THE PHARMACIST'S ROLE IN
Outpatient Pediatric Antibiotic Stewardship

ABSTRACT: Traditionally considered an inpatient activity, antimicrobial stewardship is making inroads in the community. Pharmacists and pharmacy technicians need a good understanding of antimicrobial stewardship activities and how they apply to four common pediatric infections that may be viral or bacterial—acute otitis media, acute bacterial sinusitis, pharyngitis, and community acquired pneumonia. By increasing vigilance for antibiotic misuse and promoting appropriate vaccinations, pharmacy staff become activists in the fight against microbial resistance.

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INTRODUCTION

Our faculty presents this continuing education activity in two parts. Part 1 covers common pediatric infections through the lens of antimicrobial stewardship. It discusses four common pediatric infections—acute otitis media, acute bacterial sinusitis, pharyngitis, and community acquired pneumonia—and educates pharmacy staff about current guideline recommendations that strive to reduce unnecessary antibiotic use.

Part 2 looks at antibiotic stewardship from a different angle. It recognizes that many patients need or want more than one reason to appreciate fully why prescribers may seem “stingy” with antibiotics. It also discusses antibiotic overuse and its potential repercussions to individual children and its proven affects on the environment and society at large.

The post-tests cover both parts in one document.
Acute Otitis Media

Acute otitis media (AOM) is one of the most common reasons children receive antibiotics. Prevalence is higher among children who are enrolled in daycare or have siblings because contact with others in close proximity increases the likelihood pathogens will spread. Common causative bacterial pathogens include Streptococcus pneumoniae, non-typeable Haemophilus influenzae, and Moraxella catarrhalis. The American Academy of Pediatrics (AAP) published the current AOM treatment guidelines in 2013; they provide recommendations for the treatment of AOM in otherwise healthy patients six months of age and older.

The guidelines recommend that all children who have AOM receive treatment for pain with a systemic analgesic such as acetaminophen or ibuprofen. Ear drops containing benzocaine,procaine, or lidocaine should be used only as adjunctive therapy because of limited evidence of effectiveness. Study results are unclear about whether these ear drops improve the illness, soothe symptoms related to liquid in the ear, or have a placebo effect.

Stewardship programs in outpatient settings have different characteristics than those in inpatient areas. In 2016, the CDC published unique Core Elements for ASP in Outpatient Settings. These guidelines suggest inappropriate usage in these settings is often related to knowledge gaps, patient expectations that they need antibiotics, lack of sufficient time to see patients, and/or concern regarding patient satisfaction scores if patients do not receive antibiotic prescriptions. Community pharmacists who are confident in their knowledge of current recommendations for the treatment of infectious diseases can assume an important role in outpatient stewardship.

This continuing education activity reviews recommended treatment for four common bacterial infections (acute otitis media, bacterial sinusitis, pharyngitis, and community-acquired pneumonia) and vaccines’ role in prevention in children.
Specific groups of children (see Table 1), including those with severe presentation should also receive antibiotics. Severe presentations of AOM include temperature of 102.2°F (39°C) or higher, severe ear pain that restricts normal activity (e.g. sleep), or ear pain that persists for more than 2 days. Additionally, other patients diagnosed with AOM can either receive antibiotics or be observed to ensure that their symptoms improve as expected. Further, even when antibiotic therapy is initiated, clinicians should reevaluate the patient within 48 to 72 hours to assess appropriate response to therapy.

If a child is not responding to therapy, the prescriber should reassess and consider stepping up therapy to include antibiotics that overcome the suspect reason for therapy failure. Antibiotics that should be considered include amoxicillin/clavulanate acid (Augmentin), linezolid, levofloxacin, and clindamycin.

The guidelines recommend amoxicillin as first-line therapy at a dose of 80 to 90 mg/kg/day divided twice daily. In older children, the maximum dose is 1000 mg/dose. Inner ear concentrations of amoxicillin have a much longer half-life than serum concentrations, which allows twice daily dosing. Alternative recommendations are summarized in Table 2.

Patients with conjunctivitis, recent use of amoxicillin, and those who have failed to respond to appropriately-dosed amoxicillin therapy are more likely to have infections caused by H. influenzae. Because almost 50% of H. influenzae produce beta-lactamase, the guidelines recommend these patients receive amoxicillin/clavulanic acid.

In patients with penicillin allergy, clindamycin, cefuroxime, or a third generation cephalosporin (e.g. cefdinir, cefpodoxime) are alternative antibiotics. Importantly, clindamycin is an alternative antibiotic that only provides coverage against S. pneumoniae. Other antibiotics that are sometimes considered in AOM treatment because they are able to target penicillin-resistant S. pneumoniae are levofloxacin and linezolid. These are reserved to be only used when other antibiotics fail or when drug allergy prohibits the use of other antibiotics.

When filling prescriptions for combination antibiotics, pharmacy staff should exercise care; substitutions are not appropriate because each tablet strength has a different ratio of primary antibiotic to β-lactamase inhibitor. For example, a prescription written for amoxicillin/clavulanic acid 500 mg cannot be substituted as two amoxicillin/clavulanic acid 250 mg tablets because the amount of clavulanic acid in the 500 mg tablet (125 mg) is the same as the amount of clavulanic acid (125 mg) in the 250 mg tablet. Administering two 250 mg tablets would provide the correct amount of amoxicillin, but double the prescribed amount of clavulanic acid. Therefore, it is important to dispense combination antibiotic prescriptions as written.

