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LEARNING OBJECTIVES

Upon successful completion of this lesson, you should be able to:

1. select the most appropriate outpatient antibiotic regimen for any given patient diagnosed with community-acquired pneumonia
2. identify common adverse effects and drug interactions associated with antibiotics commonly used to treat community-acquired pneumonia
3. identify the role pharmacists may play in ensuring optimization of antibiotic therapy and reduction of antibiotic resistance

To successfully complete the post-test for this lesson, you will need access to a recent edition of the *Compendium of Pharmaceuticals and Specialties (CPS)* for additional information.

INSTRUCTIONS

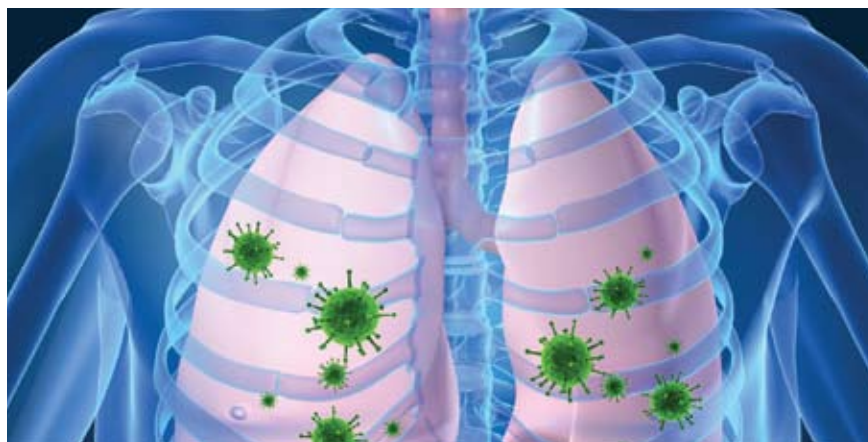
1. After carefully reading this lesson, study each question in the post-test and select the one option you believe is the best answer. Although more than one option may be considered acceptable, only one option is the *best* answer.
2. To pass this lesson, a grade of at least 70% (14 out of 20) is required. If you pass, your CEU(s) will be recorded with the relevant provincial authority(ies). (Note: some provinces require individual pharmacists to notify them.)

ANSWERING OPTIONS

- A. For immediate results, answer online at www.pharmacygateway.ca.
- B. Mail or fax the printed answer card to (416) 764-3937. Your reply card will be marked and you will be advised of your results within six to eight weeks in a letter from *Pharmacy Practice*.

Following the guidelines: Community-acquired pneumonia

By Yvonne M. Shevchuk, BSP, PharmD, FCSHP



Antibiotics are frequently prescribed for both upper and lower respiratory tract infections. Many of these infections are viral and therefore, antibiotics are not appropriate. However, pneumonia is often caused by bacterial pathogens and appropriate management of these infections is important for pharmacists to understand.

Community-acquired pneumonia (CAP) refers to pneumonia that has developed in patients who are outside the hospital or who have not resided in a long-term care facility for more than 14 days before symptoms develop.¹ Approximately 80% of patients with CAP are treated as outpatients.² This lesson will focus on the management of adult patients, with particular emphasis on the appropriate selection and use of antibiotics. Patients ill enough to be hospitalized will not be discussed, nor will patients who are otherwise institutionalized.

CAP is a potentially serious condition. It is a major cause of death in North America and the leading cause of death due to infection. It also causes significant morbidity, and the economic costs are high due to loss of productivity, cost of medications and cost of hospitalization.³ As a result, many organizations and institutions have attempted to improve the quality of care of patients with pneumonia by issuing guidelines or introducing care pathways. The role of these guidelines and pathways is to reduce variability in patient care while increasing effi-

ciency and efficacy in the management of these patients.^{4,5} Most guidelines and care pathways have been tested and studied in institutions rather than in the outpatient setting, however the same principles apply.⁶ The most recent North American guidelines designed specifically for CAP were developed jointly by the Infectious Disease Society of America (IDSA) and American Thoracic Society (ATS).⁷ Although "American," the guidelines had considerable input from Canadian physicians and are applicable to Canada. Recommendations do not refer to patients ≤ 18 years of age, immunocompromised patients, patients receiving cancer chemotherapy or long-term

