

The Medical Letter[®]

on Drugs and Therapeutics

Volume 63

January 25, 2021

ISSUE No.
1616

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The Medical Letter®

on Drugs and Therapeutics

Volume 63 (Issue 1616)

January 25, 2021

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▶ Antibacterial Drugs for Community-Acquired Pneumonia

Treatment of community-acquired pneumonia (CAP) is usually empiric, with selected antibiotic regimens directed against some of the most common causative pathogens. Recommended empiric regimens are listed in Table 2; recommended antibiotic dosages for treatment of CAP are listed in Tables 3 and 4. Joint guidelines for treatment of CAP by the American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) were updated in 2019.¹

BACTERIAL PATHOGENS – The organisms responsible for CAP are often not identified, but *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and “atypical” organisms (*Mycoplasma pneumoniae*, *Legionella* species, and *Chlamydomphila pneumoniae*) have traditionally been the most common causative bacterial pathogens. In the US, pneumococcal vaccination has substantially reduced the rates of respiratory and other infections caused by *S. pneumoniae*.²

Methicillin-resistant *S. aureus* (MRSA) and resistant gram-negative organisms, such as *Pseudomonas aeruginosa*, can cause CAP. Patients with previous respiratory isolation of one of these pathogens and/or recent hospitalization and parenteral antibiotic treatment are at increased risk.¹

INFLUENZA AND COVID-19 – Influenza and SARS-CoV-2 can also cause CAP. While these viruses are circulating in the community, patients with symptoms of acute respiratory illness should be tested for both viruses and receive appropriate treatment based on test results, risk of complications, and severity of illness.³⁻⁵ If secondary bacterial pneumonia is suspected, empiric antibiotic therapy should be started.⁶

TREATMENT OF OUTPATIENTS – For outpatient treatment of CAP in otherwise healthy adults **without comorbidities** (chronic heart, lung, liver or renal disease, diabetes, alcoholism, malignancy, or asplenia), current guidelines recommend oral treatment with high-dose

Table 1. CAP-Related Spectrum of Activity for Some Antibiotics

Cephalosporins (cefepodoxime, cefuroxime, cefotaxime, ceftriaxone, ceftazidime)
▶ <i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i> (not MRSA), <i>Moraxella catarrhalis</i> , <i>Haemophilus influenzae</i>
▶ Ceftazidime is also active against MRSA and ceftriaxone-resistant <i>S. pneumoniae</i>
▶ No activity against atypical pathogens ¹
Fluoroquinolones (levofloxacin, moxifloxacin, gemifloxacin, delafloxacin)
▶ <i>S. pneumoniae</i> , <i>S. aureus</i> (not MRSA), <i>M. catarrhalis</i> , <i>H. influenzae</i> , and atypical pathogens ¹
▶ Delafloxacin has activity against MRSA
Macrolides (azithromycin, clarithromycin)
▶ <i>H. influenzae</i> and atypical pathogens ¹
▶ High rate of <i>S. pneumoniae</i> resistance in the US
Penicillins (amoxicillin, amoxicillin/clavulanate, ampicillin/sulbactam)
▶ <i>S. pneumoniae</i>
▶ Amoxicillin/clavulanate and ampicillin/sulbactam are active against <i>H. influenzae</i> strains that produce β -lactamase
▶ No activity against atypical pathogens ¹
Doxycycline
▶ <i>S. pneumoniae</i> (resistance rates rising in US)
▶ <i>S. aureus</i> , <i>H. influenzae</i> , <i>M. catarrhalis</i> , and atypical pathogens ¹
MRSA = methicillin-resistant <i>Staphylococcus aureus</i>
1. Atypical pathogens: <i>Legionella</i> species, <i>Mycoplasma pneumoniae</i> , <i>Chlamydomphila pneumoniae</i> (formerly <i>Chlamydia pneumoniae</i>).

amoxicillin (1 g tid) or doxycycline (see Table 2). For many years, monotherapy with an oral macrolide such as azithromycin was a regimen of choice for treatment of CAP, but the rate of macrolide-resistant *S. pneumoniae* is now >40% in many areas in the US; current guidelines recommend that oral macrolide monotherapy be considered only in areas where pneumococcal resistance rates to macrolides are <25%.¹ High-dose amoxicillin monotherapy provides coverage against *S. pneumoniae*, but it has no activity against atypical pathogens; some experts would add a macrolide or doxycycline if infection with an atypical pathogen is suspected.

