000 (from 147 fewer to 98 more) | ⊕⊕OO LOW | CRITICAL |
| **Clinical response[1] (cure/improved), intention-to-treat population, up to 18 days after treatment** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | serious[4] | serious[5] | none | 64/107 (59.8%) | 73/110 (66.4%) | NICE analysis: RR 0.90 (0.73 to 1.11) | 66 fewer per 1000 (from 179 fewer to 73 more) | ⊕OOO VERY LOW | CRITICAL |
| **Adverse events, intention-to-treat population, up to 18 days after treatment** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | serious[4] | serious[6] | none | 82/110 (74.5%) | 72/111 (64.9%) | NICE analysis: RR 1.15 (0.96 to 1.37) | 97 more per 1000 (from 26 fewer to 240 more) | ⊕OOO VERY LOW | CRITICAL |
| **Adverse events related to treatment** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | serious[4] | serious[6] | none | 33/110 (30.0%) | 28/111 (25.2%) | NICE analysis: RR 1.19 (0.77 to 1.83) | 48 more per 1000 (from 58 fewer to 209 more) | ⊕OOO VERY LOW | CRITICAL |
| **All-cause mortality, intention-to-treat population** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | serious[4] | serious[7] | none | 17/110 (15.5%) | 11/111 (9.9%) | NICE analysis: RR 1.56 (0.77 to 3.18) | 55 more per 1000 (from 23 fewer to 216 more) | ⊕OOO VERY LOW | CRITICAL |
| **Pneumonia associated mortality** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | serious[4] | serious[7] | none | 1/110 (0.9%) | 2/111 (1.8%) | NICE analysis: RR | 9 fewer per 1000 (from 17 | ⊕OOO VERY LOW | CRITICAL |

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Piperacillin/tazobactam | Imipenem/cilastatin | Relative (95% CI) | Absolute | | |
| | | | | | | | | | 0.50 (0.05 to 5.48) | fewer to 81 more) | | |
| **Bacteriological response (eradication of baseline pathogens), intention-to-treat population, up to 18 days after treatment** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | serious[4] | very serious[8] | none | 9/107 (8.4%) | 10/110 (9.1%) | NICE analysis: RR 0.93 (0.39 to 2.19) | 6 fewer per 1000 (from 55 fewer to 108 more) | ⊕OOO VERY LOW | IMPORTANT |
| **Abbreviations:** CI, confidence interval; RR, relative risk | | | | | | | | | | | | |

[1] Clinical response was assessed in terms of production and characteristics of respiratory secretions, body temperature, need for mechanical ventilation/additional oxygen and lung radiography.
[2] Schmitt et al. 2006. Duration of study treatment was between 5 and 21 days
[3] Downgraded 1 level: selection bias, sequence generation was not reported in the study and participants were not comparable at baseline with a higher percentage of people who were in piperacillin/tazobactam required mechanical ventilation (28.1%) compared with 19.1% people in imipenem/cilastatin. The trial terminated early.
[4] Downgraded 1 level: 23% of people required mechanical ventilation at baseline (may have ventilator-associated pneumonia).
[5] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable benefit with imipenem/cilastatin.
[6] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable harm with piperacillin/tazobactam.
[7] Downgraded 1 level: at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm
[8] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with appreciable benefit or appreciable harm

## Table 8: GRADE profile – tetracycline versus carbapenem

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Tigecycline[1] | Imipenem/cilastatin | Relative (95% CI) | Absolute | | |
| **Sub-group analysis: Clinical cure (non-VAP) - tigecycline 100 mg followed by 50 mg, clinically modified intention-to-treatment population, at the test-of-cure visit (10 to 21 days after completion of treatment)** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | no serious indirectness | no serious imprecision | none | 217/313 (69.3%) | 223/313 (71.2%) | NICE analysis: RR 0.97 (0.88 to 1.08) | 19 fewer per 1000 (from 94 fewer to 56 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Sub-group analysis: Clinical cure (non-VAP) - tigecycline 100 mg followed by 50 mg, clinically evaluable population, at the test-of-cure visit (10 to 21 days after completion of treatment)** | | | | | | | | | | | | |