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table 1

Antibiotics commonly used for outpatient treatment of CAP*^{26, 36-39}

Drug	Respiratory pathogens spectrum	Usual oral adult dose for pneumonia	Common adverse effects (not exhaustive)	Drug interactions* (not exhaustive)	Comments
Beta-lactams amoxicillin	<ul style="list-style-type: none"> • <i>Streptococcus pneumoniae</i> • β-lactamase negative <i>Haemophilus influenzae</i> 	• 1 g TID	<ul style="list-style-type: none"> • GI—nausea, vomiting, anorexia, epigastric distress, diarrhea • rash • hypersensitivity reactions • antibiotic-associated colitis • interstitial nephritis • transient hepatic enzyme elevations 	<ul style="list-style-type: none"> • probenecid – \uparrow serum concentration of amoxicillin • allopurinol – \uparrow incidence of rash and hyperuricemia 	<ul style="list-style-type: none"> • not active against β-lactamase-producing <i>H. influenzae</i>
amoxicillin/ clavulanate	<ul style="list-style-type: none"> • <i>S. pneumoniae</i> • <i>H. influenzae</i> • <i>Moraxella catarrhalis</i> 	• 875 mg–2 g BID (higher dose recommended for intermediate- and high-level penicillin-resistant <i>S. pneumoniae</i>)	<ul style="list-style-type: none"> • same as amoxicillin • incidence of diarrhea higher with combination • diarrhea ~25% with 500 mg TID • less frequent (~10%) with 875 mg q12h 	• same as amoxicillin	<ul style="list-style-type: none"> • ratio of amoxicillin to clavulanate varies with tablet strength • \downarrow GI SE when given with food
cefprozil and cefuroxime axetil	<ul style="list-style-type: none"> • <i>S. pneumoniae</i> • <i>H. influenzae</i> • <i>M. catarrhalis</i> 	• 500 mg BID	<ul style="list-style-type: none"> • GI—nausea, vomiting, diarrhea, bitter taste (cefuroxime axetil) • hypersensitivity reactions • antibiotic-associated colitis • interstitial nephritis • transient hepatic enzyme elevations 	<ul style="list-style-type: none"> • probenecid \uparrow serum cefuroxime levels 	<ul style="list-style-type: none"> • cefuroxime axetil – \uparrow bioavailability when given with food
Macrolides erythromycin	<ul style="list-style-type: none"> • <i>S. pneumoniae</i> • <i>Mycoplasma pneumoniae</i> • <i>Chlamydia pneumoniae</i> • <i>Legionella pneumophila</i> • <i>Bordetella pertussis</i> 	<ul style="list-style-type: none"> • base: 500 mg QID • enteric-coated pellets: 250 mg QID or 333 mg TID • polymer-coated erythromycin base: 333 mg TID • stearate: 250–500 mg BID–QID • EES: 600 mg BID–QID 	<ul style="list-style-type: none"> • GI—abdominal pain and cramping, nausea, vomiting, diarrhea • hepatotoxicity—elevated transaminases, cholestatic jaundice, hepatitis • hypersensitivity—rare • ototoxicity—rare • antibiotic-associated colitis 	<ul style="list-style-type: none"> • inhibits cytochrome P450 isoenzymes CYP1A2 and CYP3A4; use with substrates of these isoenzymes may increase plasma levels and toxicity (e.g., alprazolam, atorvastatin, carbamazepine, cisapride, cyclosporin, felodipine, lovastatin, midazolam, quinidine, sertraline, simvastatin, theophylline, verapamil) • \uparrow digoxin levels • warfarin – \uparrow INR • ergot derivatives – \uparrow ergot toxicity 	<ul style="list-style-type: none"> • take stearate and base 1 hour before or 2 hours after meals • enteric-coated and polymer-coated base may be taken without regard to meals • ethylsuccinate—take immediately after meals • food may \downarrow GI SE for all forms
clarithromycin	<ul style="list-style-type: none"> • <i>S. pneumoniae</i> • <i>M. pneumoniae</i> • <i>C. pneumoniae</i> • <i>L. pneumophila</i> • <i>B. pertussis</i> • <i>H. influenzae</i> 	<ul style="list-style-type: none"> • regular tabs: 500 mg BID • extended-release tabs (XL): 1000 mg OD 	<ul style="list-style-type: none"> • GI—same as erythromycin (may cause fewer GI adverse effects) • CNS—headache, anxiety, psychosis, confusion, insomnia, nightmares, behavioural changes, hallucinations • hepatotoxicity • hypersensitivity 	<ul style="list-style-type: none"> • inhibits cytochrome P450 isoenzymes CYP1A2 and CYP3A4; see erythromycin for possible toxicities • rifampin and rifabutin – \uparrow metabolism of clarithromycin • warfarin – \uparrow INR • digoxin – \uparrow digoxin levels • ergot derivatives – \uparrow ergot toxicity 	<ul style="list-style-type: none"> • extended-release product must be taken with food • other formulations may be taken with or without food
azithromycin	<ul style="list-style-type: none"> • <i>S. pneumoniae</i> • <i>M. pneumoniae</i> • <i>C. pneumoniae</i> • <i>L. pneumophila</i> • <i>B. pertussis</i> • <i>H. influenzae</i> 	• 500 mg first day, then 250 mg OD x 4 days (5 days total)	<ul style="list-style-type: none"> • GI—same as clarithromycin • CNS—dizziness, headache • hepatotoxicity • hypersensitivity 	<ul style="list-style-type: none"> • appears to have no effect on cytochrome P450 enzyme system • co-administration with Al or Mg antacids may result in \downarrow peak serum azithromycin; take 1 hour before or 2 hours after an antacid 	<ul style="list-style-type: none"> • tablets may be taken with or without food • considered equivalent to 10 days of beta-lactams or clarithromycin
Tetracyclines doxycycline	<ul style="list-style-type: none"> • <i>S. pneumoniae</i> • <i>H. influenzae</i> • <i>M. pneumoniae</i> • <i>C. pneumoniae</i> • <i>L. pneumophila</i> 	• 100 mg BID first day, then 100 mg OD	<ul style="list-style-type: none"> • GI—nausea, vomiting, diarrhea • esophagitis/esophageal erosion (rare) • antibiotic-associated colitis • photosensitivity • hypersensitivity 	<ul style="list-style-type: none"> • Al, bismuth, Ca and Mg—chelation causes \downarrow doxycycline absorption; separate doses by at least 2–3 hours** • phenytoin, carbamazepine, barbiturates – \downarrow half-life of doxycycline 	<ul style="list-style-type: none"> • swallow with enough fluid to avoid esophageal irritation • can be taken with food or milk • avoid use in pregnancy

