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LEARNING OBJECTIVES

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

1. Identify symptoms and differentiate manifestations of several common pediatric respiratory tract infections.
2. List the common pathogens responsible for each respiratory infection.
3. Determine which infections need antimicrobial treatment and those that require symptomatic care only.
4. Identify the empiric first-line antimicrobial treatment options.
5. Discuss the burden relating to respiratory infections including antibiotic resistance and complications.
6. Discuss the importance of tailoring antibiotics to reflect the local antibiotic resistance patterns.
7. Describe various risk factors for disease and discuss prevention strategies to reduce nosocomial transmission.

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*.

Optimizing antibiotic therapy for common childhood respiratory infections

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Introduction

Over the past six decades in North America and Europe, mortality rates have progressively fallen for most childhood acute respiratory tract infections (RTIs), namely pneumonia and bronchiolitis, while community-acquired pneumonia (CAP) remains a leading cause of childhood morbidity in many developing countries.¹⁻⁴

Most antibiotics consumed in the community are for the treatment of RTIs.⁵ The benefits of antibiotic therapy must be weighed against the associated risks of adverse events and antimicrobial resistance. In Canada, systemic efforts for controlling antibiotic resistance began in 1997, resulting in the formation of the Canadian Committee on Antibiotic Resistance (CCAR). Despite targeting a 25% reduction in antimicrobial usage for RTIs, only a modest nine per cent reduction was reported in 2006.⁶ Overall from 1996 to 2007, antibiotic consumption decreased, but an upsurge was observed from 2003 to 2005, reinforcing the need for ongoing vigilance.

From 2005 to 2007, penicillin-resistant *Streptococcus pneumoniae* (PRSP) isolates reported in Canada increased from 15.1% to 17%.^{7,8} In Canada and the U.S., 25–33% of *Haemophilus influenzae* iso-

lates produce beta-lactamases, requiring treatment with beta-lactamase-stable cephalosporins or combination antibiotics that include beta-lactamase inhibitors.^{9,10} Macrolide resistance for *S. pneumoniae* has hit an all time high of 23% in Canada (reported in 2007). Resistance correlates to an increased usage of newer macrolides and may be promoted by longer-acting agents (e.g., azithromycin) that can reside in tissues at subinhibitory concentrations.¹¹ Thus, azithromycin should be

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reserved for documented cases of atypical RTIs, to avoid increasing resistance.¹²

Antibiotic resistance and the inappropriate use of antibiotics remain issues of significant concern for pharmacists especially when treating RTIs in children. Preschool-aged children commonly experience up to 10 viral upper RTIs per year. Antibiotics are frequently prescribed for the most commonplace RTIs, namely pharyngitis, sinusitis and otitis media, which are often viral in etiology.^{13,14} Delaying or avoiding antibiotics in the first 48 hours—a strategy used for otitis media and sinusitis—has shown no major differences in symptom reduction or patient satisfaction compared to immediate antibiotic prescribing.¹⁵

Healthcare resources and societal costs increase with unnecessary visits to pediatricians and physicians at walk-in clinics and hospital emergency departments, and when community pharmacists fill unneeded antibiotic prescriptions. As well, unnecessary antibiotic exposure drives the potential for drug-related adverse events. Nearly one-quarter of emergency department visits are for antibiotic-associated drug reactions reported in children less than 15 years of age.¹⁶ Decreasing inappropriate antibiotic use could substantially reduce the number of antibiotic-associated adverse events.^{16,17}

This continuing education lesson addresses the burden and challenges of optimizing the use of antibiotics in RTIs, to minimize our resistance footprint. Emerging antibiotic resistance trends reinforce the need for pharmacists—the community experts in antibiotic therapy—to be at the helm of community antibiotic awareness programs. Pharmacists can work with physicians to ensure a pragmatic approach to prescribing antibiotics for RTIs.

This lesson also provides a clinical perspective on current treatment guidelines for common childhood RTIs. Table 1 provides a brief review of the responsible pathogens and treatment options for common childhood RTIs. Pharmacists can find antibiotic resistance information for *S. pneumoniae* and *H. influenzae* on the Canadian Bacterial Surveillance Network website available at <http://microbiology.mtsinai.on.ca>. The essential goal of this lesson is to help pharmacists provide the best possible care to the youngest patients in their pharmacy practice.

Pharyngitis

ETIOLOGY/PATHOPHYSIOLOGY

Pharyngitis is an irritation or inflammation of the pharynx that most commonly presents with acute sore throat as the chief

complaint. Bacterial pharyngitis in children is predominantly caused by group A beta-hemolytic *Streptococcus* (GABHS). Occasionally, it can be caused by group C or G *Streptococcus* or *Arcanobacterium haemolyticum*.¹⁸ GABHS is uncommon in children less than three years of age and is mostly seen in children aged five to 15 years in the fall and winter seasons.¹⁹

The primary concern of untreated GABHS in children older than three years is that it may subsequently progress to rheumatic fever or retropharyngeal abscess.^{19,20} GABHS pharyngitis may be a self-limiting disease lasting eight to 10 days. Delayed treatment (up to 9 days) can still prevent acute rheumatic fever (number needed to treat [NNT] = 4,000) and the actual risk of rheumatic fever if untreated is estimated to be 0.3–0.4%.^{18,19}

Antibiotics do not protect against acute glomerulonephritis or subsequent meningitis, but do reduce the incidence of acute otitis media (AOM), acute sinusitis and peritonsillar abscess.^{19,21,22} To avoid unnecessary complications secondary to treatment failures, antibiotic treatment of pharyngitis should be limited to children with a positive GABHS test and throat culture.^{18,19,23}

