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CLINICAL REPORT

Principles of Judicious Antibiotic Prescribing for Upper Respiratory Tract Infections in Pediatrics

abstract

FREE

Most upper respiratory tract infections are caused by viruses and require no antibiotics. This clinical report focuses on antibiotic prescribing strategies for bacterial upper respiratory tract infections, including acute otitis media, acute bacterial sinusitis, and streptococcal pharyngitis. The principles for judicious antibiotic prescribing that are outlined focus on applying stringent diagnostic criteria, weighing the benefits and harms of antibiotic therapy, and understanding situations when antibiotics may not be indicated. The principles can be used to amplify messages from recent clinical guidelines for local guideline development and for patient communication; they are broadly applicable to antibiotic prescribing in general. *Pediatrics* 2013;132:1146–1154

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KEY WORDS
respiratory tract infections, antibacterial agents

ABBREVIATIONS
AAP—American Academy of Pediatrics
AOM—acute otitis media
GAS—group A *Streptococcus*
NNT—number needed to treat
PTA—peritonsillar abscess
TM—tympanic membrane
URI—upper respiratory tract infection

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INTRODUCTION

More than 1 in 5 pediatric ambulatory visits to a physician result in an antibiotic prescription, which accounts for nearly 50 million antibiotic prescriptions annually in the United States.[1] It is widely documented that inappropriate antibiotic prescribing, especially for upper respiratory tract infections (URIs) of viral origin, is common in ambulatory care.[1–3] As many as 10 million antibiotic prescriptions per year are directed toward respiratory conditions for which they are unlikely to provide benefit.[1] Recent evidence shows that broad-spectrum antibiotic prescribing has increased and frequently occurs when either no therapy is necessary or when narrower-spectrum alternatives are appropriate.[1,2] Such overuse of antibiotics causes avoidable drug-related adverse events,[4–6] contributes to antibiotic resistance,[7,8] and adds unnecessary medical costs. This is compounded by the fact that few new antibiotics to treat antibiotic-resistant infections are under development.[9] The growing health and economic threats of antibiotic resistance make promoting judicious antibiotic prescribing, which encompasses both reducing overuse and ensuring that appropriate agents are prescribed, an urgent public health and patient safety priority (http://www.cdc.gov/drugresistance/threat-report-2013).

Clinical decision-making about whether to prescribe antibiotics for a patient with URI symptoms is a daily occurrence for ambulatory-care physicians and other health care professionals who provide care for children. Although antibiotic prescribing is a routine part of clinical

care, judicious antibiotic prescribing is challenging because it is difficult to distinguish between viral and bacterial URIs. A major objective of this clinical report is to provide a framework for clinical decision-making regarding antibiotic use for pediatric URIs. A point of emphasis is the importance of using stringent and validated clinical criteria when diagnosing acute otitis media (AOM), acute bacterial sinusitis, and pharyngitis caused by group A *Streptococcus* (GAS), as established through clinical guidelines. Additionally, this document emphasizes situations in which the use of antibiotics is not indicated, in particular for viral respiratory infections. Considering the frequency of URIs and the large proportion of antibiotic prescribing attributable to URI visits, these conditions represent a high-impact target for guidelines and other interventions designed to optimize antibiotic prescribing. The careful application of these criteria has the potential to mitigate overuse of antibiotics for pediatric URIs.

The first "Principles of Judicious Use of Antimicrobial Agents for Pediatric Upper Respiratory Tract Infections" were published in 1998 in response to concerns over the emergence and spread of antibiotic-resistant organisms.[10] The Centers for Disease Control and Prevention, in collaboration with the American Academy of Pediatrics (AAP), sought to update these principles in a current context. Antibiotic resistance remains a major public health concern, and appropriate antibiotic use is an important health care quality goal. Although the introduction of a 7-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV7) in 2000 led to large declines in the incidence of invasive pneumococcal infections,[11] an increase in the prevalence of nonvaccine serotypes, most notably serotype 19A, a commonly antibiotic-resistant serotype,[12,13] prompted the 2010 introduction of a 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13). Provider concerns about antibiotic resistance may be 1 factor leading to increasing use of broad-spectrum antibiotics. In recent years, several high-quality randomized controlled trials, meta-analyses, and new and updated clinical guidelines have been published that better define the effectiveness of antibiotic use for selected URIs, including AOM and acute bacterial sinusitis.[14–23] At the same time, new evidence highlighting the extent to which antibiotics lead to adverse events requiring medical attention[4–6] or potentially life-threatening events[24,25] has emerged.