For outpatient treatment of CAP in adults **with comorbidities** (chronic heart, lung, liver or renal disease, diabetes, alcoholism, malignancy, or

asplenia), oral treatment with a combination of a beta-lactam (amoxicillin/clavulanate, cefpodoxime, or cefuroxime) and a macrolide (azithromycin, clarithromycin) or doxycycline is recommended. Monotherapy with an oral respiratory fluoroquinolone (gemifloxacin, levofloxacin, or moxifloxacin) is another option. Patients with comorbidities, who are more likely to have had healthcare system encounters and previous antibiotic exposure, are at increased risk of infection with resistant pathogens including *H. influenzae*, *M. catarrhalis*, *S. aureus* (including MRSA), and gram-negative bacilli. Patients recently treated with an antibiotic from one of the classes included in the above regimens should receive an antibiotic from a different class.¹

TREATMENT OF HOSPITALIZED PATIENTS — In patients who are hospitalized for **nonsevere** CAP, empiric treatment with a combination of an IV beta-lactam (ampicillin/sulbactam, ceftriaxone, cefotaxime, or ceftaroline) and an IV or oral macrolide (azithromycin, clarithromycin) or monotherapy with an IV or oral respiratory fluoroquinolone (levofloxacin, moxifloxacin) is recommended. In patients who cannot take a macrolide or a fluoroquinolone, an IV beta-lactam plus IV or oral doxycycline is an alternative.

In patients who are hospitalized for **severe** CAP and do not have risk factors for infection with *P. aeruginosa* (or other resistant gram-negative pathogens) or MRSA, empiric treatment with an IV beta-lactam (ampicillin/sulbactam, cefotaxime, ceftriaxone, or ceftaroline) plus either an IV macrolide (azithromycin) or an IV respiratory fluoroquinolone (levofloxacin, moxifloxacin) is recommended.

MRSA AND OTHER RESISTANT PATHOGENS — Hospitalized patients with CAP who have risk factors for infection with MRSA or resistant gram-negative organisms such as *P. aeruginosa* may be treated empirically for such pathogens in addition to standard empiric treatment. For empiric coverage of MRSA, IV vancomycin or linezolid can be added to a recommended empiric regimen (see Table 2). For empiric coverage of *P. aeruginosa* and other gram-negative pathogens, a broad-spectrum IV beta-lactam that is also effective against *S. pneumoniae*, such as piperacillin/tazobactam or cefepime, or a carbapenem, such as imipenem, can be used. The regimen should also include an agent with activity against *Legionella* species and other atypical organisms, such as a respiratory fluoroquinolone. Cultures and/or nasal PCR should be performed to confirm the need for continued treatment.

