

# Judicious use of antibiotics for common pediatric respiratory infections

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**Background.** Antibiotic resistance among common respiratory infection-producing bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* has become a major global public health problem. The use of antibiotics, whether or not medically justified for a particular illness, contributes to the development of resistant bacteria. To help to contain the proliferation of drug-resistant bacteria, members of the CDC and the American Academy of Pediatrics (AAP) recently published principles for the judicious use of antibiotics in common pediatric respiratory infections including the common cold, otitis media, sinusitis and tonsillopharyngitis. This article reviews the CDC/AAP principles for management of these illnesses and describes results of clinical practice studies in which efforts to improve the judicious use of antibiotics were undertaken.

**Conclusions.** The success of the CDC/AAP principles in containing the increase in antimicrobial resistance depends upon their being practiced. Results of clinical practice studies indicate that judicious use of antimicrobial therapy in pediatric respiratory infections can be realized through education and persistence. More widespread educational and behavior modification efforts are necessary to reduce unnecessary prescription of antibiotics and to curtail the still burgeoning problem of bacterial resistance.

## INTRODUCTION

Antibiotic resistance among common respiratory infection-producing bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* has become a major global public health problem.<sup>1,2</sup> Although *S. pneumoniae* was uniformly sensitive to penicillin treatment during the 1980s,

approximately 20 to 35% of *S. pneumoniae* isolates in the United States are now resistant to penicillin and other classes of antibiotics.<sup>2,3</sup> These levels of resistance have become significantly higher in some regions of the U.S. Furthermore, approximately 25% of *H. influenzae* and 90% of *M. catarrhalis* in the United States produce beta-lactamase and are therefore resistant to older, non-beta-lactamase-stable antibiotics such as ampicillin and amoxicillin.<sup>3</sup>

The use of antibiotics, whether or not medically justified for a particular illness, contributes to the development of resistant bacteria. Recent completion of a course of antibiotics, for example, has been shown to increase the risk of nasopharyngeal carriage of drug-resistant *Pneumococcus*. Across four studies<sup>4-7</sup> drug-resistant *Pneumococcus* was isolated from 39 to 67% of cultures from patients recently completing a course of antibiotics but from only 8 to 21% of cultures from patients who had not recently received antimicrobial therapy. Besides increasing the risk of colonization by resistant organisms, recent antibiotic use increases the risk of contracting invasive disease caused by resistant organisms. Across six studies<sup>8-13</sup> of patients with invasive pneumococcal disease, a course of antibiotics had recently been completed in 30 to 70% of patients infected with drug-resistant *Pneumococcus* compared with only 4 to 39% of patients infected with drug-susceptible *Pneumococcus*.

These data demonstrate that unnecessary antibiotic use harms patients by increasing chances that they will be infected by drug-resistant bacteria. To help to contain the proliferation of drug-resistant bacteria, members of the CDC and the American Academy of Pediatrics (AAP) recently published principles in 1998 for the judicious use of antibiotics in common pediatric respiratory infections, including the common cold,<sup>14</sup> otitis media,<sup>15</sup> sinusitis,<sup>16</sup> and tonsillopharyngitis.<sup>17</sup> This article reviews the CDC/AAP principles for management of these illnesses and describes results of clinical practice studies in which efforts to improve the judicious use of antibiotics were undertaken.

## ANTIBIOTIC USE AND THE COMMON COLD

Most children suffer multiple episodes of the common cold per year.<sup>18-22</sup> An evaluation<sup>23</sup> of Kentucky Medicaid claims during 1992 to 1993 demonstrated

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that antibiotics were prescribed to 60% of patients suffering a common cold at a cost of \$37.5 million.