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Tigecycline[1] | Imipenem/cilastatin | Relative (95% CI) | Absolute | | |
| 1[2] | randomised trials | serious[3] | not applicable | no serious indirectness | no serious imprecision | none | 147/195 (75.4%) | 143/176 (81.3%) | NICE analysis: RR 0.93 (0.83 to 1.03) | 59 fewer per 1000 (from 145 fewer to 30 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Sub-group analysis: Clinical cure (non-VAP) – tigecycline 200 mg followed by 100 mg, clinically evaluable population, at the test-of-cure visit (10 to 21 days after completion of treatment)** | | | | | | | | | | | | |
| 1[4] | randomised trials | serious[3] | not applicable | no serious indirectness | serious[5] | none | 11/13 (84.6%) | 11/15 (73.3%) | NICE analysis: RR 1.15 (0.79 to 1.69) | 110 more per 1000 (from 154 fewer to 506 more) | ⊕⊕OO LOW | CRITICAL |
| **Sub-group analysis: Clinical cure (non-VAP) – tigecycline 150 mg followed by 75 mg, clinically evaluable population, at the test-of-cure visit (10 to 21 days after completion of treatment)** | | | | | | | | | | | | |
| 1[4] | randomised trials | serious[3] | not applicable | no serious indirectness | very serious[6] | none | 11/16 (68.8%) | 11/15 (73.3%) | NICE analysis: RR 0.94 (0.6 to 1.47) | 44 fewer per 1000 (from 293 fewer to 345 more) | ⊕OOO VERY LOW | CRITICAL |
| **Adverse events (non-VAP +VAP) - tigecycline 100 mg followed by 50 mg** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | serious[7] | no serious imprecision | none | 368/467 (78.8%) | 367/467 (78.6%) | NICE analysis: RR 1.00 (0.94 to 1.07) | 0 fewer per 1000 (from 47 fewer to 55 more) | ⊕⊕OO LOW | CRITICAL |
| **Adverse events caused discontinuation of treatment (non-VAP +VAP) - tigecycline 100 mg followed by 50 mg** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | serious[7] | serious[8] | none | 51/467 (10.9%) | 31/467 (6.6%) | NICE analysis: RR 1.65 (1.07 to 2.52) | 43 more per 1000 (from 5 more to 101 more) | ⊕OOO VERY LOW | CRITICAL |
| **Sub-group analysis: Mortality (non-VAP) - tigecycline 100 mg followed by 50 mg** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | no serious indirectness | serious[9] | none | 41/336 (12.2%) | 43/345 (12.5%) | NICE analysis: RR 0.98 (0.66 to 1.46) | 13 fewer per 1000 (from 51 fewer to 41 more) | ⊕⊕OO LOW | CRITICAL |
| **Sub-group analysis: Mortality related to study drug (non-VAP) - tigecycline 100 mg followed by 50 mg** | | | | | | | | | | | | |
| 1[2] | randomised trials | serious[3] | not applicable | no serious indirectness | serious[9] | none | 1/336 | 2/345 | NICE analysis: RR 0.51 (0.05 to 5.64) | 3 fewer per 1000 (from 6 fewer to 27 more) | ⊕⊕OO LOW | CRITICAL |
| **Mortality (non-VAP +VAP) - tigecycline 150 mg followed by 75 mg** | | | | | | | | | | | | |
| 1[4] | randomised trials | serious[3] | not applicable | serious[7] | serious[9] | none | 7/36 (19.4%) | 7/34 (20.6%) | NICE analysis: RR 0.94 (0.37 to 2.41) | 12 fewer per 1000 (from 130 fewer to 290 more) | ⊕OOO VERY LOW | CRITICAL |

**Abbreviations:** VAP – ventilator-associated pneumonia; CI, confidence interval; RR, relative risk

[1] Dose of tigecycline either: 200 mg initial dose followed by 100 mg IV every 12 hours; 150 mg initial dose followed by 75 mg IV every 12 hours; or, 100 mg initial dose followed by 50 mg IV every 12 hours

[2] Freire et al. 2010. Duration of study treatment was 7 to 14 days.
[3] Downgraded 1 level: sequence generation and concealment were not reported in the study.
[4] Ramirez et al. 2013. Study treatment was up to 14 days.
[5] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable benefit with tigecycline
[6] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable benefit with tigecycline, and no meaningful difference or appreciable benefit with imipenem/cilastatin
[7] Downgraded 1 level: results were not stratified by types of pneumonia.
[8] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable harm with tigecycline
[9] Downgraded 1 level: at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

## Table 9: GRADE profile – high dose versus low dose tetracycline

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Tigecycline low dose[1]** | **Tigecycline high dose[2]** | **Relative (95% CI)** | **Absolute** | | |
| **Sub-group analysis: Clinical cure (non-VAP) clinically evaluable population, at the test-of-cure visit (10 to 21 days after completion of treatment)** | | | | | | | | | | | | |
| 1[3] | randomised trials | serious[4] | not applicable | no serious indirectness | serious[5] | none | 11/16 (68.8%) | 11/13 (84.6%) | NICE analysis: RR 0.81 (0.54 to 1.22) | 161 fewer per 1000 (from 389 fewer to 186 more) | ⊕⊕OO LOW | CRITICAL |

**Abbreviations:** VAP, ventilator-associated pneumonia; CI, confidence interval; RR, relative risk

[1] Tigecycline low dose: 150 mg initial dose followed by 75 mg IV every 12 hours
[2] Tigecycline high dose: 200 mg initial dose followed by 100 mg IV every 12 hours
[3] Ramirez et al. 2013. Study treatment was up to 14 days.
[4] Downgraded 1 level: sequence generation and concealment were not reported in the study.
[5] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable benefit with tigecycline high dose

## Table 10: GRADE profile – quinolone versus cephalosporin

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Moxifloxacin** | **Ceftriaxone/cefuroxime axetil** | **Relative (95% CI)** | **Absolute** | | |
| **Clinical response (resolution), intention-to-treat population, at the test-of-cure visit (4 to 15 days after completion of treatment)** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | serious[4] | none | 56/77 (72.7%) | 56/82 (68.3%) | NICE analysis: RR 1.06 (0.87 to 1.30) | 44 more per 1000 (from 101 fewer to 184 more) | ⊕OOO VERY LOW | CRITICAL |
| **Clinical response (resolution), per protocol population, at the test-of-cure visit (4 to 15 days after completion of treatment)** | | | | | | | | | | | | |