This clinical report focuses on antibiotic prescribing for key pediatric URIs that, in certain instances, may benefit from antibiotic therapy: AOM, acute bacterial sinusitis, and pharyngitis. The specific recommendations are applicable to healthy children who do not have underlying medical conditions (eg, immunosuppression) placing them at increased risk of developing serious complications. The purpose of this report is to provide practitioners specific context using the most current recommendations and guidelines while applying 3 principles of judicious antibiotic use: (1) determination of the likelihood of a bacterial infection, (2) weighing the benefits and harms of antibiotics, and (3) implementing judicious prescribing strategies (Table 1).

PRINCIPLE 1: DETERMINE THE LIKELIHOOD OF A BACTERIAL INFECTION

Many aspects of the clinical history, symptoms, and signs of bacterial URIs overlap with or mirror those of viral infections or noninfectious conditions. To make a judicious decision about antibiotic use, it is essential first to determine the likelihood of a bacterial infection. When a practitioner has made the diagnosis of viral infection and has reasonably excluded the presence of concurrent bacterial infection, antibiotics should not be used because the potential for harm outweighs the potential benefit. In the specific cases of AOM, acute bacterial sinusitis, and pharyngitis, there are well-established stringent criteria that aid in distinguishing bacterial from nonbacterial causes.

AOM

The AAP and American Academy of Family Physicians released updated clinical practice guidelines for the diagnosis and treatment of AOM in 2013.[22] AOM may be defined as "the rapid onset of signs and symptoms of inflammation in the middle ear." The signs include bulging with or without erythema of the tympanic membrane (TM), and the symptoms may include otalgia, irritability, otorrhea, and fever. The diagnosis of AOM always requires a careful otoscopic examination to confirm the presence of inflammatory changes in the TM. The AAP guideline recommends that physicians diagnose AOM definitively under either of 2 conditions: (1) evidence of middle-ear effusion, as demonstrated by moderate to severe bulging of the TM, or (2) new onset of otorrhea that is not attributable to otitis externa. AOM may also be diagnosed when a child presents with only mild bulging of the TM but with additional symptoms of recent onset of ear pain or with intense erythema of the TM. Although clear visualization of the TM at times is difficult and because AOM is typically a self-limiting disease, a high degree of diagnostic certainty is essential to minimize antibiotic overuse. After AOM is diagnosed, judicious antibiotic use can be enhanced by further categorizing patients on the basis of illness severity (severe otalgia, otalgia lasting

TABLE 1 Application of Judicious Antibiotic Principles for Pediatric URIs

Principles	AOM	Acute Bacterial Sinusitis	Acute Pharyngitis
Principle 1: Determine the likelihood of a bacterial infection	Requires middle ear effusion and signs of inflammation:	URI symptoms that are either worsening, severe, or persistent	Diagnosis of GAS pharyngitis requires confirmation by rapid testing or culture
	• moderate or severe bulging of TM; or	• Worsening symptoms: worsening or new onset fever, daytime cough, or nasal discharge after improvement of viral URI	• Only test if 2 of the following are present: fever, tonsillar exudate/ swelling, swollen/tender anterior cervical nodes, absence of cough
	• otorrhea not due to otitis externa; or	• Severe symptoms: fever ≥39°C, purulent nasal discharge	• Do not treat empirically
	• mild bulging of TM with ear pain or erythema of TM	• Persistent symptoms without improvement: nasal discharge or daytime cough >10 d	
		No role for routine imaging	
Principle 2: Weigh benefits versus harms of antibiotics	Benefits: for strictly defined AOM, NNT of as few as 4 patients to achieve improvements in symptoms	Benefits: for strictly defined bacterial sinusitis, antibiotics improve symptoms at 3 and 14 d	Benefits: for confirmed GAS, antibiotics shorten symptom duration, prevent rheumatic fever and may limit secondary transmission.
	• no significant benefits in preventing complications such as mastoiditis	• no evidence that antibiotic therapy prevents complications such as brain abscess	• Limited evidence that therapy prevents complications such as PTA
First-line therapy	Amoxicillin with or without clavulanate	Amoxicillin with or without clavulanate	Amoxicillin or penicillin
	Harms: for all conditions, no benefits to therapy when bacterial infection is not likely. Increased risk of adverse events including diarrhea, dermatitis, *C difficile* colitis, antibiotic resistance		
Principle 3: Implement judicious prescribing strategies	• Consider watchful waiting for older patients (>2 y), those with unilateral disease and without severe symptoms	• Consider watchful waiting for patients with persistent symptoms only	• Once daily dosing of amoxicillin
	• Shorter-duration therapy (7 d)		
	Not recommended: azithromycin and oral third-generation cephalosporins are generally not recommended for these conditions attributable to *S pneumoniae* resistance.		