table 1

Antibiotics commonly used for outpatient treatment of CAP*26, 36-39

Drug	Respiratory pathogens spectrum	Usual oral adult dose for pneumonia	Common adverse effects (not exhaustive)	Drug interactions* (not exhaustive)	Comments
Fluoroquinolones levofloxacin	<ul style="list-style-type: none"> • <i>S. pneumoniae</i> • <i>H. influenzae</i> • <i>M. catarrhalis</i> • <i>M. pneumoniae</i> • <i>C. pneumoniae</i> • <i>L. pneumophila</i> 	<ul style="list-style-type: none"> • 500 mg daily x 7–14 days OR 750 mg OD x 5 days (guidelines specify 750 mg regimen) 	<ul style="list-style-type: none"> • GI—nausea, vomiting, diarrhea, constipation, abdominal pain • antibiotic-associated colitis • CNS stimulation (headache, dizziness, insomnia, restlessness, tremor), seizures, psychosis, ↑ intracranial pressure • tendon rupture – ↑ risk in elderly, males, patients recently on corticosteroids • CV—prolongation of QT interval • hypersensitivity reactions • phototoxicity • disturbances in blood glucose – ↑ or ↓; usually in patients on concurrent oral hypoglycemics 	<ul style="list-style-type: none"> • chelating agents or drugs → significant reduction in levofloxacin absorption*** • potential additive effect with drugs known to prolong the QT interval (e.g., azole antifungals, erythromycin, clarithromycin, amiodarone procaïnamide, quinidine, sotalol) • NSAIDs → potential ↑ risk of seizures • rare reports of warfarin and digoxin interactions; monitor patient 	<ul style="list-style-type: none"> • take with or without food • do not take within 2 hours before or 2 hours after a chelating agent or drug*** • avoid use in pregnancy
Gemifloxacin (not indicated for CAP in Canada, however a choice in American guidelines)	<ul style="list-style-type: none"> • <i>S. pneumoniae</i> • <i>H. influenzae</i> • <i>M. catarrhalis</i> • <i>M. pneumoniae</i> • <i>C. pneumoniae</i> • <i>L. pneumophila</i> 	<ul style="list-style-type: none"> • 320 mg OD 	<ul style="list-style-type: none"> • same as levofloxacin 	<ul style="list-style-type: none"> • same as levofloxacin 	<ul style="list-style-type: none"> • take with or without food • do not take within 3 hours before or 3 hours after a chelating agent or drug*** • avoid use in pregnancy
moxifloxacin	<ul style="list-style-type: none"> • <i>S. pneumoniae</i> • <i>H. influenzae</i> • <i>M. catarrhalis</i> • <i>M. pneumoniae</i> • <i>C. pneumoniae</i> • <i>L. pneumophila</i> 	<ul style="list-style-type: none"> • 400 mg OD 	<ul style="list-style-type: none"> • same as levofloxacin 	<ul style="list-style-type: none"> • same as levofloxacin 	<ul style="list-style-type: none"> • take with or without food • do not take within 4 hours before or 8 hours after a chelating agent or drug*** • avoid use in pregnancy
ciprofloxacin	<ul style="list-style-type: none"> • <i>Pseudomonas aeruginosa</i> • other Gram negative bacilli (e.g., <i>E. coli</i>, <i>Klebsiella sp</i>, <i>Enterobacter sp</i>) 	<ul style="list-style-type: none"> • 500–750 mg BID (750 mg q8h for <i>Pseudomonas</i>) 	<ul style="list-style-type: none"> • same as levofloxacin except QT prolongation not seen with ciprofloxacin 	<ul style="list-style-type: none"> • same as levofloxacin • inhibitor of CYP450 isoenzyme 1A2; ↑ theophylline levels and ↓ caffeine metabolism and ↑ effects 	<ul style="list-style-type: none"> • take with or without food • do not take with milk or yogurt • do not take within 2 hours before or 6 hours after a chelating agent or drug*** • avoid use in pregnancy • reserve for <i>P. aeruginosa</i> and resistant Gram negative bacilli
Ketolides telithromycin	<ul style="list-style-type: none"> • <i>S. pneumoniae</i> including macrolide-resistant strains • <i>H. influenzae</i> • <i>M. catarrhalis</i> • <i>C. pneumoniae</i> • <i>M. pneumoniae</i> • <i>L. pneumophila</i> • <i>B. pertussis</i> 	<ul style="list-style-type: none"> • 800 mg OD 	<ul style="list-style-type: none"> • GI—nausea, diarrhea, vomiting • ↑ transaminases and hepatotoxicity • CNS—headache, dizziness • allergic reactions • QT prolongation—variable; needs further study • myasthenia gravis • syncope 	<ul style="list-style-type: none"> • competitively binds to CYP3A4 and 2D6 isoenzymes; ↑ levels of simvastatin, lovastatin, cisapride, midazolam, likely triazolam • ↑ digoxin levels (mechanism unknown) • ketoconazole and itraconazole ↓ telithromycin levels 	<ul style="list-style-type: none"> • may be taken with or without food • reports of severe liver injury

* Most antibiotics have the potential to interact with oral contraceptives, but the risk of contraceptive failure is very low. However, due to the significant consequences of unintended pregnancy, patients should be informed of the potential interaction and how to manage it when given an antibiotic.³⁶ Breakthrough bleeding may also occur. As yet, there is no evidence that fluoroquinolones interact with oral contraceptives. ** General recommendation for tetracyclines; not necessarily specific to doxycycline. *** Drugs or agents known to chelate with fluoroquinolones include any product containing Al, Ca, Mg (e.g., antacids), iron, zinc (e.g., vitamins, minerals, dietary supplements), didanosine chewable or dispersible tablets, or powder and sucralfate. Al = aluminum; Ca = calcium; CNS = central nervous system; CV = cardiovascular; EES = erythromycin ethylsuccinate; GI = gastrointestinal; INR = International Normalized Ratio; Mg = magnesium; NSAIDs = nonsteroidal anti-inflammatory drugs; SE = side effects

(> 30 days), high-dose corticosteroid treatment, patients with congenital or acquired immunodeficiency, or those infected with HIV who have CD4 cell counts < 350/mm³.^{5,7}

There are many aspects to the care of patients with CAP discussed in various guidelines. If readers are attempting to evaluate current management of CAP in their practice setting, guidelines should be consulted for

recommendations on *all* processes of care.

Pathophysiology and presentation

Pneumonia is defined as acute inflammation of the lung parenchyma as a result of infection.⁸ It is a lower respiratory tract infection which usually develops as a result of microaspiration of oropharyngeal secretions colo-

nized with potential pathogens. Impaired host defences prevent clearance of the pathogen from the lung. Pneumonia can also develop as a result of hematogenous spread (i.e., through the bloodstream) or inhalation. These routes are much less common.^{1,8,9}

Common signs and symptoms of pneumonia include fever, cough (productive or nonproductive), dyspnea, pleuritic chest pain (described

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Following the guidelines: Community-acquired pneumonia

as stabbing pain), upper back pain and chills. The fever may be high ($> 39^{\circ}\text{C}$) or low grade. The height of the fever cannot determine the etiology. Elderly patients may not develop a significant temperature elevation in response to infection. As with many other infections, non-specific symptoms such as muscle pain, arthralgias, fatigue, nausea, vomiting, loss of appetite and headache are often present. Tachypnea and tachycardia may be present. The patient may be hypoxic with evidence of low oxygen saturation. Auscultation of the chest will detect diminished breath sounds over the affected areas, and respiratory crackles. A chest X-ray, which shows pulmonary infiltrates or consolidation, is required to make a diagnosis of pneumonia. A sputum specimen may reveal many polymorphonuclear cells and a predominant causative organism on Gram stain. The peripheral white blood cell count is often elevated. Blood cultures identify the microorganism in about 10% of cases.^{1,3,8}

Diagnosis and etiology

The diagnosis of CAP begins with identifying the symptoms mentioned above, as well as a careful history. Pneumonia may be preceded by influenza. Identification of family members who were or who are ill may indicate a source for the infection. Travel history is important to rule out pathogens such as avian influenza and SARS. The history may also identify patient exposure to harmful substances or toxins such as asbestos or anthrax.

