# Pneumonia (community-acquired): antimicrobial prescribing

## NICE guideline

## Draft for consultation, February 2019

**This guideline sets out** an antimicrobial prescribing strategy for community-acquired pneumonia. It aims to optimise antibiotic use and reduce antibiotic resistance.

The recommendations in this guideline are for the use of antibiotics to manage community-acquired pneumonia in adults, young people and children. It does not cover diagnosis. See the NICE guideline on pneumonia in adults for other recommendations on diagnosis and management of community-acquired pneumonia, including microbiological tests.

For managing other lower respiratory tract infections (including hospital-acquired pneumonia), see our web page on respiratory conditions.

See a 3-page visual summary of the recommendations, including tables to support prescribing decisions.

**Who is it for?**

- Health care professionals
- People with community-acquired pneumonia, their families and carers

The guideline contains:

- the draft recommendations
- summary of the evidence.

Information about how the guideline was developed is on the guideline's page on the NICE website. This includes the full evidence review, details of the committee and any declarations of interest.

# Recommendations

## *1.1 Managing community-acquired pneumonia*

### Treatment for adults

1.1.1 Offer an antibiotic(s) for adults with community-acquired pneumonia within 4 hours of establishing a diagnosis. When choosing an antibiotic (see the recommendations on choice of antibiotic) take account of:

- the severity assessment, in line with the NICE guideline on pneumonia
- the risk of developing complications, for example if the person has co-morbidity (such as severe lung disease or immunosuppression)
- local antimicrobial resistance and surveillance data (such as flu and mycoplasma infection rates)
- recent antibiotic use
- recent microbiological results, including colonisation with multi-drug resistant bacteria.

1.1.2 Give oral antibiotics first-line if the person can take oral medicines, and the severity of their condition does not require intravenous antibiotics.

1.1.3 Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics if possible.

1.1.4 For adults with community-acquired pneumonia, follow the recommendations on microbiological tests in the NICE guideline on pneumonia.

### Treatment for children and young people

1.1.5 Offer an antibiotic(s) for children and young people with community-acquired pneumonia within 4 hours of establishing a

diagnosis. When choosing an antibiotic (see the recommendations on choice of antibiotic) take account of:

- the severity of symptoms or signs[1]
- the risk of developing complications, for example if the child or young person has a co-morbidity (such as severe lung disease or immunosuppression)
- local antimicrobial resistance and surveillance data (such as flu and mycoplasma infection rates)
- recent antibiotic use
- recent microbiological results, including colonisation with multi-drug resistant bacteria.

1.1.6 For children and young people in hospital with community-acquired pneumonia, consider sending a respiratory sample (for example, sputum sample, nasopharyngeal swab or tracheal aspirate) for microbiological testing.

**Advice**

1.1.7 Give advice to adults, young people and children with community-acquired pneumonia about:

- possible adverse effects of the antibiotic
- seeking medical help (if the person is being treated in the community) if:
  - symptoms worsen rapidly or significantly, **or;**
  - symptoms do not start to improve within 3 days, **or**
  - the person becomes systemically very unwell.

**Reassessment**

1.1.8 If a respiratory sample has been sent for microbiological testing:

- review the choice of antibiotic(s) when results are available, **and**

[1] At the time of publication, no validated severity assessment tools are available for children with community-acquired pneumonia, and severity of symptoms or signs should be based on clinical judgement.

- change the antibiotic(s) according to results, using a narrower spectrum antibiotic, if appropriate.

1.1.9 Reassess adults, young people and children with community-acquired pneumonia if symptoms or signs do not improve as expected or worsen rapidly or significantly.

1.1.10 Send a respiratory sample (for example, sputum sample, nasopharyngeal swab or tracheal aspirate) for microbiological testing if symptoms or signs have not improved following antibiotic treatment, and this has not been done already.

**Referral and seeking specialist advice**

1.1.11 Refer adults with community-acquired pneumonia to hospital in line with the NICE guideline on pneumonia, and if they have:

- any symptoms or signs suggesting a more serious illness or condition (for example cardiorespiratory failure or sepsis), **or**
- symptoms that are not improving as expected with antibiotics, **or**
- bacteria that are resistant to oral antibiotics.

1.1.12 Consider referring children and young people with community-acquired pneumonia to hospital, or seek specialist paediatric advice on further investigation and management.

1.1.13 Seek specialist advice for adults, young people and children with community-acquired pneumonia if they cannot take oral medicines (to explore locally available options for giving intravenous antibiotics at home or in the community, rather than in hospital if this is appropriate).

See the evidence and committee discussion on antibiotic prescribing strategies and choice of antibiotics.

## *1.2 Choice of antibiotic*

1.2.1 When prescribing an antibiotic(s) for community-acquired pneumonia:

- follow table 1 for adults aged 18 years and over
- follow table 2 for children and young people under 18 years.

