

# Pneumonia (hospital-acquired): antimicrobial prescribing

16 September 2019

## Summary of the evidence

This is a summary of the evidence. For full details, see the [evidence review](#).

Hospital-acquired pneumonia is a lower respiratory tract infection that may be life threatening.

- Early-onset hospital-acquired pneumonia (less than 5 days after admission to hospital) is usually caused by *Streptococcus pneumoniae* and late-onset (more than 5 days after admission to hospital) is usually caused by microorganisms that are acquired in hospital, most commonly methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* and other non-pseudomonal gram-negative bacteria.
- No evidence from systematic reviews or randomised controlled trials (RCTs) was identified in children or young people under 18 years.

## Antibiotic prescribing strategies

- An antibiotic prescribing strategy (guided by results of immediate bronchoscopy with protected specimen brush sample culture) was not significantly different from immediate antibiotics for clinical cure and mortality up to 28 days in adults with hospital-acquired pneumonia (non-ventilated; [Herer et al. 2009](#)). Bronchoscopy was carried out within 24 hours of clinical diagnosis and gram-stain results (available 4 hours to 6 hours after bronchoscopy) were used to modify treatment.
- The total costs (antibiotics and bronchoscopy) of each strategy were not significantly different overall.
- An antibiotic prescribing strategy of using antibiotics with very broad antimicrobial cover (imipenem with cilastatin plus vancomycin) followed by de-escalation to a broad-spectrum antibiotic based on culture results was significantly better than empirical antibiotics for achieving adequate initial

antimicrobial cover. However, there were no significant differences in clinical outcomes, including mortality up to 28 days ([Kim et al. 2012](#)). This study included non-ventilated adults with hospital-acquired pneumonia and a small proportion of adults with ventilator-associated pneumonia (8.3%).

- The overall incidence of multidrug-resistant bacteria was significantly higher with very broad antimicrobial cover followed by de-escalation, compared with empirical antibiotics.

Evidence for antibiotic prescribing strategies is based on 2 RCTs (Herer et al. 2009 and Kim et al. 2012).

#### **Committee discussion on antibiotic prescribing strategies**

- The committee noted that the bronchoscopy antibiotic prescribing strategy used by Herer et al. (2009) was not consistent with clinical practice in the UK; culture results are not usually available within 24 hours and sputum cultures are more common than gram staining of bronchoscopy samples.
- The committee noted that overall there were no significant differences in clinical outcomes between the 2 prescribing strategies. Because of the lack of applicability to UK practice, and the small sample size, the committee agreed that there was insufficient evidence to show that the prescribing strategies were equivalent.
- The committee discussed evidence from Kim et al. (2012) suggesting no difference in clinical outcomes between a prescribing strategy of very-broad-spectrum antibiotics with de-escalation, compared with empirical antibiotics. However, the committee was concerned that the rate of emergence of multidrug-resistant bacteria was significantly higher with the very-broad-spectrum antibiotics followed by de-escalation strategy.
- The committee was concerned about the risk of antimicrobial resistance from using very-broad-spectrum antibiotics for longer than necessary, as well as the high rates of adverse effects in some of the included studies. Therefore, the committee concluded that a respiratory sample (for example, sputum sample, nasopharyngeal swab or tracheal aspirate)

should be taken and sent for microbiological testing if possible. This reflects current practice.

The committee agreed that when microbiological results are available, the antibiotic should be reviewed and changed accordingly (for example, if bacteria are found to be resistant), using a narrower-spectrum antibiotic, if appropriate.

## Choice of antibiotics

### Efficacy of antibiotics

- Overall, there were no differences in the clinical effectiveness (clinical cure or mortality) in a range of antibiotic comparisons in adults with hospital-acquired pneumonia:
  - penicillin with beta-lactamase inhibitor (piperacillin with tazobactam) compared with a carbapenem (imipenem with cilastatin; [Schmitt et al. 2006](#))
  - cephalosporin with beta-lactamase inhibitor (ceftazidime with avibactam) compared with a carbapenem (meropenem; [Torres et al. 2017](#))
  - tetracycline (tigecycline) compared with a carbapenem (imipenem with cilastatin; [Freire et al. 2010](#) and [Ramirez et al. 2013](#))
  - fluoroquinolone (moxifloxacin) compared with a cephalosporin (ceftriaxone followed by cefuroxime; [Hoffken et al. 2007](#))
  - cephalosporin (ceftobiprole) compared with cephalosporin plus oxazolidinone (ceftazidime plus linezolid; [Awad et al. 2014](#))
  - glycopeptide (telavancin) compared with glycopeptide (vancomycin; [Rubinstein et al. 2011](#) reported in [Rubinstein et al. 2014](#)).