While it is common in hospitalized patients to obtain blood cultures and sputum Gram stain and cultures, this is uncommon in the community for a number of reasons: some pathogens responsible for CAP cannot be cultured, not all patients are able to produce sputum samples, and less than half of sputum samples grow organisms on which to base treatment.^{7,10} Overall, the causative organism can be determined in about 50% of patients.¹¹ When dealing with otherwise healthy individuals in the community, the low yield often makes diagnostic testing impractical. As such, antibiotic choices are most often empiric (i.e., cause not known).

Age and underlying disease states may alter the proportion of cases caused by specific pathogens, but the most common causes of CAP overall are *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Haemophilus influenzae* and respiratory viruses. With the exception of viruses, empiric outpatient antibiotic regimens are aimed at these pathogens. *S. pneumoniae* is most frequently isolated overall, including the elderly. Nontypable *H. influenzae* is seen in patients with bronchopulmonary disease. *M. pneumoniae*, *C. pneumoniae* and *Legionella* species are referred to as atypical pathogens because they are not seen on Gram stain and do not grow on usual bacteriologic media. *M. pneumoniae* is the most common pathogen seen in younger (< 50 years

old), otherwise healthy patients.^{1,2,7}

Although *Staphylococcus aureus* is less frequently encountered as a cause of pneumonia, one presentation of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) infection is severe necrotizing pneumonia.^{12,13} If *S. aureus* is suspected in CAP, then CA-MRSA should be considered. These patients are usually ill enough to require hospitalization.

Other possible causes of CAP include, but are not limited to *Pseudomonas aeruginosa* and other Gram negative bacilli such as *Klebsiella pneumoniae*. These are less common and tend to occur in hospital settings and/or in specific patient populations. For example, along with other uncommon pathogens, alcoholism is a risk factor for *K. pneumoniae*, and *P. aeruginosa* is a more likely concern in patients with severe chronic obstructive or structural lung disease.^{7,9}

Testing outpatients for etiology is important if the results are likely to change the antibiotic choice or regimen. Due in part to challenges of diagnostic testing, physicians typically prescribe an antibiotic based on the knowledge that CAP will likely be caused by at least one of the four dominant bacterial pathogens described above. Covering these pathogens empirically works for most patients. If the physician has reason to suspect a different pathogen (e.g., due to a patient's health condition(s) and/or history), he or she is more likely to test for etiology. Unfortunately, organisms cannot be distinguished on the basis of clinical presentation.

A major disadvantage of not obtaining blood and sputum specimens for testing in all outpatients is the potential inability to identify antibiotic resistance issues early in therapy, and management of antibiotic failure is more difficult if the pathogen has not been identified. Diagnostic testing also allows surveillance and monitoring of etiology and antimicrobial susceptibilities. Current guidelines for empiric therapy are based on the results of such monitoring and surveillance.⁷

Management

Antibiotics are the mainstay of treatment of CAP. The goals are to: 1) eradicate the microorganisms, 2) resolve signs and symptoms, 3) reduce the risk of complications and hospitalization, 4) reduce the risk of adverse events, and 5) minimize the development of antimicrobial resistance.^{1,7,8}

The spectrum of antibiotic activity for respiratory pathogens, antibiotic dosing, and adverse effects and drug interactions for common antimicrobials used in the outpatient treatment of CAP are provided in Table 1.

In addition to antibiotic therapy, general treatment measures such as adequate hydration and nutrition, staying home from work or school to rest, and antipyretic and antitussive therapy may be required. As coughing is important to

encourage expectoration of sputum, cough suppression is not encouraged. However, in some patients, persistent coughing causes severe musculoskeletal chest pain, respiratory fatigue, and/or inability to get adequate rest. In this situation cough suppression, particularly at night, is recommended. Acetaminophen, acetylsalicylic acid or ibuprofen may be used to manage fever, myalgias, arthralgias and headache. Patients who smoke are encouraged to quit, or at least reduce the number of cigarettes they have while they are ill.^{8,9}

CHOICE OF ANTIBIOTIC

As noted, outpatients are often treated empirically for CAP. Table 2 describes the recommendations for empiric therapy from the 2007 IDSA/ATS guidelines.⁷ These guidelines are highly regarded and the most frequently used by infectious diseases practitioners.

To apply the recommendations in Table 2, the first step is to identify whether the patient was previously healthy or has specific comorbidities. The second step is to determine whether the patient has used systemic antimicrobials (for any indication) in the past three months. If he or she has, an antibiotic from a different class should be selected from Guideline 2 (Table 2) to provide coverage for drug-resistant *S. pneumoniae* (DRSP).⁷ For example, recent treatment with a fluoroquinolone, macrolide or beta-lactam increases the risk of pneumococcal resistance to the same class of antibiotic.¹⁴⁻¹⁶

ANTIBIOTIC RESISTANCE

The organism of greatest importance with respect to drug resistance in CAP is *S. pneumoniae*. Initially this was referred to as penicillin-resistant *S. pneumoniae* (PRSP), reflecting resistance to the penicillin group of antibiotics. Due to growing awareness that many PRSPs show increased resistance to other classes of antibiotics (including macrolides and fluoroquinolones), the more frequently used term is now DRSP. PRSP will have a higher minimum inhibitory concentration (MIC) to all beta-lactams. Some publications refer to these as PRSP, while others use the term beta-lactam-resistant *S. pneumoniae* to reflect this observation.¹⁷

Penicillin or beta-lactam resistance in *S. pneumoniae* is due to alteration of penicillin-binding proteins in the organism and is classified as intermediate- or high-level resistance. Increased doses of appropriate drugs (e.g., amoxicillin 1 g TID) are still useful in treating PRSP because higher doses will saturate the penicillin-binding proteins, achieving a bactericidal effect.⁷ Clavulanate does not affect penicillin binding proteins; its goal is to provide coverage for organisms which produce beta-lactamases.