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Moxifloxacin | Ceftriaxone/cefuroxime axetil | Relative (95% CI) | Absolute | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | no serious imprecision | none | 52/60 (86.7%) | 50/60 (83.3%) | NICE analysis: RR 1.04 (0.89 to 1.21) | 33 more per 1000 (98 fewer to 160 more) | ⊕⊕OO LOW | CRITICAL |
| **Serious adverse events** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | very serious[5] | none | 25/77 (33%) | 23/82 (28%) | NICE analysis: RR 1.16 (0.72 to 1.86) | 33 more per 1000 (98 fewer to 160 more) | ⊕OOO VERY LOW | CRITICAL |
| **Drug related adverse events** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | serious[5] | none | 23/77 (29.9%) | 13/82 (15.9%) | NICE analysis: RR 1.88 (1.03 to 3.45) | 140 more per 1000 (from 5 more to 388 more) | ⊕OOO VERY LOW | CRITICAL |
| **Mortality** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | serious[3] | serious[6] | none | 8/77 (10.4%) | 11/82 (13.4%) | NICE analysis: RR 0.77 (0.33 to 1.82) | 31 fewer per 1000 (from 90 fewer to 110 more) | ⊕OOO VERY LOW | CRITICAL |

**Abbreviations:** CI, confidence interval; RR, relative risk

[1] Hoffken et al. 2007. Duration of study treatment was 7 to 14 days.
[2] Downgraded 1 level: non-blind study design; terminated early due to low recruitment rate
[3] Downgraded 1 level: the time between hospitalisation and diagnosis of hospital-acquired pneumonia ranged from 0 to 107 days; therefore an unknown percentage of participants who acquired pneumonia before hospitalisation are likely to have community-acquired pneumonia
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable benefit with moxifloxacin
[5] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable harm with moxifloxacin.
[6] Downgraded 1 level: at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

## Table 11: GRADE profile – cephalosporin versus cephalosporin plus oxazolidinone

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Ceftobiprole | Ceftazidime/linezolid | Relative (95% CI) | Absolute | | |
| **Sub-group analysis: Clinical cure (non-VAP), intention-to-treat population, at the test of cure visit (7 to 14 days after completion of treatment)** | | | | | | | | | | | | |

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Ceftobiprole | Ceftazidime/linezolid | Relative (95% CI) | Absolute | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | no serious indirectness | no serious imprecision | none | 171/287 (59.6%) | 167/284 (58.8%) | NICE analysis: RR 1.01 (0.88 to 1.16) | 8 more per 1000 (from 73 fewer to 88 more) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Sub-group analysis: Clinical cure (non-VAP), clinically evaluable population, at the test of cure visit (7 to 14 days after completion of treatment)** | | | | | | | | | | | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | no serious indirectness | no serious imprecision | none | 154/198 (77.8%) | 141/185 (76.2%) | NICE analysis: RR 1.02 (0.91 to 1.14) | 16 more per 1000 (from 69 fewer to 100 more) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Treatment-related adverse events (non-VAP+VAP)** | | | | | | | | | | | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | serious[2] | serious[3] | none | 96/386 (24.9%) | 98/386 (25.4%) | NICE analysis: RR 0.98 (0.77 to 1.25) | 5 fewer per 1000 (from 58 fewer to 63 more) | ⊕⊕OO LOW | CRITICAL |
| **Sub-group analysis: Mortality (non-VAP) - 30-day all-cause mortality** | | | | | | | | | | | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | no serious indirectness | serious[4] | none | 48/287 (16.7%) | 51/284 (18.0%) | NICE analysis: RR 0.93 (0.65 to 1.33) | 13 fewer per 1000 (from 63 fewer to 59 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Sub-group analysis: Mortality (non-VAP) - pneumonia-specific mortality** | | | | | | | | | | | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | no serious indirectness | serious[4] | none | 17/287 (5.9%) | 16/284 (5.6%) | NICE analysis: RR 1.05 (0.54 to 2.04) | 3 more per 1000 (from 26 fewer to 59 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Sub-group analysis: Microbiological eradication (non-VAP)** | | | | | | | | | | | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | no serious indirectness | no serious imprecision | none | 179/269 (66.5%) | 181/267 (67.8%) | NICE analysis: RR 0.98 (0.87 to 1.1) | 14 fewer per 1000 (from 88 fewer to 68 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |

**Abbreviations:** VAP – ventilator-associated pneumonia; CI, confidence interval; RR, relative risk

[1] Awad et al 2014. Duration of study treatment was 7 to 14 days.
[2] Downgraded 1 level: results were not stratified by types of pneumonia.
[3] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable harm with ceftazidime/linezolid.
[4] Downgraded 1 level: at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