>48 hours, or temperature ≥39°C), laterality of infection (bilateral versus unilateral), and age (≤23 months vs ≥24 months). Patients with more severe symptoms, bilateral involvement, and younger age are more likely to benefit from antibiotics. Watchful waiting is reasonable for patients who are older and have nonsevere, unilateral disease.

Acute Bacterial Sinusitis

The AAP[23] and the Infectious Diseases Society of America[21] recently developed evidence-based clinical guidelines for the diagnosis and treatment of acute bacterial sinusitis. These guidelines support use of strict diagnostic criteria to distinguish bacterial from viral URIs. In particular, acute bacterial sinusitis is diagnosed on the basis of symptoms that are (1) persistent and not improving, (2) worsening, or (3) severe. Persistent symptoms are most common and include nasal discharge (of any quality) or daytime cough not improving by 10 days. Worsening symptoms include a worsening or new onset of fever, daytime cough, or nasal discharge after improvement of a typical viral URI. Severe symptoms include persistent fever (temperature ≥39°C) and purulent nasal discharge for at least 3 days. These clinical criteria are the basis for the diagnosis of acute bacterial sinusitis. Because many children with viral URI will have radiographic abnormalities, imaging should not be performed routinely.

Acute Pharyngitis

Pharyngitis, or sore throat, may be accompanied by other nonspecific symptoms including cough, congestion, and fever. The most important diagnostic consideration is whether β-hemolytic GAS is the cause. Unlike AOM and acute bacterial sinusitis, the diagnosis of GAS infection can be confirmed with laboratory testing (either a rapid-antigen detection test or culture).[26,27] Scoring systems (Modified Centor or McIsaac Scores[28]) can assist in identifying candidates for testing. Patients with 2 or more of the following features should undergo testing: (1) absence of cough, (2) presence of tonsillar exudates or swelling, (3) history of fever, (4) presence of swollen and tender anterior cervical lymph nodes, and (5) age younger than 15 years. Children with URI signs and symptoms, including cough, nasal congestion, conjunctivitis, hoarseness, diarrhea, or oropharyngeal lesions (ulcers, vesicles) more likely have viral illnesses and not GAS infection and should not be tested for GAS. Testing should generally not be performed in children younger than 3 years in whom GAS rarely causes pharyngitis and in whom rheumatic fever is uncommon. GAS should not be diagnosed in the

absence of testing, even among patients with all of the aforementioned clinical criteria, with rare exceptions (eg, symptomatic and household contact with confirmed GAS pharyngitis). The importance of limiting testing to children with appropriate clinical criteria is further supported by the fact that colonization rates can reach 15% to 20% even among asymptomatic children.

Common Cold, Nonspecific URI, Acute Cough Illness, and Acute Bronchitis

Symptoms of the common cold, nonspecific URI, and bronchitis may overlap with or mirror those of bacterial URIs and can include cough, congestion, and sore throat. Collectively, these viral conditions account for millions of office visits per year. Acute bronchitis, in particular, is a cough illness that is diagnosed during more than 2 million pediatric office visits annually, and antibiotics are prescribed more than 70% of the time.[1] Application of diagnostic clinical criteria for AOM, sinusitis, and pharyngitis should aid clinicians in excluding these conditions. Management of the common cold, nonspecific URI, acute cough illness, and acute bronchitis should focus on symptomatic relief. Antibiotics should not be prescribed for these conditions.

PRINCIPLE 2: WEIGH BENEFITS VERSUS HARMS OF ANTIBIOTICS

If a bacterial infection is determined to be likely, the next step is to compare the evidence about the benefits of antibiotic therapy for each condition to the potential for harms. Relevant outcomes to consider for benefits include the cure rate, symptom reduction, prevention of complications, and secondary cases. Outcomes for harms include antibiotic-related adverse events (eg, abdominal pain, diarrhea, rash), *Clostridium difficile* colitis, development of resistance, and cost.

AOM

Benefits

Several high-quality randomized controlled trials and meta-analyses have been published since the publication of the first principles of judicious use of antibiotics.[18–20,29–33] Collectively, these have emphasized the following: (1) at least half of patients with AOM will recover without antibiotic therapy; (2) recovery is more likely and is hastened for children who receive antibiotic therapy compared with placebo; and (3) recovery without antibiotic therapy is less likely for younger children, those with bilateral versus unilateral disease, and those with more severe signs and symptoms. These observations underlie the rationale for treatment recommendations for AOM.