CLINICAL FEATURES

The clinical manifestations of bacterial pharyngitis in children older than three years are often nonspecific, but typically include an acute onset of sore throat, pain on swallowing, tonsillitis with non-adherent exudates, and enlarged and tender anterior cervical glands. Other symptoms may include a history of fever or scarlatiniform rash.^{19,21,24} The throat soreness typically gets worse over two to three days and then gradually subsides within a week. Children complaining of a sore throat and fever for three days or more should be referred to a physician. Children older than five years are more likely to present with headache.²⁵ Viral etiology is suggested by symptoms such as conjunctivitis, cough, hoarseness, diarrhea or rhinorrhea.^{19,21} The signs and symptoms of viral and bacterial etiologies overlap, hence predictive scoring systems have been developed to limit antibiotic use by determining the probability of pharyngitis based on clinical presentation and age.^{24,26,27} However, these predictive scoring systems require further evaluation and validation in the pediatric population. For example, the presence of all four Centor criteria (fever, absence of cough, tender cervical adenopathy and tonsillar exudates) has a positive predictive value for group A streptococcal pharyngitis of only 56%, constituting only 10% of sore

throat cases seen in practice.²⁸

GABHS testing (i.e., rapid *Streptococcus* antigen test) is performed by throat swab, with results in minutes, while it generally takes at least two to three days to obtain throat culture results. About 20% of school age children are asymptomatic chronic carriers of GABHS (and would have a positive GABHS test); therefore, antibiotics should only be prescribed for children with clinical symptoms of GABHS pharyngitis who have a positive throat culture. Linder's study found GABHS testing was associated with lower antibiotic prescribing rate, but GABHS testing is less accurate than culture, which may lead to unnecessary antibiotic prescribing.²⁹ Throat cultures have been found to be cost effective in lieu of rapid *Streptococcus* antigen tests.³⁰ Antigen tests have a high specificity (98–99%), but a sensitivity of only 70%, which translates to a potential for 30% false-negative results.²⁰ Laboratory confirmation of GABHS (by throat culture) prior to initiating antibiotic treatment is best practice, as delayed therapy is associated with decreased re-infection and relapse rates.¹⁸ Children receiving immediate treatment were twice as likely to relapse with group A *Streptococcus* within four months than were children receiving delayed treatment.^{31,32} Followup cultures are not routinely recommended unless the case is related to a community outbreak or if there is repeated transmission within families.¹⁸

MANAGEMENT

Antibiotic therapy decreases the severity of symptoms, the duration of symptoms by about one day (mean 16 hours), the risk of transmission after 24 hours of therapy and the likelihood of developing rheumatic fever.^{18,19,22} GABHS is invariably susceptible to penicillin (< 1% resistance).¹⁸ Since penicillin VK is more resistant to gastric acid, it is preferred over penicillin G. Erythromycin or clindamycin are alternate agents that can be used in penicillin allergy. Clarithromycin is usually recommended in place of erythromycin, since clarithromycin is better tolerated. The standard duration of therapy for the listed medications (Table 1) is 10 days.^{18,19}

The possibility of resistance to macrolide agents among GABHS isolates is an emerging concern. Although erythromycin resistance among GABHS isolates has been decreasing since 2006, reaching a level of 11.6% in 2008 according to British Columbia Biomedical Laboratories data, this trend correlates to a decreased utilization of erythromycin. The selective pressure realized by increasing use of newer mac-

rolides is concerning, because their long duration at suboptimal antimicrobial concentrations could select for resistance to erythromycin more efficiently. Resistance to macrolides often indicates resistance to clindamycin (2.1% in 2008), as well.³³ Use of cephalosporins and broader-spectrum penicillins (e.g., ampicillin, amoxicillin) should be avoided as this may increase resistance. Patients failing to respond to treatment after 72 hours should be evaluated for relapse, noncompliance or complications (e.g., retropharyngeal abscess). Late relapsing or recurrent pharyngitis should be confirmed by a new throat culture and can be treated with amoxicillin-clavulanate, which has extended activity that covers anaerobes and beta-lactamase producing bacteria.¹⁸

Sinusitis

ETIOLOGY/PATHOPHYSIOLOGY

Sinusitis is among the most commonly encountered childhood diseases. It is characterized as an acute or chronic condition involving inflammation and/or mucosal thickening of one or more of the paranasal sinus cavities.^{18,21} The causes of sinusitis include allergy, viruses, bacteria and, rarely, fungi.³⁵ Acute sinusitis can persist for up to four weeks, with a maximum of three episodes per year. Chronic sinusitis is characterized by frequent recurrence, or symptoms that persist for longer than 12 weeks, with nasal discharge, cough and headache.^{18,34}

Obtaining cultures by nasopharyngeal aspirate is not routinely recommended. This invasive procedure is painful and cultures do not correlate well with causative pathogens. Sinus plain x-rays are also not routinely recommended. CT scan may be used for diagnosis of complications of acute sinusitis or chronic sinusitis that does not respond to treatment. Maxillary tenderness and bilateral opaque maxillary sinuses on radiography suggest maxillary sinus involvement.³⁴

Risk factors predisposing children to sinusitis include undeveloped sinuses, immune deficiency, asthma and gastroesophageal reflux disease. The most common organisms responsible for acute sinusitis are similar to AOM: *S. pneumoniae*, *H. influenzae* and *Moraxella catarrhalis*. Occasionally, pathogens found in chronic infections include *Staphylococcus aureus*, group A streptococci and anaerobes.¹⁸

CLINICAL FEATURES

Increased nasal discharge is a distinct feature of acute sinusitis; however, discharge colour cannot be used to differentiate between bacterial and viral causes.³⁵

Other features of acute bacterial sinusitis include fever, prolonged daytime cough, irritability, lethargy and facial pain.³⁵ Children may demonstrate fewer symptoms as a result of the combined effect of having a shallow sinus and a wider ostium, which prevents the occurrence of pressure symptoms.³⁶ A preceding two-week history of viral upper RTI with persistent symptoms without improvement is reported in 0.2–2% of cases.¹⁸