Table 2. Empiric Antibiotic Regimens for CAP¹⁻³

Outpatients	
Without comorbidities⁴	
▶	Oral high-dose amoxicillin ⁵
▶	Oral doxycycline ⁵
With comorbidities⁴	
▶	An oral beta-lactam (amoxicillin/clavulanate, cefpodoxime, cefuroxime) PLUS an oral macrolide (azithromycin, clarithromycin)
▶	An oral beta-lactam (amoxicillin/clavulanate, cefpodoxime, cefuroxime) PLUS oral doxycycline
▶	Oral respiratory fluoroquinolone monotherapy ⁶ (levofloxacin, moxifloxacin, gemifloxacin)
Hospitalized Patients	
Nonsevere^{7,8}	
▶	An IV beta-lactam (ampicillin/sulbactam, cefotaxime, ceftriaxone, ceftaroline) PLUS a macrolide (IV/PO azithromycin, PO clarithromycin)
▶	An IV or oral respiratory fluoroquinolone monotherapy ⁶ (levofloxacin, moxifloxacin)
▶	An IV beta-lactam (ampicillin/sulbactam, cefotaxime, ceftaroline, ceftriaxone) PLUS IV/PO doxycycline ⁹
Severe^{7,8,10}	
▶	An IV beta-lactam (ampicillin/sulbactam, cefotaxime, ceftriaxone, ceftaroline) PLUS a macrolide (IV azithromycin)
▶	An IV beta-lactam (ampicillin/sulbactam, cefotaxime, ceftriaxone, ceftaroline) PLUS an IV respiratory fluoroquinolone ⁶ (levofloxacin, moxifloxacin)

1. JP Metlay et al. Am J Respir Crit Care Med 2019; 200:e45.

2. See Tables 3 and 4 for CAP-specific dosage recommendations.

3. Omadacycline, a new tetracycline, and lefamulin, a new pleuromutilin, are FDA-approved for treatment of CAP, but data on their use are limited. Current guidelines do not recommend either of these drugs for routine empiric treatment.

4. Chronic heart, lung, liver or renal disease, diabetes, alcoholism, malignancy, or asplenia.

5. An oral macrolide (azithromycin, clarithromycin) is an alternative if local pneumococcal resistance rates are <25%.

6. Gemifloxacin has a high rate of rash; Medical Letter reviewers prefer levofloxacin or moxifloxacin. Delafloxacin, a newer PO/IV fluoroquinolone antibiotic FDA-approved for treatment of CAP, is an alternative.

7. Addition of vancomycin or linezolid should be considered for patients with prior respiratory isolation of methicillin-resistant *Staphylococcus aureus* (MRSA), or in those who have been hospitalized and treated with IV antibiotics within the previous 90 days.

8. Piperacillin/tazobactam, cefepime, imipenem, or meropenem can be used as the beta-lactam for coverage of *P. aeruginosa* or some other resistant gram-negative pathogens in patients with prior respiratory isolation of one of these pathogens or for those who have been hospitalized and treated with IV antibiotics within the previous 90 days.

9. Option for patients with contraindications to both macrolides and fluoroquinolones.

10. Defined as septic shock requiring vasopressors, respiratory failure requiring mechanical ventilation, or ≥ 3 of the following: respiratory rate ≥ 30 breaths/minute, $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 250 , multilobar infiltrates, confusion or disorientation, uremia, leukopenia, thrombocytopenia, hypothermia, or hypotension requiring aggressive fluid resuscitation.

ADVERSE EFFECTS — **Beta-lactam antibiotics** (penicillins and cephalosporins) can cause rash, diarrhea, nausea, vomiting, allergic reactions, hemolytic anemia, neutropenia, cholestatic hepatitis, serum sickness, and seizures.

Doxycycline can cause GI disturbances and photosensitivity. Use in children <8 years old can inhibit bone growth and cause permanent discoloration of teeth and enamel hypoplasia.

Table 3. Dosage and Cost of Some Oral Antibiotics for Empiric Treatment of CAP in Outpatients