**Table 1. Antibiotics for adults aged 18 years and over**

| **Antibiotic[1]** | **Dosage and course length[2]** |
|---|---|
| **First choice antibiotic if low-severity (based on clinical judgement and CRB65 score 0, or CURB65 score 0 or 1)[3]** | |
| Amoxicillin | 500 mg three times a day orally or IV[4] for 5 days in total[5] |
| **Alternative antibiotics if low-severity, for penicillin allergy or if amoxicillin unsuitable (for example, atypical pneumonia suspected)[3]** | |
| Clarithromycin | 500 mg twice a day orally or IV[4] for 5 days in total[5] |
| Erythromycin (in pregnancy) | 500 mg four times a day orally for 5 days[5] |
| Doxycycline | 200 mg on first day, then 100 mg once a day orally for 5 days[5] |
| **First choice antibiotics if moderate-severity (based on clinical judgement and CRB65 score 1 or 2, or CURB65 score 2); guided by microbiological results when available[3]** | |
| Amoxicillin ***with (if atypical pneumonia suspected):*** | 500 mg three times a day orally or IV[4] (higher doses can be used – see BNF) for 5 days in total[5] |
| Clarithromycin[6] ***or*** | 500 mg twice a day orally or IV[4] for 5 days in total[5] |
| Erythromycin[6] (in pregnancy) | 500 mg four times a day orally for 5 days[5] |
| **Alternative antibiotics if moderate-severity, for penicillin allergy; guided by microbiological results when available[3]** | |
| Clarithromycin | 500 mg twice a day orally or IV[4] for 5 days in total[5] |
| Azithromycin | 500 mg once a day orally for 3 days[5] |
| **First choice antibiotics if high-severity (based on clinical judgement and CRB65 score 3 or 4, or CURB65 score 3 to 5); guided by microbiological results when available[3]** | |
| Co-amoxiclav ***with*** | 500/125 mg three times a day orally or 1.2 g three times a day IV[4] for 5 days in total[5] |
| Clarithromycin ***or*** | 500 mg twice a day orally or IV[4] for 5 days in total[5] |
| Erythromycin (in pregnancy) | 500 mg four times a day orally for 5 days[5] |
| **Alternative antibiotics if high-severity, for penicillin allergy; guided by microbiological results when available[3]** | |
| Levofloxacin | 500 mg twice a day orally or IV[4] for 5 days in total[5] |
| [1]See BNF and MHRA advice for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding, and administering intravenous antibiotics.<br>[2]Oral doses are for immediate-release medicines. | |

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|---|
| [3]Give oral antibiotics first-line if the person can take oral medicines, and the severity of their condition does not require intravenous antibiotics.<br>[4]Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics if possible.<br>[5]Stop antibiotic treatment after a total of 5 days (3 days with azithromycin) unless the person is not clinically stable (based on clinical judgement, taking account of presence of fever in last 48 hours, BP, heart rate, respiratory rate and oxygen saturations).<br>[6]Consider adding a macrolide to amoxicillin if atypical pneumonia suspected. Review when susceptibilities available and stop the macrolide if atypical bacteria are not isolated. |
| Abbreviations: BP, blood pressure; IV, intravenous; C(U)RB65, **c**onfusion, (**u**rea >7 mmol/l), **r**espiratory rate ≥ 30/min, low systolic [<90 mm Hg] or diastolic [≤60 mm Hg] **b**lood pressure, age >**65** |

## Table 2. Antibiotics for children and young people under 18 years

| **Antibiotic[1]** | **Dosage and course length[2]** |
|---|---|
| **Children under 3 months** | |
| Refer to paediatric specialist and treat with intravenous antibiotics in line with the NICE guideline on fever in under 5s. | |
| **Children aged 3 months and over** | |
| **First choice antibiotic if non-severe symptoms or signs (based on clinical judgement)[3]** | |
| Amoxicillin | Oral doses:<br>3 to 11 months, 125 mg three times a day for 5 days[4]<br>1 to 4 years, 250 mg three times a day for 5 days[4]<br>5 to 17 years, 500 mg three times a day for 5 days[4]<br>IV dose[5]:<br>3 months to 17 years, 30 mg/kg three times a day (maximum 500 mg per dose) |
| **Alternative antibiotics if non-severe symptoms or signs, for penicillin allergy or if amoxicillin unsuitable (for example, atypical pneumonia suspected)[3]** | |
| Clarithromycin | Oral doses, 3 months to 11 years:<br>Under 8 kg, 7.5 mg/kg twice a day for 5 days[4]<br>8 to 11 kg, 62.5 mg twice a day for 5 days[4]<br>12 to 19 kg, 125 mg twice a day for 5 days[4]<br>20 to 29 kg, 187.5 mg twice a day for 5 days[4]<br>30 to 40 kg, 250 mg twice a day for 5 days[4]<br>IV dose[5], 3 months to 11 years:<br>7.5 mg/kg twice a day (maximum 500 mg per dose)[4]<br>12 to 17 years:<br>250 mg to 500 mg twice a day orally or 500 mg twice a day IV[5] for 5 days in total[4] |
| Erythromycin (in pregnancy) | 8 to 17 years, 250 mg to 500 mg orally four times a day for 5 days |
| Doxycycline | 12 to 17 years, 200 mg on first day, then 100 mg once |

| | |
|---|---|
| | a day orally for 5 days [4] |
| **First choice antibiotic(s) if severe symptoms or signs (based on clinical judgement); guided by microbiological results when available[3]** | |
| Co-amoxiclav | Oral doses:<br>3 to 11 months, 0.5 ml/kg of 125/31 suspension three times a day for 5 days[4]<br>1 to 5 years, 10 ml of 125/31 suspension three times a day or 0.5 ml/kg of 125/31 suspension three times a day for 5 days[4]<br>6 to 11 years, 10 ml of 250/62 suspension three times a day or 0.3 ml/kg of 250/62 suspension three times a day for 5 days[4]<br>12 to 17 years, 500/125 mg three times a day for 5 days[4]<br>IV dose[5]:<br>3 months to 17 years, 30 mg/kg three times a day (maximum 1.2 g per dose three times a day)[4] |
| ***with (if atypical pneumonia suspected):*** | |
| Clarithromycin ***or*** | See oral and IV doses above; for 5 days in total[5] |
| Erythromycin (in pregnancy) | See oral doses above; for 5 days in total[5] |
| **Alternative antibiotics if severe symptoms or signs (based on clinical judgement), for penicillin allergy; guided by microbiological results when available[3]** | |
| Consult local microbiologist | |
| [1]See BNF for children and MHRA advice for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding, and administering intravenous antibiotics.<br>[2]Oral doses are for immediate-release medicines. The age bands apply to children of average size and, in practice, the prescriber will use the age bands in conjunction with other factors such as the severity of the condition being treated and the child's size in relation to the average size of children of the same age.<br>[3]Give oral antibiotics first-line if the person can take oral medicines, and the severity of their condition does not require intravenous antibiotics.<br>[4]Stop antibiotic treatment after a total of 5 days unless the person is not clinically stable.<br>[5]Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics if possible. | |
| Abbreviations: BP, blood pressure; IV, intravenous | |

1 See the committee discussion on choice of antibiotic and antibiotic course
2 length.

# Terms used in the guideline

### Severity assessment in adults

A judgement by the managing clinician as to the likelihood of adverse outcomes. This is based on a combination of clinical understanding and knowledge in addition to a mortality risk score. There may be situations when the mortality score does not accurately predict mortality risk and clinical judgement is needed. For example an adult with a low mortality risk score who has an unusually low oxygen level, may be considered to have a severe illness. See the NICE guideline on pneumonia.

