
Comments by Jack L. Paradise, MD

The most common reason for antimicrobial use in United States children is treatment of otitis media.1 Of 44.5 million office-based prescriptions for antimicrobials in 1986 for children younger than 10 years of age, 42% were for otitis media,2 and of the estimated 20 million visits in 1990 for otitis media by children younger than 14 years of age, antimicrobials were prescribed at >80%.3,4 In a recent prospective study, antimicrobial treatment of otitis media accounted for >90% of all antimicrobial use during the first 2 years of life.5

Foundations for rational use of antimicrobials for acute otitis media (AOM) were first laid down in the United States in a series of five reports6–10 in Pediatrics over a 14-year period beginning in 1956. Each of the reports concerned the bacteriology of AOM as determined from aspiration and culture of middle ear exudate. Taken as a group, these reports in my judgment constitute the most important contribution of an otolaryngologic nature to appear in the 50-year history of Pediatrics. Today, when otitis media constitutes the most common reason for office visits by children,3 it seems remarkable that during the 8 years of publication of Pediatrics before 1956, only two reports in any way involving otitis media were published: one, a case report describing chronic suppurative otitis media as one element of what came to be termed the Wiskott–Aldrich syndrome,11 and the other, a brief discussion of the diagnosis and management of secretory otitis media (otitis media with effusion [OME]).12

An additional bit of historical perspective is necessary as preface to a discussion of the five selected reports. Early in the 20th century, the organisms implicated most commonly in AOM were the group A β-hemolytic streptococcus (Streptococcus pyogenes)
and the pneumococcus (Streptococcus pneumoniae); other frequently encountered organisms considered pathogenic included staphylococci, other varieties of streptococci, Haemophilus influenzae, and coliform bacilli. Treatment consisted primarily of measures to relieve pain, and in cases that seemed severe, myringotomy. By the late 1930s, sulfanilamide had been shown to be effective in treating streptococcal AOM—in one study, reducing the proportion of cases requiring mastoidectomy from 69% to 8%—and sulfapyridine had shown promise in treating pneumococcal AOM. Nonetheless, in the discussion of the treatment of AOM in a standard pediatric textbook of that time, almost two pages were devoted to myringotomy but only a single paragraph to sulfanamide therapy. Sulfonamides remained the only antimicrobial drugs available for treating AOM until the mid-1940s, when penicillin first became available. By the time volume 1 of Pediatrics was published in 1948, antibacterial therapy with sulfonamides or penicillin had become, among pediatricians, the predominant mode of treating AOM. A standard pediatric textbook of that time stated that such therapy had “reduced materially the incidence of suppurative otitis media and also of mastoiditis,” such therapy had “reduced materially the incidence of suppurative otitis media and also of mastoiditis,” and sulfapyridine had shown promise in treating pneumococcal AOM. Nonetheless, in the discussion of the treatment of AOM in a standard pediatric textbook of the time, almost two pages were devoted to myringotomy but only a single paragraph to sulfanamide therapy. Sulfonamides remained the only antimicrobial drugs available for treating AOM until the mid-1940s, when penicillin first became available. By the time volume 1 of Pediatrics was published in 1948, antibacterial therapy with sulfonamides or penicillin had become, among pediatricians, the predominant mode of treating AOM. A standard pediatric textbook of that time stated that such therapy had “reduced materially the incidence of suppurative otitis media and also of mastoiditis,” and it also noted “a growing tendency toward conservatism” regarding the use of myringotomy. However, only in connection with myringotomy was bacterial culture of middle ear contents mentioned.

In 1956, in “A Bacteriologic Investigation of Otitis Media in Infancy,” Edward Mortimer and Reich Watterson at Cleveland City Hospital reported findings of the first study in the United States to use tympanocentesis for diagnostic purposes in children with AOM. Previous such studies had been undertaken only in Scandinavia. Mortimer and Watterson found, as did the the Scandinavian investigators, that in children younger than 2 years of age, the most commonly recovered pathogen was S pneumoniae, and the next most common, nontypeable H influenzae. They considered staphylococci, diphtheroids, and other miscellaneous organisms recovered from the aspirates to be contaminants because they were cultured also from the surface of the tympanic membrane before aspiration. Not infrequently as well, cultures of middle ear exudate were sterile. Clinically, Mortimer and Watterson pointed out that the relative severity of the otitis, as judged by the appearance of the eardrum, did not correlate well with the presence or absence of organisms on culture. They also noted that “it was unusual to find an organism in the middle ear that was not also present in the nose and/or the throat.” Their report included a figure showing the type of otoscope and the aspiration equipment they used.

Ten years later, in “Otitis Media in the Practice of Pediatrics: Bacteriological and Clinical Observations,” John Coffey reported findings gathered over a 1-year period in his private pediatric practice in Natchez, MS. Coffey collected middle ear specimens by tympanocentesis from 267 infants and children with purulent otitis media, and found that in addition to S pneumoniae and H influenzae, Moraxella catarrhalis (then called Neisseria catarrhalis) appeared to be the cause of a substantial number of cases. Relatively few cases were attributable to S pyogenes. Coffey made a number of important observations including 1) that a majority of the children had apparently been free of ear pain; 2) that a number of children—primarily those in whom H influenzae was cultured from the middle ear—had associated conjunctival discharge; 3) that those with bulous myringitis, an entity thought previously to be attributable to viral infection, in fact had positive cultures for S pneumoniae and/or H influenzae; 4) that none of the children from whose aspirates M catarrhalis was isolated were acutely ill or febrile; and 5) that of the children whose cultures showed no growth, most had a history of recurrent otitis media, many had received antimicrobial treatment, and many had viscid middle ear effusions characteristic of OME. In instances of relapse or recurrence of otitis media, Coffey often found middle ear pathogens other than those recovered originally. Finally, he gently reminded readers that “the number of cases found varies directly with the diligence with which they are sought.” The observation that M catarrhalis was a middle ear pathogen had been made previously in Finland by Grönroos, but Coffey appears to have been the first anywhere to report the presence of the organisms intracellularly in middle ear exudate.