This statistic is particularly distressing in the context of the strong evidence showing that the common cold, most often caused by viruses such as rhinoviruses and coronaviruses, does not respond to antibiotics. Studies<sup>24-32</sup> conducted from the 1950s to the late 1990s in thousands of patients consistently demonstrate no effect of antibiotic use on the course or outcome of the common cold. In one of the studies, a modest but statistically significant benefit of doxycycline over placebo was noted for improvement in rhinorrhea on the fifth day of therapy but not on the tenth day. These data, which indicate that antibiotic use for common colds is unwarranted, provide the evidence base for the CDC/APA first principle of judicious use of antibiotics for the common cold (Table 1): "Antimicrobial agents should not be given for the common cold."

Most clinicians realize that antibiotics should not be given to treat episodes of the cold *per se*; however, they may prescribe antibiotics in order to prevent bacterial complications of the cold. The efficacy of antibiotics in preventing bacterial complications of the common cold has not been systematically studied, but the evidence accumulated to date suggests that antibiotics are not particularly effective in preventing bacterial complications of viral infections. For example, a metaanalysis<sup>33</sup> of randomized, controlled trials conducted in a variety of clinical settings demonstrates that antibiotic treatment of children with nonspecific upper respiratory

infections neither shortens the length of upper respiratory illness nor prevents development of bacterial pneumonia.

Familiarity with signs and symptoms of the common cold helps clinicians to minimize inappropriate antibiotic prescribing for normal manifestations of this typically viral illness. However, despite clinicians' awareness of the precepts that mucopurulent rhinitis is one of the most common symptoms of the cold and usually does not signify the need for treatment with antibiotics, many continue to prescribe antibiotics at the first sign of mucopurulent rhinitis. For example, more than 7 in 10 family practitioners and more than 5 in 10 pediatricians indicated in a 450-physician survey<sup>34</sup> conducted in 1994 that they immediately prescribe antibiotics for infants with green mucopurulent rhinitis lasting 1 day.

The CDC/AAP members formulated the second principle of judicious use of antibiotics for the common cold (Table 1) in order to curb such prescribing behavior: "Mucopurulent rhinitis (thick, opaque, or discolored nasal discharge) frequently accompanies the common cold. It is not an indication for antimicrobial treatment unless it persists for >10 to 14 days." The superfluity of antibiotic treatment based on presence of mucopurulence is illustrated by the results of a 1984 study<sup>35</sup> comparing cephalexin with placebo treatment in 142 children with mucopurulent nasopharyngitis. Five to 6 days after initiation of therapy, cephalexin and placebo groups did not differ with respect to presence of purulent nasal discharge (76% of cephalexin patients; 63%

**TABLE 1.** The Centers for Disease Control/American Academy of Pediatrics (CDC/AAP) principles for judicious use of antimicrobials in common respiratory infections