Risk factors for beta-lactam resistant *S. pneumoniae* are ages less than two years or > 65 years, beta-lactam therapy within the last

three months, alcoholism, co-morbidities, immunosuppressive illness or drugs, and exposure to a child who routinely spends time with other children (e.g., a daycare centre). Of the risk factors identified, recent antibiotic treatment is likely the most significant factor.⁷

Macrolide resistance in *S. pneumoniae* has also emerged and is steadily increasing.^{6,18} Rates of fluoroquinolone resistance are low, but are on the rise, particularly in elderly patients.^{7,17} As noted, resistance to beta-lactams can be overcome with increased doses. This is in contrast to macrolides and fluoroquinolones (ciprofloxacin and levofloxacin) where resistance can result in clinical failure. Treatment failures as a result of resistance to gemifloxacin and moxifloxacin have yet to be reported.^{7,18,19}

Resistance may be seen in other microorganisms causing CAP. For example, *H. influenzae* may produce beta-lactamases which inactivate penicillins. In this case, the addition of clavulanate to amoxicillin will overcome this mechanism of resistance.

Referring to Table 2, macrolides such as erythromycin, clarithromycin and azithromycin are a common choice for CAP because of activity against both *S. pneumoniae* and atypical pathogens. In patients with no co-morbidities, any macrolide is acceptable. If empiric coverage of *H. influenzae* is needed (e.g., patients with chronic lung disease), then either clarithromycin or azithromycin is required (with a beta-lactam), because erythromycin is not active against this organism.⁷

Amoxicillin (plus a macrolide) is one of the empiric choices in patients who have co-morbidities or who have received an alternate antibiotic class in the last three months. It has excellent activity against *S. pneumoniae* including strains with intermediate resistance

to beta-lactams. This, along with amoxicillin's relatively low cost, long history of experience, and excellent safety profile (including that in pregnancy) makes this drug one of the more commonly used antibiotics. For reasons noted earlier, amoxicillin clavulanate is an effective alternative to amoxicillin. All beta-lactam drugs lack activity against atypical pathogens, therefore, are not used alone empirically.⁷

Doxycycline can be used as an alternative to the macrolides in patients with or without co-morbidities. As shown in Table 1 it has activity against common respiratory pathogens such as *S. pneumoniae* (although resistance to this organism may be seen) and atypical organisms.

In patients with co-morbidities or at risk for DRSP, respiratory fluoroquinolones (moxifloxacin, levofloxacin and gemifloxacin) are one of the choices. Although respiratory fluoroquinolones have potent activity against *S. pneumoniae*, as well as activity against atypical organisms and *H. influenzae*, concern that widespread use will result in rising rates of resistance has led to recommendations that fluoroquinolones should not be used in patients without co-morbidities or risk factors for DRSP.^{20,21}

Ciprofloxacin should be used only if *P. aeruginosa* or resistant Gram negative bacilli are suspected or documented. Although it is a fluoroquinolone, ciprofloxacin has poor activity against *S. pneumoniae* and resistance to ciprofloxacin is higher than that found with levofloxacin or moxifloxacin.

The optimal duration of therapy is unknown, but is generally one to two weeks in outpatients.^{7,22} If complications develop, this may prolong therapy. Duration of therapy continues to evolve with shorter regimens being proposed to reduce selection pressure (in very basic terms, the emergence of additional resistant

bacteria secondary to the antibiotic-induced changes in normal flora).²³ For example, a physician may suggest an antibiotic be stopped after a patient with uncomplicated pneumococcal pneumonia has been afebrile for three days.⁹ A five-day regimen of levofloxacin 750 mg has been shown to be equivalent to a 500 mg course for 10 days.²⁴ Five days of gemifloxacin produces outcomes similar to a seven-day course.²⁵ The five-day course of azithromycin is *not* an example of a short course. Due to its unique pharmacokinetics, the antimicrobial effect of azithromycin lasts much longer than five days.²⁶

MINIMIZING ANTIBIOTIC RESISTANCE

Antibiotic resistance is a major health threat, with predictions it will only get worse.²⁷ With the appearance of "superbugs" and the growing problem of multidrug resistance, all health professionals need to understand the implications of antibiotic resistance and seriously consider strategies to reduce inappropriate antibiotic use.

CAP is not immune to this phenomenon, of multidrug resistance. Steps can be taken however to slow rising rates of resistance in this potentially serious condition (Table 3).^{28,29}

The guidelines for empiric therapy of CAP consider not only the microorganisms causing the infection, but also the issue of antibiotic resistance.⁷ If patients are at risk of infection with a drug-resistant organism, then empiric choices change. As well, consideration is given to minimizing antibiotic pressure to produce new resistance (e.g., discouraging the widespread use of fluoroquinolones).

Antibiotic resistance patterns may be geographic and healthcare providers should be familiar with local antibiotic resistance patterns.^{7,27} Many regional health authorities produce antibiograms—charts showing local patterns of resistance. Some show composite resistance patterns, while others separate organisms obtained from hospitalized patients from those in the community. This local resistance data can be used to help select the most appropriate antibiotic from the guidelines.