Multiple meta-analyses indicate that children receiving antibiotic therapy are more likely to achieve clinical success in terms of symptom resolution compared with placebo with a number needed to treat (NNT) of 7 or 8 patients.[18,33] Two recent randomized controlled trials among younger children that used even more stringent diagnostic criteria demonstrated that children who received antibiotics had more favorable symptom scores than those who received placebo, achieved faster symptom recovery, and had significantly lower rates of clinical failure as measured by otoscopic examination and persistence of symptoms, with an NNT closer to 4.[19,20] Nonetheless, it is important to note that in numerous studies of antibiotic efficacy for AOM, the majority of patients have symptoms that ultimately resolve spontaneously regardless of therapy and without complications. The potential for preventing complications, such as mastoiditis, may contribute, in part, to the clinical decision to use antibiotics for AOM. However, across the aforementioned controlled studies and meta-analyses, antibiotics have not demonstrated significant benefit in preventing these rare but serious complications. Observational data from the United Kingdom including more than 1 million AOM episodes indicates that when mastoiditis occurs, it typically is present at time of initial clinical presentation to care.[34] The estimated NNT to prevent 1 episode of mastoiditis is nearly 5000.[34]

The AAP recommends antibiotic therapy for children diagnosed with AOM on the basis of presence of established clinical criteria. Observation can be considered for selected children, particularly children older than 2 years with nonsevere symptoms and unilateral disease.

Acute Bacterial Sinusitis

Benefits

The evidence base evaluating the effectiveness of antibiotics for treatment of acute bacterial sinusitis in children is limited and mixed. Three randomized controlled trials have assessed the effectiveness of antibiotics versus placebo for clinically diagnosed acute bacterial sinusitis in children, 2 of which have been published since the 1998 principles of judicious use of antibiotics.[14,17,35] Two trials concluded that antibiotics significantly improved the likelihood of symptom resolution after both 3 and 14 days,[14,35] but 1 study revealed no benefit of antibiotics over placebo.[17] Key differences in the study design between these studies likely contributed to the differences in outcomes; the trials showing benefit included patients with more severe symptoms and applied more strict diagnostic criteria. This emphasizes the importance of careful attention to clinical diagnosis because antibiotics confer no clinical benefit for patients

without diagnostic criteria suggesting acute bacterial sinusitis.

The benefit of antibiotic therapy in preventing suppurative complications, such as orbital cellulitis or intracranial abscess, is unproven. Individual efficacy trials lack the statistical power to demonstrate effectiveness against these rare complications, and a meta-analysis of randomized controlled trials in children and adults found no significant association between antibiotic use and the rate of complications.[36]

The AAP recommends antibiotic therapy for children with clinical features of acute bacterial sinusitis, especially those with symptoms that are worsening or severe. Observation with close follow-up or antibiotic therapy can be considered for those with persistent symptoms (>10 days).

GAS Pharyngitis

Benefits

Antibiotic treatment of acute pharyngitis has been studied with respect to the effects on symptom resolution, transmission, and prevention of complications, including rheumatic fever. Five randomized controlled studies and 1 meta-analysis have examined the effect of immediate antibiotics on resolution of symptoms, 1 of which was completed since publication of the first principles of judicious use of antibiotics.[37–41] These studies provide strong evidence that antibiotic therapy for children with pharyngitis and confirmation of GAS shortens the duration of symptoms, including sore throat and headache, by approximately 1 day. These benefits are apparent within as few as 3 days. However, the benefits of antibiotic therapy on shortening duration of fever are uncertain. Although data are somewhat limited, antibiotic therapy for index cases of GAS may reduce horizontal transmission and thereby prevent secondary cases.[40,42] These benefits are especially relevant in large households, child care settings, schools, and military settings.

Historically, the primary motivation for prescribing antibiotics for GAS pharyngitis was prevention of rheumatic fever. Randomized controlled trials in children before 1975 showed a fourfold benefit in preventing the onset of rheumatic fever, which occurred in approximately 3% of untreated patients.[43] Although localized outbreaks have occurred in recent decades, the incidence of rheumatic fever in most developed countries has declined dramatically.[44] Some of this decline might be attributable to better recognition and antibiotic treatment,[45] but more likely this relates to a decline in the prevalence of rheumatogenic strains of GAS.[46]

Antibiotics may also have a role in preventing suppurative complications associated with GAS pharyngitis, such as peritonsillar abscess (PTA), AOM, and acute sinusitis. One meta-analysis suggested that antibiotic treatment prevents PTA; however, the majority of cases were derived from a single study conducted in 1951.[43] Data from a large observational cohort conducted in the United Kingdom suggest that antibiotic treatment may prevent development of PTA, but with an NNT >4000.[47]

The AAP recommends antibiotic therapy for children with pharyngitis confirmed to be caused by GAS.