Evidence for efficacy of antibiotics is based on 6 RCTs (Schmitt et al. 2006, Torres et al. 2017, Freire et al. 2010, Ramirez et al. 2013, Hoffken et al. 2007 and Awad et al. 2014) and 1 post-hoc analysis of an RCT (Rubinstein et al. 2014).

## Safety of antibiotics

- 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](#) for more information.
- People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics ([BNF, August 2019](#)).
- Macrolides (for example, clarithromycin) should be used with caution in people with a predisposition to QT interval prolongation ([BNF, August 2019](#)).
- Tetracyclines (for example, doxycycline), can deposit in growing bone and teeth (by binding to calcium) causing staining and occasionally dental hypoplasia. They should not be given to pregnant or breastfeeding women, and use in children under 12 years is either contraindicated or cautioned for use in severe or life-threatening infections where there are no alternatives ([BNF, August 2019](#)).
- Co-trimoxazole is associated with rare but serious side effects including blood disorders and Stevens–Johnson syndrome. It is cautioned for use in older people because there is an increased risk of serious adverse effects, and in those with a predisposition to hyperkalaemia. Monitoring of blood counts is recommended with prolonged treatment ([BNF, August 2019](#)).
- Fluoroquinolones have restrictions and precautions around their use because of rare reports of disabling and potentially long-lasting or irreversible side effects affecting musculoskeletal and nervous systems ([MHRA Drug Safety Update, March 2019](#)). They may also be associated with a small increased risk of aortic aneurysm and dissection, particularly in older people ([MHRA Drug Safety Update, November 2018](#)).
- Glycopeptide (for example, vancomycin and teicoplanin) doses are based on body weight. Therapeutic drug monitoring and monitoring of various patient parameters including blood count, urinalysis, auditory function,

hepatic function and renal function is recommended depending on the particular glycopeptide ([BNF, August 2019](#)).

- Severe optic neuropathy can occur with linezolid, particularly if used for longer than 28 days. Blood disorders have also been reported and weekly full blood counts are recommended ([BNF, August 2019](#)).
- Overall, there were no significant differences in adverse effects in the studies between antibiotics or classes of antibiotics in people with hospital-acquired pneumonia.
- Treatment-related adverse events were significantly higher with moxifloxacin compared with a cephalosporin (intravenous ceftriaxone then oral cefuroxime; 30% versus 16%, number needed to harm [NNH] 7 [range 3 to 84]).
- Significantly more people stopped treatment because of adverse events with tigecycline than with imipenem with cilastatin (10.9% versus 6.6%, NNH 23 [range 12 to 150]).
- See the [summaries of product characteristics](#) for information on contraindications, cautions, drug interactions and adverse effects of individual medicines.

#### **Committee discussion on choice of antibiotics**

- The committee agreed that prompt antibiotic treatment should be offered to everyone with hospital-acquired pneumonia.
- The committee discussed the definition of hospital-acquired pneumonia. Because it includes people with pneumonia that develops 48 hours or more after hospital admission and that was not incubating at hospital admission, the committee agreed that the NICE guideline on community-acquired pneumonia should be followed for people with symptoms or signs of pneumonia starting on days 1 or 2 after hospital admission.
- The committee discussed the timing of antibiotic treatment and was aware of current practice to offer antibiotics within 4 hours. No systematic reviews or RCTs were identified, and the committee agreed that there was no reason to change current practice. However, they noted that the

timing should be within 4 hours of an established diagnosis to avoid inappropriate use of broad-spectrum antibiotics.