Adapted with permission.<sup>14-17</sup>

Illness	CDC/AAP Principles
Common cold	<ol style="list-style-type: none"> <li>1. Antimicrobial agents should not be given for the common cold.</li> <li>2. Mucopurulent rhinitis (thick, opaque or discolored nasal discharge) frequently accompanies the common cold. It is not an indication for antimicrobial treatment unless it persists for &gt;10-14 days.</li> </ol>
Otitis media	<ol style="list-style-type: none"> <li>1. Episodes of otitis media should be classified as acute otitis media or otitis media with effusion.</li> <li>2. Antimicrobials are indicated for treatment of acute otitis media; however, diagnosis requires documented middle ear effusion and signs or symptoms of acute local or systemic illness.</li> <li>3. Uncomplicated acute otitis media may be treated with a 5- to 7-day course of antimicrobials in certain patients older than 2 years of age.</li> <li>4. Antimicrobials are not indicated for initial treatment of otitis media with effusion; treatment may be indicated if effusions persist for <math>\geq 3</math> mo.</li> <li>5. Persistent middle ear effusion after therapy for acute otitis media is expected and does not require retreatment.</li> <li>6. Antimicrobial prophylaxis should be reserved for control of recurrent acute otitis media, defined by <math>\geq 3</math> distinct and well-documented episodes/6 mo or <math>\geq 4</math> episodes/12 mo.</li> </ol>
Sinusitis	<ol style="list-style-type: none"> <li>1. Clinical diagnosis of bacterial sinusitis requires prolonged nonspecific upper respiratory signs and symptoms (i.e. rhinosinusitis and cough without improvement for &gt;10-14 days) or more severe upper respiratory tract signs and symptoms (i.e. fever <math>\geq 39^\circ\text{C}</math>, facial swelling, facial pain).</li> <li>2. The common cold often includes radiologic evidence of sinus involvement; therefore, radiographs should be used and interpreted with caution. They may be indicated when episodes of sinusitis are recurrent, when complications are suspected, or when the diagnosis is unclear.</li> <li>3. Initial antimicrobial treatment of acute sinusitis should be with the most narrow spectrum agent that is active against the likely pathogens.</li> </ol>
Pharyngitis	<ol style="list-style-type: none"> <li>1. Diagnosis of group A streptococcal pharyngitis should be based on results of appropriate laboratory tests in conjunction with clinical and epidemiologic findings.</li> <li>2. Antimicrobial therapy should not be given to a child with pharyngitis in the absence of diagnosed group A streptococcal or other bacterial infection.</li> <li>3. A penicillin remains the drug of choice for treating group A streptococcal pharyngitis.</li> </ol>

of placebo patients), incidence of complications (7% of cephalexin patients; 8% of placebo patients), or parental opinion of the benefit of medication (36% of cephalexin parents; 31% of placebo parents).

### ANTIBIOTIC USE IN OTITIS MEDIA

Acute otitis media is the most commonly diagnosed illness in children and the chief indication for antibiotic prescriptions in the United States.<sup>36</sup> It is often a self-limiting illness. However, because the efficacy of antibiotics compared with placebo in producing bacterial eradication and clinical improvement in acute otitis media has been convincingly demonstrated, most clinicians prescribe antimicrobial therapy to reduce patients' suffering and return them to normal functioning. This practice is supported by the finding, from a metaanalysis<sup>37</sup> of 33 randomized, controlled clinical trials enrolling more than 5400 children, that the use of antibiotics for acute otitis media increased the recovery rate over that without antibiotics by 14% (though spontaneous recovery without antibiotics occurred in the majority of patients not given them). In addition to the desire to effect a clinical cure and to restore the patient rapidly to normal activities, the goals of preventing progression to chronic disease and the occurrence of rare but dangerous sequelae such as meningitis and bacteremia favor the use of antibiotics for this illness.

In deciding whether or not to prescribe antibiotics, it is important to classify otitis media as *acute otitis media*, defined as the presence of middle ear fluid associated with clinical manifestations of local or systemic illness, or *otitis media with effusion*, defined as presence of middle ear fluid not accompanied by clinical manifestations of infection. Otitis media with effusion, which often follows a bout of acute otitis media or a viral upper respiratory infection, may persist for weeks or months.<sup>15, 38</sup> While there is a strong rationale for prescribing antibiotics to patients suffering from acute otitis media, there is no evidence that antibiotics affect the course of otitis media with effusion. Whether or not children are administered antibiotic therapy for otitis media with effusion, middle ear fluid is present in 1 of 2 children at 1 month; 1 in 5 at 2 months; and 1 in 10 at 3 months after cessation of therapy for acute otitis media.<sup>39</sup> Because the decision to use or not to use antibiotics in otitis media hinges on differentiation of acute otitis media from otitis media with effusion, members of the CDC/AAP indicate that as the first principle of judicious use of antibiotics in otitis media, "episodes of otitis media should be classified as acute otitis media or otitis media with effusion" (Table 1). In addition, the CDC/AAP principles for judicious use of antimicrobial agents for otitis media state that "antimicrobials are not indicated for initial treatment of otitis media with effusion; treatment may be indicated

if effusions persist for  $\geq 3$  months" and "persistent middle ear effusion after therapy for acute otitis media is expected and does not require retreatment" (Table 1).