Allergic rhinitis is a common predisposing factor for sinusitis; therapy aimed at decreasing allergic mucosal edema stops recurrent sinusitis symptoms. As well, in patients with underlying asthma, impaired nasal function increases post-nasal drip and irritant burden on the lower airways, thereby causing asthma exacerbations.^{36–39} Treatment of sinusitis may significantly decrease exacerbations of chronic asthma.^{40,41}

MANAGEMENT

In selecting antibiotic therapy for acute sinusitis, agents should have activity against *S. pneumoniae*, the most common pathogen. The first-line antibiotic is amoxicillin, with dosing tailored to local resistance patterns and child risk factors.^{18,34} High-dose amoxicillin (Table 1) is suitable for children with daycare attendance and/or recent antibiotic exposure in the past three months. In children with beta-lactam allergy, trimethoprim-sulfamethoxazole (TMP-SMX) may be considered, but *S. pneumoniae* resistance to this combination is increasing.¹⁸ Children with recurrent sinusitis within three months or with no improvement after 72 hours on high-dose amoxicillin should be treated with amoxicillin plus amoxicillin-clavulanate (Table 1). This combination provides comprehensive anaerobic coverage with activity effective against beta-lactamases.^{18,34} Cephalexin, cefaclor, cefixime, ceftriaxone and erythromycin should not be chosen due to poor activity of these agents against penicillin-intermediate and resistant strains of *S. pneumoniae*. In addition, clindamycin should be avoided in acute sinusitis treatment since it has no activity against *H. influenzae* or *Moraxella* species. Macrolide therapy is also considered less efficacious than amoxicillin-clavulanate.^{18,42}

Studies evaluating the clinical benefit of antibiotic treatment in children who are diagnosed with acute uncomplicated sinusitis by clinical criteria without radiograph images support the first-line use of amoxicillin, while insufficient evidence supports the use of broad-spectrum antibiotics.^{43–45} Wald's study found antibiotics to be superior to placebo in a population defined by

positive radiographs and symptoms of nasal discharge or cough that were not improving after at least 10 days. The overall difference in cure rates between children receiving placebo and those receiving antibiotics at the end of 10 days of therapy was about 20%.⁴⁴ Despite the fact that these studies were reported before the era of increased resistance among *Streptococcus* isolates, the rates of spontaneous resolution were high for acute uncomplicated sinusitis. The benefit of antibiotic therapy remains controversial as 70% of cases resolve spontaneously.¹⁸

Otitis media

ETIOLOGY/PATHOPHYSIOLOGY

AOM is the most frequently diagnosed bacterial infection in early childhood. In British Columbia, the number of otitis media-related physician visits per child in a three-year followup period of a cohort of 50,474 children was 1.14 (38 visits per 100 child-years), and acute and recurrent otitis media accounted for 49.3% and 7.8% of cases, respectively.⁴⁶ On average, at least 80% of children will be diagnosed with AOM at least once by three years of age, with the incidence peaking at ages six to 24 months.^{21,47}

Otitis media is an inflammation of the middle ear signified by local or systemic findings, with a bulging or inflamed tympanic membrane. Otitis media often develops (30% of cases) following an upper RTI.⁴⁸ Most episodes of AOM occur when clearance of congestion from the nasopharynx is impaired, resulting in pressure changes and obstruction in the Eustachian tube, since children tend to have a relatively shorter and more horizontal ear canal. As well, children are more prone to AOM than adults due to a decreased immunity level and more frequent episodes of upper RTIs and allergies.^{21,47}

The leading bacterial isolates from cultures of the middle ear fluid in AOM include *S. pneumoniae* (27–52%), *H. influenzae* (16–52%) and *M. catarrhalis* (2–27%).⁴⁷ Other less common causes include *S. aureus* and group A *Streptococcus*, as well as the atypical organisms *Chlamydia trachomatis* and *Mycoplasma pneumoniae*. Since the introduction of the heptavalent pneumococcal conjugate vaccine (PCV7) in 2000, the microbiology of AOM has shifted towards gram-negative pathogens, namely beta-lactamase producing *H. influenzae* in children who have received PCV7.^{49,50} *S. pneumoniae* cannot be ignored, as it is more prominent in children older than two years because PCV7 only covers 40% of serotypes in this age group.⁵¹ It is also important to note that no bacterial pathogen may be identified in up

table 1

Antibiotics for treatment of common community-acquired pediatric respiratory infections^{18,27,41,52,88,101}