<table>
<thead>
<tr>
<th>Table 1. Conditions under Which Patients Should Receive Antibiotics for AOM³</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Severe presentation of AOM</td>
</tr>
<tr>
<td>• Recurrent AOM</td>
</tr>
<tr>
<td>• Bilateral AOM in patients six to 24 months</td>
</tr>
<tr>
<td>• AOM diagnosis in ill-appearing child</td>
</tr>
<tr>
<td>• Other bacterial illness is suspected</td>
</tr>
<tr>
<td>• Uncertain follow-up</td>
</tr>
</tbody>
</table>

AOM = Acute otitis media

Antibiotics that are not currently recommended to treat AOM include macrolides (e.g. erythromycin, azithromycin) and sulfamethoxazole/trimethoprim (cotrimoxazole or Bactrim).

PAUSE AND PONDER:
How many prescriptions for antibiotic suspension do you fill? Do you usually know the child’s diagnoses? Do you ask?
Acute Bacterial Sinusitis
The American Academy of Pediatrics published acute bacterial sinusitis clinical guidelines in 2013 (see Table 3). The guidelines are based on identification of the pathogenic organism responsible for the infection using analysis of blood/sputum samples from the patient. Common pathogens causing sinusitis in children are similar to AOM as both are upper respiratory tract infections. Level of resistance in the community plays an important role in choosing an appropriate antimicrobial.

Local laboratories tend to classify organisms as high resistance or low resistance. High resistance results in decreased antibiotic efficacy against bacterial pathogens because the bacteria possess mechanisms that evade or destroy the antibiotic. Conversely, antibiotics effectively eradicate low resistance bacteria without as much difficulty.

In certain instances, such as S. pneumonia that is not susceptible to penicillins, presence of moderate to severe illness, age younger than two years, daycare attendance, or recent antibiotic use, level of resistance is likely high. The preferred antibiotic in these circumstances would be high-dose amoxicillin. Low likelihood of resistance to antibiotics would be defined as infrequent use of amoxicillin within the community or little to no personal use of amoxicillin. In this situation, low-dose amoxicillin (45 mg/kg/day in divided doses administered every 12 hours) is recommended.

Other antibiotics that may be considered for acute bacterial sinusitis are cephalosporins, linezolid, and clindamycin. Cephalosporins are more commonly used as alternative antibiotics while linezolid and clindamycin are reserved as last-line options. Prescribers may switch from amoxicillin to a cephalosporin if the patient has a documented penicillin allergy or to evade possible antimicrobial resistance to the penicillin drug class. Duration of therapy to treat acute bacterial sinusitis varies widely from a minimum of 10 days to 28 days. Systematic studies have not determined an optimal length of therapy for treating acute bacterial sinusitis in the pediatric population.

AOM’s common causative bacterial pathogens include Stretococcus pneumoniae, non-typeable Haemophilus influenzae, and Moraxella catarrhalis.

Common pathogens causing sinusitis in children are similar to AOM as both are upper respiratory tract infections.

Table 2. Guideline-Directed Care for Acute Otitis Media

<table>
<thead>
<tr>
<th>Indication</th>
<th>Routine</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line AOM treatment</td>
<td>Amoxicillin</td>
<td>1. Amoxicillin in past 30 days or if conjunctivitis also present: amoxicillin/clavulanate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Penicillin allergy, but able to tolerate cephalosporins: cefpodoxime, cefdinir, or cefuroxime</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Beta-lactam allergy (unable to tolerate penicillins and cephalosporins): clindamycin</td>
</tr>
<tr>
<td>Failure after at least 48 hours of treatment</td>
<td>Amoxicillin/clavulanate</td>
<td>1. If failed amoxicillin/clavulanate, ceftriaxone x 3 days is preferred, alternatively can consider oral clindamycin +/- cephalosporin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. If failed cephalosporin or if failed more than one above measure: levofloxacin or linezolid maybe considered</td>
</tr>
</tbody>
</table>

AOM = acute otitis media

Table 3: Antibiotic Recommendations for Acute Bacterial Sinusitis in Children

<table>
<thead>
<tr>
<th>Indication</th>
<th>Routine</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial therapy</td>
<td>Low dose amoxicillin (45 mg/kg/day)</td>
<td>1. Areas with high resistance rates: high-dose amoxicillin/clavulanate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Penicillin allergy: cefdinir, cefpodoxime, or cefuroxime</td>
</tr>
<tr>
<td>Lack of response to initial therapy</td>
<td>Increase amoxicillin dose or consider amoxicillin/clavulanate or Cephalosporin</td>
<td>1. Consider clindamycin or linezolid for resistant pneumococcus as most of the above cover H. influenzae and M. catarrhalis well</td>
</tr>
</tbody>
</table>

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Community-Acquired Pneumonia