**Table 12: GRADE profile – cephalosporin with beta-lactamase inhibitor versus carbapenem**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Ceftazidime/avibactam | Meropenem | Relative (95% CI) | Absolute | | |
| **Clinical cure (non-VAP), clinically modified intention to treat population, at the test-of-cure visit (21-25 days after randomisation)** | | | | | | | | | | | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | no serious | no serious imprecision | none | 162/238 (68.3%) | 175/242 (72.3%) | NICE analysis: RR 0.94 (0.84 to 1.06) | 43 fewer per 1000 (from 116 fewer to 43 more) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Clinical cure (non-VAP), clinically evaluable population, at the test-of-cure visit (21-25 days after randomisation)** | | | | | | | | | | | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | no serious | no serious imprecision | none | 137/177 (77.4%) | 148/187 (79.1%) | NICE analysis: RR 0.98 (0.88 to 1.09) | 16 fewer per 1000 (from 95 fewer to 71 more) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Adverse events (non-VAP+VAP) - any AEs** | | | | | | | | | | | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | serious[2] | no serious imprecision | none | 302/405 (74.6%) | 299/403 (74.2%) | NICE analysis: RR 1.01 (0.93 to 1.09) | 7 more per 1000 (from 52 fewer to 67 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Adverse events (non-VAP+VAP) – any, not including people who died due to disease progression** | | | | | | | | | | | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | serious[2] | very serious[3] | none | 25/405 (6.2%) | 22/403 (5.5%) | NICE analysis: RR 1.13 (0.65 to 1.97) | 7 more per 1000 (from 19 fewer to 53 more) | ⊕OOO VERY LOW | CRITICAL |
| **Adverse events (non-VAP+VAP) - any serious AEs** | | | | | | | | | | | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | serious[2] | serious[4] | none | 75/405 (18.5%) | 54/403 (13.4%) | NICE analysis: RR 1.38 (1.00 to 1.91) | 51 more per 1000 (from 0 more to 122 more) | ⊕⊕OO LOW | CRITICAL |
| **Adverse events (non-VAP+VAP) - any leading to discontinuation** | | | | | | | | | | | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | serious[2] | very serious[3] | none | 16/405 (4.0%) | 11/403 (2.7%) | NICE analysis: RR 1.45 (0.68 to 3.08) | 12 more per 1000 (from 9 fewer to 57 more) | ⊕OOO VERY LOW | CRITICAL |
| **Adverse events (non-VAP+VAP) – considered related to treatment** | | | | | | | | | | | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | serious[2] | serious[4] | none | 66/405 (16.3%) | 54/403 (13.4%) | NICE analysis: RR 1.22 (0.87 to 1.70) | 29 more per 1000 (from 17 fewer to 94 more) | ⊕⊕OO LOW | CRITICAL |
| **Mortality (non-VAP +VAP) - all cause mortality** | | | | | | | | | | | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | serious[2] | serious[5] | none | 38/405 (9.4%) | 30/403 (7.4%) | NICE analysis: RR 1.26 (0.80 to 1.99) | 19 more per 1000 (from 15 fewer to 74 more) | ⊕⊕OO LOW | CRITICAL |
| **Mortality (non-VAP +VAP) - death due to disease progression** | | | | | | | | | | | | |

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Ceftazidime/avibactam | Meropenem | Relative (95% CI) | Absolute | | |
| 1[1] | randomised trials | no serious risk of bias | not applicable | serious[2] | serious[5] | none | 13/405 (3.2%) | 8/403 (2.0%) | NICE analysis: RR 1.62 (0.68 to 3.86) | 12 more per 1000 (from 6 fewer to 57 more) | ⊕⊕OO LOW | CRITICAL |

**Abbreviations:** VAP – ventilator-associated pneumonia; CI, confidence interval; RR, relative risk

[1] Torres et al 2017. Duration of study treatment was 7 to 14 days.
[2] Downgraded 1 level: results were not stratified by types of pneumonia.
[3] Downgraded 2 levels: at a default minimum important difference of 25% relative risk increase, effect estimate is consistent with no appreciable benefit or harm
[4] Downgraded 1 level: at a default minimum important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable harm with ceftazidime/avibactam
[5] Downgraded 1 level: at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

## Table 13: GRADE profile – glycopeptide versus glycopeptide

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Telavancin | Vancomycin | Relative (95% CI) | Absolute | | |
| **Clinical cure, clinically evaluable population, up to 14 days after completion of treatment** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | no serious indirectness | no serious imprecision | Yes[3] | 201/242 (83.1%) | 233/277 (84.1%) | NICE analysis: RR 0.99 (0.91 to 1.07) | 8 fewer per 1000 (from 76 fewer to 59 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Adverse events (at least 1 AE), up to 14 days after completion of treatment** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | no serious indirectness | no serious imprecision | Yes[3] | 422/535 (78.9%) | 424/541 (78.4%) | NICE analysis: RR 1.01 (0.95 to 1.07) | 8 more per 1000 (from 39 fewer to 55 more) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Adverse events resulted in discontinuation of study, up to 14 days after completion of treatment** | | | | | | | | | | | | |
| 1[1] | randomised trials | serious[2] | not applicable | no serious indirectness | serious[4] | Yes[3] | 38/535 (7.1%) | 27/541 (5.0%) | NICE analysis: RR 1.42 (0.88 to 2.30 | 21 more per 1000 (from 6 fewer to 65 more) | ⊕⊕OO LOW | CRITICAL |

**Abbreviations:** CI, confidence interval; RR, relative risk

[1] Rubinstein et al 2014. Duration of study treatment was 7 to 21 days. The analysis reported was based on clinically evaluable population.
[2] Downgraded 1 level: post-hoc analysis of primary trials which included both people who had hospital-acquired pneumonia (non-VAP) and VAP, and data on people with non-VAP were extracted for the purpose of the analysis. Selective reporting (the primary endpoint in the all-treated population was not reported in the study)
[3] Vancomycin dosage could be modified per site-specific guideline
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable harm with telavancin.