### CRB65

CRB65 is used in primary care to assess 30-day mortality risk in adults with pneumonia. The score is calculated by giving 1 point for each of the following prognostic features: **c**onfusion, **r**espiratory rate ≥ 30/min, low systolic [< 90 mm Hg] or diastolic [≤ 60 mm Hg] **b**lood pressure, age >**65**). Risk of death is stratified as follows:

- 0: low risk (less than 1% mortality risk)
- 1 or 2: intermediate risk (1–10% mortality risk)
- 3 or 4: high risk (more than 10% mortality risk).

### CURB65

CURB65 is used in hospital to assess 30-day mortality risk in adults with pneumonia. The score is calculated by giving 1 point for each of the following prognostic features: (**c**onfusion, **u**rea > 7 mmol/l, **r**espiratory rate ≥ 30/min, low systolic [< 90 mm Hg] or diastolic [≤ 60 mm Hg] **b**lood pressure, age >**65**). Risk of death is stratified as follows:

- 0 or 1: low risk (less than 3% mortality risk)
- 2: intermediate risk (3–15% mortality risk)
- 3 to 5: high risk (more than 15% mortality risk).

Adults with score of 1 and particularly 2 are at increased risk of death (should be considered for hospital referral) and people with a score of 3 or more are at high risk of death (require urgent hospital admission).

**Pneumonia severity index**

Pneumonia severity index (PSI) is a predictive score of the 30-day mortality risk in adults with pneumonia. It is based on 20 variables which are used to provide a score between I and V. Adults in classes I to III are usually considered to be at low risk of mortality.

## Summary of the evidence

This is a summary of the evidence, for full details see the evidence review.

- Community-acquired pneumonia is a lower respiratory tract infection that is most commonly caused by bacterial infection (British Thoracic Society [BTS] guideline on community-acquired pneumonia in adults, 2009).
- The main bacterial pathogen is *Streptococcus pneumoniae* (clinical knowledge summaries [CKS] – chest infections, 2015), however *Mycoplasma pneumonia* occurs in outbreaks approximately every 4 years in the UK and is much more common in school-aged children and young people (BTS 2009).
- While bacterial infection is the most common cause of community-acquired pneumonia, approximately 13% of cases are caused by viral infection (BTS 2009).
- Low-severity community-acquired pneumonia in adults includes people with pneumonia severity index (PSI) score of I or II, CRB65 score 0 or CURB65 score 0 or 1. Moderate- to high-severity community-acquired pneumonia in adults includes people with PSI score of III to V, CRB65 score 1 to 4 or CURB65 score 2 to 5.
- The severity of infection was not always clearly defined in the studies, but was often based on clinical judgement. The management setting (community or hospital) was used to indicate the severity of symptoms when this was not described in the studies (either through severity assessment scores or clinical judgement).

### *Antibiotic prescribing strategies*

- In adults with moderate- to high- severity community-acquired pneumonia, an antibiotic prescribing strategy guided by results of pneumococcal and *Legionella pneumophilia* urine antigen tests was not significantly different from a strategy that used broad-spectrum antibiotics without antigen testing for the outcomes of mortality, clinical relapse and hospital admissions (1 RCT, Falguera et al. 2009).
- In adults with mixed severity community-acquired pneumonia, a strategy of stopping antibiotics based on guidelines was not different to physician-guided stopping for a range of outcomes, including mortality, symptoms, recurrence, length of hospital stay and adverse events Stopping antibiotics based on guidelines was associated with a longer total antibiotic course length (including intravenous and oral antibiotics) but with a shorter time taking intravenous antibiotics (2 RCTs, Uranga et al. 2016 and Aliberti et al. 2017).
- In children aged 1 month to 5 years with severe community-acquired pneumonia, a strategy of intravenous antibiotics then switching to oral antibiotics (based on a specified drop in body temperature and stable clinical signs) reduced hospital stay by about 1 day, compared with standard care (intravenous then switching to oral antibiotics at least 48 hours after dissipation of fever). There was no difference in readmissions (1 non-inferiority RCT, In-iw et al. 2015).

**Committee discussions on antibiotic prescribing strategies**

- The committee discussed the evidence for antibiotic prescribing strategies in adults, young people and children with community-acquired pneumonia.
- The committee discussed that the study designs were not appropriate for determining which antibiotic prescribing strategies were most effective, because the antibiotics used in the studies on prescribing strategies had very broad antibacterial cover.

- As there were no major differences identified between stopping antibiotics based on guidelines and stopping antibiotics based on clinical judgement, the committee agreed that clinical judgement should be used when deciding when to stop antibiotic treatment, which should usually be after 5 days.
- The committee agreed that the criteria used in the study by Uranga et al. (2016) (fever in the last 48 hours, blood pressure, heart rate, respiratory rate and oxygen saturations) should be considered during decision making (see committee discussion on antibiotic course length).
- The committee discussed the evidence in children suggesting a reduced length of hospital stay with switching from intravenous to oral antibiotics when clinical signs were stable compared with switching following 48 hours of dissipation of fever. However, as other important clinical outcomes were not reported (such as mortality or cure), and no evidence was available in adults for this prescribing strategy, the committee agreed that if applicable, the decision for switching from intravenous to oral antibiotics in adults, young people and children should be based on clinical judgement (see evidence summary and committee discussion section on route of administration).
- The committee was aware that the NICE guideline on pneumonia makes recommendations on microbiological testing for adults.
- In children and young people with severe symptoms or signs, the committee agreed that a broad-spectrum antibiotic would be needed initially to cover the range of possible pathogens, including the addition of a macrolide if atypical pneumonia was suspected (see committee discussion on choice of antibiotics).
- The committee were concerned about the risk of antimicrobial resistance from using broad-spectrum antibiotics for longer than necessary. Therefore, the committee agreed that in children and young people managed in hospital (who were more likely to be on broad spectrum antibiotics), sending a respiratory sample for microbiological testing should be considered. They recognised that

obtaining a respiratory sample is not always possible, especially in young children.