Other strategies that attempt to slow rising rates of resistance include using antibiotics only when indicated, shortening the duration of therapy, and using the narrowest-spectrum antibiotic possible.^{28,29} If the results of sputum or blood cultures indicate a specific pathogen, switching the patient to an antibiotic with a narrower spectrum of activity may reduce costs, adverse effects and antibiotic resistance.⁷ Unfortunately, this is not common practice in the outpatient setting. On a practical level, once a patient fills a prescription for a 10-day course of a broad-spectrum antibiotic, it is costly and inconvenient to switch three days later to a narrow-spectrum drug when the culture and sensitivity results are returned. This is a difficult obstacle to overcome in the community setting.

table 2

Empirical antibiotics for community-acquired pneumonia—outpatient treatment*

Patient characteristics	Antibiotic choice
1. patients previously healthy and no use of antimicrobials within the previous 3 months (i.e., no risk of DRSP)	<ul style="list-style-type: none"> • a macrolide (azithromycin, clarithromycin or erythromycin) OR <ul style="list-style-type: none"> • doxycycline
2. patients with presence of co-morbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class in this category should be selected); or other risks for DRSP infection	<ul style="list-style-type: none"> • a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, levofloxacin [750 mg]) OR <ul style="list-style-type: none"> • a beta-lactam plus a macrolide <ul style="list-style-type: none"> - high-dose amoxicillin (e.g., 1 g TID) or amoxicillin clavulanate (e.g., 2 g BID) is preferred - alternatives to amoxicillin or amoxicillin/clavulanate include ceftriaxone or cefuroxime (500 mg BID) - doxycycline is an alternative to the macrolide
3. patients in regions with a high rate (> 25%) of infection with high-level (MIC ≥ 16 µg/mL) macrolide-resistant <i>Streptococcus pneumoniae</i>	<ul style="list-style-type: none"> • consider the use of agents listed above (in 2.) for any patient, including those without co-morbidities

*Adapted from the Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults⁷
DRSP = drug-resistant *Streptococcus pneumoniae*; MIC = minimum inhibitory concentration

Prevention

Pneumonia is a serious complication of influenza. Over the long term (10 influenza seasons), influenza immunization has resulted in a 27% reduction in the risk of hospitalization for pneumonia or influenza, and a 48% reduction in the risk of death in persons aged ≥ 65 years old living in the community.³⁰ All individuals who are at risk for influenza complications, household contacts of patients at high risk and healthcare workers should be immunized yearly against influenza infection. Specific information regarding influenza immunization can be found on the website of the National Advisory Committee on Immunization Statement on Influenza Vaccination.³¹

Pneumococcal polysaccharide vaccine is also recommended for all individuals > 65 years of age and for those with high-risk concurrent diseases. Specific information about this vaccine can be found on the Public Health Agency of Canada's Canadian Immunization Guide web page.³² Pharmacists can become actively involved in identifying patients who should be immunized and can facilitate their immunization by making recommendations to the patient, the patient's family or physician, and by hosting immunization clinics in the pharmacy.³³

Some organisms that cause CAP may be contagious. However, none of the four common CAP bacterial organisms is contagious in the classic sense seen with a cold. At the same time, CAP may be spread by inhalation and patients should be reminded of general measures to help prevent transmission. One obvious measure is for the patient to cover his or her mouth and nose when coughing. Handwashing by both the patient and family

or other contacts is also important. Other suggestions include the patient having his or her own face cloth and having contacts avoid eating or drinking from the same dishes. Staying at home when sick is another measure to help break the chain of transmission.^{7,27}

The pharmacist's role

Antibiotics are one of the most common prescriptions pharmacists see. As such, pharmacists can play a major role in CAP by facilitating effective antibiotic therapy, taking measures to reduce resistance and helping patients make the best use of these drugs. While many of the following principles apply to all antibiotics, some are specific to CAP.

Inappropriate antibiotic use is a major driver in the perpetuation of antimicrobial resistance both in CAP and other infections. Pharmacists should discourage the use of antibiotics for conditions where there is a high likelihood the infection is viral, and should support the physician's decision not to prescribe antibiotics in such situations. If a diagnosis such as CAP is made, where bacterial pathogens are likely and antibiotics are warranted, pharmacists can make themselves aware of the current guidelines and local antimicrobial susceptibility data. They should encourage the use of agents suggested in the guidelines and be able to explain the rationale for particular choices.

Once an antibiotic has been prescribed, pharmacists can check the patient profile to check if he or she has used one within the past three months. Since patients sometimes go to different pharmacies, it is advisable to also ask patients for this information. The physician should be informed if the prescribed antibiotic class has been used recently, and the pharmacist should have alternatives in mind.

In order to implement the above suggestions, the pharmacist needs to know if an antibiotic is intended for CAP. This information is needed before the prescription is filled. The most obvious approach is to simply ask the patient when the prescription is handed in (e.g., "What did your doctor tell you about why he prescribed this for you?"). A more ambitious approach is to encourage physicians to put the purpose of the drug on the label. Doing this in tandem with an educational awareness campaign about CAP and its guidelines and/or local susceptibility data not only helps patients but facilitates public relations with physicians in the area, many of whom may not be aware of the guidelines.

When the antibiotic choice has been determined, the patient's profile needs to be examined for drug allergies and interacting medications, and the dose confirmed for the patient's age, weight and renal function. A careful allergy history should be taken to determine the nature and severity of any past reactions. Many patients will indicate an allergy to an antibiotic when in fact the true

reaction was intolerance (e.g., gastrointestinal upset with erythromycin, a common side effect especially with erythromycin base). In contrast, patients who give a history of urticaria, chest tightness or breathing problems and severe rash likely have a true allergy to penicillin and should avoid beta-lactam antibiotics.³⁴ Again, appropriate recommendations for any changes in the prescription can be made at this time. The pharmacist should also review over-the-counter medication use with the patient to detect or prevent problems, especially potential drug interactions (Table 1).