# Appendix I: Studies not prioritised

| Study reference | Reason for deprioritisation |
|---|---|
| Rea-Neto Alvaro, Niederman Michael, Lobo Suzana Margareth, Schroeder Eric, et al (2008) Efficacy and safety of doripenem versus piperacillin/tazobactam in nosocomial pneumonia: a randomized, open-label, multicenter study. Current medical research and opinion 24(7), 2113-26 | Doripenem is not available in the UK; another study is available providing evidence on carbapenems compared with a penicillin combination antibiotic |

# Appendix J: Excluded studies

| Study reference | Reason for exclusion |
|---|---|
| Bao H, Lv Y, Wang D, Xue J, and Yan Z (2017) Clinical outcomes of extended versus intermittent administration of piperacillin/tazobactam for the treatment of hospital-acquired pneumonia: a randomized controlled trial. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 36(3), 459-466 | Inappropriate or unclear methodology (intervention not the interest of the review) |
| Barriere Steven L (2014) The ATTAIN trials: efficacy and safety of telavancin compared with vancomycin for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia. Future microbiology 9(3), 281-9 | Not a systematic review (a narrative report of a trial study) |
| Barriere Steven L, Stryjewski Martin E, Corey G Ralph, Genter Fredric C, and Rubinstein Ethan (2014) Effect of vancomycin serum trough levels on outcomes in patients with nosocomial pneumonia due to Staphylococcus aureus: a retrospective, post hoc, subgroup analysis of the Phase 3 ATTAIN studies. BMC infectious diseases 14, 183 | No comparator (same antibiotic, comparisons were made by vancomycin serum level) |
| Bassetti M, Righi E, Rosso R, Mannelli S, Di Biagio , A , Fasce R, Pallavicini F Bobbio, Marchetti F, and Viscoli C (2006) Efficacy of the combination of levofloxacin plus ceftazidime in the treatment of hospital-acquired pneumonia in the intensive care unit. International journal of antimicrobial agents 28(6), 582-5 | Not a clinical trial |
| Chuan Junlan, Zhang Yuan, He Xia, Zhu Yuxuan, Zhong Lei, Yu Dongke, and Xiao Hongtao (2016) Systematic Review and Meta-Analysis of the Efficacy and Safety of Telavancin for Treatment of Infectious Disease: Are We Clearer?. Frontiers in pharmacology 7, 330 | Inappropriate or unclear methodology (study populations) |
| Dalhoff Klaus, Ewig Santiago, Gideline Development, Group , Abele-Horn Marianne, Andreas Stefan, Bauer Torsten T, von Baum , Heike , Deja Maria, Gastmeier Petra, Gatermann Soren, Gerlach Herwig, Grabein Beatrice, Hoffken Gert, Kern Winfried, Kramme Evelyn, Lange Christoph, Lorenz Joachim, Mayer Konstantin, Nachtigall Irit, Pletz Matthias, Rohde Gernot, Rosseau Simone, Schaaf Bernhard, Schaumann Reiner, Schreiter Dirk, Schutte Hartwig, Seifert Harald, Sitter Helmut, Spies Claudia, and Welte Tobias (2013) Adult patients with nosocomial pneumonia: epidemiology, diagnosis, and treatment. Deutsches Arzteblatt international 110(38), 634-40 | Not a systematic view of RCTs |
| De Cock , E , Krueger W A, Sorensen S, Baker T, Hardewig J, Duttagupta S, Muller E, Piecyk A, Reisinger E, and Resch A | Inappropriate or unclear methodology (study population) |

