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Antibiotic Recommendations for Acute Otitis Media and Acute Bacterial Sinusitis: Conundrum No More

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Abstract

There has been a substantial change in the prevalence and microbiologic characteristics of cases of acute otitis media secondary to the widespread use of pneumococcal conjugate vaccines. Current trends in nasopharyngeal colonization and the microbiology of acute otitis media support a change in the recommendation for antibiotic management of acute otitis media and acute bacterial sinusitis in children.

Keywords

acute otitis media (AOM); acute bacterial sinusitis (ABS); antibiotics; vaccine

Acute otitis media (AOM) and acute bacterial sinusitis (ABS) are two of the most frequent indications for initiating antimicrobial therapy in young children. The two conditions share substantial similarities in epidemiology, pathogenesis and microbiology. Consequently, recommendations for treatment are similar, although based on microbiologic data available only for AOM.

Pathogenesis of AOM and ABS

The pathogenesis of AOM and ABS almost always relate directly to a preceding viral upper respiratory in both conditions.[2,3] Common respiratory viruses of childhood including human rhinovirus, respiratory syncytial virus, human metapneumovirus, coronavirus, human bocavirus, adenovirus, parainfluenza, enterovirus and influenza infect the upper respiratory tract and cause symptomatic infection characterized by nasal discharge and nasal congestion, with or without cough.[3] During viral upper respiratory tract infection there is inflammation of the mucous membranes that line the nose, the sinus cavities, the middle ear and the Eustachian tube.[1] The swelling and inflammation of these mucosal linings leads to an impairment of Eustachian tube function in the case of AOM and functional or mechanical obstruction of the paranasal sinus ostia during sinusitis. The result of the functional obstruction to the middle ear and sinuses is the development of a negative pressure in each cavity. Simultaneously, the virus infection is also associated with an enhanced density of colonization of the nasopharynx with the common bacterial pathogens associated with each

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of these infections, *i.e.*, *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis*.[4] With an imbalance of the pressure relationships between the nasopharynx and middle ear and the nasopharynx and the sinus cavity, a transient relief of the obstruction favors aspiration of secretions (heavily contaminated with bacteria) from the nasopharynx into the middle ear and sinus cavity, respectively. Because of the impairment of the Eustachian tube function and the functional obstruction of the sinus ostia, this material cannot simply be eliminated by normal mucociliary action. Instead, the bacteria have an opportunity to further multiply and set up a secondary bacterial infection of the middle ear and paranasal sinuses. As testimony to this proposed pathogenesis, we and others have documented that the nasopharynx in children with URI is colonized with one or more of these bacterial pathogens nearly ninety percent of the time and that the density of these pathogens increase exponentially when viral infection occurs.[4,5]

Bacteriology of AOM and ABS and impact of Pneumococcal Conjugate Vaccines

There is general familiarity with the common pathogens that cause AOM and ABS. The relative prevalence of these otopathogens/sinopathogens as a cause of AOM was fairly stable until licensure of the first pneumococcal conjugate vaccine PCV7 in the year 2000 (Table 1).[6] Although the vaccine was intended to eliminate or decrease cases of invasive pneumococcal disease such as pneumococcal meningitis and pneumococcal bacteremia, it had an unanticipated impact on the incidence and microbiologic characteristics of AOM which was directly related to the alteration in nasopharyngeal colonization with vaccine and non-vaccine strains of *S. pneumoniae*. In the early years after PCV7 was licensed, there was a decrease in nasopharyngeal colonization with vaccine strains of *S. pneumoniae* and a subsequent decrease in the prevalence of *S. pneumoniae* as a cause of AOM.[6,7] In the late period after PCV7 was licensed (2008-2010), there was the emergence of virulent non-vaccine strains of *S. pneumoniae* (especially serotype 19A) which caused both an increase in severe invasive disease as well as an increase in cases of AOM. However, since the licensure of PCV13, in 2010, there has been a sustained decline in nasopharyngeal colonization with vaccine strains of *S. pneumoniae*. Although non-vaccine strains of *S. pneumoniae* have emerged (serotype 15 A,B,C, 21, 23B and 35B)[7–9] there appears to be a relatively stable rate of these strains as a cause of AOM resulting in an all-time low of *S. pneumoniae* as a cause of AOM.[6,10–12] With the decrease of nasopharyngeal colonization with vaccine strains, there has also been a decrease in AOM caused by pen-R *S. pneumoniae*.[13,14] Both of these observations underscore the basic principle that nasopharyngeal colonization with *S. pneumoniae* is a necessary prelude to the development of either AOM or ABS with that organism.