Community-acquired pneumonia (CAP) is usually a viral respiratory tract infection in children, especially children younger than four years of age.\(^7\) When CAP is bacterial in nature, the most common cause in children is \textit{S. pneumoniae}. The possibility of bacterial CAP due to \textit{M. pneumoniae} or \textit{C. pneumoniae} is rare in young children and if present in older children, it is debatable if treatment improves outcome. The Infectious Diseases Society of America released clinical guidelines for the treatment of CAP in 2011. These guidelines apply to children older than three months of age.\(^7,8\)

For viral CAP, unless influenza is suspected, parents should provide supportive care measures and healthcare providers should educate them concerning symptoms that require additional or immediate medical attention. When influenza is suspected, the preferred antiviral is oseltamivir dosed by age and weight given twice a day for five days.\(^7,8\)

With suspected bacterial CAP, high-dose amoxicillin (90 mg/kg/day) is the preferred antibiotic due to its ability to cover \textit{S. pneumoniae}.\(^7,8\) In areas where there is increased pneumococcal resistance it is recommended that the amoxicillin component be divided in three doses to maximize the bactericidal activity. For unvaccinated pediatric patients, amoxicillin/clavulanic acid should replace amoxicillin to provide additional coverage against beta-lactamase producing \textit{H. influenzae} type b.\(^7,8\)

Other antibiotics that can be used but should be reserved as second or third-line antibiotics are cephalosporins, doxycycline, and levofloxacin. Traditionally, clinicians have avoided tetracyclines in children younger than eight because of a risk of tooth enamel discoloration. Although recent data suggests that the risk of teeth staining in children from short courses is low, doxycycline should generally only be used in CAP in children 8 years and older because there are other safer alternatives available.\(^7,8\)

Pharyngitis

Pharyngitis (inflammation of the throat) is one of the most common complaints among children.\(^9\) Viral pharyngitis is common and only supportive therapy is necessary. Children aged five through 15 years are at increased risk for \textit{Streptococcus pyogenes} or group A \textit{Streptococcus} (GAS) pharyngitis or strep throat. Especially in these patients, it is important to differentiate GAS pharyngitis with viral pharyngitis because up to 30% of the population is colonized with non-pathogenic GAS, a common colonizer of normal gut flora.\(^9,10\)

Some signs differentiate viral and bacterial pharyngitis. Viral pharyngitis is likely to cause a general viral upper respiratory syndrome plus sore throat, whereas in GAS pharyngitis, respiratory symptoms besides sore throat are rare. Patients who have GAS paryngitis should start treatment within a few days as untreated pharyngitis can lead to acute rheumatic fever (ARF), acute glomerulonephritis, peritonsillar abscess, cervical lymphadenitis, and mastoiditis. These infections develop if group A strep spreads from the pharynx to nearby physical structures.\(^9,11\)

The Infectious Disease Society of America published clinical guidelines for the treatment of pharyngitis in 2012.\(^10\) It is worth noting that appropriate antibiotic use decreases the incidence of all complications related to GAS pharyngitis other than the incidence of post-streptococcal glomerulonephritis (PSGN). The incidence of PSGN is not improved with the use of antibiotics because it is caused by the immune system’s reaction to fighting group A streptococcus rather than a bacterial etiology.\(^12\)

Pediatric patients who have symptoms of GAS pharyngitis

| Table 4. Antibiotic Recommendations for Community Acquired Pneumonia\(^6\) |
|---------------------------------|-----------------|------------------|
| **Indication**                  | **Routine**     | **Alternatives** |
| Vaccinated infant /child        | Either no antibiotic or high-dose amoxicillin (divided 2 to 3 times a day based on local resistance) | 1. If influenza is suspected: oseltamivir  
2. Penicillin allergy: cefdinir, cefpodoxime, doxycycline (age > 8 years), or levofloxacin for 5 days based on patient specific factors  
3. Rarely coverage for \textit{Mycoplasma pneumoniae} or other intracellular organisms is needed in older children /adolescents: azithromycin |
| Unvaccinated infant /child      | High dose amoxicillin-clavulanate divided in 3 daily doses | |

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Pediatric Vaccines to Reduce Respiratory Illness in Children

Vaccinations can prevent many childhood bacterial infections and limit their spread. Immunizations that are routinely recommended can prevent the incidence or severity of the common respiratory infections caused by influenza, pneumococcal species (e.g. targeting \textit{S. pneumoniae}), and \textit{Haemophilus influenzae} type b (Hib).\textsuperscript{14,15} PCV13 is recommended as a four-dose series at ages two months, four months, six months, and 12 to 15 months. Additionally, children two years old or older who are immunocompromised or have other high-risk factors for pneumococcal disease should receive the pneumococcal polysaccharide vaccine (PPSV23).\textsuperscript{11}

Influenza vaccine is recommended annually beginning at the age of six months.\textsuperscript{11}

Since its approval, pneumococcal conjugate vaccine (PCV13) has decreased pneumococcal-related AOM by 55% to 57% and CAP by 29% to 32% in children.\textsuperscript{15,16} PCV13 is recommended as a four-dose series at ages two months, four months, six months, and 12 to 15 months. Additionally, children two years old or older who are immunocompromised or have other high-risk factors for pneumococcal disease should receive the pneumococcal polysaccharide vaccine (PPSV23).\textsuperscript{11}