Drug	Some Formulations	Usual Adult Dosage ¹	Cost ²
Cephalosporins			
Cefpodoxime proxetil – generic	100, 200 mg tabs	200 PO mg bid	\$64.90
Cefuroxime axetil – generic	250, 500 mg tabs	500 PO mg bid	21.40
Fluoroquinolones			
Delafloxacin – <i>Baxdela</i> (Melinta)	450 mg tabs	450 mg PO bid	726.50
Gemifloxacin – <i>Factive</i> (Oscient)	320 mg tabs	320 mg PO once/day	199.30
Levofloxacin – generic	250, 500, 750 mg tabs; 25 mg/mL soln	750 mg PO once/day	4.30
Moxifloxacin – generic	400 mg tabs	400 mg PO once/day	36.90
Macrolides			
Azithromycin – generic <i>Zithromax</i> (Pfizer)	250, 500, 600 mg tabs; 100, 200 mg/5 mL susp 250, 500 mg tabs; 100, 200 mg/5 mL susp	500 mg PO on day 1, then 250 mg once/day ³	8.30 12.80
Clarithromycin – generic extended-release – generic	250, 500 mg tabs; 125, 250 mg/5 mL susp 500 mg ER tabs	500 mg PO bid 1000 mg PO once/day	28.00 62.80
Pleuromutilin			
Lefamulin – <i>Xenleta</i> (Nabriva)	600 mg tabs	600 mg PO bid	1375.00
Penicillins			
Amoxicillin – generic	500, 875 mg tabs; 250, 500 mg caps; 125, 250 mg chew tabs; 125, 200, 250, 400 mg/5 mL susp	1 g PO tid	5.10
Amoxicillin/clavulanate – generic	250, 500, 875/125 mg tabs; 200/28.5 mg, 400/57 mg chew tabs; 200/28.5 mg/5 mL, 250/62.5 mg/5 mL, 600/42.9 mg/5 mL, 400/57 mg/5 mL susp	500/125 mg PO tid or 875/125 mg bid	18.60
extended-release – generic	1000/62.5 mg ER tabs	2000/125 mg PO bid	67.00
Tetracyclines			
Doxycycline – generic <i>Vibramycin</i>	50, 75, 100 mg tabs, caps; 25 mg/5 mL susp	100 mg PO bid	9.40 9.00
Omadacycline – <i>Nuzyra</i> (Paratek)	150 mg tabs	300 mg PO once/day	2167.10

ER = extended release; soln = solution; susp = suspension

1. Dosage adjustments may be needed for renal or hepatic impairment.

2. Approximate WAC for 5 days' treatment at the lowest usual adult dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. January 5, 2021. Reprinted with permission by First Databank, Inc. All rights reserved. ©2021. www.fdbhealth.com/policies/drug-pricing-policy.

3. Dosage for outpatients. Recommended dosage for hospitalized patients is 500 mg once daily.

Azithromycin and **clarithromycin** can cause GI disturbances, headache, dizziness, vaginitis, and QT-interval prolongation. Clarithromycin can also cause dysgeusia and hepatic enzyme elevations. The FDA has warned that use of clarithromycin may increase the risk of cardiovascular morbidity and mortality in patients with heart disease.⁷

Fluoroquinolones can cause GI disturbances, tremors, rash, oral and vaginal *Candida* infections, eosinophilia, neutropenia, leukopenia, increased aminotransferase and serum creatinine levels, insomnia, photosensitivity reactions, and peripheral neuropathy. They have also been associated with hyperglycemia and severe hypoglycemia, especially in older adults and in patients with diabetes. Central nervous system effects including seizures, delirium, agitation, nervousness, and disturbances in attention, memory, and orientation have occurred. Other serious

adverse effects include tendinitis, tendon rupture, aortic aneurysm, exacerbation of myasthenia gravis, *Clostridioides difficile*-associated diarrhea, and (except for delafloxacin) QT-interval prolongation and torsades de pointes.⁸

DRUG INTERACTIONS – Coadministration of antacids or products containing calcium, magnesium, or iron can decrease absorption of **doxycycline** and **fluoroquinolones**. Administration should be separated by several hours.

Concurrent use of **azithromycin**, **clarithromycin**, or **fluoroquinolones** with other QT-interval-prolonging drugs can result in additive effects.⁹

Use of **fluoroquinolones** with antihyperglycemic drugs may increase the risk of hypoglycemia. Concurrent use of fluoroquinolones and nonsteroidal anti-inflammatory drugs (NSAIDs) may lower the seizure threshold.

