Streptococcal Otitis Media: From Epidemiology to Pathogenesis

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(SSee the article by Segal et al. on pages 35–41)

Segal and colleagues, from the productive pediatric infectious diseases unit in Beer-Sheva, Israel, report their analysis of data from over 11,300 children with acute otitis media (AOM) from whom specimens of middle-ear fluid had been obtained and cultured [1]. Their particular goal was to assess the role of group A β-hemolytic Streptococcus (GAS), or Streptococcus pyogenes, in these cases of infection. As might have been predicted from smaller series conducted earlier, Haemophilus influenzae and Streptococcus pneumoniae predominated as causative pathogens, but cultures from ~3% of episodes of AOM yielded GAS, of which two-thirds yielded GAS only, and the remainder yielded a combination of GAS and another pathogen. Children with GAS AOM differed significantly from other children in the study: they were somewhat older, were more likely to be Jewish than they were Bedouin (the 2 distinct ethnic groups represented in this study population), less often presented during Fall months, were more likely to have unilateral AOM, less often had fever, and were less likely to have other systemic or respiratory manifestations, were less likely to have recurrent AOM and to have received recent antibiotic therapy, were more likely to have acute drainage from the ears, and were at a much greater risk for developing mastoiditis.

Over the past several decades, a number of much smaller studies have reported isolation of GAS from ~2%–5% of cultures of middle-ear fluid specimens obtained from children with AOM (e.g., in a study from Japan, 5% of culture-positive children were infected with GAS [2]; in a study from Costa Rica, 1.8% [3]; and in studies from the United States, rates of 2% [4], 4% [5], 4% [6], and 5% have been reported [7]). This is consistent with the findings of Segal et al. in Israel [1]. Thus, in contrast to the very striking role of GAS as the major bacterial agent of acute pharyngitis, it appears that, in recent decades, GAS has been fairly consistently the fourth-most predominant pathogen causing pediatric AOM, after S. pneumoniae, H. influenzae, and M. catarrhalis.

This was not always so; historically, GAS was the predominant bacterial isolate recovered from middle-ear fluid specimens from patients who had AOM with or without otorrhea. In her landmark study published in 1924 in the Journal of Infectious Diseases [8], Eugenia Valentine reported data for 100 episodes of AOM in 77 patients from San Francisco from whom specimens were obtained by tympanocentesis and cultured; 53 cultures yielded GAS, of which 50 grew GAS only and 3 grew GAS with staphylococci. Valentine recovered 22 isolates of staphylococci and only 9 isolates of pneumococci [8]. No information regarding sterilization or cleaning of the external ear canal before performing tympanocentesis was provided, and because a number of diphtheroids were also recovered, the role of staphylococci here is unclear. Valentine cited 6 European and US studies dating back to 1903, most (but not all) of which also emphasized the dominant role of β-hemolytic streptococci in this regard. In that era, before Rebecca Lancefield developed the serologic grouping system that differentiates group A from other β-hemolytic streptococci on the basis of differences in the cell-wall carbohydrate [9], it is highly likely that GAS comprised the vast majority of the β-hemolytic streptococcal isolates that were recovered.

One of the more striking findings reported by Segal et al. [1] is the association of GAS AOM with increased risk of development of mastoiditis. Although the number of cases of acute mastoiditis is small (4 of 346 episodes of GAS AOM resulted in mastoiditis, compared with 8 of 3651 episodes of infection with S. pneumoniae, 1 of 3999 episodes of infection with H. influenzae, and 0 of 394 episodes of infection with M. catarrhalis; the attack rates were 11.6, 2.2, 0.3, and 0 cases per

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1000 episodes, respectively), this association also supports the findings of previous studies. A 2003 study from Beer-Sheva reported that 33% of 43 cases of acute pediatric mastoiditis were due to *S. pneumoniae* and 26% were due to GAS [10]. A multicenter Israeli study of acute mastoiditis (almost all cases in children) [11] identified 15 patients infected with *S. pneumoniae*, 14 infected with GAS, and 13 infected with *S. aureus*, and a small study [12] from Portugal found comparable data. In 1980, Ginsburg and colleagues [13], from Dallas, Texas, also recovered *S. pneumoniae* most often, and recovered GAS and *S. aureus* nearly as often.