- The committee noted that evidence was identified in adults only, and for a limited number of head-to-head antibiotic comparisons. They agreed that recommendations for children and young people should be based on its experience and extrapolation of evidence in adults, taking account of any relevant medicines safety concerns.
- Given the clinical expertise needed for assessing and managing hospital-acquired pneumonia in very young children (under 1 month), the committee agreed that the choice of antibiotic in these children should be based on local resistance data and specialist microbiological advice.
- Overall, the limited evidence showed no differences in clinical effectiveness between different broad-spectrum antibiotics or classes of antibiotics, with some small differences in the rates of adverse effects. The committee noted the high rates of adverse events for many broad-spectrum antibiotics included in the studies.
- The committee discussed the most common causes of hospital-acquired pneumonia. They agreed that cause is often uncertain because many people do not have a microbiological diagnosis.
- They recognised that *S. pneumoniae* is the most common cause in people who develop hospital-acquired pneumonia within 5 days of hospital admission. The risk of having a multidrug-resistant infection with *P. aeruginosa*, MRSA or extended-spectrum beta-lactamases (ESBLs) increases in people who develop the infection after more than 5 days of being in hospital, although resistance rates vary locally.
- Therefore, the committee agreed that for people with symptoms or signs of pneumonia starting on days 3 to 5 after hospital admission who are not at high risk of resistance, it may be appropriate to follow the NICE guideline on community-acquired pneumonia for recommendations on the choice of antibiotic, based on their clinical judgement. This would give the option to treat some people with amoxicillin, which is a narrower-spectrum antibiotic with activity against *S. pneumoniae*.

- Based on experience, the committee agreed that there are several factors that need to be taken into account when choosing an antibiotic, including the severity of symptoms or signs. The committee did not know of any validated tools for assessing the severity of hospital-acquired pneumonia, and therefore agreed that this should be based on clinical judgement.
- The committee also agreed that some people are at higher risk of developing complications, for example, people with a comorbidity such as severe lung disease or immunosuppression.
- The committee recognised that, when available, local antimicrobial resistance data are an important consideration in hospital-acquired pneumonia, including at hospital and ward-based level (particularly in high-risk areas such as intensive care, high-dependency units, haematology or oncology).
- The committee also agreed that recent use of broad-spectrum antibiotics and recent contact with healthcare services before the current hospital admission were also highly likely to increase the risk of resistant pathogens.
- The committee agreed that taking account of these factors would optimise the appropriate use of broad-spectrum antibiotics and minimise the risk of antimicrobial resistance.
- The committee agreed that an antibiotic should be started empirically, so as not to delay treatment for an infection with a high-mortality risk.
- The committee agreed that the choice of antibiotic should be based on its experience of which antibiotics are effective against likely pathogens and cause the least harm, with the narrowest spectrum possible to minimise the risk of antimicrobial resistance and adverse effects. However, the committee discussed that people with severe symptoms or signs and those at higher risk of resistance will need broad-spectrum antibiotics with high activity against likely organisms.
- Based on its experience, the committee recommended **co-amoxiclav** as **first-choice antibiotic** for people with non-severe symptoms or signs who are not at higher risk of resistance; co-amoxiclav is a broad-

spectrum antibiotic that combines a penicillin with a beta-lactamase inhibitor and has good activity against common pathogens, such as *S. pneumoniae* and *Haemophilus influenzae*. The committee also recognised the extensive clinical experience of its effectiveness in this population.