Despite CDC/AAP efforts to curb antibiotic prescribing for otitis media with effusion, up to 8 million prescriptions per year are filled in the United States for otitis media with effusion.<sup>15</sup> The persistence of this unnecessary prescribing may be attributed in part to the difficulty in diagnosing acute otitis media, for which diagnostic criteria abound. One review<sup>40</sup> identified 18 sets of criteria in 26 clinical trials and 147 sets in 165 pediatric clinical settings. Because middle ear fluid and local infection are hallmark signs of acute otitis media and together suggest the presence of bacterial illness, the members of the CDC/AAP advise that "diagnosis requires documented middle ear effusion *and* signs or symptoms of acute local or systemic illness" (Table 1).

The members of the CDC/AAP recommend that pneumatic otoscopy be used to assess the position, color, translucency and mobility of the tympanic membrane. Otoscopic evidence of an inflamed middle ear, however, is not sufficient to justify a diagnosis of acute otitis media. Symptoms such as otorrhea, a bulging yellow or red tympanic membrane and ear pain, all of which may signal existence of local infection, or systemic symptoms such as fever need also to be present. Nonspecific symptoms such as rhinorrhea, cough, irritability and headache can occur with many respiratory and nonrespiratory illnesses of bacterial and nonbacterial origin and provide inadequate basis for a diagnosis of acute otitis media.

Antibiotic therapy should be directed at the most likely pathogens, including nontypable *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*. Although the CDC/AAP principles do not recommend which antibiotics to prescribe once acute otitis media has been diagnosed, they do advocate reducing the duration of antibiotic therapy from the traditional (in the United States) 10 days to a 5- to 7-day course in uncomplicated cases (Table 1). The equivalent efficacy of shortened courses compared with traditional courses of antibiotic therapy for acute otitis media has been consistently demonstrated across studies reviewed elsewhere<sup>41, 42</sup> and in this Supplement.<sup>43</sup> Benefits of 5- to 7-day relative to 10-day therapy include reduced drug costs, improved compliance and—most importantly in the context of judicious use of antibiotics—decreased risk of fostering the development and spread of resistant organisms. The shortened course of antibiotics, appropriate for the majority of children suffering from acute otitis media, may be inadvisable for some patient groups including children less than 2 years of age or with tympanic membrane perforation and those prone to recurrent or persistent infection. The evidence for equivalent effi-

cacy of shortened and traditional courses of antimicrobial therapy in these patients, few of whom have been studied in clinical trials conducted to date, is mixed.<sup>41-43</sup>

Like the recommendation to shorten the duration of antibiotic therapy in appropriate patients, the final CDC/AAP principle for judicious use of antimicrobial therapy in acute otitis media is intended to reduce the risk of encouraging the proliferation of resistant bacteria: "Antibiotic prophylaxis should be reserved for control of recurrent acute otitis media" (Table 1). Although daily prophylactic treatment with low doses of antibiotics has been demonstrated to decrease the incidence of episodes of acute otitis media, the benefit of antimicrobial prophylaxis is small. One metaanalysis demonstrates that prophylactic antibiotic therapy for acute otitis media reduced the number of episodes by approximately 1 episode per year. Members of the CDC/AAP advise that the possible benefits of prophylactic therapy be carefully considered in the context of the risks of fostering antibiotic resistance and that prophylactic therapy be limited to patients most likely to have frequent recurrences.