The patient should be counselled on how to take the antibiotic, how long the course of therapy is, the importance of completing the entire course even if the patient feels better, common adverse effects, and expectations of therapy. Improvement should be seen in three to five days. Tell the patient to look for decreased fever and sputum production, decreased malaise, nausea, vomiting and lethargy, and improvement in the cough. It is not unusual for cough to persist for a number of weeks following completion of antibiotic therapy, and the patient may not have returned to his or her usual state of well-being by the end of the antibiotic course; but, there should be improvement. If the fever persists more than three days, or the patient notes worsening cough, dyspnea, pleuritic chest pain or increasing sputum production, medical attention should be sought.¹

The importance of completing the full course of an antibiotic, even if symptoms subside or disappear before the antibiotic is finished, cannot be overemphasized. Using the shortest duration of therapy does not mean individual patients should decrease their prescribed length of antibiotic treatment. Explaining why it is important to complete an antibiotic course makes it more likely patients will follow this advice. It is also helpful to discuss the importance of taking the prescribed number of doses each day and help patients incorporate dose-taking into their daily routine. Evidence suggests a call back to the patient after three or four days may be helpful to evaluate whether the infection is responding to therapy and any adverse events have emerged, as well as to encourage completion of the entire regimen.³⁵

A followup chest X-ray may be ordered by the physician two to three weeks after completion of therapy to evaluate resolution of the pneumonia, especially in patients with co-morbidities or complications.¹⁰ It is important to note that chest X-ray resolution lags behind clinical improvement. In other words, a repeat chest X-ray may still suggest pneumonia, even when symptoms have diminished. For this reason, patients should never be advised to get an early chest X-ray for symptoms such as a lingering cough.

table 3

Minimizing antibiotic resistance*^{2,7,14-16,27-29}

- Identify the pathogen as much as possible.
- Use local antibiotic resistance pattern information when available.
- Use antibiotics only when indicated.
- Follow guidelines for outpatient CAP management with antibiotics.
- Use adequate antibiotic doses.
- Use antibiotics for the shortest duration possible.
- Choose an antibiotic with the narrowest spectrum.
- Facilitate individual patient's antibiotic completion.
- Monitor drug interactions, especially those that can reduce absorption.
- Vaccinate high-risk patients (influenza and pneumococcal).
- Prevent transmission to others.

* prepared for outpatient use; hospitals have additional infection-control procedures that are not listed here

Summary

Community-acquired pneumonia is a serious condition commonly treated on an outpatient basis. The selection of inappropriate antibiotics for treatment of CAP continues to be seen daily

in the community despite availability of clinical practice guidelines to help direct therapy. Pharmacists should be familiar with appropriate antibiotic choices for CAP and understand the rationale for these choices. By educating and

assisting physicians, nurse practitioners and patients regarding antibiotic choices, pharmacists can play a key role in optimizing outcomes in patients with CAP and in slowing the development of resistance to antibiotics. **PP**

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Questions

To answer online, go to www.pharmacygateway.ca, CE section, CE Online, Pharmacy Practice

M.S. is a 52-year-old insulin dependent diabetes mellitus male patient diagnosed with CAP. He reports symptoms of fever, dyspnea, productive cough and fatigue. His current medications include regular and NPH insulin, acetylsalicylic acid, ramipril and atorvastatin. His diabetes is well-controlled, and he has not received antibiotics in the last six months.

1 Based on the 2007 Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines, an appropriate antibiotic regimen for M.S. would be:

- a) doxycycline 100 mg BID x 1 day, then 100 mg OD
- b) cefprozil 500 mg BID plus clarithromycin 500 mg BID
- c) levofloxacin 750 mg OD
- d) either a) or b)
- e) either b) or c)

2 On review of M.S.'s medication profile, which of the following may be of potential concern?

- a) Levofloxacin may produce hyper- or hypoglycemia.
- b) Doxycycline may increase atorvastatin concentrations.
- c) Clarithromycin may inhibit the metabolism of ramipril.
- d) Both a) and b)
- e) Both b) and c)

3 When counselling M.S., all of the following points should be mentioned except:

- a) He will need a chest X-ray in one week.
- b) If his fever lasts longer than three days, he should see his doctor.

- c) If his shortness of breath increases, he should see his doctor.
- d) He should monitor his blood glucose levels frequently.
- e) He should call you if he develops severe diarrhea.

4 CAP is the leading cause of death due to infection.

- a) true
- b) false

Z.T. is a 26-year-old pregnant female diagnosed with CAP. She complains of fever, chills, pleuritic chest pain, nonproductive cough, anorexia and fatigue. She is otherwise healthy and does not recall taking antibiotics in the past year. Her only current medications are a prenatal vitamin and folic acid. She is in the second trimester of her pregnancy.

5 The most appropriate antibiotic for treating Z.T.'s pneumonia is:

- a) doxycycline 100 mg BID x 1 day, then 100 mg OD
- b) erythromycin 333 mg TID
- c) ciprofloxacin 500 mg BID
- d) moxifloxacin 400 mg OD
- e) telithromycin 800 mg OD

6 Z.T.'s physician obtained a sputum culture. The lab result is *Streptococcus pneumoniae* intermediate-level resistance to penicillin and resistance to tetracycline. Considering this information, the most appropriate antibiotic choice is:

- a) amoxicillin 1 g TID
- b) azithromycin 500 mg OD x 1 d, then 250 mg OD
- c) erythromycin 333 mg TID

- d) levofloxacin 750 mg OD
- e) none of the above

7 Without diagnostic testing, antibiotic therapy often results in treatment failure in outpatients with CAP.

- a) true
- b) false

8 Antimicrobial resistance is an increasing concern with respect to management of CAP. Which of the following strategies is/are important for minimizing resistance?

- a) Adjust the drug to a narrower-spectrum antibiotic when microbiologic etiology is determined.
- b) Increase the duration of antimicrobial therapy to ensure all organisms are eradicated.
- c) Increase the use of fluoroquinolones to ensure coverage of penicillin-resistant *S. pneumoniae*.
- d) Both a) and b) are important.
- e) All of the above are important.

9 Reference is made to atypical microorganisms when discussing the etiology of CAP. All of the following statements regarding these organisms is/are true except:

- a) They are so named because they are less likely than typical organisms to cause CAP in otherwise healthy individuals.
- b) These organisms stain poorly with Gram's stain and do not grow on usual microbiologic media.
- c) These organisms cannot be distinguished from usual bacterial pathogens on the basis of clinical presentation.
- d) Both a) and b)
- e) Both b) and c)

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PHARMACY PRACTICE NATIONAL CONTINUING EDUCATION PROGRAM

Following the guidelines: Community-acquired pneumonia

10 QT interval prolongation has been associated with which of the following antibiotics?

- a) clarithromycin
- b) levofloxacin
- c) doxycycline
- d) both a) and b)
- e) all of the above

J.T. is an 83-year-old male who has been a regular at your pharmacy for many years. He has severe arthritis for which he takes a nonsteroidal anti-inflammatory drug (NSAID), a disease-modifying antirheumatic drug (DMARD) and prednisone 10 mg OD. He also takes antacids prn for stomach upset related to his arthritis medications. Today, a nurse from a long-term care facility (LTCF) phones to confirm what medications he is on, as he is running out of the ones he brought with him two days ago when he first moved to the LTCF. When you list J.T.'s prescriptions, the nurse asks if you have anything on file for amoxicillin or other antibiotics. Apparently J.T. had an empty bottle for amoxicillin 500 mg TID x 10 d for chest infection, but it was filled at another pharmacy about two months ago. Although he has no fever, today he complains of most other symptoms of pneumonia.