The likelihood of Hib diseases including CAP have decreased in recent years due to the availability of several brands of HiB vaccine. Guidelines recommended starting the Hib series at two months of age followed by three or four dose series (depending on brand administered) with booster completion at 12 to 15 months of age.\textsuperscript{11}

\textbf{Table 5. Circumstances in which Antibiotics are Recommended for GAS Eradication.}\textsuperscript{10}

- Community outbreak of ARF, poststreptococcal glomerulonephritis, or invasive GAS infections
- Outbreaks of GAS in closed community
- Presence of family or personal history of ARF
- Family with high anxiety about GAS
- Tonsillectomy is being considered because of GAS carriage

\begin{tabular}{|l|}
\hline
Abbreviations: ARF = acute rheumatic fever; GAS = Group A Streptococcus \\
\hline
\end{tabular}
Stewardship: Incorporating Principles into Practice

Pharmacists already perform many of essential roles in outpatient stewardship on a daily basis. Pharmacists
- provide education to parents regarding over-the-counter management of cough and colds
- review antibiotic therapies to optimize drug therapy as part of medication therapy management
- review prescriptions for interactions and allergies
- educate parents regarding appropriate usage and expected side effects.

Pain management is an important factor in appropriate treatment of AOM and pharyngitis. Pharmacists can provide parents with appropriate education about pain medications for their children and how to dose them effectively. Pharmacists’ community accessibility gives parents opportunities to ask questions and tailor therapy for their children.6,10

Many people are unaware that antibiotics are used for bacterial infections rather than viral infections; in 2003, 57% of the public believed “antibiotics are not an effective treatment for viral infections.”17 A 2011 study revealed improvement, with 67% of the public agreeing that antibiotics are inappropriate for viral infections. However, more improvement is needed.18 For example, pediatric CAP is commonly caused by viruses. If patients were to take antibiotics for viral infections, it would not help but could instead only cause adverse effects.

Viral infections can be as severe as bacterial infections. Coughs, colds, viral pharyngitis, and many cases of pediatric CAP are caused by viruses for which targeted treatments are unavailable. If young children contract influenza, pharmacy staff should recommend parents consult a pediatrician promptly to determine if oseltamivir is indicated.7 In cases when pediatricians do not prescribe antibiotics, the pharmacist can dispel the myth that the decision to use an antibiotic is based on the infection’s severity (i.e. the more severe the infection, the more greater the likelihood antibiotics will help). This is a not true. Additionally, pharmacists can also help parents find options for symptomatic management. Finally, pharmacists should always remind parents to seek additional medical help if a child presents with fever > 38°C (100.4°F) along with a cough or cold.2

Last, it is also important for community pharmacists to learn about local antibiotic susceptibility rates in their geographic locations.2 A local hospital laboratory that cares for children would be a place to start; ask for an antibiogram. This information can assist pharmacists in assessing and optimizing dosing for children with AOM, sinusitis, and CAP.

Patient Counseling

Finally, the pharmacist and pharmacy staff have unique responsibilities to counsel families on proper antibiotic use, storage, dosing, and side effects when dispensing medications. Proper storage of antibiotics is important for a variety of reasons such as maintaining stability and taste. Table 6 lists the proper storage requirements, duration, and food considerations needed for antibiotic suspensions.

Along with timing doses to be given with or without food, other considerations include timing of concurrent medications or supplements. Cefdinir and levofloxacin suspensions should be separated from antacids and iron supplements by at least two hours to avoid chelation of the antibiotics by cations. Parents of pediatric patients should also be aware that cefdinir suspensions discolor stool to look reddish, but this should not be confused for blood in stool.5,21 Rifampin also discolors bodily fluids (skin, urine, sweat, saliva, tears, and feces) to an orangish color and may permanently stain soft contact lenses.13

Nausea and gastrointestinal adverse effects are most commonly reported for beta-lactam antibiotics.4,21 Allergic reactions are also possible and often initially present as a rash. Fluoroquinolones are saved as “last resort” antibiotics in children because their labeling includes a boxed warning for tendonitis, tendon rupture, and worsening of myasthenia gravis. Boxed warnings also note the potential for peripheral neuropathy that may be irreversible in both children and adults.22,24 Fluoroquinolones are also associated with serious cardiac, dermatologic, and hypersensitivity reactions.22,24 Linezolid is reserved as a last-line antibiotic because it has drug-food and drug-drug interactions and associations with hematologic suppression.3

<table>
<thead>
<tr>
<th>Antibiotic Suspension</th>
<th>Method of Storage</th>
<th>Duration of Stability</th>
<th>Food Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>Refrigerator for taste</td>
<td>14 days</td>
<td>Take without food</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>Refrigerator for stability</td>
<td>10 days</td>
<td>Take with food</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Room temperature</td>
<td>10 days</td>
<td>Take without food</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>Room temperature</td>
<td>10 days</td>
<td>Take with or without food</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>Refrigerator</td>
<td>14 days</td>
<td>Take with food</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Refrigerator</td>
<td>10 days</td>
<td>Take with food</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Do NOT refrigerate</td>
<td>14 days</td>
<td>Take without food</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Room temperature</td>
<td>21 days</td>
<td>Take without food</td>
</tr>
</tbody>
</table>
Ibuprofen should be avoided in children who are not eating or drinking fluids sufficiently as it is associated with gastrointestinal ulcers and acute kidney injury. Aspirin should be avoided in children until the age of 12 due to the risk of causing Reye’s syndrome (a condition that causes confusion, liver damage, and swelling in the brain when triggered by aspirin use during a viral illness or infection). Products containing codeine are now contraindicated in children younger than 12 years of age and should be avoided in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease due to increased risk of serious breathing problems.