Common Cold, Nonspecific URI, Acute Cough Illness, and Acute Bronchitis

Because the predominant etiologies for these conditions are viruses, antibiotic therapy is not indicated. Because of uncertainty about the relevance of the diagnosis of acute bronchitis for children, data are limited. Nonetheless, a large meta-analysis concluded that there was no benefit to antibiotic therapy (including for delayed prescriptions) for patients with nonspecific cough and cold.[48]

Harms of Antibiotic Therapy

It is crucial to account for the potential for antibiotics to cause harm when used for treatment of URIs. The significance of potential harms should be directly balanced against the potential for benefit on a case-by-case basis. The importance of harms associated with antibiotic use is directly related to (1) an assessment of the magnitude of potential benefit (eg, greater benefit achieved for young children with bilateral AOM than unilateral) and (2) the extent to which uncertainty remains in the diagnosis. The preponderance of evidence for benefits of antibiotic therapy in treatment of bacterial URIs relates to attenuation of symptoms. When it is unclear whether the URI represents an acute bacterial infection, in general, the harms of antibiotic use have the potential to outweigh benefits. The importance of applying stringent clinical criteria to establish the diagnosis of a bacterial infection aids in differentiating children with nonspecific URI and common cold. Prescribing antibiotics for nonspecific URI and colds generally does not provide benefit and only exposes these children to potential harm.

Antibiotics are responsible for the largest number of unplanned medical visits for medication-related adverse events among children, which exceeds 150 000 per year and incurs substantial potential morbidity and cost.[4] Antibiotic-associated adverse events can range from mild (diarrhea and rash), to more severe (Stevens-Johnson syndrome), to life-threatening (anaphylaxis or sudden cardiac death) reactions. Most clinical trials conducted to assess the treatment of AOM, sinusitis, and pharyngitis have used amoxicillin or amoxicillin-clavulanate,

and these remain the first-line recommended agents for antibiotic therapy for these conditions. Studies comparing antibiotic treatment to placebo for AOM suggest a modestly increased rate of adverse events among treated patients, particularly diarrhea and rash. Two meta-analyses estimated rate differences of approximately 5% for adverse events.[18,32] Not included in these are the results from 2 recent trials using amoxicillin-clavulanate (older studies frequently used amoxicillin), which demonstrated even higher rates of diarrhea and dermatitis among patients receiving antibiotic therapy.[19,20] Among studies of sinusitis, in the most recent trial that demonstrated a benefit of antibiotic therapy, adverse events (defined as rash, diarrhea, vomiting, and abdominal pain) occurred in 44% of patients treated with high-dose amoxicillin-clavulanate compared with 14% in the placebo group.[14]

The adverse events described previously occur relatively frequently, although are relatively mild in most cases. Antibiotics can produce serious allergic reactions such as Stevens-Johnson syndrome.[25] There is rapidly growing evidence that antibiotic exposures early in life may disrupt the microbial balance of the intestines and other parts of the body in such a way as to contribute to long-term adverse health effects, such as inflammatory bowel disease, obesity, eczema, and asthma.[49–51] A recent study highlighted risk of sudden death in adults treated with azithromycin, likely related to drug-associated prolongation of the QT interval.[24] Azithromycin is not a first-line antibiotic for any pediatric URI and is the antibiotic most likely to be used inappropriately (inadequate coverage for the most common pathogens causing AOM and sinusitis).[1] The incidence of *C difficile* colitis in hospitalized children has increased substantially during the past decade.[52] Although children with comorbid conditions are at greatest risk, community-onset infections occur,[53] with recent antibiotic exposure as an important risk factor.

The relationship between antibiotic exposure and development of antibiotic resistance at the level of the individual patient and at the level of the community is well established.[7,8] Because of limited therapeutic options, antibiotic-resistant infections are difficult to treat and, in some cases, are associated with poor clinical outcomes.[54] Application of stringent diagnostic criteria and use of therapy only when the diagnosis and potential benefits are well established is essential to minimizing the impact of antibiotic overuse on resistance in individuals and within communities.

PRINCIPLE 3: IMPLEMENT JUDICIOUS PRESCRIBING STRATEGIES

When evidence suggests that antibiotics may provide benefit, several aspects of judicious prescribing should be considered. These include selecting an appropriate antibiotic agent that treats the most likely pathogens (including accounting for local resistance patterns), selecting the appropriate dose, and treating for the shortest duration required. Additionally, physicians may consider the role of observation and use of delayed prescribing strategies.