- The committee agreed that when microbiological results are available, the antibiotic should be reviewed and changed according to results (for example, if bacteria are found to be resistant or atypical pathogens are not isolated), using a narrower spectrum antibiotic, if appropriate.
- In children and young people with non-severe symptoms or signs, the committee agreed that most would respond to first line antibiotics, and therefore a respiratory sample would not be routinely needed to guide antibiotic choice.

## *Choice of antibiotic*

### Efficacy of antibiotics

#### *Low-severity community-acquired pneumonia in adults*

- There were no differences in the clinical effectiveness of the following antibiotic comparisons (course length varied but usually ranged from 7 to 14 days) in adults with low-severity community-acquired pneumonia:
  - clarithromycin compared with amoxicillin (Pakhale et al. 2014)
    clarithromycin compared with erythromycin (Pakhale et al. 2014)
  - azithromycin compared with clarithromycin (Pakhale et al. 2014)
  - azithromycin compared with co-amoxiclav (Paris et al. 2008)
  - azithromycin compared with levofloxacin (Pakhale et al. 2014)
  - a cephalosporin (cefuroxime or cefditoren) compared with co-amoxiclav (Maimon et al. 2008)
  - levofloxacin compared with ceftriaxone plus azithromycin (Raz-Pasteur et al. 2015).
- Some differences were seen for some efficacy outcomes for other antibiotic comparisons in adults with low-severity community-acquired pneumonia.
  - Amoxicillin improved clinical cure rates (in intention to treat analysis only) and complete resolution at 30 days, compared with phenoxymethylpenicillin (Llor et al. 2017).

  - Cefixime significantly reduced respiratory rate, radiological consolidations and bacterial isolates compared with ciprofloxacin, but there was no significant differences in temperature reduction or pulse rate (Ige et al. 2015).

Evidence for efficacy of antibiotics for low-severity community-acquired pneumonia in adults is based on 3 systematic reviews (Pakhale et al. 2014, Maimon et al. 2008 and Raz-Pasteur et al. 2015), 1 RCT (Ige et al. 2015) and 2 non-inferiority RCTs (Llor et al. 2017 and Paris et al. 2008).

***Moderate- to high-severity community-acquired pneumonia in adults***

- There were no differences in the clinical effectiveness of the following antibiotic comparisons (course length varied but usually ranged from 7 to 14 days) in adults with moderate- to high- severity community-acquired pneumonia:
  - a macrolide compared with antibiotics targeted at non-atypical pathogens (penicillins, beta-lactam plus beta-lactamase inhibitors, cephalosporins and carbapenems; Eliakim-Raz et al. 2012)
  - a fluoroquinolone compared with antibiotics targeted at non-atypical pathogens (penicillins, beta-lactam plus beta-lactamase inhibitors and cephalosporins; Eliakim-Raz et al. 2012)
  - levofloxacin compared with tigecycline (Nemeth et al. 2015)
  - levofloxacin compared with doxycycline (Nemeth et al. 2015)
  - ofloxacin compared with erythromycin (Skalsky et al. 2013)
  - moxifloxacin compared with levofloxacin (Yuan et al. 2012)
  - ertapenem compared with ceftriaxone (Bai Nan et al. 2014)
  - a macrolide compared with a beta-lactam antibiotic plus macrolide (Raz-Pasteur et al. 2015)
  - a fluoroquinolone compared with a beta-lactam antibiotic plus fluoroquinolone (Raz-Pasteur et al. 2015)
  - ceftriaxone plus azithromycin compared with ceftriaxone plus a macrolide (clarithromycin or erythromycin; Tamm et al. 2007)

  - ceftobiprole compared with ceftriaxone plus linezolid (in suspected methicillin-resistant *Staphylococcus aureus* (MRSA) infection (Nicholson et al. 2012).
- Some differences were seen for some efficacy outcomes for other antibiotic comparisons in adults with moderate- or high-severity community-acquired pneumonia:
  - Antibiotics targeted at atypical pathogens (macrolides and fluoroquinolones) compared with antibiotics targeted at non-atypical pathogens (penicillins, beta lactam plus beta-lactamase inhibitors, cephalosporins and carbapenems): overall there were no significant differences in mortality or clinical failure, but there was significantly less bacteriological failure with antibiotics targeted at atypical pathogens. Some minor differences were seen in subgroup analyses, including significantly lower clinical failure with antibiotics targeted at atypical pathogens in adults with *Legionella pneumophilia* infection (Eliakim-Raz et al. 2012).
  - Ceftriaxone compared with ceftaroline fosamil: there was no significant difference in mortality, but clinical cure was significantly increased with ceftriaxone (El Hajj et al. 2017).
  - A fluoroquinolone (levofloxacin or moxifloxacin) compared with a beta-lactam antibiotic plus macrolide: there were no significant differences in mortality or microbiological failure, but clinical failure was significantly reduced with a fluoroquinolone (result not significant in adults with pneumococcal pneumonia; Raz-Pasteur et al. 2015).
  - A beta-lactam antibiotic (co-amoxiclav or cefuroxime) plus upfront clarithromycin (upfront dual therapy) compared with a beta-lactam antibiotic (co-amoxiclav or cefuroxime) plus clarithromycin only when a positive *Legionella pneumophila* urine sample was confirmed (test-dependant dual therapy): there was no significant difference in mortality or clinical stability; in people with an atypical (but not non-atypical) infection, upfront dual therapy was significantly better for achieving clinical stability compared with test-dependant dual therapy; there were no significant differences in admission to intensive care, incidence of

complicated pleural effusion, length of hospital stay or long-term readmission rates.