For children who present with pharyngitis, it is important to counsel parents/guardians to hydrate their child properly with six to eight glasses of water per day. Topical analgesics/gargles or, hard candies/lozenges (in children six years and older) can soothe the throat. Children under the age of six should not be given lozenges or hard candies, as they are possible choking hazards.

Communicating with Healthcare Providers
Medication therapy management for common respiratory infections is important. Initially, pharmacists may have to reach out frequently to clinicians who lack understanding of or harbor misconceptions about pharmacist responsibilities. Face to face communication is best. In outpatient pharmacy, barriers to communication between the pharmacist and other healthcare providers often exist. In community pharmacy, the main mode of communication is the telephone; rarely does the pharmacist have the opportunity to communicate in person with community pediatricians. Before filling prescriptions for antibiotics, the pharmacist should gather all necessary information to determine if antibiotics are appropriate. With each antibiotic prescription, the following information should be obtained:

- patient weight
- allergies
- current working diagnosis
- recent or current medications.

This information can be obtained from the pediatrician or child’s parent. The pharmacist can then review an antibiotic guide such as the Connecticut Children’s Medical Centers’ Empiric Outpatient Antimicrobial Guide (http://www.cidrap.umn.edu/asp/clinicaltools/empiric-outpatient-antimicrobial-guide) to evaluate antibiotic choice and dose for that patient.

Establishing open communication relationships with healthcare providers promotes information sharing. Ideally, doctor-pharmacist collaboration should go hand-in-hand; understanding each other’s professional roles can be beneficial not only to improving workflow, but also to improve patient outcomes.

Maintaining a consistent flow of information from the provider’s office to the pharmacist would allow for better patient care, which leads into the next communication barrier.

When communicating with healthcare professionals, it is best to avoid using abbreviations. Although we all work in healthcare, many abbreviations have more than one meaning and may be used in a different context in settings other than pharmacies. Avoiding abbreviations can prevent miscommunication or misunderstand and allow for more effective communication.

Methods to Improve Workflow
According to the CDC’s Core Elements of Outpatient Antibiotic Stewardship, “action is necessary to transform policy and practice into measurable outcomes.” Applying antimicrobial stewardship knowledge to routine workflow prevents emerging antibiotic resistance. Incorporating techniques summarized below can improve workflow and overall patient treatment experience.

1. Work with prescribers to communicate routinely and help them understand the pharmacists’ role in antibiotic treatment. If prescribers agree to provide the indication along with patient weight and allergies on all prescriptions, this can improve care.

2. Pharmacists can also counsel parents on children’s medications prior to reconstituting the suspension to make sure they understand the medication’s importance and storage requirements.

3. Counsel families on appropriate adjunctive over-the-counter medications such as pain medications to take with antibiotics and help children feel more comfortable during treatment of their infection. When other symptomatic medications are appropriate, it is important that parents receive necessary information on those as well.

4. Use storage and food auxiliary labels appropriately and consistently for antibiotic medications to ensure that antibiotics remain stable and effective throughout the entire prescribed course of treatment. Parents should also understand that antibiotics should be disposed of following discontinuation of the antibiotic and resolution of the infection.
Part 2
DECREASING “RESISTANCE” TO ANTIBiotic STEWARDSHIP: THREE MORE REASONS
Sara E. Miller and Jeannette Wick

Every year, children receive an estimated 11.4 million unnecessary antibiotic prescriptions. Inappropriate antibiotic use contributes to antimicrobial resistance, which causes costly, resource-consuming, hard-to-cure illnesses with increased risk of complications. Infections with bacteria resistant to antibiotics kill at least 23,000 people annually.

To reduce the dangers of antibiotic resistance, the Centers for Disease Control and Prevention (CDC) defines “Core Elements of Outpatient Antibiotic Stewardship,” fundamentals that pharmacists can use to develop innovative stewardship programs. Antimicrobial stewardship programs promote evidence-based prescribing and proper patient use of antibiotics to decrease microbial resistance and the spread of resistant infections. They also improve patient outcomes.

The companion continuing education activity discusses the importance of antibiotic stewardship in children with an emphasis on preventing antibacterial resistance. This activity offers three additional reasons to promote antibacterial stewardship.