The treatment of AOM and acute bacterial sinusitis illustrates several key aspects of judicious antibiotic use. Amoxicillin has traditionally been the recommended first-line agent for these conditions because *Streptococcus pneumoniae* is the most important cause. However, in some communities, the prevalence of amoxicillin-resistant β-lactamase-producing *Haemophilus influenzae* among bacterial URIs has increased significantly.[55] This underlies (in part) the recommendation to consider amoxicillin-clavulanate in certain instances (eg, severe symptoms, recent [<6 weeks] antibiotic exposure, known high local prevalence of amoxicillin-resistant *H influenzae*). It is important to note, however, that the benefits of antibiotic therapy appear to be greatest for patients with *S pneumoniae* infection, compared with other bacterial causes of URI, including *H influenzae* and *Moraxella* species, which may have higher rates of spontaneous resolution.[16] In recognition of the possibility of a higher rate of adverse events caused by amoxicillin-clavulanate compared with amoxicillin, some physicians may choose to use amoxicillin as the first-line agent in most instances.

An understanding of local epidemiology and resistance patterns is especially important for understanding appropriate antibiotic selection. The rates of pneumococcal resistance to macrolides[56] and oral third-generation cephalosporins[57,58] make these agents poor choices for treating most children with suspected bacterial URIs. Emergence of macrolide resistance to GAS is also an important problem, although susceptibility testing is not routinely performed.

The role of observation (also termed "wait and see" or "delayed prescribing") instead of immediate antibiotic therapy is an important consideration for children with AOM and acute bacterial sinusitis. Studies among patients with AOM have shown that this approach reduces antibiotic use, is well accepted by families, and, when supported by close follow-up, does not result in worse clinical outcomes.[22] Observation therapy may be considered as an alternative strategy to immediate therapy for AOM and sinusitis for older patients without severe symptoms.[22,23] The use of this approach is an opportunity to engage in shared decision-making with patients and families to include a discussion

about the potential benefits and risks associated with immediate antibiotic therapy.

Another important consideration for judicious antibiotic use is overall magnitude of exposure. Relatively short courses of therapy may achieve the same clinical benefits as longer courses while minimizing the risks of adverse events and development of resistance and lead to better compliance. Important examples are the use of once-daily amoxicillin for GAS pharyngitis[26] (vs 2 or 3 times daily dosing but the same daily dose of 50 mg/kg) and short-course therapy (eg, 7 days vs 10 days) for older children with AOM.[22]

CONCLUSIONS

This clinical report discusses principles of judicious antibiotic use for pediatric URIs. There is a strong emphasis on appropriate diagnosis, which is the foundation for making judicious decisions about prescribing antibiotics. Although focused on specific URIs, the main message has broader application for antibiotic use in general. These principles can be used to promote educational efforts for physicians, amplify the messages from recent clinical guidelines, assist with communication about appropriate antibiotic use to patients and families, and support local guideline development for judicious antibiotic use.

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REFERENCES

1. Hersh AL, Shapiro DJ, Pavia AT, Shah SS. Antibiotic prescribing in ambulatory pediatrics in the United States. *Pediatrics*. 2011;128(6):1053–1061
2. Grijalva CG, Nuorti JP, Griffin MR. Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. *JAMA*. 2009;302(7):758–766
3. Nyquist AC, Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. *JAMA*. 1998;279(11):875–877
4. Bourgeois FT, Mandl KD, Valim C, Shannon MW. Pediatric adverse drug events in the outpatient setting: an 11-year national analysis. *Pediatrics*. 2009;124(4). Available at: www.pediatrics.org/cgi/content/full/124/4/e744
5. Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis*. 2008;47(6):735–743
6. Cohen AL, Budnitz DS, Weidenbach KN, et al. National surveillance of emergency department visits for outpatient adverse drug events in children and adolescents. *J Pediatr*. 2008;152(3):416–421
7. Hicks LA, Chien YW, Taylor TH, Jr, Haber M, Klugman KP Active Bacterial Core Surveillance (ABCs) Team. Outpatient antibiotic prescribing and nonsusceptible Streptococcus pneumoniae in the United States, 1996–2003. *Clin Infect Dis*. 2011;53(7):631–639
8. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ*. 2010;340:c2096
9. Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(1):1–12
10. Dowell SF, Marcy SM, Philips WR. Principles of judicious use of antimicrobial agents for pediatric upper respiratory tract infections. *Pediatrics*. 1998;101(suppl 1):163–165
11. Pavia M, Bianco A, Nobile CG, Marinelli P, Angelillo IF. Efficacy of pneumococcal vaccination in children younger than 24 months: a meta-analysis. *Pediatrics*. 2009;123(6). Available at: www.pediatrics.org/cgi/content/full/123/6/e1103
12. Centers for Disease Control and Prevention (CDC). Invasive pneumococcal disease in

children 5 years after conjugate vaccine introduction—eight states, 1998–2005. *MMWR Morb Mortal Wkly Rep*. 2008;57(6):144–148