Infection	Indications for antibiotic treatment	Pathogens	Antibiotic	Oral pediatric dosage (max mg/day)
Pharyngitis	<p>When to treat with an antibiotic: Symptoms and signs: sore throat, fever, pharyngeal tonsillar erythema, exudates, tender enlarged lymph nodes, absence of cough</p> <p>Confirm diagnosis with throat culture</p>	<p><i>Streptococcus pyogenes</i> (group A Strep)</p>	<p>First line: • Penicillin VK¹</p> <p>For β-lactam allergy: Erythromycin or clindamycin</p> <p>Failure/relapse: Failure to respond after 72 hours of antibiotics or</p> <p>Early relapse: 2-7 days post-therapy</p> <p>Erythromycin or clindamycin</p> <p>Late relapse or recurrence: • Amoxicillin-clavulanate or clindamycin, erythromycin, penicillin VK</p>	<p>40 mg/kg/day in 2 or 3 divided doses (750 mg/day) Duration 10 days</p> <p>40 mg/kg/day in 3 divided doses 20 mg/kg/day in 3 divided doses Duration 10 days</p> <p>Change in antibiotic may not be required; check noncompliance or suppurative complications</p> <p>Repeat throat swab—only treat if positive for group A streptococci</p> <p>40 mg/kg/day in 3 divided doses 20 mg/kg/day in 3 divided doses (1.8 g/day) Duration 10 days</p> <p>40 mg/kg/day² in 3 divided doses 20 mg/kg/day in 3 divided doses 40 mg/kg/day in 3 divided doses 40 mg/kg/day³ in 2 or 3 divided doses Duration 10 days</p>
Sinusitis	<p>When to treat with an antibiotic: Acute symptoms (< 4 weeks) and prior history of URTI⁴ (with purulent nasal discharge or daytime cough; severe illness with fever, cough, irritability, lethargy, facial pain) not improving after 10 days or worsening after 5-7 days.</p>	<p><i>Streptococcus pneumoniae</i></p> <p>nontypeable <i>Haemophilus influenzae</i></p> <p><i>Moraxella catarrhalis</i></p> <p>Occasionally <i>Staphylococcus aureus</i>, group A streptococci, anaerobes</p>	<p>Acute first line: • Amoxicillin High-risk children⁵ • Amoxicillin</p> <p>For β-lactam allergy: • TMP-SMX⁶</p> <p>Failure alternatives: reevaluate patient and switch to second-line antibiotic: • Amoxicillin plus amoxicillin-clavulanate or</p> <p>• Cefuroxime axetil</p> <p>For β-lactam allergy⁷: • Azithromycin or clarithromycin</p>	<p>Standard dose: 40 mg/kg/day (500 mg 3 times a day)</p> <p>High dose: 90 mg/kg/day (1000 mg 3 times a day) Duration 10 days</p> <p>6-12 mg/kg/day (320mg/day) based on TMP component x 10 days</p> <p>Failure to respond after 72 hours of antibiotics or < 6 weeks between episodes</p> <p>45 mg/kg/day of amoxicillin plus additional 45 mg/kg/day of amoxicillin component (7:1 formulation) Duration 10 days</p> <p>30 mg/kg/day in 2 or 3 divided doses for 10 days</p> <p>10 mg/kg on day 1(500 mg/day), then 5 mg/kg daily (250 mg/day) x 4 days 15 mg/kg/day in 2 divided doses (500 mg/day for weight up to 40 kg) Duration 10 days</p> <p style="text-align: right;">Table 1 continued on next page</p>

to 30% of patients, since viruses play a significant role in AOM etiology.^{21,34,47}

Complications of AOM include hearing loss, tympanic membrane perforation, otorrhea, recurrent otitis media, persistent middle ear effusion and mastoiditis. Risk factors associated with the development of AOM include increased exposure to other children (e.g., daycare setting, older siblings at home), exposure to cigarette smoking in the household or to seasonal allergens, and ethnic origin (e.g., more common in the First Nations population).^{21,24,47,52} Exclusive breast feeding for three to six months can decrease the incidence of AOM by 13%, with protective effects lasting up to 12 months.³⁴

MANAGEMENT

Despite the microbiological shift towards beta-lactamase producing strains of *H. influenzae*, oral amoxicillin is still the first-

line treatment for uncomplicated AOM, even in children vaccinated with PCV7 (Table 1).⁴⁹ Amoxicillin retains the best activity against *S. pneumoniae*, including penicillin-intermediate strains. Dosing depends on whether the patient is considered to be at low or high risk for drug-resistant *S. pneumoniae* (DRSP).¹⁸ Clinical cure is often demonstrated even when beta-lactamase producing organisms are cultured. High-dose amoxicillin (maximum 90 mg/kg/day) is recommended in children with recent antibiotic exposure and/or daycare centre attendance, or recurrent AOM (6 weeks to 3 months apart).¹⁸ Clinicians overestimate the extent to which clinical failure is due to antibiotic resistance, often relying on second-line medications to cover resistant organisms.⁵³ Treatment with amoxicillin-clavulanate (7:1 formulation) or cefuroxime axetil is recommended when failure occurs while on amoxicillin. DRSP

is more likely the cause of failure, rather than beta-lactamase producing *H. influenzae* or possibly the presence of a mixed infection despite adequate amoxicillin therapy. This fact emphasizes the importance of maintaining excellent *S. pneumoniae* coverage. Adding amoxicillin (45 mg/kg/day) to amoxicillin/clavulanate provides additional DRSP coverage (versus either used alone), while providing additional coverage for beta-lactamase *H. influenzae*. Cefuroxime axetil and cefprozil have reasonable activity against *H. influenzae*, including beta-lactamase producing strains, but are broader spectrum and less effective than amoxicillin against DRSP. Common reasons for treatment failures include non-compliance, due to too frequent daily dosing, poor palatability of antibiotics and adverse gastrointestinal effects. Agents not routinely recommended include cephalixin, cefaclor, ceftriaxone, cefixime,