Often, people need to understand situations on a personal level before they understand the problem’s urgency and embrace solutions. In the case of pediatric antibiotic prescribing, parents often need to know what could happen to their own children, and the implications of unnecessary antibiotics for society at large. These explanations need to be provided in ways that are reasonable and measured, and don’t frighten people unnecessarily. Pharmacists can educate and empower patients, families, and providers to reduce or eliminate inappropriate antibiotic use by

● raising awareness of antibiotic adverse effects
● emphasizing consequences of misuse, and
● explaining irreversible environmental effects.

Antibiotic Adverse Effects

More than 30% of children taking antibiotics for at least 14 days experience an adverse event (AE) that warrants therapy change. Pediatrics are inherently at high risk for AEs. Multiple medications, comorbidities, and longer duration of therapies further increase risk.

Antibiotics cause more pediatric emergency department (ED) visits than any other medication. They account for 56% of visits in children younger than 5 years old, and 32% in those aged six to 19 years old. Reasons for ED visits include AEs and accidental ingestions. Amoxicillin-containing, sulfonamide-containing, and cephalosporin antibiotics are implicated most often. Few studies of severe antibiotic reactions have been conducted in pediatrics, but antimicrobials, particularly minocycline and amoxicillin/clavulanate, are known to cause 45% of drug hepatotoxicity. Experts hope to heighten awareness of this potential AE, and recommend monitoring blood counts and liver function tests during long-term therapy.

Most antibiotic effects are mild and self-limiting, but diarrhea and rash can be hallmarks for more severe AEs. Providers should counsel on conditions under which parents or caregivers must seek immediate medical care for diarrhea and rash (See Table 1). Table 2 lists possible side effects of common antibiotics prescribed to pediatrics.

| Table 1. When to Seek Medical Care for Antibiotic-Associated Diarrhea or Rash

<table>
<thead>
<tr>
<th>Children need additional medical attention if they develop these symptoms of <strong>DIARRHEA:</strong></th>
<th>Caregivers should stop administering the drug and seek emergency care if a <strong>RASH:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bloody stool, very liquid stool, or stool that burns the peri-anal area</td>
<td>• Appears painful, purple, or dark colored</td>
</tr>
<tr>
<td>• Explosive diarrhea</td>
<td>• Develops on the face or mucous membranes</td>
</tr>
<tr>
<td>• Signs of systemic dehydration</td>
<td>• Is accompanied by tongue swelling, a fever (&gt;104°F), shortness of breath, joint pain, or low blood pressure</td>
</tr>
<tr>
<td>• Painful evacuation</td>
<td>• Loss of appetite</td>
</tr>
<tr>
<td>• Loss of appetite</td>
<td>• Inability to drink or urinate</td>
</tr>
<tr>
<td>• Any diarrhea that continues for two weeks or more</td>
<td></td>
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</tbody>
</table>
Providers often develop decreased mindfulness, a phenomenon about patient satisfaction lead to inappropriate prescribing. Knowledge gaps, patient expectations, lack of time, and concern unnecessarily. Prescribing consumes money, time and resources. U.S. spends more than $10.7 billion on antibiotics; inappropriate infections including otitis media, bronchitis, and sinusitis. Prescriptions are used inappropriately for common respiratory indications persists. Inappropriate medication dosing is the most common pediatric medical error because of complex weight-based dosing and age-dependent formulations. Over the counter topical antibiotics like bacitracin are not appropriate for routine care due to risk of allergy and anaphylaxis. Pharmacist can discourage parents/patients from using these products, and educate them that the best way to treat a minor cut or scrape is to clean it with mild soap and water and apply plain petrolatum if they need an emollient. Patients need to see a healthcare provider if a cut or scrape will not stop bleeding; is painful to the touch for more than 24 to 72 hours; or inflammation suggestive of infection develops. Consequences of Antibiotic Misuse Inappropriate medication dosing is the most common pediatric medical error because of complex weight-based dosing and age-dependent formulations. Overall, pediatric antibiotic prescribing has decreased in recent years, but prescribing for inappropriate indications persists. About 58% of pediatric antibiotic prescriptions are used inappropriately for common respiratory infections including otitis media, bronchitis, and sinusitis. The U.S. spends more than $10.7 billion on antibiotics; inappropriate prescribing consumes money, time and resources unnecessarily. Knowledge gaps, patient expectations, lack of time, and concern about patient satisfaction lead to inappropriate prescribing. Providers often develop decreased mindfulness, a phenomenon called alert fatigue, when electronic Clinic Decision Support programs routinely generate alerts about potential interactions and clinically acceptable dosing parameters. Clinicians may shrug off the alert, or have knowledge gaps, so they don’t completely understand the alert’s potential repercussions. Clinically, high false positive rates cause alert fatigue and clinicians override approximately 77% of alerts. Once a healthcare provider overrides an alert, it’s unlikely that any other safety measure will catch an error. Experts are urging pharmacists to incorporate—and pay attention to—antibiotic overdose alerts because 38% of pediatric antibiotic alerts are true overdoses. For optimal patient safety, providers must recognize knowledge gaps and wake up to alert fatigue. Although antibiotic overdoses don’t usually cause pediatric deaths, even one death is too many. All parents and providers should know how to approach overdose situations. Speedy contact with an emergency response team or the National Capital Poison Center by phone (1-800-222-1222) or on the website can save a life.