GAS mastoiditis clearly is not a new observation. In his 8-volume textbook of pediatrics published from 1923 to 1926 [14], Dr. Isaac Abt of Chicago noted, during the preantibiotic era, that 1%–2% of patients with scarlet fever developed acute mastoiditis as a complication. Drs. George and Gladys Dick, in their 1938 monograph on scarlet fever [15], cited AOM and “operative mastoiditis” as frequent complications of scarlet fever, occurring in 14.1% and 2.3% of cases of scarlet fever, respectively. They also noted that the signs and symptoms of ear disease may precede the rash. These historic publications highlight the risk of mastoiditis in those with what we now know to be GAS infection, and report frequencies of mastoiditis similar to that found by Segal et al. [1], who observed 4 cases of mastoiditis among 346 children with GAS AOM.

A crucial question relates to the pathogenesis of GAS AOM. The data presented by Segal et al. [1] suggest that middle-ear infection caused by GAS differs somewhat from otitis media caused by *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*. The lower rates of recurrent disease, recent receipt of antibiotics, and upper-respiratory-tract symptoms all seem to argue against dysfunction of the eustachian tube as the major contributor to GAS AOM. The older age of the patients, the acute onset of symptoms, and the lack of other respiratory-tract complaints are more similar to features of acute GAS pharyngitis. Given that the pharyngeal and middle-ear respiratory epithelia (simple squamous cells on the internal surface of the tympanic membrane and stratified squamous cells in much of the pharynx, including the tonsillar surfaces) are similar and are connected by the eustachian tube, direct invasion of the epithelial cells of the middle ear by GAS, similar to the direct invasion of pharyngeal epithelial cells, may be possible. It is probable that GAS otitis media is preceded by pharyngeal colonization, if not bona fide symptomatic infection, with GAS. The increased frequency of mastoiditis among patients infected with GAS seems likely to be the result of the known invasiveness and virulence of the organism. Since mastoiditis is clearly a critical factor in the rare instance of development of GAS meningitis, understanding the pathogenesis of AOM by this organism is important. Perhaps the differences in rates of GAS AOM and mastoiditis between the Jewish and Bedouin populations in Israel are related to immunogenetic differences in the populations studied. Certainly Kotb and colleagues [16] demonstrated that the variability in severity of invasive GAS infection is related to specific HLA haplotypes. One might also speculate that certain individuals are uniquely susceptible because they have increased numbers of receptors for GAS or specific streptococcal virulence factors on middle-ear or mastoid epithelial cells.

Specifically absent from the older reports and from the article by Segal et al. [1] are more-detailed data about the GAS strains isolated from children with either AOM or acute mastoiditis; such data might help to clarify the pathogenetic issues. PCR-based *emm* typing data (or serologic M-typing, as originally developed by Dr. Lancefield [17]) would indicate whether the spectrum of GAS organisms obtained from middle-ear or mastoid sites is as broad as that of those isolated from the pharynx [18], or whether it is more limited. Perhaps certain of the ~200 *emm* types of GAS are particularly ototropic or “mastoidotropic.” Additionally, evaluation of strains recovered from these sites for the expression of some of the many known virulence factors of GAS organisms would be of interest. One might predict lower than average antimicrobial resistance rates among GAS AOM isolates because patients with GAS AOM are less likely to have recently received antibiotics, compared with patients who have AOM of other etiologies, but the antimicrobial resistance profiles of the pathogens that cause AOM and mastoiditis are not known. Given the suggestions that bacterial factors associated with cell invasiveness or internalization, such as the gene *prtF1*, may also be associated with macrolide resistance [19], it will be worthwhile to assess the resistance patterns of isolates of GAS from ear infections and mastoiditis. Finally, if GAS AOM is indeed the middle-ear correlate of GAS pharyngitis, are patients with untreated GAS AOM at risk for developing acute rheumatic fever?

The answer to this question may have implications for the recent recommendation that AOM be managed with “watchful waiting” [20].

*Streptococcus pyogenes*, the infectious agent that causes the broadest range of infections of any known pathogen, continues to challenge us clinically and scientifically. The article by Segal et al. [1] is thought-provoking, should stimulate additional studies, and provides further impetus for the development of an effective GAS vaccine.

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