13. Kyaw MH, Lynfield R, Schaffner W, et al; Active Bacterial Core Surveillance of the Emerging Infections Program Network. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant Streptococcus pneumoniae. *N Engl J Med*. 2006;354(14):1455–1463
14. Wald ER, Nash D, Eickhoff J. Effectiveness of amoxicillin/clavulanate potassium in the treatment of acute bacterial sinusitis in children. *Pediatrics*. 2009;124(1):9–15
15. American Academy of Pediatrics. Subcommittee on Management of Sinusitis and Committee on Quality Improvement. Clinical practice guideline: management of sinusitis. *Pediatrics*. 2001;108(3):798–808
16. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. *Pediatrics*. 2004;113(5):1451–1465
17. Garbutt JM, Goldstein M, Gellman E, Shannon W, Littenberg B. A randomized, placebo-controlled trial of antimicrobial treatment for children with clinically diagnosed acute sinusitis. *Pediatrics*. 2001;107(4):619–625
18. Coker TR, Chan LS, Newberry SJ, et al. Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review. *JAMA*. 2010;304(19):2161–2169
19. Hoberman A, Paradise JL, Rockette HE, et al. Treatment of acute otitis media in children under 2 years of age. *N Engl J Med*. 2011;364(2):105–115
20. Tähtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med*. 2011;364(2):116–126
21. Chow AW, Benninger MS, Brook I, et al; Infectious Diseases Society of America. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis*. 2012;54(8):e72–e112
22. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics*. 2013;131(3). Available at: www.pediatrics.org/cgi/content/full/131/3/e964
23. Wald ER, Applegate KE, Bordley C, et al; American Academy of Pediatrics. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. *Pediatrics*. 2013;132(1). Available at: www.pediatrics.org/cgi/content/full/132/1/e262
24. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med*. 2012;366(20):1881–1890
25. Goldman JL, Jackson MA, Herigon JC, Hersh AL, Shapiro DJ, Leeder JS. Trends in adverse reactions to trimethoprim-sulfamethoxazole. *Pediatrics*. 2013;131(1). Available at: www.pediatrics.org/cgi/content/full/131/1/e103
26. American Academy of Pediatrics. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2012
27. Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012;55(10):1279–1282
28. Fine AM, Nizet V, Mandl KD. Large-scale validation of the Centor and McIsaac scores to predict group A streptococcal pharyngitis. *Arch Intern Med*. 2012;172(11):847–852
29. Damoiseaux RA, van Balen FA, Hoes AW, Verheij TJ, de Melker RA. Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children aged under 2 years. *BMJ*. 2000;320(7231):350–354
30. Le Saux N, Gaboury I, Baird M, et al. A randomized, double-blind, placebo-controlled noninferiority trial of amoxicillin for clinically diagnosed acute otitis media in children 6 months to 5 years of age. *CMAJ*. 2005;172(3):335–341
31. Vouloumanou EK, Karageorgopoulos DE, Kazantzi MS, Kapaskelis AM, Falagas ME. Antibiotics versus placebo or watchful waiting for acute otitis media: a meta-analysis of randomized controlled trials. *J Antimicrob Chemother*. 2009;64(1):16–24
32. Glasziou PP, Del Mar CB, Sanders SL, Hayem M. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev*. 2004;(1):CD000219
33. Rovers MM, Glasziou P, Appelman CL, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet*. 2006;368(9545):1429–1435
34. Thompson PL, Gilbert RE, Long PF, Saxena S, Sharland M, Wong IC. Effect of antibiotics for otitis media on mastoiditis in children: a retrospective cohort study using the United Kingdom general practice research database. *Pediatrics*. 2009;123(2):424–430
35. Wald ER, Chiponis D, Ledesma-Medina J. Comparative effectiveness of amoxicillin and amoxicillin-clavulanate potassium in acute paranasal sinus infections in children: a double-blind, placebo-controlled trial. *Pediatrics*. 1986;77(6):795–800
36. Falagas ME, Giannopoulou KP, Vardakas KZ, Dimopoulos G, Karageorgopoulos DE. Comparison of antibiotics with placebo for treatment of acute sinusitis: a meta-analysis of randomised controlled trials. *Lancet Infect Dis*. 2008;8(9):543–552
37. Zwart S, Rovers MM, de Melker RA, Hoes AW. Penicillin for acute sore throat in children: randomised, double blind trial. *BMJ*. 2003;327(7427):1324
38. el-Daher NT, Hijazi SS, Rawashdeh NM, al-Khalil IA, Abu-Ektaish FM, Abdel-Latif DI. Immediate vs. delayed treatment of group A beta-hemolytic streptococcal pharyngitis with penicillin V. *Pediatr Infect Dis J*. 1991;10(2):126–130
39. Krober MS, Bass JW, Michels GN. Streptococcal pharyngitis. Placebo-controlled double-blind evaluation of clinical response to penicillin therapy. *JAMA*. 1985;253(9):1271–1274
40. Pichichero ME, Disney FA, Talpey WB, et al. Adverse and beneficial effects of immediate treatment of group A beta-hemolytic streptococcal pharyngitis with penicillin. *Pediatr Infect Dis J*. 1987;6(7):635–643
41. Nelson JD. The effect of penicillin therapy on the symptoms and signs of streptococcal pharyngitis. *Pediatr Infect Dis*. 1984;3(1):10–13
42. Kikuta H, Shibata M, Nakata S, et al. Efficacy of antibiotic prophylaxis for intrafamilial transmission of group A beta-hemolytic streptococci. *Pediatr Infect Dis J*. 2007;26(2):139–141
43. Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for sore throat. *Cochrane Database Syst Rev*. 2004;(2):CD000023
44. Robertson KA, Volmink JA, Mayosi BM. Antibiotics for the primary prevention of acute rheumatic fever: a meta-analysis. *BMC Cardiovasc Disord*. 2005;5(1):11
45. Massell BF, Chute CG, Walker AM, Kurland GS. Penicillin and the marked decrease in morbidity and mortality from rheumatic fever in the United States. *N Engl J Med*. 1988;318(5):280–286
46. Shulman ST, Stollerman G, Beall B, Dale JB, Tanz RR. Temporal changes in streptococcal M protein types and the near-disappearance of acute rheumatic fever in the United States. *Clin Infect Dis*. 2006;42(4):441–447
47. Petersen I, Johnson AM, Islam A, Duckworth G, Livermore DM, Hayward AC. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with