Misuse of systemic antibiotics in patients younger than five is one of the top reasons for calls to Poison Control. Antibiotic suspensions have appealing colors and flavors that may increase the risk that a child will be attracted to the bottle and possibly drink part or all of its contents; this increases risk of overdose. The most common causes of unintentional exposure include administering a dose twice by accident or giving doses too close together; giving the wrong medication or someone else’s medication; and confusing dosage units.

### Table 2. Antibiotic Side Effects in Pediatrics

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Antibiotic Names</th>
<th>Common Side Effects</th>
<th>Rare Side Effects*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>Penicillin, amoxicillin, amoxicillin/clavulanate, ampicillin</td>
<td>N/V/D, rash, abdominal pain, black hairy tongue, candidiasis, <em>C. difficile</em></td>
<td>Hepatic and renal dysfunction, anemia, neutropenia, extrinsic tooth discoloration (from liquid formulations)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Cephalexin, cefuroxime, ceftriaxone, cefdinir, cefpodoxime</td>
<td>N/V/D, rash, dyspepsia, abdominal pain, genital pruritus, <em>C. difficile</em></td>
<td>Seizure, hepatic and renal dysfunction, anemia, hemorrhage (primarily from cefamycins)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Azithromycin, clarithromycin, erythromycin</td>
<td>N/V/D, rash vomiting, abdominal pain, <em>C. difficile</em></td>
<td>Hepatic and renal dysfunction, anemia, ototoxicity, <em>torsades de point</em></td>
</tr>
<tr>
<td>Sulfonamide derivatives</td>
<td>Trimethoprim/sulfamethoxazole</td>
<td>Photosensitivity, nausea, vomiting, abdominal pain, rash, <em>C. difficile</em></td>
<td>Hepatic and renal dysfunction, anemia, hyperkalemia</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Ciprofloxacin, levofloxacin</td>
<td>Photosensitivity, rash, musculoskeletal effects</td>
<td>Tendon, joint and muscle pain, a “pins and needles” tingling or pricking sensation, confusion, and hallucinations</td>
</tr>
<tr>
<td>Tetracycline derivatives</td>
<td>Doxycycline</td>
<td>N/V/D, phototoxicity, rash</td>
<td>Effects on tooth development, growth, and color before age 8</td>
</tr>
</tbody>
</table>

*All antibiotics have the potential to cause hypersensitivity reactions

**ABBREVIATIONS:** N/V/D = nausea vomiting diarrhea
Clinical effects of excessive oral antibiotics include stomach upset and diarrhea, for which pediatricians often recommend supportive care (hydration and rest). If the exposure is ophthalmic or dermal, advise parents to flush the area with water before contacting poison control.12

Pediatric antibiotic dosing is complex, so provider knowledge of pediatric-specific tolerability and pharmacokinetic parameters is critical.7 Pharmacists and other healthcare providers should ask questions about the patient’s medical history, coinfections, symptoms, time of ingestion, and suspected amount of ingestion (pill count, spill volume, and sometimes, mouth color/odor).12 Pharmacists can remind parents by providing key information:

- Consider it an emergency if the child gasps for air, collapses, seizes, or isn’t waking up.
- Handle any emergency overdose (described in the bullet above) by calling 911 for immediate care before poison control.
- In all overuse circumstances, pay attention to the child’s airway, breathing and circulation.12

Antibiotics have “Environmental Side Effects”

This may surprise readers: Antimicrobials are now ubiquitous in the environment.13 The largest use of antimicrobial agents outside human medicine is in food animals. Children are at high risk of developing infections with resistant organisms linked directly to the agricultural use of antimicrobials.13

Historically, the U.S. Food and Drug Administration (FDA) has allowed use of antibiotics in farm animals to stimulate growth and to treat, control, and prevent infections.14 Resistant bacteria that spread from food and animals cause about one in five resistant infections in humans.15,16 To combat antimicrobial resistance, the FDA released voluntary guidance on judicious use of medically important antibiotics in food-producing animals (poultry, swine, or cattle) in 2017.14

The media has been replete with stories about antibiotic resistant bacteria in food on our grocery store shelves, and in fast food.17,18 Meat producers and popular fast food restaurants have capitalized on the recommendation—and on growing concern among health-minded Americans—to voluntarily phase out antimicrobials for growth stimulation by using and advertising “antibiotic free” meat.19

To limit further resistance, the FDA suggests veterinary oversight when using antimicrobial therapy in food-producing animals. Note the FDA now prohibits use of fluoroquinolones and certain cephalosporins in poultry because of high risk of resistance development.20 Figure 1 shows mechanisms resistant bacteria spread through the environment.15

Pause and Ponder:

What do you know about antibiotics in our food supply and in the environment?
Do you know enough?