| Study reference | Reason for exclusion |
|---|---|
| (2009) Cost-effectiveness of linezolid vs vancomycin in suspected methicillin-resistant Staphylococcus aureus nosocomial pneumonia in Germany. Infection 37(2), 123-32 | |
| Equils Ozlem, da Costa , Christopher , Wible Michele, and Lipsky Benjamin A (2016) The effect of diabetes mellitus on outcomes of patients with nosocomial pneumonia caused by methicillin-resistant Staphylococcus aureus: data from a prospective double-blind clinical trial comparing treatment with linezolid versus vancomycin. BMC infectious diseases 16, 476 | Inappropriate or unclear methodology (study population) |
| Franzetti F, Antonelli M, Bassetti M, Blasi F, Langer M, Scaglione F, Nicastri E, Lauria F N, Carosi G, Moroni M, and Ippolito G (2010) Consensus document on controversial issues for the treatment of hospital-associated pneumonia. International Journal of Infectious Diseases 14(SUPPL. 4), S55-S65 | Not a systematic review (a narrative review) |
| Frippiat F, Musuamba F T, Seidel L, Albert A, et al (2015) Modelled target attainment after meropenem infusion in patients with severe nosocomial pneumonia: The PROMESSE study. Journal of Antimicrobial Chemotherapy 70(1), 207-216 | Inappropriate or unclear methodology (study population) |
| Gandjini H, McGovern Pc, Yan Jl, and Dartois N (2012) Clinical efficacy of two high tigecycline dosage regimens vs. imipenem/cilastatin in hospital-acquired pneumonia: results of a randomised phase II clinical trial. Clinical microbiology and infection 18, 64 | Abstract only |
| Huang David B, File Thomas M, Jr , Torres Antoni, Shorr Andrew F, et al (2017) A Phase II Randomized, Double-blind, Multicenter Study to Evaluate Efficacy and Safety of Intravenous Iclaprim Versus Vancomycin for the Treatment of Nosocomial Pneumonia Suspected or Confirmed to be Due to Gram-positive Pathogens. Clinical therapeutics 39(8), 1706-1718 | Inappropriate or unclear methodology (study population) |
| Ioannidou Eleni, Siempos Ilias I, and Falagas Matthew E (2007) Administration of antimicrobials via the respiratory tract for the treatment of patients with nosocomial pneumonia: a meta-analysis. The Journal of antimicrobial chemotherapy 60(6), 1216-26 | Inappropriate or unclear methodology (study population) |
| Jiang H, Tang R N, and Wang J (2013) Linezolid versus vancomycin or teicoplanin for nosocomial pneumonia: meta-analysis of randomised controlled trials. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 32(9), 1121-8 | Inappropriate or unclear methodology (study population) |
| Joshi Manjari, Metzler Michael, McCarthy Mary, Olvey Stephen, Kassira Wedad, and Cooper Angel (2006) Comparison of piperacillin/tazobactam and imipenem/cilastatin, both in combination with tobramycin, administered every 6 h for treatment of nosocomial pneumonia. Respiratory medicine 100(9), 1554-65 | Inappropriate or unclear methodology (study population) |
| Jung Young Ju, Koh Younsuck, Hong Sang-Bum, Chung Joo Won, et al (2010) Effect of vancomycin plus rifampicin in the treatment of nosocomial methicillin-resistant Staphylococcus aureus pneumonia. Critical care medicine 38(1), 175-80 | Inappropriate or unclear methodology (study population) |
| Kalil Andre C, Murthy Madhu H, Hermsen Elizabeth D, Neto Felipe K, Sun Junfeng, and Rupp Mark E (2010) Linezolid versus vancomycin or teicoplanin for nosocomial pneumonia: a systematic review and meta-analysis. Critical care medicine 38(9), 1802-8 | Inappropriate or unclear methodology (study population) |

| Study reference | Reason for exclusion |
|---|---|
| Kalil Andre C, Klompas Michael, Haynatzki Gleb, and Rupp Mark E (2013) Treatment of hospital-acquired pneumonia with linezolid or vancomycin: a systematic review and meta-analysis. BMJ open 3(10), e003912 | Inappropriate or unclear methodology (study population) |
| Labelle Aj, Schoenberg N, Skrupky L, and Kollef M (2012) Five versus seven day antibiotic course for the treatment of pneumonia in the intensive care unit. American journal of respiratory and critical care medicine 185, | Abstract only |
| Lal Ashima, Jaoude Philippe, and El-Solh Ali A (2016) Prolonged versus Intermittent Infusion of beta-Lactams for the Treatment of Nosocomial Pneumonia: A Meta-Analysis. Infection & chemotherapy 48(2), 81-90 | Not a systematic review of RCTs |
| Lee Chun-Yuan, Huang Chung-Hao, Lu Po-Liang, Ko Wen-Chien, Chen Yen-Hsu, and Hsueh Po-Ren (2017) Role of rifampin for the treatment of bacterial infections other than mycobacteriosis. The Journal of infection | Inappropriate or unclear methodology (study population) |
| Liapikou Adamantia, and Torres Antoni (2014) Pharmacotherapy for lower respiratory tract infections. Expert opinion on pharmacotherapy 15(16), 2307-18 | Not a systematic review (A narrative review) |
| Liu Dong, Zhang Jing, Liu Hai-Xia, Zhu Ying-Gang, and Qu Jie-Ming (2015) Intravenous combined with aerosolised polymyxin versus intravenous polymyxin alone in the treatment of pneumonia caused by multidrug-resistant pathogens: a systematic review and meta-analysis. International journal of antimicrobial agents 46(6), 603-9 | Not a systematic review of RCTs |
| Lü Y, Yan Z, Wang Dh, Dong Wl, Yang Y, and Xia R (2013) Treatment study of hospital acquired pneumonia by optimizing dosing regimen of piperacillin/tazobactam: prolonged vs. regular infusion. Zhonghua wei zhong bing ji jiu yi xue 25(8), 479-483 | Non-English language |
| Ma L, Zhang X, Zhao X, Zhao L, and Qiao Y (2017) Comparison of efficacy of linezolid and vancomycin for treatment of hospital-acquired pneumonia: A meta-analysis. Biomedical Research (India) 28(8), 3420-3426 | Inappropriate or unclear methodology (study population) |
| Marquet K, Liesenborgs A, Bergs J, Vleugels A, and Claes N (2015) Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: A systematic review and meta-analysis. Critical Care 19(1), 63 | Inappropriate or unclear methodology (study population) |
| Nannini Esteban C, Corey G Ralph, and Stryjewski Martin E (2012) Telavancin for the treatment of hospital-acquired pneumonia: findings from the ATTAIN studies. Expert review of anti-infective therapy 10(8), 847-54 | Not a systematic review (a narrative report of a trial study) |
| Niederman Ms, Wunderink Rg, Chastre Je, Kollef M, et al (2011) Outcomes of vancomycin weight based dosing by trough concentrations for the treatment of hospital acquired pneumonia caused by methicillin-resistant staphylococcus aureus. American journal of respiratory and critical care medicine 183. | Abstract only |
| Niederman Michael S, Chastre Jean, Solem Caitlyn T, Wan Yin, et al (2014) Health economic evaluation of patients treated for nosocomial pneumonia caused by methicillin-resistant Staphylococcus aureus: secondary analysis of a multicenter randomized clinical trial of vancomycin and linezolid. Clinical therapeutics 36(9), 1233-1243.e1 | Outcome of interest not reported |

