### Indication
| Bacterial pneumonia | ICD11 code: CA40.0Z |

### INN
- Doxycycline

### Medicine type
- Chemical agent

### Antibiotic groups
- ACCESS

### List type
- Core

### Formulations
- Oral > Liquid: 25 mg per 5 mL (anhydrous) (EMLc); 50 mg per 5 mL (anhydrous) (EMLc)
- Oral > Solid: 50 mg (as hyclate) (EMLc); 100 mg (as hyclate)
- Parenteral > General injections > unspecified: 100 mg in vial powder for injection

### EML status history
- First added in 2017 (TRS 1006)

### Sex
- All

### Age
- Also recommended for children

### Age restriction
- Use in children under 8 years of age only for life-threatening infections when no alternatives exist.

### Therapeutic alternatives
- The recommendation is for this specific medicine

### Patent information
- Patents have expired in most jurisdictions
- Read more about patents.

### Wikipedia
- Doxycycline

### DrugBank
- Doxycycline

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### Expert Committee recommendation

The Expert Committee endorsed the inclusion of amoxicillin and phenoxymethylpenicillin as first-choice therapy options and of amoxicillin + clavulanic acid or doxycycline as second-choice therapy in mild to moderate CAP. For severe CAP in adults, the Expert Committee endorsed the inclusion of ceftriaxone or cefotaxime in combination with clarithromycin (EML) as first-choice and amoxicillin + clavulanic acid in combination with clarithromycin as second-choice therapy. For severe CAP in children, the Expert Committee endorsed the inclusion of amoxicillin + clavulanic acid; ceftriaxone or cefotaxime (EMLc); and gentamicin in combination with benzylpenicillin, ampicillin or amoxicillin (EMLc).

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### Background

Community-acquired pneumonia (CAP) refers to pneumonia that is acquired in the community rather than within the health-care system. Patients of advanced age or with comorbid conditions or greater severity of illness are more likely to be hospitalized. Although there is consensus that Streptococcus pneumoniae is the most common bacterial cause of CAP, the need for so-called "atypical coverage" of pathogens such as Chlamydia pneumoniae, Mycoplasma or Legionella with antibiotics such as macrolides or fluoroquinolones has been controversial. The emergence of macrolide and fluoroquinolone resistance in the community has created concern, and the need for these medicines in addition to antibiotics with antipneumococcal coverage has been debated. The following summary considers the CAP syndrome review conducted by the McMaster Group, and the review of CAP guidelines for paediatrics conducted by the WHO Department of Maternal, Newborn, Child and Adolescent Health.
Adult outpatient therapy

A 2014 Cochrane review covering 11 randomized controlled trials (RCTs) of 3352 participants older than 12 years with a diagnosis of CAP reported that, for outpatients, there was no advantage of one antibiotic over another for efficacy when the comparison was either between fluoroquinolones and macrolides or between different macrolides (1). However, there were substantially fewer adverse events with clarithromycin than with erythromycin (odds ratio (OR) 0.3; 95% confidence interval (CI) 0.2–0.46). The application therefore did not propose erythromycin for inclusion on the EML for this indication. Among 423 patients, substantially more adverse events with azithromycin (42/211) than with levofloxacin (26/212) (OR 1.78; 95% CI 1.04 to 3.03) (1). Although adverse events such as nausea and vomiting are not in themselves life-threatening, they can have an important impact on adherence. There was no comparison of clarithromycin with levofloxacin. Given these adverse effects, and the fact that the U.S. Food & Drug Administration (FDA) has warned about fatal cardiovascular events (2), the application did not propose azithromycin for inclusion on the EML for this indication. A review of 16 RCTs (4989 patients), which mostly assessed outpatients with mild to moderate CAP, found no difference in mortality between those treated with macrolides and those given fluoroquinolones (risk ratio (RR) 1.03: 95% CI 0.63–1.68), although gastrointestinal adverse events were more common with macrolides (3). The wide confidence intervals do not exclude a clinically important effect, however, and the findings therefore do not help in differentiating between these antibiotic classes. Adult inpatient therapy