table 1 *continued*

Infection	Indications for antibiotic treatment	Pathogens	Antibiotic	Oral pediatric dosage (max mg/day)
Otitis media	When to treat with an antibiotic: 1. Recent (usually abrupt) onset of signs and symptoms of middle-ear inflammation and effusion AND 2. Presence of middle-ear effusion 3. Signs or symptoms of middle-ear inflammation Age group: 1. < 6 mo: antibiotics 2. 6 mo - 2 yrs: antibiotics (10-day treatment) if diagnosis certain and severe illness 3. > 2 yrs: Watchful waiting for 48-72 hours or antibiotics (5 days of treatment) if diagnosis certain and severe illness	<i>Streptococcus pneumoniae</i> nontypeable <i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i>	First line: Amoxicillin High-risk children: Second-line alternatives: Non-anaphylactic penicillin allergy • Cefuroxime axetil Severe penicillin/ beta-lactam allergy TMP-SMX Failure on standard dose amoxicillin Amoxicillin plus amoxicillin/clavulanate Failure on high-dose amoxicillin Amoxicillin/clavulanate or • Cefuroxime axetil Severe penicillin/ beta-lactam allergy Azithromycin or Clarithromycin Failure of second-line agents: ceftriaxone or clindamycin	Standard dose: 40 mg/kg/day High dose: 90 mg/kg/day Duration 5 days 30 mg/kg/day in 2 divided doses Duration 5 days 6-12 mg/kg/day (TMP component) in 2 divided doses Duration 5 days 45 mg/kg/day plus 45 mg/kg/day (amoxicillin component; 7:1 formulation) Duration 10 days 40 mg/kg/day (4:1 formulation) Duration 10 days 30 mg/kg/day in 2 divided doses Duration 10 days 10 mg/kg day 1, then 5 mg/kg daily x 4 days 15 mg/kg/day (500 mg/day for weight up to 40 kg) x 10 days 50 mg/kg/day IM x 3 days 20-30 mg/kg/day
Pneumonia > 3 months to 5 years of age	When to treat with an antibiotic: Signs include fever, tachypnea, tachycardia, crackles, bronchial breath sounds, and dullness to percussion. Signs of pleural effusion may also be present. Nasal flaring, use of accessory muscles, and cyanosis are common in infants. Symptoms include malaise, cough, dyspnea, and chest pain. Cough typically is productive in older children and dry in infants. Infants may exhibit nonspecific irritability and restlessness	<i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> Group A or B streptococci , Enterobacteriaceae, <i>Haemophilus influenzae</i> , <i>Staphylococcus aureus</i>	Amoxicillin Mild⁸ High-risk children Severe penicillin/ beta-lactam allergy Clarithromycin Erythromycin or Azithromycin Treatment failure • Cefuroxime axetil or amoxicillin/clavulanate +/- erythromycin ⁹	Standard dose: 40 mg/kg/day (500 mg 3 times a day) High dose: 90 mg/kg/day (1000 mg 3 times a day) Duration 7-10 days 15 mg/kg/day in 2 divided doses (500mg/day for weight up to 40 kg) Duration 7-10 days 40 mg/kg/day in 4 divided doses (2000 mg/day) Duration 7-10 days 10 mg/kg day 1 (500 mg/day), then 5 mg/kg daily x 4 days (250 mg/day) 30 mg/kg/day (500 mg twice day) 40 mg/kg/day in 3 divided doses 40 mg/kg/day in 4 divided doses x 7-10 days
Pneumonia > 5 years of age	When to treat with an antibiotic: See above	<i>Streptococcus pneumoniae</i> <i>Chlamydia pneumoniae</i> <i>Mycoplasma pneumoniae</i> Group A streptococci , <i>Haemophilus influenzae</i> , <i>Staphylococcus aureus</i>	Age > 5 years: Mild⁸ Clarithromycin Erythromycin or Azithromycin or Age > 8 years: Doxycycline Treatment failure • Cefuroxime axetil or amoxicillin/clavulanate + erythromycin ⁹	15 mg/kg/day in 2 divided doses (500mg/day for weight up to 40 kg) Duration 7-10 days 40 mg/kg/day (2 g/day) Duration 7-10 days 10 mg/kg day 1 (500 mg/day), then 5 mg/kg daily x 4 days (250 mg/day) 4 mg/kg/day divided every 12 hrs (200 mg/day) Duration 7-10 days 30 mg/kg/day in 2 divided doses 40 mg/kg/day in 3 divided doses 40 mg/kg/day in 4 divided doses Duration 7-10 days

1. Penicillin V is preferred over penicillin G as it is more resistant to gastric acid. Ampicillin and amoxicillin are often used for treatment of group A streptococcal pharyngitis, but they provide an unnecessarily broad spectrum of activity compared to penicillin; 2. Pediatric doses should not exceed the recommended adult dose (usually 3g/day). Dose children who weigh ≥ 38 kg according to adult recommendations; 3. Penicillin VK should be effective, but agents with beta-lactamase inhibition may be superior. Macrolide and clindamycin resistance to group A streptococci is increasing; 4. URFI = upper respiratory tract infection; 5. High-risk children: Higher dose should be used in children with recent antibiotic exposure (within the past 3 months) and/or daycare attendance; 6. TMP-SMX = trimethoprim-sulfamethoxazole; Consider increasing S. pneumoniae resistance to TMP-SMX. If beta-lactam allergy and previous exposure to antibiotics, then use azithromycin or clarithromycin (not erythromycin); 7. Macrolide use should be restricted, as resistance is increasing and they generally have poor/no activity against H. influenzae and S. pneumoniae; 8. Moderate to severe: recommend hospital admission for intravenous therapy; 9. Chest X-ray to rule out empyema

clindamycin, tetracycline, rifampin and erythromycin.¹⁸ The recommended duration of treatment for AOM is five days, or 10 days for patients at high risk of recurrence

or complications.⁵⁴ TMP-SMX is commonly used in penicillin-allergic children, but resistance is higher than 20% for isolates of *S. pneumoniae* (reported in 2007).⁵⁵ Pro-

phylactic antibiotics are no longer recommended for recurrent AOM, as prophylaxis provides only a slight benefit, reducing occurrence by about one episode per year.¹⁸