the UK General Practice Research Database. *BMJ*. 2007;335(7627):982

48. Spurling GK, Del Mar CB, Dooley L, Foxlee R, Farley R. Delayed antibiotics for respiratory infections. *Cochrane Database Syst Rev*. 2013;4:CD004417
49. Kronman MP, Zaoutis TE, Haynes K, Feng R, Coffin SE. Antibiotic exposure and IBD development among children: a population-based cohort study. *Pediatrics*. 2012;130(4). Available at: www.pediatrics.org/cgi/content/full/130/4/e794
50. Tsakok T, McKeever TM, Yeo L, Flohr C. Does early life exposure to antibiotics increase the risk of eczema? A systematic review [published online ahead of print June 21, 2013]. *Br J Dermatol*. doi:doi:10.1111/bjd.12476
51. Jedrychowski W, Perera F, Maugeri U, et al. Wheezing and asthma may be enhanced by broad spectrum antibiotics used in early childhood. Concept and results of a pharmacoepidemiology study. *J Physiol Pharmacol*. 2011;62(2):189–195
52. Lessa FC, Gould CV, McDonald LC. Current status of Clostridium difficile infection epidemiology. *Clin Infect Dis*. 2012;55(suppl 2):S65–S70
53. Khanna S, Baddour LM, Huskins WC, et al. The epidemiology of Clostridium difficile infection in children: a population-based study. *Clin Infect Dis*. 2013;56(10):1401–1406
54. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis*. 2006;42(suppl 2):S82–S89
55. Pichichero ME, Casey JR. Evolving microbiology and molecular epidemiology of acute otitis media in the pneumococcal conjugate vaccine era. *Pediatr Infect Dis J*. 2007;26(10 suppl):S12–S16
56. Jenkins SG, Farrell DJ. Increase in pneumococcus macrolide resistance, United States. *Emerg Infect Dis*. 2009;15(8):1260–1264
57. Pottumarthy S, Fritsche TR, Jones RN. Comparative activity of oral and parenteral cephalosporins tested against multidrug-resistant Streptococcus pneumoniae: report from the SENTRY Antimicrobial Surveillance Program (1997–2003). *Diagn Microbiol Infect Dis*. 2005;51(2):147–150
58. Fritsche TR, Biedenbach DJ, Jones RN. Update of the activity of cefditoren and comparator oral beta-lactam agents tested against community-acquired Streptococcus pneumoniae isolates (USA, 2004–2006). *J Chemother*. 2008;20(2):170–174

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