Evidence for efficacy of antibiotics for moderate-to high-severity community-acquired pneumonia in adults is based on 7 systematic reviews (Eliakim-Raz et al. 2012, Nemeth et al. 2015, Skalsky et al. 2013, El Hajj et al. 2017, Yuan et al. 2012, Bai Nan et al. 2014 and Raz-Pasteur et al. 2015) and 4 non-inferiority RCTs (Garin et al. 2014, Nicholson et al. 2012 and Tamm et al. 2007).

***Non-severe community-acquired pneumonia in children and young people***

- Evidence (1 systematic review, Lodha et al. 2013) was identified on the following antibiotic comparisons (course length varied but usually ranged from 4 to 10 days) for treatment of non-severe community-acquired pneumonia, for which no significant differences were found for the efficacy outcomes reported:
  - azithromycin compared with erythromycin
  - azithromycin compared with co-amoxiclav
  - clarithromycin compared with erythromycin
  - co-trimoxazole compared with amoxicillin
  - cefpodoxime compared with co-amoxiclav
- For other antibiotic comparisons in children and young people with non-severe community-acquired pneumonia, some differences were seen in the following efficacy outcomes.
  - Co-amoxiclav was significantly better than amoxicillin for improving cure rate (94% versus 60%), and improving poor or no response rate (2% versus 20%) in children aged 2 to 12 years.
  - Amoxicillin was significantly better than chloramphenicol for improving cure rate in children aged 2 to 59 months.

***Severe community-acquired pneumonia in children and young people***

- Evidence (Lodha et al. 2013 unless otherwise stated) was identified on the following antibiotic comparisons for treatment (course length varied but

usually ranged from 3 to 10 days) of severe or very severe community-acquired pneumonia in children and young people, for which no significant differences were found for the outcomes reported:

  - amoxicillin compared with an unspecified penicillin
  - amoxicillin compared with ampicillin
  - amoxicillin compared with cefuroxime
  - amoxicillin compared with clarithromycin
  - levofloxacin compared with beta-lactam antibiotics (co-amoxiclav or ceftriaxone)
  - cefuroxime compared with clarithromycin
  - co-trimoxazole compared with chloramphenicol
  - ceftaroline fosamil compared with ceftriaxone (Cannavino et al. 2016).
  - benzylpenicillin plus gentamicin compared with co-amoxiclav
  - an unspecified penicillin plus chloramphenicol compared with ampicillin
  - benzylpenicillin plus chloramphenicol compared with chloramphenicol
  - an unspecified penicillin plus gentamicin compared with chloramphenicol
  - chloramphenicol plus an unspecified penicillin compared with ceftriaxone
  - ceftriaxone plus vancomycin compared with ceftaroline fosamil (Blumer et al. 2016).

- For other antibiotic comparisons in children and young people with severe community-acquired pneumonia, some differences were seen in the following efficacy outcomes
  - Ampicillin plus gentamicin was significantly better than chloramphenicol in children with very severe pneumonia, aged 2 to 59 months for clinical failure at all time points, but there was no significant difference in mortality. Significantly fewer children given ampicillin plus gentamicin needed to change antibiotics before day 21.
  - A penicillin (unspecified) plus gentamicin was not significantly different to chloramphenicol for mortality in children with severe community-acquired pneumonia, aged 1 to 59 months, but readmissions were significantly lower with a penicillin plus gentamicin.

Evidence for efficacy of antibiotics for severe community-acquired pneumonia in children and young people is based on 1 systematic review (Lodha et al. 2013) and 2 RCTs (Cannavino et al. 2016 and Blumer et al. 2016).

**Safety of antibiotics**

- Antibiotic-associated diarrhoea is estimated to occur in 2 to 25% of people taking antibiotics, depending on the antibiotic used (NICE CKS on 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 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).
- Macrolides should be used with caution in people with a predisposition to QT interval prolongation (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. This includes a recommendation to not use them for mild or moderately severe infections unless other antibiotics cannot be used.
- Fluoroquinolones may be associated with a small increased risk of aortic aneurysm and dissection, particularly in older people (MHRA Drug Safety Update, November 2018).
- Overall, adverse effects of antibiotics were similar in the studies, although some differences were seen for the following antibiotic comparisons in people with severe community-acquired pneumonia:
  - Adverse events were significantly higher with azithromycin compared with levofloxacin (19.9% versus 12.3%) and erythromycin compared with

clarithromycin (45.7% versus 21.4%; Pakhale et al. 2014), and abdominal pain was significantly worse with azithromycin compared with co-amoxiclav (9.6% versus 1.5%; Paris et al. 2008), in adults with low-severity community-acquired pneumonia.

  - Adverse events, treatment discontinuations and diarrhoea were significantly lower with a fluoroquinolone compared with beta-lactam antibiotic plus a macrolide in adults with moderate- to high-severity community-acquired pneumonia (Raz-Pasteur et al. 2015).
  - Adverse events were significantly lower with a macrolide compared with a beta-lactam antibiotic plus macrolide in adults with moderate- to high-severity community-acquired pneumonia (Raz-Pasteur et al. 2015).
  - Adverse events were significantly higher with ceftrobiprole compared with ceftriaxone plus linezolid in adults with suspected methicillin-resistant *Staphylococcus aureus* (MRSA) infection (Nicholson et al. 2012).
  - Adverse events were significantly lower with azithromycin compared with co-amoxiclav in children with non-severe community-acquired pneumonia (Lodha et al. 2013).
  - Significantly more children with severe community-acquired pneumonia had 1 or more adverse events with ceftriaxone plus vancomycin compared with ceftaroline fosamil (Blumer et al. 2016).

- See the summaries of product characteristics for information on contraindications, cautions, drug interactions and adverse effects of individual medicines.

**Committee discussions on choice of antibiotics**

- The committee noted that using the care setting as a proxy for the severity of community-acquired pneumonia may not always be appropriate, and that some studies in outpatients may include people with moderate-severity community-acquired pneumonia, or a mixed severity population. They recognised that hospital admission criteria in other countries may differ from UK practice.

- The committee discussed the pathogens which cause community-acquired pneumonia, and noted that *Streptococcus pneumoniae* is the most common cause. Based on their experience, the committee noted that atypical pathogens are the causative organism in around 10 to 15% of moderate- to high-severity infections.