CLINICAL TRIALS AND CONTROVERSIES

Several decision trees and treatment algorithms have been developed for the treatment of AOM, including the Ear Card system and the Observation Option Toolkit for accurate assessment of children with AOM.⁵⁶⁻⁶⁰ Treatment guidelines are based upon age and severity of symptoms, as well as on the presence of high-risk factors for resistance or history of recurrent episodes.¹⁸ Children six months to two years of age with definite signs of infection and children with severe infection upon presentation should receive antibiotics immediately.⁵⁶ A review of recent literature suggests that antibiotics are not necessary in many cases of AOM provided that there is good followup.¹⁸ Most cases (80%) of AOM resolve spontaneously within three days without treatment.^{18,56} The NNT for one child to benefit (resolution of symptoms one day sooner, on average) from initial antibiotic therapy is between seven and 20.⁶¹ The standard initial treatment of AOM in the Netherlands does not include antibiotics, which has decreased the emergence of DRSP without increasing complications.⁶¹ Clinical resolution will occur in a significant number of cases without antibiotics with “watchful waiting” in children with fever, ear pain but no bulging tympanic membrane.⁶²⁻⁶⁵ Children with AOM who are at low risk for serious sequelae include those older than two years of age with mild unilateral AOM, no toxicity or severe pain, late presentation (> 36 hours), no chronic disease, no otorrhea, no history of chronic or recurrent AOM and the availability of good followup.⁶⁶ The observation approach was well accepted in an emergency department study setting and it reduced antibiotic exposure by 67%.⁶⁷⁻⁶⁹ The delayed prescription strategy not only saves considerable expense, but also potentially lowers the development of antibiotic resistance resulting from the treatment of a primarily self-limiting upper RTI. Children with AOM who were routinely given amoxicillin for seven to 10 days gained about 3.5 hours of quality-adjusted life at an additional cost of U.S.\$22.90 compared with children managed with delayed prescription.⁷⁰

Prevention of otitis media by the advent of pneumococcal conjugate vaccines would be advantageous to reduce antibiotic consumption and reduce complications such as mastoiditis. However, the introduction of the heptavalent pneumococcal conjugate vaccine (PCV7) has been associated with only a modest decrease (i.e., 6–7%) in AOM episodes.⁷¹⁻⁷⁶ Serotypes covered by the vaccine will lead to a reduction in nasal carriage of these resistant isolates.⁷⁷ A

significant reduction in overall incidence of acute otitis media (34%) was reported in the POET study using an 11-valent pneumococcal conjugate vaccine, which is not currently available in Canada. The 11-valent vaccine uses a protein D of *H. influenzae* as a carrier (PncPD11) for enhanced activity.⁷⁸ In addition to reducing the incidence of the first episode of AOM, it also reduced the occurrence of AOM due to non-typable *H. influenzae* (NTHi). The absolute reduction of all AOM episodes was 6.7% (NNT=15). Four doses of the vaccine per child (or 60 doses in total) were needed to prevent one episode of AOM.⁷⁹ Future pneumococcal conjugate vaccines in the pipeline include 10-valent (approved by Health Canada in late 2008) and 13-valent vaccines. They are expected to deliver a broader public health benefit, since they contain serotypes 1, 5 and 7F, which are responsible for an estimated five to 25% of all invasive pneumococcal infections; they also contain carrier proteins for enhanced protection against NTHi.

The benefits of the pneumococcal conjugate vaccine are derived primarily from preventing invasive disease and resistant infections.⁶⁶ Modest decreases in the incidence of acute otitis media are seen as ancillary benefits of the PCV7 vaccine.⁸⁰ Declining trends in the incidence of uncomplicated AOM, treatment failure, and relapse in children (2 months to 12 years) during the past decade have been credited to increased antibiotic prescribing scrutiny.^{81,82}

Community-acquired pneumonia

ETIOLOGY/PATHOPHYSIOLOGY

CAP accounts for numerous emergency department and physician office visits, and remains a major cause of pediatric hospitalization (741 per 100,000 population from 1996–1998 in Canada).⁸³ The standard World Health Organization algorithm for acute RTIs specifies two signs as entry criteria for examining a child under five years for possible pneumonia: cough, and difficult or fast breathing.⁸⁴

Causative pathogens for CAP differ by age group. For neonates (birth to 20 days) the most common pathogens are group B *Streptococcus* and gram-negative enteric bacteria obtained via vertical transmission at birth. For infants aged three weeks to three months, the most common pathogens are *S. pneumoniae* and *C. trachomatis*. Less common pathogens in this age group include *H. influenzae* type B, *M. catarrhalis* and *S. aureus*.⁸⁴ For infants older than four months and preschool-age children,

viruses (respiratory syncytial virus, parainfluenza, and influenza) are the most frequent cause of CAP. For children five years and older, pathogens associated with CAP include *S. pneumoniae*, group A streptococci, *M. pneumoniae* and *Chlamydia pneumoniae*.^{85,86}

CLINICAL FEATURES

Features of CAP include the presence of high fever, acute respiratory symptoms, or both, with evidence of parenchyma infiltrates on a chest radiograph.⁸⁵⁻⁸⁸ Studies looking at predictors of CAP have found that increased erythrocyte sedimentation rate and an assay for C-reactive protein (CRP) are not helpful in differentiating viral from bacterial sources of infection.⁸⁹⁻⁹¹ The threshold values needed for CRP to correlate with a positive predictive bacterial pneumonia are quite high, in the range of 400–600 mg/L.⁹¹

MANAGEMENT

The etiology of CAP is rarely identified in a timely manner, thus treatment is usually empirical. Knowledge of the prevailing local antimicrobial susceptibility patterns can be used to guide empiric treatment. Amoxicillin (40 mg/kg/day in divided doses) retains the best coverage of all oral beta-lactam agents against *S. pneumoniae*, including intermediate-resistant strains. Amoxicillin has no activity against *S. aureus* or beta-lactamase producing *H. influenzae*. Higher doses of amoxicillin (90 mg/kg/day, divided every eight hours) should be given to children with recent antibiotic exposure (within the previous 3 months) or daycare attendance. Using the higher dosage provides coverage for penicillin-nonsusceptible strains. Macrolides are a treatment option for children with a beta-lactam allergy. However, the previous use of macrolides (especially azithromycin) within three months may result in multiresistant *S. pneumoniae*.^{18,88,92,93} The optimal duration of outpatient therapy for uncomplicated pneumonia ranges from seven to 10 days depending on clinical response. If the child's condition deteriorates or does not improve in two or three days, the possibility of other pathogens or a complication (empyema or abscess) should be considered.⁹³ Children with a seizure disorder or underlying neuromuscular disease who may have aspirated should receive amoxicillin or amoxicillin-clavulanate to cover anaerobes.⁹³

The pharmacist's role

Community pharmacists are in the opportune position to assist physicians in the selection of the appropriate first-line

therapy for a RTI (Table 1). Pharmacists should be aware of local resistance patterns, as resistant strains of *H. influenzae* and *S. pneumoniae* have been reported by provincial laboratories (<http://microbiology.mtsinai.on.ca>). Drug-resistant *S. pneumoniae* develop through the genetic alteration of penicillin-binding cell wall proteins, which decreases the affinity of beta-lactam antibiotics for target binding sites.³³ High-dose amoxicillin ensures adequate drug levels to overcome many of the resistant pneumococci. For *H. influenzae* and *M. catarrhalis*, beta-lactamase production imposes resistance to amoxicillin requiring the addition of clavulanate for activity. By reinforcing compliance with antibiotic therapy, pharmacists can decrease the potential for resistance, relapse and re-infection.