After any mammal consumes an antibiotic, it has to eliminate it via urine or stool. Human sewage treatment plants often do not remove residue, and when animal eliminate onto or into the soil, residue contaminates ground water. Fluoroquinolones, macrolides, and tetracyclines persist in water supplies, diffusing into the entire body of water and accumulating in increasingly higher concentrations.21 Mechanisms including high efficiency membranes, chlorination, and high UV radiation successfully decrease bacteria’s ability to survive in wastewater but they are costly and used in only newer sewage treatment plants. Researchers must prioritize developing wastewater treatment plants that remove all antibiotic disintegrates effectively and efficiency.22

Increasing antibiotic use causes immediate direct and indirect long term effects in the environment. Many factors influence the antibiotics’ environmental impact including the concentration, exposure time, receiving ecosystem (e.g. soil or water), and co-occurrence with other antibiotics or contaminants. Antibiotics’ direct bactericidal and bacteriostatic effects on microbes kill entire microbial populations that have valid and important ecological functions, such as maintenance of soil and water quality.21

Also, sewage treatment plants contain diverse bacterial communities with several hundred species, increasing risk of resistant gene transfer.23 Once a microbial population acquires resistance genes, it’s impossible to reestablish complete drug sensitivity, even if humans are able to reduce antibiotics in the environment.21

Indirect effects of antibiotics in the environment include consequent development of multi-resistant bacteria, death of aquatic environments, and adverse effects on birds and bees. Researchers indicate they haven’t yet identified all of antibiotics’ indirect long-term effects in the ecosystem.21

Antibiotics flushed down the toilet directly harm the environment. Pharmacists should find safe medication disposal sites around the community to recommend to patients:

- Walgreens has an online resource to find the nearest safe medication disposal kiosk.
- The U.S. Drug Enforcement Administration (DEA) sponsors National Prescription Drug Take Back Day. Promoting safe medication disposal is an easy way to help preserve our environment.
Figure 1

**How Antibiotic Resistance Happens**

1. Lots of germs. A few are drug resistant.
2. Antibiotics kill bacteria causing the illness, as well as good bacteria protecting the body from infection.
3. The drug-resistant bacteria are now allowed to grow and take over.
4. Some bacteria give their drug-resistance to other bacteria, causing more problems.

**Examples of How Antibiotic Resistance Spreads**

- Animals get antibiotics and develop resistant bacteria in their guts.
- Drug-resistant bacteria can remain on meat from animals. When not handled or cooked properly, the bacteria can spread to humans.
- Fertilizer or water containing animal feces and drug-resistant bacteria is used on food crops.
- Drug-resistant bacteria in the animal feces can remain on crops and be eaten. These bacteria can remain in the human gut.
- Simply using antibiotics creates resistance. These drugs should only be used to treat infections.

- George gets antibiotics and develops resistant bacteria in his gut.
- George stays at home and in the general community. Spreads resistant bacteria.
- George gets care at a hospital, nursing home or other inpatient care facility.
- Resistant germs spread directly to other patients or indirectly on unclean hands of healthcare providers.
- Resistant bacteria spread to other patients from surfaces within the healthcare facility.

Centers for Disease Control and Prevention. Available at https://www.cdc.gov/drugresistance/about.html
**Take Action Together**

Antibiotic resistance is a growing global threat; prescribers and patients must acknowledge national goals for improving outpatient antibiotic prescribing. It’s a particularly troubling (and frustrating) situation because researchers have produced no new antibiotic class in almost 30 years. This means our antibiotic selection is limited. The White House National Action Plan for Combating Antibiotic-Resistant Bacteria aims to reduce inappropriate antibiotic outpatient use by 50% and a Healthy People 2020 objective discourages antibiotic use for inappropriate indications, including pediatric ear infections and common colds.  

Effective parent-provider communication has potential to reduce inappropriate antibiotic prescribing using rapport-building, exchange of critical information, and shared-decision making. Researchers must study effective strategies further to prevent inappropriate antibiotic prescribing and its effects on healthcare costs, patient visits, and antibiotic resistance. Pharmacists who counsel children and their caregivers can and should discuss antimicrobial resistance when they dispense antibiotics. As with all things, sometimes people need to be nudged a little harder to appreciate a problem’s urgency. Discussing adverse effect avoidance, the potential for accidental poisonings, and environmental effects can underscore the urgency. Figure 2 suggest ways pharmacies can step up their involvement.

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**Figure 1. Advancing Pharmacists and Pharmacy Technicians Role in Antibiotic Stewardship**

**Best**

1. **Be COMMUNITY CHAMPIONS** and talk about individual and societal risks of antibiotic overuse
2. **Collaborate** with local pediatricians to enhance information transfer and improve patient safety
3. **Examine your workflow** to ensure you are taking advantage of every opportunity to implement the principles of Antimicrobial Stewardship.

**Better**

1. **Always ask for age, weight, and allergies** on kids’ prescriptions for antibiotics
2. **Post signage** about antimicrobial resistance in prominent places in the pharmacy
3. **Know the guidelines for common pediatric infections**

**Good**

1. **Be familiar with antimicrobial resistance** and potential antibiotic adverse effects and toxicities
2. **Educate patients** about the differences between bacterial and viral infections
REFERENCES

PART 1
FUNDAMENTALS OF ANTIMICROBIAL STEWARDSHIP FOR OUTPATIENT PEDIATRIC INFECTIOUS DISEASES


REFERENCES

PART 2
DECREASING “RESISTANCE” TO ANTIBIOTIC STEWARDSHIP: THREE MORE REASONS