***Adults with community-acquired pneumonia***

- The committee discussed the evidence on choice of antibiotics in adults with low-severity community-acquired pneumonia and in adults with moderate- to high-severity community-acquired pneumonia.
- The committee was aware that the CRB65 (in primary care) and CURB65 (in hospital) mortality risk scores are recommended in the NICE guideline on pneumonia for assessing the risk of mortality in adults with community-acquired pneumonia. The committee discussed evidence which used the pneumonia severity index (PSI) to assess severity, however, they agreed that CRB65 and CURB65 scores should be used in conjunction with clinical judgement to assess severity in adults, as this is current routine practice.
- Based on limited evidence showing no major differences in clinical effectiveness between antibiotics or classes of antibiotics, the committee agreed that the choice of antibiotic should largely be driven by their experience of which antibiotics have good activity against likely pathogens and cause the least harm, with as narrow spectrum as possible to minimise the risk of antimicrobial resistance.
- Based on their experience, the **first choice antibiotic** for adults with low-severity community-acquired pneumonia is **amoxicillin** (a penicillin), which has good activity against *Streptococcus pneumoniae* and is associated with fewer adverse effects and relatively low resistance rates. Amoxicillin is routinely used as first-line treatment and the committee agreed that there was no evidence to support changing current practice.
- **Alternative antibiotics** are **clarithromycin** (a macrolide), **erythromycin** (an alternative macrolide in pregnancy) and **doxycycline** (a tetracycline), for people with low-severity community-acquired pneumonia and

penicillin allergy, or when amoxicillin may not be appropriate, for example if an atypical infection is suspected. These antibiotics have good activity against *Streptococcus pneumoniae*, however due to their broader spectrum of activity (and because some of them also have additional safety warnings) the committee agreed that these antibiotics should be used only when there is a clinical reason not to use amoxicillin.

- Although evidence for doxycycline was not identified in people with low-severity community-acquired pneumonia, the committee agreed that evidence identified in hospitalised adults could include a mixed severity population. From their experience, the committee agreed that doxycycline is an appropriate choice as an alternative to a macrolide.
- From their experience, the committee agreed that although the available evidence does not differentiate between people with moderate-severity disease and those with high-severity disease, there is a clinical distinction between these groups which require different treatment options. Therefore, separate recommendations on antibiotic choice were made for moderate-severity and high-severity community-acquired pneumonia.
- The committee recognised that there was not clear evidence that the addition of a macrolide to amoxicillin was effective for treating adults with moderate- to high-severity community-acquired pneumonia, although this was current routine practice. However, the committee had concerns about the consistency and quality of the evidence identified.
- Based on their experience, the **first choice antibiotic** for adults with moderate-severity community-acquired pneumonia is **amoxicillin** (a penicillin), with the addition of a macrolide if atypical infection is suspected**.** Choices of macrolides are **clarithromycin** or **erythromycin** (in pregnancy). The committee based this decision on their experience of current practice, and because dual therapy with amoxicillin plus a macrolide provides broader spectrum of activity which is more likely to target atypical pathogens. In this population when the causative pathogen is not known, the risk of adverse effects and increased

antimicrobial resistance with dual therapy is likely to be outweighed by the clinical benefit.

- Based on their experience, the committee agreed that if dual therapy with amoxicillin plus a macrolide is given to people with moderate-severity community-acquired pneumonia, this should be reviewed when microbiological results are available. The macrolide can be stopped if an atypical infection is not isolated, due to the increased risk of resistance and adverse effects with dual therapy.
- **Alternative antibiotics** for adults with moderate-severity community-acquired pneumonia and penicillin allergy are **clarithromycin** or **azithromycin** (a macrolide) alone**.** This is based on the committee's experience that these antibiotics have good activity against *Streptococcus pneumoniae*, as well as other atypical infections. The committee noted that there are no reasonable alternatives for dual therapy in adults who are unable to take a penicillin, for example due to penicillin allergy.
- The committee noted that adults with high-severity community-acquired pneumonia will be managed in a high-dependency or an intensive care unit, and are easily distinguishable from adults with moderate-severity community-acquired pneumonia.
- The committee discussed evidence that fluoroquinolone monotherapy (levofloxacin or moxifloxacin) was as effective as beta-lactam plus macrolide dual therapy for people with moderate- to high-severity community-acquired pneumonia. However, they noted the safety concerns with fluoroquinolones, such as tendon damage and aortic aneurysm, and that the licence is restricted in community-acquired pneumonia, for use when other medicines cannot be prescribed or have been ineffective.
- Based on their experience, the **first choice antibiotic** for adults with high-severity community-acquired pneumonia is **co-amoxiclav** (a penicillin with a beta-lactamase inhibitor) **with clarithromycin** or **erythromycin** (in pregnancy). This provides broad spectrum gram negative cover, and the high risk of mortality in this population outweighs

the potential adverse effects and increased risk of antimicrobial resistance.

- The **alternative antibiotic** for adults with high-severity community-acquired pneumonia and penicillin allergy is **levofloxacin**. The committee recognised that *Legionella pneumophilia* infection is more common in this population and levofloxacin monotherapy would be an appropriate alternative. The committee agreed that the high risk of mortality without appropriate treatment in this population outweighed the safety concerns.

***Children and young people with community-acquired pneumonia***

- The committee was not aware of any validated severity assessment tools for children and young people with community-acquired pneumonia. Therefore, the severity of symptoms and signs should be assessed by clinical judgement.
- Based on the evidence identified and their experience, the committee agreed that it was appropriate to make separate recommendations for non-severe and severe community-acquired pneumonia.
- Given the specialist expertise needed for treatment of children under 3 months with community-acquired pneumonia, the committee agreed that these children should be managed by a paediatric specialist and treated with intravenous antibiotics in line with the NICE guideline on fever in under 5s.
- Overall, the committee agreed there was limited evidence relevant to UK practice, and that this evidence also had major limitations.
- Therefore, the committee agreed that the choice of antibiotics in children and young people should largely be driven by their experience of which antibiotics have good activity against likely pathogens and cause the least harm, with as narrow spectrum as possible to minimise the risk of antimicrobial resistance.
- The committee discussed evidence that co-amoxiclav was more effective than amoxicillin for children with non-severe community-acquired pneumonia. However, the committee noted that this was based on 1

small RCT within a systematic review, and a lower than expected response rate to amoxicillin was reported compared with other studies in children, which may have been due to sub-therapeutic dosing.