The severity of illness and concerns about complications mean that the approach to hospitalized patients differs from that to outpatients. Coverage for atypical pathogens has been a source of controversy. A 2012 Cochrane review (28 RCTs; 5939 participants) of empirical therapy for CAP in hospitalized adults showed that atypical coverage offered no additional benefit compared with typical coverage in reducing deaths (4): there was no difference between groups for mortality (RR 1.14; 95% CI 0.84–1.55). However, only one study compared a beta-lactam with a beta-lactam plus a macrolide. The width of the confidence intervals exceeds that specified by the applicants for similarity (i.e. within 5%) and these results therefore do not contribute to antibiotic selection. Although there was no difference in overall adverse events between the groups, gastrointestinal events were less common in the atypical group (RR 0.70; 95% CI 0.53–0.92). A 2015 review (16 RCTs; 4809 participants) reported no difference in mortality between fluoroquinolones and beta-lactam/macrolide combinations (RR 0.99; 95% CI 0.70–1.40), but wide confidence intervals limited inferences (5). However, a reduction in clinical failure with fluoroquinolones was reported (RR 0.72; 95% CI 0.57–0.91). Overall, while these findings may be useful in helping clinicians to select antibiotics, the large number of antibiotics being compared was not considered by the applicants to be helpful for informing selection of antibiotics for the EML. The lack of additional benefit of atypical antimicrobials in patients with CAP with mild to moderate illness was also demonstrated in a recent non-inferiority cluster RCT (6). The trial randomized patients to beta-lactams, a combination of beta-lactams and atypical antibiotics, or to fluoroquinolones. The 90-day mortality was 9.0%, 11.1% and 8.8%, respectively. Compared to the beta-lactam strategy, the risk differences (RD) for 90-day mortality were 1.9% (90% CI –0.6 to 4.4) with the beta-lactam/macrolide strategy and –0.6% (90% CI –2.8 to 1.9) with the fluoroquinolone strategy. The results indicated non-inferiority of the beta-lactam strategy. These data are of particular relevance, because it does not appear that adding atypical antibiotics to beta-lactam antibiotics makes a clinically important difference, at least for patients presenting with mild to moderate CAP. Whether atypical coverage is required for CAP has been an important concern; another question is whether there is a difference between fluoroquinolones and macrolides. A review of five RCTs for inpatients addressed this question and reported no difference between fluoroquinolones and macrolides for mortality (RR 1.13; 95% CI 0.65–1.98) (7). The confidence intervals are relatively wide and the results do not allow either protection or harm from fluoroquinolones compared with macrolides to be inferred. Children A 2013 Cochrane review of antibiotics within an outpatient or hospital setting (29 RCTs; 14 188 children) showed that cure rates with amoxicillin were similar to those with sulfamethoxazole + trimethoprim (SMX–TMP) (odds ratio (OR) 1.03; 95% CI 0.56–1.89) (8). In this review, “cure” referred to an absence of symptoms at the end of treatment, “failure” was the presence of a sign at the end of treatment, and “relapse” was defined as recurrence of disease in follow-up of a patient after cure. Given the wide confidence intervals (i.e. >10%), these data were not considered by the applicants to inform the proposal of antibiotics for the EML. Amoxicillin resulted in better cure rates than amoxicillin + clavulanic acid (RR 10.44; 95% CI 0.29–38.2), suggesting that amoxicillin alone may be preferred. Failure rate at 21 days was greater for chloramphenicol compared with ampicillin and gentamicin (OR 1.43; 95% CI 1.03–1.98). The applicants considered that this important evidence supported non-inclusion of chloramphenicol on the EML and inclusion of ampicillin and gentamicin. Cure rate was significantly greater for amoxicillin compared with cefpodoxime (OR 0.20; 95% CI 0.08–0.53), which argues for the inclusion of amoxicillin and against the inclusion of oral third-generation cephalosporins on the EML. Another systematic review examined antibiotic therapy for pneumonia in children in low- and middle-income countries. The pooled estimate of two studies involving...
Proposed antibiotics for CAP were based on evidence from systematic reviews and are similar to recommendations in clinical practice guidelines – with the exception of azithromycin, which is not proposed for the EML because of safety concerns reported by the FDA (2). The applicants stated that, although no systematic review evidence was found for vancomycin, its inclusion for empirical therapy when MRSA is suspected, as suggested by the guidelines, was reasonable. To minimize the occurrence of antibiotic resistance, and taking into consideration efficacy, safety, cost and availability, the application proposed the use of amoxicillin, amoxicillin + clavulanic acid, or phenoxymethylpenicillin as first-line empirical (core) therapy for mild to moderate CAP. The BTS guidelines recommend doxycycline as an alternative first-line to macrolides as well as ceftriaxone or ampicillin + sulbactam for patients in intensive care. The BTS guidelines recommend amoxicillin as first choice for oral antibiotic therapy in children and propose amoxicillin + clavulanic acid, cefaclor, erythromycin, azithromycin and clarithromycin as alternatives (12). They suggest that macrolide antibiotics may be added at any age if there is no response to first-line empirical therapy or if either Mycoplasma or Chlamydia pneumonia is suspected or in very severe disease. They recommend amoxicillin + clavulanic acid for pneumonia associated with influenza. The WHO Department of Maternal, Newborn, Child and Adolescent Health reviewed its existing guidelines for treatment of CAP in children. This undertaking was informed by a systematic review of the current evidence of efficacy, safety and feasibility of antibiotic treatment options. Following expert consultation, the following recommendations were made with regard to antibiotic treatment of pneumonia in children: • Fast breathing pneumonia: amoxicillin oral liquid or tablets, at least 40 mg/kg twice daily (80 mg/kg per day) x 5 days; in areas with low HIV prevalence, oral amoxicillin for 3 days. • Severe pneumonia: - first-line: IM/IV ampicillin 50 mg/kg or benzylpenicillin injection 50 000 units/kg, every 6 hours for at least 5 days and IM/IV gentamicin, 7.5 mg/kg once a day for at least 5 days; - second-line: IV ceftriaxone. For HIV-infected individuals, 10 days’ therapy is recommended.