Pharmacists can educate a child's caregiver about the importance of proper refrigeration of some antibiotic suspensions, to ensure potency and successful treatment. They should also be aware of antibiotic side effect profiles. Amoxicillin-clavulanate is often associated with rash, vomiting and significant diarrhea (> 10 mg/kg/day of clavulanate).^{18,34} If cefuroxime axetil suspension is not tolerated due to poor palatability, then pharmacists can recommend using tablets instead or consider alternatives such as cefprozil suspension. Cefprozil has a better taste, but has inferior coverage compared to cefuroxime for *H. influenzae* and penicillin-intermediate-resistant *S. pneumoniae*.²¹

Pharmacists can promote symptomatic care measures, such as acetaminophen, ibuprofen and warm compresses to reduce

facial pain in sinusitis. They should educate caregivers about the proper dosing of acetaminophen (10–15 mg/kg per dose every 4–6 hours) and ibuprofen (5–10 mg/kg per dose every 8 hours). Ibuprofen can be helpful at night because of its longer duration of action. A topical analgesic, such as benzocaine or lidocaine eardrops, may be a useful adjunct to oral analgesia to provide rapid relief of ear pain in children with otitis media.^{94,95}

Symptomatic care measures that pharmacists should advise parents against include the use of antihistamines and decongestants in children less than 12 years old with sinusitis or otitis media.^{21,96} Although short-term topical or systemic decongestants can reduce congestion and the risk of secondary bacterial sinusitis in adolescents, the prolonged use of topical agents (> 5 days) should be avoided as it may lead to rebound congestion.²¹ Antihistamines have no role in the management of acute sinusitis in children because they dry the sinus secretions and may decrease mucociliary clearance.³⁶

Pharmacists may suggest saline nasal drops or spray as a safe therapy to help promote drainage of secretions; intranasal corticosteroids are not advisable because they provide only modest benefits and have the potential for systemic adverse effects.^{37,43,97} Oral corticosteroids used in conjunction with antibiotic therapy resolve otitis media with middle ear effusions more effectively than antibiotics alone.⁹⁸ In a randomized study, children with GABHS pharyngitis who received dexamethasone as add-on therapy to antibiotics showed a more rapid improvement

in general condition and level of activity; those who received three daily doses of dexamethasone also demonstrated resolution of throat pain. However, despite these results, dexamethasone treatment is not without risks; more studies are needed to determine whether oral dexamethasone treatment for uncomplicated streptococcal pharyngitis is both safe and beneficial.⁹⁹

Pharmacists are accessible to caregivers and can assist in identifying the warning symptoms that may signify the need for medical attention in children who have acute respiratory illnesses. These include difficulty breathing, rapid onset of symptoms, fever, cough and wheezing.¹⁰⁰

Summary

The initiation of appropriate treatment of common pediatric RTIs is of primary importance to prevent the emergence of antimicrobial resistance. Pharmacists can play an active role and take responsibility for antibiotic management in their communities by tailoring antibiotic selection to local resistance patterns. For this statement to mean more than a modicum of truth, we need to take small incremental steps towards active antibiotic stewardship. Pharmacists working together with physicians can alter the future antimicrobial resistance landscape by reducing the antibiotic usage footprint in our communities.

References available online at www.pharmacygateway.ca (Go to Continuing Education, CE Archives, *Pharmacy Practice CE Lessons*, April/May 2009.)

Questions

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

1 Which of the following is the most common pathogen seen in community-acquired pneumonia in children over the age of five?

- a) *Haemophilus influenzae*
- b) *Streptococcus pneumoniae*
- c) *Moraxella catarrhalis*
- d) *Staphylococcus aureus*

2 Which of the following describes the mechanism of antimicrobial resistance for penicillin-resistant *S. pneumoniae*?

- a) production of an enzyme known as beta-lactamase
- b) alteration of penicillin-binding proteins in cell wall
- c) active efflux or inactivation of drug by bacteria
- d) increased permeability of the bacteria into the cell

3 *S. pneumoniae* resistance to penicillins may be overcome by:

- a) addition of a beta-lactamase inhibitor, such as clavulanate, to amoxicillin

b) administering small doses of amoxicillin more frequently

- c) administering high-dose amoxicillin
- d) administering intravenous penicillin

4 Is the following statement true or false? Chronic sinusitis is diagnosed when symptoms of sinusitis persist for six weeks, and often involves the pathogens *S. aureus*, anaerobes and resistant organisms.

- a) true
- b) false

5 Which of the following is true regarding the use of macrolides in CAP?

- a) Erythromycin is the preferred macrolide for the treatment of CAP.
- b) Previous use of macrolides (especially azithromycin) within three months may result in multi-resistant *S. pneumoniae*.
- c) Erythromycin has better activity against *H. influenzae* compared to clarithromycin.

d) Macrolides have no activity against atypical pathogens such as *M. pneumoniae*, *Chlamydia pneumoniae* and *Legionella*.