Current Data on Microbiology of AOM and Nasopharyngeal Colonization with Otopathogens

Although there is only one center in the U.S. performing tympanocentesis regularly,[6] there are international data related to the microbiology of AOM and multiple reports accruing with regard to patterns of nasopharyngeal colonization with *S. pneumoniae* and *H. influenzae*

throughout the U.S. and world. First, there is evidence that the overall incidence of AOM is decreasing as a response to pneumococcal conjugate vaccines.[6,11,12,15] This decline is largely due to a dramatic decrease in cases of AOM attributable to *S. pneumoniae* (including pen-R *S. pneumoniae*) as documented both in the U.S.,[6,14,16] Iceland[17] and Israel (south and central).[11–13] Going hand-in-hand with these observations are reports from Israel,[18] France[7,19] and the U.S.[6,8,20] indicating there is a substantial decrease in nasopharyngeal colonization with vaccine strains of *S. pneumoniae* with a relative increase in non-vaccine strains. In all but one of these studies,[8] there was a concurrent decrease in penicillin and ceftriaxone resistant strains of *S. pneumoniae*.

Simultaneously with these reports of decreasing *S. pneumoniae* are increasing reports of *H. influenzae*[6,21,22] and in particular beta-lactamase producing *H. influenzae* from Rochester N.Y.[6] In the latest data released from Rochester, *H. influenzae* accounts for 60%, *S. pneumoniae* 20% and *M. catarrhalis*, 15% of cases of AOM (Table 1).[6]

Unfortunately, there are very limited published data in the U.S. regarding the prevalence of beta-lactamase producing *H. influenzae*. In an ongoing clinical study of children with sinusitis being conducted in Pittsburgh, PA, Madison, WI and Bardstown, KY, 31 (44%) of 71 nasopharyngeal isolates obtained from 228 children from March, 2016 to December, 2017 were beta-lactamase positive.[23] Annual tabulation of microbiology results from Children's Hospital of Colorado for the years 2014-2016 shows that 34% of 231 isolates of *H. influenzae* are beta-lactamase positive.[24] Finally, a 2016 publication from University of Texas Medical Branch Galveston, states that a third to a half of *H. influenzae* recovered from middle ear fluids produce beta-lactamase.[25]

Time to Change

Given these data, it is time to change empiric recommendations for the initial antibiotic management of AOM and ABS. The standard recommendation has been high dose amoxicillin at 80-90 mg/kg/day in two divided doses.[26] The desire to continue to use amoxicillin as first line therapy in uncomplicated cases of AOM and ABS is related to its safety, general effectiveness, reasonable cost and narrow spectrum. The recommendation to use high dose amoxicillin relates to concerns about pen-R *S. pneumoniae*. Given that the prevalence of *S. pneumoniae* as a cause of AOM is at an all-time low, and that the proportion of cases of pen-R *S.pneumoniae* is low as well, regular or low dose amoxicillin (45 mg/kg/day in 2 divided doses) will suffice. However, the other important issue is that beta-lactamase producing *H. influenzae* and *M. catarrhalis* are resistant to amoxicillin. Fortunately, the 2013 AOM guideline acknowledges that when there is reason to suspect that the cause of AOM is *H. influenzae*, the recommendation switches from amoxicillin to a selection that has enhanced beta-lactamase coverage; while amoxicillin-clavulanate is the most suitable choice, alternatives include cefuroxime and cefpodoxime.[26] In addition, standard dose amoxicillin-clavulanate may be expected to have the same or lower rate of diarrhea than the high dose formulation.[27]

Given the combination of an increase in *H. influenzae* and decrease in pen-R *S. pneumoniae*, we should be ready to endorse regular dose amoxicillin-clavulanate as the preferred

treatment (45 mg/kg/day in two divided doses of 400mg/57mg) for children with AOM and ABS. Having made this recommendation in the first quarter of 2018, we should underscore that this is a very dynamic situation which requires careful monitoring.[28] It was 7 years after licensure of PCV7 that the peak impact of the emergence of serotype 19A of *S. pneumoniae* with its associated virulence was realized. Although we must be alert to changes, current data suggest that the prevalence of the observed serotype replacements for *S. pneumoniae* do not mandate high dose amoxicillin-clavulanate.

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Table 1

Bacteriology of Acute Otitis Media [*]

Bacterial Species	Prevalence (%) 1999	Prevalence (%) 2017
Streptococcus pneumoniae	40-45	15-25
Haemophilus influenzae	25-30	50-60
Moraxella catarrhalis	12-15	12-15
Streptococcus pyogenes	3-5	3-5
Sterile [+]	15-20	15-20

[*] Data shown in this table represent summary information provided within references 6, 7, 11 and 12.

[+] Although conventional microbiologic techniques fail to demonstrate positive cultures in 15-20% of samples of middle ear fluid, PCR techniques applied to sterile specimens indicate the presence of microbiota. [Xu Q, Kaur R, Casey JR, Adlowitz DG, Pichichero ME, Zeng M. Identification of *Streptococcus pneumoniae* and *Haemophilus influenzae* in culture-negative middle ear fluids from children with acute otitis media by combination of multiplex PCR and multi-locus sequencing typing. *Int J Pediatr Otohinolaryngol* 2011;75:239-244.]