- For adults with non-severe symptoms or signs who are not at higher risk of resistance, with penicillin allergy or in whom co-amoxiclav is unsuitable (for example, because of local resistance data), the committee agreed that the choice of an **alternative antibiotic** should be based on local resistance data and specialist microbiological advice only. They agreed that options include:
  - doxycycline (a tetracycline)
  - cefalexin (a cephalosporin; not suitable if there is a risk of penicillin-resistant pneumococci)
  - co-trimoxazole (trimethoprim plus a sulfonamide)
  - levofloxacin (a fluoroquinolone; only to be used when switching from IV antibiotics, following specialist advice).
- Co-trimoxazole and levofloxacin are not licensed for hospital-acquired pneumonia, so use would be off-label.
- In children and young people with penicillin allergy or in whom co-amoxiclav is unsuitable, the **alternative antibiotic** is **clarithromycin** (a macrolide); this has good activity against common pathogens and is appropriate for use in children and young people. However, the committee recognised that other options may be suitable based on local resistance data and specialist microbiological advice.
- The committee agreed that specialist advice should be sought for young women who are pregnant with penicillin allergy or in whom co-amoxiclav is unsuitable, because they were not able to specify an alternative antibiotic for this population.
- Based on its experience, the committee recognised that many broad-spectrum antibiotics would be appropriate as **first-choice intravenous antibiotics** for people with severe symptoms or signs, or who are at higher risk of resistance. It agreed that the choice should be based on



local resistance data and following specialist microbiological advice.

Options include:

- **piperacillin with tazobactam** (an antipseudomonal penicillin with a beta-lactamase inhibitor)
  - **ceftazidime** (a third-generation cephalosporin)
  - **ceftriaxone** (a third-generation cephalosporin)
  - **cefuroxime** (a second-generation cephalosporin; in adults)
  - **meropenem** (a carbapenem; in adults)
  - **ceftazidime with avibactam** (a third-generation cephalosporin with a beta-lactamase inhibitor; in adults)
  - **levofloxacin** (in adults).
- These antibiotics have good activity against common pathogens in this population, including multidrug-resistant *P. aeruginosa*, ESBLs and some carbapenemase-producing gram-negative bacteria.
  - The committee discussed that a small number of people with hospital-acquired pneumonia may have suspected or confirmed infection with MRSA. Therefore, based on their experience, the committee agreed that for these people, 1 of the following **antibiotics** with activity against MRSA should be added to the treatment regimen:
    - **vancomycin** (a glycopeptide)
    - **teicoplanin** (a glycopeptide)
    - **linezolid** (an oxazolidinone; if vancomycin cannot be used, following specialist advice only). Linezolid is not licensed in children and young people under 18 years, so use would be off-label.
  - Based on its experience, the committee recommended the same **oral antibiotics** (discussed above) for people with severe symptoms or signs or at higher risk of resistance who have initially received intravenous antibiotics, to complete the antibiotic course when intravenous antibiotics are no longer required.
  - The committee recognised that hospital-acquired pneumonia requires careful monitoring. It agreed by consensus that a person's condition

should be reassessed if symptoms do not improve as expected or worsen rapidly or significantly at any time.

The committee agreed that for people with symptoms that are not improving as expected with antibiotics, or who are known to have multidrug-resistant bacteria, specialist advice from a microbiologist should be sought.

## **Antibiotic course length, dosage and route of administration**

- No systematic reviews or RCTs were identified that compared antibiotic course lengths, dosage or route of administration.

### **Committee discussions on antibiotic course length, dosage and route of administration**

- The committee agreed that the shortest course that is likely to be effective should be prescribed to reduce the risk of antimicrobial resistance and adverse effects from broad-spectrum antibiotics. However, hospital-acquired pneumonia is a serious infection with a high-mortality risk and needs effective treatment.
- Based on its experience and extrapolation of evidence for people with community-acquired pneumonia (see the NICE guideline on community-acquired pneumonia), the committee agreed that a total course of 5 days of antibiotics was the minimum required.
- The committee agreed that antibiotic treatment should be reviewed at 5 days. Stopping the antibiotic should be considered on an individual basis if the person is judged to be clinically stable.
- Based on its experience, the committee agreed that usual BNF and BNF for children doses for hospital-acquired pneumonia, or severe susceptible infections should be used.
- In line with the [NICE guideline on antimicrobial stewardship](#) and [Public Health England's Start smart – then focus](#), oral antibiotics should be given first line if the person can take them, and if the severity of their infection does not require intravenous antibiotics. The use of intravenous antibiotics should be reviewed by 48 hours (taking into account the

person's response to treatment and any microbiological results) and switched to oral treatment where possible.

For people with severe symptoms or signs or at higher risk of resistance, the committee agreed that intravenous antibiotics should always be given initially.

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