#### ANTIBIOTIC USE IN SINUSITIS

Acute sinusitis most often arises as a complication of upper respiratory tract infections; acute bacterial sinusitis complicates 0.5 to 5% of viral respiratory infections such as the common cold.<sup>44</sup> The number of prescriptions written in the United States for acute sinusitis in 1992, a year during which 25.9 million individuals sought medical attention for upper respiratory infections, was 12.9 million.<sup>36</sup> According to the 0.5 to 5% incidence cited above, 0.13 to 1.3 million episodes of bacterial sinusitis in 1992 would be predicted to have complicated upper respiratory infections and to have warranted antibiotic therapy. The 12.9 million prescriptions actually written for acute sinusitis that year thus reflect a staggering incidence of overdiagnosis and overtreatment of acute sinusitis.

The first two CDC/AAP principles for judicious use of antimicrobial therapy in sinusitis (Table 1) are directed primarily at preventing its overdiagnosis, which often occurs when symptoms of the common cold or other upper respiratory tract infections are attributed to bacterial sinusitis. The CDC/AAP principles state that clinical diagnosis of bacterial sinusitis requires "prolonged nonspecific upper respiratory signs and symptoms (*i.e.* rhinosinusitis and cough without improvement for >10 to 14 days) or more severe upper respiratory tract signs and symptoms (*i.e.* fever  $\geq 39^{\circ}\text{C}$ , facial swelling, facial pain).<sup>45</sup> The requirement for persistent (lasting >10 to 14 days) nonspecific upper respiratory signs and symptoms is based on the demonstration that symptoms of viral upper respiratory tract infections such as the common cold, often symp-

tomatically indistinguishable from sinusitis and up to 200 times more common, last approximately 9 days.<sup>45</sup> The CDC/AAP instruction that nonspecific upper respiratory signs and symptoms should be "without improvement" for >10 to 14 days is important; children whose runny nose and cough improve by the tenth day of illness are probably suffering a viral upper respiratory infection. Lack of abatement of symptoms beyond the typical time of resolution of respiratory viral infections may suggest, but does not invariably indicate, the existence of bacterial sinusitis.

Members of the CDC/AAP recommend only occasional use of sinus radiographs as a diagnostic tool for sinusitis because sinus radiographs may appear abnormal (by manifesting, for example, thickening of the mucosa or opacification) not only in sinusitis, but also in other conditions such as the common cold. The second CDC/AAP principle advises that ". . . radiographs should be used and interpreted with caution. They may be indicated 1) when episodes of sinusitis are recurrent; 2) when complications are suspected; or 3) when the diagnosis is unclear" (Table 1). In these situations, signs of sinus inflammation in the presence of protracted symptoms of infection may help to increase confidence in the diagnosis of sinusitis.

The final CDC/AAP principle for treatment of bacterial sinusitis indicates, "initial antimicrobial treatment of acute sinusitis should be with the most narrow-spectrum agent that is active against the likely pathogens" (Table 1). Like acute otitis media, sinusitis is most frequently caused by nontypable *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*. Amoxicillin is often an initial choice. However, because many of the organisms that cause sinusitis are now resistant to amoxicillin, a beta-lactamase-stable antibiotic effective against *Pneumococcus* such as amoxicillin/clavulanate or the cephalosporin cefuroxime axetil could be considered if patients do not clinically respond to initial therapy within 48 to 72 h.

#### ANTIBIOTIC USE IN TONSILLOPHARYNGITIS

Sore throat, the cardinal symptom of bacterial tonsillopharyngitis, also occurs in many nonspecific upper respiratory infections of viral origin, a fact that complicates diagnosis. Group A *Streptococcus*, the primary bacterial cause of pharyngitis, is responsible for the sore throat and other symptoms in one or two of 10 patients;<sup>46</sup> infections in most of the remainder of patients are generally attributable to viruses.<sup>17</sup> Antibiotic treatment of Group A *Streptococcus* is important in preventing progression of bacterial tonsillopharyngitis to rheumatic fever and in returning the sufferer to normal daily activities. Because most sore throats are caused by viruses, however, members of the CDC/AAP recommend that careful "diagnosis of Group A streptococcal pharyngitis should be made using a laboratory

test in conjunction with clinical and epidemiologic findings" (first principle) and that "antimicrobial therapy should not be given to a child with pharyngitis in the absence of diagnosed Group A streptococcal or other bacterial infection" (second principle) (Table 1).