| Study reference | Reason for exclusion |
|---|---|
| Opal S M (2012) Review: Short-course antibiotics in hospital-acquired pneumonia do not affect mortality. Annals of Internal Medicine 156(6), JC3-JC13 | Commentary |
| Pascale G, Fortuna S, Montini L, Occhionero A, et al (2013) Linezolid continuous infusion in obese patients with nosocomial pneumonia. Intensive care medicine. 39, S270 | Abstract only |
| Paul Mical, Daikos George L, Durante-Mangoni Emanuele, Yahav Dafna, et al (2018) Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. The Lancet. Infectious diseases 18(4), 391-400 | Inappropriate or unclear methodology (study population) |
| Pineda Lilibeth A, Saliba Ranime G, El Solh , and Ali A (2006) Effect of oral decontamination with chlorhexidine on the incidence of nosocomial pneumonia: a meta-analysis. Critical care (London, and England) 10(1), R35 | Outcome of interest not reported |
| Polyzos Konstantinos A, Mavros Michael N, Vardakas Konstantinos Z, Makris Marinos C, Rafailidis Petros I, and Falagas Matthew E (2012) Efficacy and safety of telavancin in clinical trials: a systematic review and meta-analysis. PloS one 7(8), e41870 | Inappropriate or unclear methodology (study population) |
| Pooley N, Chadda S, Madrigal Am, Kuessner D, and Posthumus J (2014) A network meta-analysis comparing the efficacy and safety of ceftobiprole and selected comparators in the treatment of hospital-acquired pneumonia. Value in health. 17(7), A588 | Abstract only |
| Pothirat C, Champunot R, and Inchai J (2006) The optimal duration of antibiotic treatment for hospital acquired pneumonia a comparative study between the two antibiotic discontinuation policies. Chest 130(4 Suppl), 106s | Abstract only |
| Pugh Richard, Grant Chris, Cooke Richard P. D, and Dempsey Ged (2015) Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. The Cochrane database of systematic reviews (8), CD007577 | Inappropriate or unclear methodology (study population) |
| Qu Xiao-Yu, Hu Ting-Ting, and Zhou Wei (2015) A meta-analysis of efficacy and safety of doripenem for treating bacterial infections. The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases 19(2), 156-62 | Inappropriate or unclear methodology (study population) |
| Restrepo M I (2009) Efficacy of intravenous infusion of doripenem. Clinical Infectious Diseases 49(SUPPL. 1), S17-S27 | Not a RCT |
| Rice Dennis A. K, Kaniga Kone, Lee Michael, and Redman Rebecca (2013) Activity of doripenem versus comparators in subjects with baseline bacteraemia in six pooled phase 3 clinical trials. International journal of antimicrobial agents 41(4), 388-92 | Inappropriate or unclear methodology (study population) |
| Rubinstein E, Corey Gr, Boucher Hw, and Niederman Ms (2009) Telavancin for the treatment of hospital-acquired pneumonia in severely ill and older patients: the ATTAIN studies. Critical care (london, and england) ume 13 Suppl 1P310 (Abstract number), | Abstract only |
| Rubinstein Ethan, Lalani Tahaniyat, Corey G Ralph, Kanafani Zeina A, et al and Group Attain Study (2011) Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 52(1), 31-40 | Inappropriate or unclear methodology (study population) |
| Rubinstein Ethan, Corey G Ralph, Stryjewski Martin E, and Kanafani Zeina A (2011) Telavancin for the treatment of serious | Not a systematic review (a narrative review) |