Table 4. Dosage and Cost of Some IV Antibiotics for Empiric Treatment of CAP in Hospitalized Patients

Drug	Some Formulations	Usual Adult Dosage ¹	Cost ²
Cephalosporins			
Cefotaxime – generic	1 g vials	1-2 g IV q8h	\$75.50
Ceftaroline – <i>Teflaro</i> (Allergan)	400, 600 mg vials	600 mg IV q12h	2118.20
Ceftriaxone – generic	250 mg, 500 mg, 1 g, 2 g, 10 g vials; 1, 2 g/50 mL soln	1-2 g IV once/day	17.70
Fluoroquinolones			
Delafloxacin – <i>Baxdela</i> (Melinta)	300 mg vials	300 mg IV q12h	1325.00
Levofloxacin – generic	250 mg/50 mL, 500 mg/100 mL, 750 mg/150 mL soln; 25 mg/mL vials	750 mg IV once/day	40.00
Moxifloxacin – generic <i>Avelox IV</i> (Bayer)	400 mg/250 mL soln	400 mg IV once/day	225.20 255.30
Macrolides			
Azithromycin – generic <i>Zithromax</i>	500 mg vials	500 mg IV once/day	27.90 30.20
Pleuromutilins			
Lefamulin – <i>Xenleta</i> (Nabriva)	150 mg vials	150 mg IV q12h	1025.00
Penicillins			
Ampicillin/sulbactam – generic <i>Unasyn</i> (Pfizer)	1.5, 3, 15 g vials	1.5-3 g IV q6h	100.60 152.80
Tetracyclines			
Doxycycline – generic <i>Doxy</i> (Fresenius)	100 mg vials	100 mg IV q12h	204.20 210.00
Omadacycline – <i>Nuzyra</i> (Paratek)	100 mg vials	200 mg IV on day 1, ³ then 100 mg once/day	2196.10

soln = solution

1. Dosage adjustments may be needed for renal or hepatic impairment.

2. Approximate WAC for 5 days' treatment at the lowest usual adult dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. January 5, 2021. Reprinted with permission by First Databank, Inc. All rights reserved. ©2021. www.fdbhealth.com/policies/drug-pricing-policy.

3. 200 mg loading dose is infused over 60 minutes. Alternative loading dose is 100 mg IV infused over 30 minutes twice on day 1.

PREGNANCY – Amoxicillin or amoxicillin/clavulanate plus azithromycin can be used for outpatient treatment of pregnant women with CAP. Pregnant women who are hospitalized for CAP can be treated with an IV beta-lactam plus azithromycin.

Doxycycline, clarithromycin, and fluoroquinolones should be avoided, if possible, in pregnant women. Doxycycline can cause fetal tooth discoloration and enamel hypoplasia and can inhibit bone growth. Clarithromycin is teratogenic in animals. Fluoroquinolones have caused arthropathy in animal studies, but observational data in pregnant women suggest that teratogenic effects are unlikely to occur at therapeutic doses.

NEWER ANTIBIOTICS – Data supporting the efficacy of newer FDA-approved antibiotics for treatment of CAP, including the fluoroquinolone delafloxacin (*Baxdela*), the tetracycline omadacycline (*Nuzyra*),¹⁰ and the pleuromutilin lefamulin (*Xenleta*),¹¹ are limited. Until more data become available, empiric regimens with a longer record of efficacy and safety are preferred.

DURATION OF ANTIMICROBIAL THERAPY – Antibiotic treatment should be continued until clinical stability is achieved (usually within 48-72 hours) and for at least 5 days. Short courses of treatment (5-7 days) appear to be similar in efficacy to longer courses (8-10 days).¹² When switching from IV to oral therapy, the same drug or a drug from the same class should be used.

ADJUNCTIVE CORTICOSTEROIDS – No data are available supporting the use of adjunctive corticosteroids for treatment of mild to moderate CAP. Data on whether they improve clinical outcomes in patients with severe CAP are mixed; until more evidence becomes available, they probably should not be used routinely, except in patients with CAP and refractory septic shock.¹³ ■

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