- Based on their experience, the **first choice antibiotic** for children and young people with community-acquired pneumonia and non-severe symptoms or signs is **amoxicillin**, which is effective against the most common causative pathogens and is well tolerated. The committee also recognised the clinical experience of the effectiveness of amoxicillin in children and young people, and its common use in current practice.
- **Alternative antibiotics** are **clarithromycin**, **erythromycin** (in pregnancy) and **doxycycline** (12 to 17 years only) for children and young people with non-severe symptoms or signs and penicillin allergy, or if amoxicillin is unsuitable (for example, if atypical pneumonia is suspected). These antibiotics have good activity against *Streptococcus pneumoniae*, however due to their broader spectrum of activity the committee agreed that these antibiotics should be used only when there is a clinical reason not to use amoxicillin.
- The committee highlighted that the evidence identified for children and young people with severe community-acquired pneumonia was conducted in low-income countries, where severe pneumonia may be more common. The committee was aware that children with severe community-acquired pneumonia in the UK will usually have underlying respiratory conditions. Therefore the evidence identified may not be directly relevant to UK practice.
- Based on their experience, the **first choice antibiotic** for children and young people with severe community-acquired pneumonia is **co-amoxiclav**, with the addition of **clarithromycin** or **erythromycin** (in pregnancy) if atypical infection is suspected. The committee discussed that children and young people with severe symptoms or signs are likely to be at higher risk of treatment failure with amoxicillin, and therefore need dual therapy to target a range of possible causative organisms, including atypical pathogens. In this population when the causative pathogen is not known, the risk of adverse effects and increased

antimicrobial resistance with dual therapy is likely to be outweighed by the clinical benefit.

- The committee agreed that children and young people with severe community-acquired pneumonia and penicillin allergy, is likely to be a small population and specialist microbiological advice should be sought.

***Safety netting for all people with community-acquired pneumonia***

- The committee recognised that community-acquired pneumonia is potentially a life-threatening infection and that a person's condition may change rapidly.
- The committee agreed that advice should be given to adults, young people and children about
  - the possible adverse effects of the antibiotic, and
  - about seeking medical help (if the person is being treated in the community) if symptoms worsen rapidly or significantly, do not start to improve within 3 days, or they become systemically very unwell.
- They agreed by consensus that adults, young people and children should be reassessed if symptoms or signs do not improve as expected or worsen rapidly or significantly. If symptoms or signs have not improved following antibiotic treatment, a respiratory sample should be sent for microbiological testing if this has not been done already. The committee were aware that obtaining a respiratory sample may not always be possible.
- The committee was aware of recommendations from NICE guidelines on pneumonia and sepsis that cover when to refer people to hospital.
- The committee agreed by consensus that adults with symptoms that are not improving as expected with antibiotics, or who have bacteria that are resistant to oral antibiotics should be referred to hospital if they are being treated in the community.
- The committee recognised that not all children and young people need to be managed in hospital, and referral should be based on clinical judgement as no evidence was identified. They agreed that community-acquired pneumonia is less common in children and young people, and

that referral to hospital or seeking specialist paediatric advice on further investigation and management should be considered.

- The committee also agreed by consensus that for adults, young people and children with community-acquired pneumonia who cannot take oral antibiotics, specialist advice should be sought, to explore locally available options for giving intravenous antibiotics at home or in the community, rather than in hospital, if this is appropriate.

## *Antibiotic dosage*

- Low-dose antibiotics were not significantly different from high-dose antibiotics for any clinical or bacteriological outcomes reported, in adults with low-severity community acquired pneumonia:
  - levofloxacin 500 mg once a day compared with levofloxacin 750 mg once a day; 1 non-inferiority RCT, Zhao et al. 2016).
  - co-amoxiclav 875/125 mg three times a day compared with co-amoxiclav 2000/125 mg twice a day, including in a subgroup analysis of adults with atypical pathogens, *S. pneumoniae* or *H. influenzae* infection (1 non-inferiority RCT, Siquier et al. 2006).
- Low-dose amoxicillin (45 mg/kg/day divided into 3 doses) was not significantly different to high-dose amoxicillin (90 mg/kg/day divided into 3 doses) for clinical improvement in young children (2 to 59 months) with non-severe community-acquired pneumonia (1 non-inferiority RCT, Hazir et al. 2007).
- Amoxicillin given twice a day (total 50 mg/kg/day) was not significantly different to amoxicillin given three times a day at the same dose (total 50 mg/kg/day) for clinical failure rates in young children (2 to 59 months) with non-severe community-acquired pneumonia (1 non-inferiority RCT, Vilas-Boas et al. 2014).
- Low-dose benzylpenicillin (200,000 IU/kg/day divided into 4 doses) was not significantly different to high-dose benzylpenicillin (400,000 IU/kg/day divided into 4 doses) for duration of hospital stay, duration of intravenous treatment or C-reactive protein levels in young children (3 months to 15

years) with severe community-acquired pneumonia (1 RCT, Amarilyo et al. 2014).

- No evidence from systematic reviews or RCTs was identified in adults with moderate- or high-severity community acquired pneumonia.

**Committee discussions on antibiotic dosage**

- Based on evidence showing no differences between low-dose and high-dose antibiotics, and their experience, the committee agreed that usual British National Formulary (BNF) doses for community-acquired pneumonia (or respiratory tract infections) should usually be used. However, they recognised the importance of consulting BNF, BNF for children and MHRA advice for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding, and for information on administering intravenous antibiotics.
- The committee noted that no evidence was identified in adults with moderate- or high-severity community-acquired pneumonia, and only 1 small RCT in young children with severe community-acquired pneumonia was identified. Based on their experience and the higher risk of mortality in people with a severe infection, the committee agreed that where a range of doses are given, the higher dose is appropriate for these people.
- Based on clinical experience and evidence in adults with low-severity community-acquired pneumonia that high-dose erythromycin is associated with more adverse effects, the committee agreed that the usual BNF dose for erythromycin should be used when this is recommended as an option for women and young women aged 8 years and over who are pregnant.

