COMMENTARY: ANTIBIOTIC RECOMMENDATIONS FOR ACUTE OTITIS MEDIA AND ACUTE BACTERIAL SINUSITIS IN 2013—THE CONUNDRUM

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The pathogens that cause acute otitis media (AOM) and acute bacterial sinusitis are well known to primary care practitioners.1,2 The source of microbiologic data are cultures of middle ear fluid that are obtained by the performance of tympanocentesis, a procedure that can be safely undertaken in the office setting after specific training of clinicians, and with appropriate measures to manage pain for the child.3,4 Unfortunately, in contrast to AOM, there has been very little study of the microbiology of acute bacterial sinusitis as this requires a more invasive procedure usually performed by pediatric otolaryngologists under local or general anesthesia.4 Two publications in the early 1980s described the microbiology of acute bacterial sinusitis in children in the United States, based on the results of maxillary sinus aspiration.5,6 Subsequently, discussions of the microbiology and recommendations for antibiotic management of acute bacterial sinusitis have leaned heavily on recommendations and data developed for AOM.1

Pathogenesis and Physiology of Acute Otitis Media and Acute Bacterial Sinusitis

The willingness to rely on data derived from tympanocentesis as a guide to the microbiology of acute bacterial sinusitis relates to the similarity of AOM and acute bacterial sinusitis with regard to anatomy, physiology and pathogenesis. Parsons noted, more than 15 years ago, that the middle ear is a paranasal sinus as the Eustachian tube acts in a similar fashion to the ostia of the paranasal sinuses. In both cases, the common preceding event is a viral upper respiratory infection.7 The mucosal swelling of the Eustachian tube and sinus ostia lead to (1) impairment of drainage of the secretions, which are produced by the lining of the middle ear and the paranasal sinuses, respectively; (2) a disorder of the pressure relationships between the cavities of the middle ear, paranasal sinuses and the nose and (3) the development of negative pressure within the middle ear or paranasal sinuses, which favors aspiration of mucus and bacteria from the nasopharynx into the middle ear space or paranasal sinuses. Ordinarily this material would drain out again, but, when there is Eustachian tube dysfunction, impaired ciliary activity and a functional or mechanical obstruction of the sinus ostia, bacteria multiply and AOM or acute bacterial sinusitis develops.

Tympanocentesis—Infrequently Performed

Antimicrobial recommendations for the treatment of AOM and acute bacterial sinusitis depend on the age of the child, recent antibiotic use, regional variations in antibiotic susceptibility and resistance patterns and knowledge of the current microbiology. Therefore, the alarming news with regard to antibiotic recommendations for both AOM and acute bacterial sinusitis is that there are very few remaining medical centers where tympanocentesis is performed routinely. Locations in the United States that historically generated the bulk of data regarding the microbiology of AOM were in Pittsburgh, Pennsylvania,8–10 Boston, Massachusetts,11–13 Bardstown, Kentucky14,15 and Rochester, New York.16–18 The decrease in centers at which tympanocentesis is performed most probably reflects few recent introductions of antibiotics that might be useful in the management of AOM—and therefore no requirement to demonstrate their ability to eradicate pathogens or compare them to standard therapies. This state of affairs leaves us in a very precarious situation with regard to selection of antimicrobial agents for treatment of 2 of the most common clinical infections in childhood because we have no up-to-date microbiology on which to base treatment decisions.

History of Microbiology and Treatment of AOM

Historically, the relative proportion of bacterial agents in AOM was Streptococcus pneumoniae at 40%, Haemophilus influenzae at 25% and Moraxella catarrhalis at 12%.9 The original distribution of bacterial pathogens in acute bacterial sinusitis was S. pneumoniae at 30% and H. influenzae and M. catarrhalis at 20% each.9 Streptococcus pyogenes was a minor cause of both entities, accounting for 2% to 4% of cases.

For many years, amoxicillin 45 mg/kg/day in 3 divided doses was the drug of choice for AOM. The preference for amoxicillin relates to its excellent safety profile, relatively narrow spectrum, low cost and general effectiveness.2 The first challenge to the effectiveness of amoxicillin arose in the mid-1970s when the issue of β-lactamase production emerged. The decision to continue to recommend amoxicillin for children with AOM was based on a calculation which involved multiplying the proportion of cases of AOM caused by H. influenzae, by the proportion of isolates that were β-lactamase positive; the rate of probable spontaneous cure was also taken into consideration. In the past, when H. influenzae caused 25% of cases of AOM and β-lactamase production occurred in 20%–30% of isolates, it could be calculated that a middle ear isolate would be resistant to amoxicillin in 6% of cases. Although M. catarrhalis produces β-lactamase nearly 100% of the time, it was isolated less frequently and was thought to have a very high rate of spontaneous resolution. Accordingly, amoxicillin remained a good choice.