| Study reference | Reason for exclusion |
|---|---|
| gram-positive infections, including hospital acquired pneumonia. Expert opinion on pharmacotherapy 12(17), 2737-50 | |
| Sandrock Christian E, and Shorr Andrew F (2015) The role of telavancin in hospital-acquired pneumonia and ventilator-associated pneumonia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 61 Suppl 2, S79-86 | Not a systematic review (a narrative review) |
| Scott Lesley J (2013) Telavancin: a review of its use in patients with nosocomial pneumonia. Drugs 73(16), 1829-39 | Not a systematic review (a narrative review) |
| Siempos I I, Vardakas K Z, Manta K G, and Falagas M E (2007) Carbapenems for the treatment of immunocompetent adult patients with nosocomial pneumonia. The European respiratory journal 29(3), 548-60 | Inappropriate or unclear methodology (study population) |
| Silvestri L, Weir I, Gregori D, Taylor N, Zandstra D, Van Saene , J J, Van Saene , and H K (2014) Effectiveness of oral chlorhexidine on nosocomial pneumonia, causative micro-organisms and mortality in critically ill patients: a systematic review and meta-analysis. Minerva anestesiologica 80(7), 805-20 | Not a systematic review (a narrative review) |
| Sorbello A, Komo S, and Valappil T (2010) Noninferiority margin for clinical trials of antibacterial drugs for nosocomial pneumonia. Drug Information Journal 44(2), 165-176 | Not a systematic review of RCTs |
| Steinmetz T, Eliakim-Raz N, Goldberg E, Leibovici L, and Yahav D (2015) Association of vancomycin serum concentrations with efficacy in patients with MRSA infections: a systematic review and meta-analysis. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 21(7), 665-73 | Not a systematic review of RCTs |
| Talaie Haleh, Jabari Hamid Reza, Shadnia Shahin, Pajouhmand Abdolkarim, et al (2008) Cefepime/clindamycin vs. ceftriaxone/clindamycin for the empiric treatment of poisoned patients with aspiration pneumonia. Acta bio-medica : Atenei Parmensis 79(2), 117-22 | Inappropriate or unclear methodology (study population) |
| Wang Yan, Zou Yamin, Xie Jiao, Wang Taotao, Zheng Xiaowei, He Hairong, Dong Weihua, Xing Jianfeng, and Dong Yalin (2015) Linezolid versus vancomycin for the treatment of suspected methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a systematic review employing meta-analysis. European journal of clinical pharmacology 71(1), 107-15 | Inappropriate or unclear methodology (study population) |
| Wu (2017) The clinical efficacy of integrated traditional chinese and western medicine treatment of hospital-acquired pneumonia. Biomedical research (india) 28(9), 3957-3961 | Comparator is not antibiotic or placebo (Chinese medicine) |
| Trupka Tracy, Fisher Kristen, Micek Scott T, Juang Paul, and Kollef Marin H (2017) Enhanced antimicrobial de-escalation for pneumonia in mechanically ventilated patients: a cross-over study. Critical care (London, and England) 21(1), 180 | Inappropriate or unclear methodology (study population) |
| Walkey Allan J, O'Donnell Max R, and Wiener Renda Soylemez (2011) Linezolid vs glycopeptide antibiotics for the treatment of suspected methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a meta-analysis of randomized controlled trials. Chest 139(5), 1148-1155 | Inappropriate or unclear methodology (study population) |
| Wang Z, Shan T, Liu Y, Ding S, et al (2014) Comparison of 3-hour and 30-minute infusion regimens for meropenem in patients with hospital acquired pneumonia in intensive care unit: a randomized | Non-English language |

| Study reference | Reason for exclusion |
|---|---|
| controlled clinical trial. Zhonghua wei zhong bing ji jiu yi xue 26(9), 644-649 | |
| Welte T, Scheeren Twl, Rodriguez A, Demange A, and Engelhardt M (2014) Efficacy of ceftobiprole in intensive care unit (ICU) patients with hospital-acquired pneumonia (HAP). European respiratory journal 44, | Abstract only |
| Wood G Christopher, and Swanson Joseph M (2007) Aerosolised antibacterials for the prevention and treatment of hospital-acquired pneumonia. Drugs 67(6), 903-14 | Not a systematic review (a narrative review) |
| Wood G Christopher (2011) Aerosolized antibiotics for treating hospital-acquired and ventilator-associated pneumonia. Expert review of anti-infective therapy 9(11), 993-1000 | Not a systematic review (a narrative review) |
| Wunderink Richard G, Niederman Michael S, Kollef Marin H, Shorr Andrew F, et al (2012) Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a randomized, controlled study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 54(5), 621-9 | Inappropriate or unclear methodology (study population) |
| Xu Li, Wang Ya-Li, Du Shuai, Chen Lin, Long Li-Hui, and Wu Yan (2016) Efficacy and Safety of Tigecycline for Patients with Hospital-Acquired Pneumonia. Chemotherapy 61(6), 323-30 | Not a systematic review of RCTs |
| Yakovlev S V, Stratchounski L S, Woods G L, Adeyi B, et al (2006) Ertapenem versus cefepime for initial empirical treatment of pneumonia acquired in skilled-care facilities or in hospitals outside the intensive care unit. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 25(10), 633-41 | Inappropriate or unclear methodology (study population) |
| Zhang Y, Ding R, and Zhang J (2017) Clinical evaluation of prolonged infusion versus standard infusion of meropenem in the treatment of hospital-acquired pneumonia in elderly patients. Chinese journal of infection and chemotherapy 17(6), 623-628 | Non-English language |