6 Which of the following is/are true regarding the reasons for treatment failure in RTIs?

- a) Too frequent daily dosing, leading to noncompliance.
- b) Poor palatability of antibiotics and adverse gastrointestinal side effects.
- c) Improper storage of some antibiotic suspensions.
- d) All of the above.

7 In atopic patients, controlling allergic rhinitis with antihistamines should help decrease episodes of acute sinusitis.

- a) true
- b) false

Questions

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

8 A four-year-old child comes to the clinic with her first case of otitis media. She presents with fever and otalgia, without a bulging tympanic membrane. She has no other siblings at home and has had no previous antibiotics in the past three months. Which one of the following recommendations would you suggest to the physician for treatment?

- Blood cultures should be taken to identify the causative organism.
- Antibiotics are not warranted at this time. Patient advised to return if symptoms continue beyond 48 hours or worsen.
- Azithromycin should be started to provide coverage for *Mycoplasma*.
- Intramuscular ceftriaxone should be given once daily for three doses.

9 The child (see question 8 above) returns to the clinic after 48 hours with symptoms not resolved and worsening of ear pain. Which of the following would be the most appropriate recommendation regarding her treatment considering she has no history of drug allergies?

- high-dose amoxicillin
- standard-dose amoxicillin
- azithromycin or trimethoprim-sulfamethoxazole
- tympanocentesis and culture for sensitivities

10 A six-year-old child is diagnosed with his fourth case of otitis media in 12 months. Would you recommend low-dose and long-course prophylaxis with beta-lactam antibiotics for AOM to decrease the risk of PRSP carriage?

- yes
- no

11 Which of the following recommendations regarding pneumococcal vaccine is most appropriate for a child 12 months of age with no previous vaccination?

- administer pneumococcal conjugate vaccine
- administer pneumococcal polysaccharide vaccine
- too late for catch up immunization, recommend deferring vaccination until a later date with influenza vaccine
- do not vaccinate as the child is not in the range of recommended ages

12 A five-year-old child is diagnosed with mild community-acquired pneumonia that was preceded by a RTI. The child does not require hospitalization but lives in an area of high

pneumococcal resistance. Which of the following interventions would you recommend as initial treatment considering he has no history of drug allergies?

- low-dose amoxicillin
- high-dose amoxicillin
- amoxicillin-clavulanate
- azithromycin

13 Which of the following is true regarding *S. pneumoniae* resistance to macrolides?

- Macrolide resistance has been shown to have a negative impact on treatment outcomes.
- S. pneumoniae* macrolide resistance is not prevalent in the United States and Canada.
- Risk of *S. pneumoniae* macrolide resistance increases with previous treatment exposure.
- All of the above.

14 Which of the following describes the preventive role pharmacists can take to minimize the development of resistance?

- Pharmacists can guide physicians and other healthcare professionals in selection of appropriate antibiotics.
- Pharmacists can educate patients and improve compliance with antimicrobial agents.
- Pharmacists can get involved in community programs to promote appropriate antibiotic use.
- All of the above.

15 Which of the following statements is/are true regarding the treatment management of otitis media?

- Amoxicillin/clavulanate dosed 40 mg/kg/day should be given in at least three divided doses to maximize the time that concentrations remain greater than the minimum inhibitory concentration (MIC).
- Due to increasing antibiotic resistance, antibiotic prophylaxis is no longer recommended for the management of recurrent otitis media.
- Five-day treatment is recommended in children more than two years old.
- All of the above.

16 Which of the following is not a contributing factor to antimicrobial resistance?

- delayed initiation of antimicrobial therapy
- inappropriate antibiotic selection
- inappropriate dose of antibiotic
- previous antibiotic therapy in the past three months

17 Which of the following is a true statement regarding the antibiotic treatment for acute sinusitis?

- Antibiotics are moderately effective for acute sinusitis.
- Antibiotics are not effective in the management of acute sinusitis.
- Only amoxicillin-clavulanate is effective for the treatment of acute sinusitis.
- Only macrolides are effective for the treatment of acute sinusitis.

18 A five-year-old child presents to the clinic with a two-day history of fever, complaining of sore throat and abdominal pain, but no cough. On exam, swollen tonsils and tender anterior cervical lymphadenopathy are seen. The culture result was strongly positive for group A streptococcal infection. Which of the following is the best intervention to recommend to the physician?

- watchful waiting or wait-and-see approach, no antibiotics
- oral amoxicillin
- oral amoxicillin-clavulanate
- oral penicillin VK 40 mg/kg/d in 2 or 3 divided doses

19 For most children the benefits of administration of the pneumococcal vaccine and the primary reason for vaccination would be for:

- reduction of risk of AOM
- reducing the risk of complications from AOM
- prevention of invasive pneumococcal disease and resistant infections
- all the above

20 Which of the following is true regarding appropriate diagnostic tools for evaluating respiratory tract infections?

- Bacterial cultures of samples from the nasopharynx and throat have little predictive value in CAP.
- Increased erythrocyte sedimentation rate and assay for C-reactive protein (CRP) are helpful in differentiating a viral from bacterial CAP infection.
- The threshold values needed for CRP correlating with a positive predictive bacterial pneumonia are quite low (< 400–600 mg/L).
- All of the above.

ce faculty

THIS MONTH

Optimizing antibiotic therapy for common childhood respiratory infections

AUTHORS

Susanne works as clinical pharmacy specialist where she is involved in treatment plans for adult and pediatric patients with respiratory illnesses admitted through the emergency department. She has also been involved in research projects at the BC Centre for Disease Control. Currently she is a representative on the Infection Control Committee whose purpose is to recommend standards and policies for infection control at the hospital. As part of her hospital practice, she is also involved in several infectious disease projects, including planning for influenza, hospital-acquired pneumonia and *Clostridium difficile* outbreaks.

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

This lesson is valid until April 7, 2012. Information about antibiotic therapy for common childhood respiratory infections may change over the course of this time. Readers are responsible for determining the most current aspects of this topic.

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