Emergence of Penicillin-resistant S. pneumoniae

The emergence of penicillin-resistant S. pneumoniae in the 1990s became a challenge to the dose of amoxicillin that was prescribed. The mechanism of resistance, alteration of penicillin binding proteins, may be overcome, largely, by raising the dose of amoxicillin to increase concentrations of antibiotic in middle ear or sinus fluid. This became the stimulus to increase the dose of amoxicillin from 45 mg/kg/day to 90 mg/kg/day in situations in which it was anticipated that penicillin-nonsusceptible S. pneumoniae might be present (eg, in children <2 years of age, those subjected to recent antibiotic exposure [<30 days] or attendance at day care).2

Soon after licensure of the pneumococcal conjugate vaccine (PCV7) in 2000, there were some changes in the relative prevalence of the microbes that cause AOM, that is, a decrease in the prevalence of S. pneumoniae (including penicillin-nonsusceptible S. pneumoniae)20 and a relative increase in the prevalence of H. influenzae. Data from 3 major surveillance programs in the United States showed slight variations in the frequency of β-lactamase-positive H. influenzae from 27% to 43%.21,22 Although these data may not be directly comparable to isolates obtained exclusively by tympanocentesis or sinus aspiration, they describe a trend.
Likewise, studies by Casey and Pichichero and Block et al demonstrated an increase in the proportion of AOM due to nontypeable *H. influenzae* and an absolute increase in the proportion of isolates that were β-lactamase positive. This trend was altered briefly between 2005 and 2010, with the emergence of penicillin-resistant infections caused by *S. pneumoniae* of serotype 19A. However, the inclusion of serotype 19A in PCV13 has reversed the escalation of this serotype as a cause of invasive and local diseases. Now we can anticipate, and several pieces of information support the notion, that there will be a further decrease in the prevalence of *S. pneumoniae* (including penicillin-nonsusceptible *S. pneumoniae*) and a further increase in *H. influenzae* secondary to the use of PCV13, which was licensed in 2010 and has enjoyed a rapid increase in use. If the decrease in prevalence of *S. pneumoniae* (and highly penicillin-resistant *S. pneumoniae*) persists, the recommended dose of amoxicillin could then be reduced to 45 mg/kg/day in 2 divided doses once again. It is essential to recognize that this is a very dynamic situation and that there is a possibility that the few nonvaccine strains of *S. pneumoniae*, which are resistant to penicillin, may, similar to serotype 19A, become more prevalent. This possibility underscores the importance of the continuous availability of current data that reflects local and national microbiologic trends.

### Current Data

Unfortunately, there are very few data by which to judge the prevalence of penicillin-nonsusceptible *S. pneumoniae* or β-lactamase production among the *H. influenzae* in 2013. The single center in the United States where tympanocentesis continues to be performed is in Rochester, NY. In that center, there is evidence that as predicted, recovery of *S. pneumoniae* from middle ear fluid has dramatically decreased, and *H. influenzae* and *M. catarrhalis* have increased to account for 90% of isolates. The surprising data are that the prevalence of β-lactamase producing organisms is quite high, in the range of 70–80%. In addition, cumulative microbiologic data published annually by Dr. Mary Glode from Denver Children’s Hospital shows 68% of *H. influenzae* isolates are β-lactamase producing (personal communication August 22, 2012). Furthermore, in 2011, a small sample of nasopharyngeal isolates obtained between 2008 and 2010 from children meeting clinical criteria for acute bacterial sinusitis in Pittsburgh, PA, showed (16 of 33) 48% of children harboring β-lactamase-positive *H. influenzae* (personal communication, N. Shaikh, September 26, 2012). Finally, a recent study reported from Boston, MA, showed nasopharyngeal carriage of pneumococcal serotypes contained in PCV13 has decreased as use of the vaccine has become more widespread. It is noteworthy that the latter 2 studies reflect respiratory tract mucosal colonization, which may be slightly different than middle ear or sinus isolates.

### The Conundrum

Two clinical trials of amoxicillin/clavulanate, 1 standard dose and 1 high dose in children with AOM showed similar rates of superiority of antibiotic over placebo. In addition, a trial of high-dose amoxicillin/clavulanate in children with clinically diagnosed sinusitis demonstrated the efficacy of this antibiotic over placebo. If the sparse current microbiologic data that are available truly reflect general trends, *H. influenzae* now accounts for 60–70% of cases of AOM and 60–70% of these may be β-lactamase producing.

The questions are: Should we use amoxicillin or amoxicillin/clavulanate? Should we recommend high dose or standard dose amoxicillin? In the absence of data derived from tympanocentesis, these are difficult questions to answer. Although neither nasopharyngeal nor throat cultures have been a useful guide to recommendations for the treatment of specific patients with AOM or acute bacterial sinusitis, they may be useful on a population basis in formulating recommendations in different regions of the United States. Accordingly, we urge that medical centers within various geographic areas begin to generate these data to provide guidance regarding antimicrobial choices. In the meanwhile, on the basis of the limited data that are available, it seems reasonable to recommend standard dose of amoxicillin–clavulanate (45 mg/kg/day in 2 divided doses) as preferred initial therapy for children with AOM and acute bacterial sinusitis.

### References