11 Since J.T. does not have a fever, he is unlikely to have pneumonia.

- a) true
- b) false

12 If J.T. does have pneumonia, which of the following would be an appropriate antibiotic regimen at this point?

- a) amoxicillin 1 g TID
- b) amoxicillin/clavulanate 2 g BID
- c) cefuroxime 500 mg BID
- d) b) and c) together
- e) none of the above

13 J.T. does have pneumonia and his doctor prescribes levofloxacin 500 mg po OD x 10 days. Which of the following are potential drug-related problems with this prescription?

- a) Given his co-morbidities and other risk factors, levofloxacin is a poor choice to begin J.T.'s CAP treatment.
- b) Failure to respond may occur if J.T. takes his antacid within two hours of his antibiotic dose.
- c) Given other drugs J.T. takes, levofloxacin may put him at increased risk for seizures.
- d) Both b) and c)
- e) All of the above

W.C. is a 21-year-old male with a long-standing history of severe asthma with numerous "bouts" of pneumonia. He looks unwell today. While requesting a refill of his nasal corticosteroid for allergies, he tells you he will be back after seeing the doctor about the

possibility of another chest infection. Your profile shows W.C.'s last antibiotic was four months ago.

14 Appropriate antibiotic therapy to cover a pathogen often seen in patients such as W.C. includes:

- a) enteric-coated erythromycin 250 mg QID
- b) moxifloxacin 400 mg OD
- c) ciprofloxacin 750 mg q8h
- d) either a) or b)
- e) any of the above

15 W.C. returns to the pharmacy with a prescription for levofloxacin 500 mg OD x 10 days. You notice he has a bottle of iron pills in his hand. Which of the following would you suggest to the doctor about W.C.'s prescription?

- a) Change W.C.'s levofloxacin dose to 750 mg OD x 5 days.
- b) Add azithromycin to W.C.'s regimen as his age puts him at greater risk for resistance to fluoroquinolones.
- c) Change the prescription to something like telithromycin, as W.C.'s corticosteroid use puts him at greater risk for levofloxacin-induced tendon rupture.
- d) Both a) and c)
- e) All of the above

16 What information would you discuss with W.C. about levofloxacin?

- a) Sun protection measures should be reviewed as levofloxacin may cause photosensitivity.
- b) He may take the drug with or without food.
- c) Before buying iron, W.C. should be told he cannot take it while he is on levofloxacin.
- d) Both a) and b)
- e) All of the above

L.M. is a 35-year-old lawyer who asks you for acetaminophen with codeine. She tells you she needs the acetaminophen for fever, aching muscles and a pain in her chest. She is also hoping the codeine will reduce a cough that interferes with her work plus keeps her up at night. All of her symptoms have been getting worse over the past week. She is otherwise healthy, using only alprazolam 0.5 mg BID-TID to help her stay calm, plus a contraceptive patch. You suggest to L.M. that she see her doctor about her current symptoms, but she says she is too busy and is sure it will eventually pass.

17 Which of the following is/are true?

- a) One reason L.M. should be referred is that her symptoms suggest the possibility of CAP.
- b) To encourage referral, tell L.M. her symptoms

could be a potentially serious infection that may need an antibiotic to avoid complications.

- c) If L.M. has CAP, one likely pathogen is *M. pneumoniae*.
- d) Both a) and b)
- e) All of the above

18 L.M. accepts your offer to use your phone to call her doctor and now has an appointment for 5:00 p.m. Considering L.M.'s busy schedule and reluctance to take time to see her doctor, with which of the following antibiotics is she more likely to be compliant?

- a) erythromycin enteric-coated pellets 250 mg
- b) clarithromycin 500 mg
- c) azithromycin 250 mg
- d) either b) or c)
- e) any of the above

19 L.M. returns that evening with a prescription for clarithromycin extended-release 1000 mg OD x 7 d. Before you fill it, she tells you she had an allergic reaction to a drug called erythromycin and wonders if she has an allergy to all "mycin" types of drugs. Her profile shows she had erythromycin base about one year ago. Apparently, the reaction was stomach pains, cramping, diarrhea, nausea and some vomiting. What would you tell L.M. about these symptoms?

- a) Her symptoms one year ago were not a true allergy but rather a side effect that is most common with the kind of erythromycin she took.
- b) All antibiotics have the potential to cause stomach problems, but the drug she had in the past is particularly bothersome.
- c) Clarithromycin is less likely than erythromycin to cause stomach-related problems.
- d) Both a) and c)
- e) All of the above

20 What advice does L.M. need about her clarithromycin?

- a) She must take it with food. Taking it with her main meal of the day will help reduce stomach problems and help her remember each day's dose.
- b) Like all antibiotics, clarithromycin may decrease the effectiveness of her contraceptive and/or cause breakthrough bleeding. She should be given advice about additional methods of birth control.
- c) The effectiveness of L.M.'s alprazolam may be reduced by clarithromycin. Although rare, clarithromycin by itself may add to anxiety. She will need to monitor this and adjust her alprazolam dose accordingly.
- d) Both a) and b)
- e) Both a) and c)

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THIS MONTH

Following the guidelines: Community-acquired pneumonia

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All lessons are reviewed by a minimum of six pharmacists for accuracy, currency and relevance to current pharmacy practice.

This lesson is valid until March 24, 2011. Information about community-acquired pneumonia may change over the course of this time. Readers are responsible for determining the most current aspects of this topic.

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