Diagnosis of Group A streptococcal infection should be based on the results of a throat swab culture (the recommended standard) or antigen-detection test. Because antigen-detection tests may give false-negative results, a culture should also be taken in the presence of a negative antigen-detection test.

To help curb unnecessary antibiotic use, the CDC/AAP guidelines caution against the initiation of antimicrobial therapy while awaiting the results of a throat culture or antigen-detection test. If a culture or antigen-detection test is returned with negative results, patients are nevertheless likely to continue to take the unnecessary antibiotic as prescribed because the physician does not advise cessation of antibiotic therapy and/or the patient decides to continue antibiotic therapy despite the negative test and physician recommendations to stop.

Members of the CDC/AAP recommend a 10-day course of penicillin the "drug of choice for treating group A streptococcal pharyngitis" due to its low cost, narrow spectrum of activity and proven efficacy (Table 1). In patients whose flora may be resistant to penicillin therapy, treatment with beta-lactamase-stable agents such as cephalosporins may be indicated. Group A *Streptococcus* resistance has not been identified to date after use of beta-lactam antibiotics; however, macrolide resistance has been observed.

#### JUDICIOUS USE OF ANTIBIOTICS IN CLINICAL PRACTICE

The success of these principles in containing the increase in antimicrobial resistance depends upon their being practiced. Although most physicians are aware of these principles, they may nevertheless continue to prescribe unnecessary antibiotics. Parental pressure is one frequently cited reason for physicians to prescribe antibiotics to children. In Schwartz and colleagues' survey<sup>34</sup> of 450 pediatricians and family practitioners, two of the top four reasons physicians cited for giving prompt antibiotic therapy were related to parental pressure ("pressure from mothers to prescribe an antibiotic" and "the desire to allow employed parents to return to work earlier"). Despite citing these medically unjustified reasons for prescribing antibiotic therapy, the majority of family practitioners (89%) and pediatricians (97%) in this study indicated that they were concerned about the role of unnecessary antibiotics in fostering bacterial resistance.

A study<sup>47</sup> conducted in 5 pediatric practices in Arkansas suggests that educational programs may impact both parental and physician behavior in favor of

more judicious use of antibiotics. Physicians, office staff and parents of children with respiratory infections viewed an 8-minute videotape designed to educate them about the CDC/AAP principles of judicious use of antimicrobial therapy. At the end of the 9-month study period, the majority of parents who viewed the videotape reported a significant increase in understanding of the reasons that unnecessary antibiotic use should be eliminated, and frequency of physician use of antibiotics for viral infections had dropped to 4% from 25% at study start.

In addition to parental pressure, the desire to reduce return office visits for bacterial infections that may arise as complications of nonspecific viral infections may motivate excessive antibiotic prescribing. A 1-year study<sup>48</sup> of 383 children with respiratory tract infections suggests that this frequently cited concern is unfounded. Seventy-seven percent (77%) of children with respiratory symptoms did not receive antibiotics at the initial visit, while 23% of children received antibiotics for presumed or confirmed bacterial infections. Unscheduled return office visits related to the initial visit occurred in 29 and 44% of children not receiving and receiving antibiotics at the initial visit, respectively. There was no difference between children not receiving and receiving antibiotics in the incidence of bacterial infections during the 1-year follow-up period. Thus, withholding prescriptions from children with respiratory symptoms but no documented bacterial infection did not result in either a higher rate of return office visits related to the initial visit or to an increase in bacterial infections.

The encouraging results from these two clinical practice studies indicate that judicious use of antimicrobial therapy in pediatric respiratory infections can be realized through education and persistence. More widespread educational and behavior modification efforts are necessary to reduce unnecessary prescription of antibiotics and curtail the still burgeoning problem of bacterial resistance.

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