**Rationale for antibiotic selection**

Proposed antibiotics for CAP were based on evidence from systematic reviews and are similar to recommendations in clinical practice guidelines – with the exception of azithromycin, which is not proposed for the EML because of safety concerns reported by the FDA (2). The applicants stated that, although no systematic review evidence was found for vancomycin, its inclusion for empirical therapy when MRSA is suspected, as suggested by the guidelines, was reasonable. To minimize the occurrence of antibiotic resistance, and taking into consideration efficacy, safety, cost and availability, the application proposed the use of amoxicillin, amoxicillin + clavulanic acid, or phenoxymethylpenicillin as first-line empirical (core) therapy for mild to moderate CAP. “Targeted” antibiotics were defined in the application as those necessary in cases of more severe illness, when alternatives to first-line options are required (e.g. penicillin allergy), and in specific situations where the likelihood of a particular organism warrants use. Intravenous formulations such as benzylpenicillin, cefotaxime or ceftriaxone are proposed for inclusion on the EML as targeted antibiotics for severe CAP. Doxycycline is targeted since it an alternative to first-line antibiotics. In settings where melioidosis is
Committee considerations

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. The Expert Committee considered the antibiotics proposed in the application and selected first- and second-choice antibiotics for community-acquired pneumonia, in line with WHO guidelines, for inclusion on the EMLc. The Committee considered the various antibiotics proposed in the application from the McMaster Group using the guiding principle of parsimony and selected first- and second-choice antibiotics for this indication for inclusion on the EML. Piperacillin + tazobactam, levofloxacin, vancomycin and ceftazidime were excluded. Recommended first- and second-choice antibiotics are reported above. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents.

EML recommendations: Bacterial pneumonia

**First choice**

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<tr>
<th><strong>COMMUNITY-ACQUIRED PNEUMONIA - MILD TO MODERATE</strong></th>
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<tbody>
<tr>
<td>amoxicillin</td>
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<td>phenoxybenzylpenicillin</td>
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<tr>
<th><strong>COMMUNITY-ACQUIRED PNEUMONIA - SEVERE [CHILDREN]</strong></th>
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<tr>
<td>amoxicillin co-prescribed with gentamicin</td>
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<tr>
<td>cefotaxime</td>
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<tr>
<td>ampicillin co-prescribed with gentamicin</td>
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<tr>
<td>benzylpenicillin co-prescribed with gentamicin</td>
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<tr>
<td>ceftriaxone</td>
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<td>amoxicillin + clavulanic acid</td>
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**Second choice**

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<thead>
<tr>
<th><strong>COMMUNITY-ACQUIRED PNEUMONIA - SEVERE</strong></th>
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<tbody>
<tr>
<td>doxycycline</td>
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<tr>
<td>amoxicillin + clavulanic acid</td>
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cefotaxime co-prescribed with clarithromycin
ceftriaxone co-prescribed with clarithromycin
amoxicillin + clavulanic acid co-prescribed with clarithromycin