## *Antibiotic course length*

- Short-course antibiotics (3 to 7 days) were not significantly different to long-course antibiotics (10 to 14 days) for mortality or clinical failure in

adults with low- to moderate-severity community-acquired pneumonia (1 systematic review, Li et al. 2007).

- Short-course amoxicillin (3 days) was not significantly different to long-course amoxicillin (8 days) for clinical cure, bacteriological or radiological success, and length of hospital stay, in adults with low- to moderate-severity community-acquired pneumonia (1 RCT, El Moussaoui et al. 2006).
- Short-course antibiotics (amoxicillin or co-trimoxazole for 3 days) were not significantly different to a 5 day course of the same antibiotic for clinical cure or relapse, in young children (2 to 59 months) with non-severe community-acquired pneumonia. The same results were seen when amoxicillin and co-trimoxazole were analysed separately (1 systematic review, Haider et al. 2011).
- Short-course amoxicillin (3 days) was significantly worse than a 10 day course of amoxicillin (at the same dose) for treatment failure (4/10 versus 0/56) in young children (6 to 59 months) with non-severe community-acquired pneumonia (1 RCT, Greenberg et al. 2014).
- Short-course amoxicillin (5 days) was not significantly different to a 10 day course of amoxicillin (at the same dose) for treatment failure in young children (6 to 59 months) with non-severe community-acquired pneumonia. However, C-reactive protein at day 5 to 7 was significantly worse with the 5 day course (1 RCT, Greenberg et al. 2014).
- No evidence from systematic reviews or RCTs was identified in adults or children with severe community-acquired pneumonia.

**Committee discussions on antibiotic course length**

- The committee agreed that the shortest course that is likely to be effective should be prescribed to reduce the risk of antimicrobial resistance and minimise the risk of adverse effects. However, an effective course length is important in community-acquired pneumonia as this can be a life-threatening infection.
- The committee discussed evidence for antibiotic course length in adults, young people and children with community-acquired pneumonia. Overall,

there did not appear to be major differences between short- and long-course antibiotics, but they noted some inconsistency in the evidence for adults and children. They were also aware that no evidence was identified in children and young people with severe community-acquired pneumonia.

- The committee agreed that there were several limitations which reduced the applicability of the evidence to UK practice (for example, evidence on antibiotic comparisons not recommended or available in the UK, or a lack of critical outcome reporting).
- The committee noted the Uranga et al. (2016) study carried out in adults, which found that antibiotics given for a minimum of 5 days, with a strategy of stopping treatment if fever was absent for 48 hours, and there was no more than 1 associated sign of clinical instability, was not different to usual physician's practice (see committee discussion on antibiotic prescribing strategies).
- Based on their experience and the risks of antimicrobial resistance with longer courses, the committee agreed by consensus that a 5 day course of recommended antibiotics was appropriate to treat community-acquired pneumonia for adults, young people and children. The only exception to this is azithromycin in adults, for which a 3-day course is appropriate because of its long half-life.
- However, the committee did recognise that in some individual circumstances a longer course may be required. In adults, they agreed that antibiotic treatment should be stopped at 5 days (3 days for azithromycin) unless the person is not clinically stable (based on clinical judgement, taking account of the presence of fever within 48 hours blood pressure, heart rate, respiratory rate and oxygen saturations).
- In children and young people, no evidence on specific review criteria was identified, therefore the committee agreed by consensus that antibiotic treatment should be stopped after 5 days unless the person is not clinically stable, based on clinical judgement.

- The committee could not determine an upper limit on antibiotic course length, as this will be determined in individual circumstances, based on time taken to reach clinical stability.

## *Antibiotic route of administration*

- Intravenous antibiotics with switch to oral antibiotics after 2 to 4 days if there was clinical improvement was not significantly different to continuous intravenous antibiotics for mortality, treatment success, or recurrence of infection in adults with moderate- to high severity community-acquired pneumonia. However, there were significantly fewer days in hospital and adverse events with the switch to oral antibiotics (1 systematic review, Athanassa et al. 2008).
- Oral antibiotics (amoxicillin or co-trimoxazole) were not significantly different to injectable penicillins for clinical failure rate in children and young people (1 month to 18 years) with non-severe community-acquired pneumonia (1 systematic review, Lodha et al. 2013).
- Oral antibiotics (amoxicillin or co-trimoxazole) were significantly better than injectable penicillins for mortality (0.05% versus 0.56%), in children and young people (3 months to 18 years) with severe community-acquired pneumonia. However, there were no significant differences in the rates of cure, clinical failure, hospitalisation or relapse, including when oral amoxicillin was analysed separately (Lodha et al. 2013).

**Committee discussions on antibiotic route of administration**

- The committee discussed evidence on route of administration, which found that oral antibiotics (or intravenous antibiotics with switch to oral antibiotics) are as effective as continuous intravenous antibiotics for adults, young people and children with community-acquired pneumonia.
- Based on this evidence and taking account of the principles of antimicrobial stewardship, the committee agreed that oral antibiotics should be given first-line for most people, unless they cannot take oral

medicines (for example if they are vomiting), or the severity of infection means that intravenous antibiotics are required.

- For people with non-severe symptoms or signs, intravenous antibiotics may be required if the person is unable to take oral medicines.
- In line with the NICE guideline on antimicrobial stewardship and Start smart – then focus, the committee agreed that if intravenous antibiotics are used initially, this 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.

# Other considerations

## *Medicines adherence*

- Medicines adherence may be a problem for some people taking antibiotics that need frequent dosing or longer treatment duration. See the NICE guideline on medicines adherence.

## *Resource implications*

- Recommended antibiotics are all available as generic formulations, see Drug Tariff for costs.

See the evidence review for more information.