The connection between initial bacteriologic findings in AOM and the outcome of specific treatments was first made in 1969 by Bjorn Nilson and colleagues at Johns Hopkins, in “Acute Otitis Media: Treatment Results in Relation to Bacterial Etiology.” In a double-blind, randomized trial, they assigned 306 children younger than 3 years of age with AOM to receive either penicillin V, penicillin V plus a sulfonamide, or ampicillin. Clinical response was correlated with the type of organism isolated from the initial middle ear aspirate. Patients with otitis generally, irrespective of culture results, and patients with pneumococcal otitis fared equally well with each of the three regimens. However, patients in whom the infecting organism was H influenzae fared better with either the penicillin-sulfa combination or ampicillin than with penicillin V alone. Correspondingly, most patients receiving ampicillin achieved bacteriostatic serum levels for the strains of H influenzae initially isolated, whereas most patients receiving penicillin V did not. This report by Nilson and colleagues appears to have offered the first reported evidence of the superiority of one antimicrobial over another in treating otitis media caused by a specific pathogen.

Later in 1969 came the next development in the use of information derived from tympanocentesis to rationalize antimicrobial therapy for otitis media. In “The In Vivo Sensitivity Test—Bacteriology of Middle Ear Exudate During Antimicrobial Therapy in Otitis Media,” Virgil Howie and John Ploussard reported data derived from initial and repeat tympanocentesis in patients with otitis media in their private practices in Huntsville, AL. Starting from the premise that “the ultimate test of the efficacy of antibiotic therapy is its ability to eradicate the organism at the site of infection,” Howie and Ploussard...
contributed by pediatric practitioners. These individuals recognized the need for new knowledge; they brought to bear keen clinical skills to make important observations; and they had the initiative and the courage, and took the time in the course of their practices, to perform the necessary investigative procedures and to record, analyze, and report their findings. This is not to depreciate the contributions of those working in academic settings, but rather to acknowledge not only the practitioners’ contributions to our understanding, but also the exceptional effort required to overcome the obstacles to research inherent in pediatric practice.

A timely lesson to be derived from these studies is that tympanocentesis is a procedure well within the purview of everyday pediatric practice. As clinicians treating children with AOM, we currently confront a major problem of antimicrobial resistance, particularly on the part of S pneumoniae.25 In especially refractory cases, there is no reasonable substitute for diagnostic tympanocentesis (or myringotomy) to enable identification of the offending organism (if any) and determination of its antimicrobial sensitivities, so that treatment can be directed accordingly. Incising the tympanic membrane in children with AOM to relieve pressure and accomplish drainage became a lost art for most pediatricians trained after the advent of the antimicrobial era, and few currently practicing primary care clinicians perform the procedure. Even fewer, in my experience, feel comfortable undertaking diagnostic tympanocentesis. That is a limitation that cries out for remedying. If treatment is to be rationalized maximally, pediatricians must incorporate tympanocentesis into their armamentarium. To do so, they will need at minimum to acquire a surgical head for their otoscopes, no different from the type pictured 42 years ago in the report by Mortimer and Watterson5 and pictured again in another report in Pediatrics 25 years later.23 A more recent report had as its goal improving general familiarity with a convenient tympanocentesis apparatus and with appropriate technique for performing the procedure.24

An unanswered research question involving tympanocentesis concerns the optimal design for comparative trials of antimicrobials in treating AOM. Most experts would agree that children entering such trials should undergo initial tympanocentesis and aspiration of middle ear contents so that the infecting organism(s) can be identified. Experts do not agree, however, on whether such trials should be designed to measure primarily clinical outcomes or whether, instead, they should focus primarily on bacteriologic outcomes as determined by the results of repeat tympanocentesis 3 to 5 days after therapy has been instituted, much as originally described by Howie and Ploussard.9 Marchant and colleagues have called attention to three interrelated factors that argue for a primary focus on bacteriologic outcomes: 1) the well known fact that some patients with AOM fail to improve clinically despite treatment with an antimicrobial effective against the infecting organism, whereas others improve despite treatment with an ineffective antimicrobial; 2) limited correlations between clinical efficacy (measured by the presence or absence of symptoms as noted at a visit 3 to 6 days after the onset of therapy) and bacteriologic efficacy (measured at the same visit by tympanocentesis and culture in the comparative trials of antimicrobials that they conducted); and 3) in the same trials, greater differences between drugs in bacteriologic efficacy than in clinical efficacy. Accordingly, Marchant and colleagues concluded that between-drug differences can be demonstrated more readily with bacteriologic than with clinical outcome measures, and therefore that tests of differences between bacteriologic outcomes would require smaller sample sizes than would tests of differences between clinical outcomes.25

The proposition appears to be persuasive, but the
validity of its evidential basis depends on a number of assumptions including 1) that symptomatic response at 3 to 6 days is a consistently valid indicator of concurrent middle ear status and also a valid predictor of middle ear status that is obtained at the termination of therapy or at any given point thereafter; 2) that in any individual episode of AOM treated with a given antimicrobial drug, symptomatic status on each of days 3 to 6 is invariably the same (My clinical experience would suggest otherwise); 3) that in any such episode, middle ear bacteriologic status on each of days 3 to 6 also is invariably the same; 4) that the time between the repeat tympanocentesis and the most recent preceding dose of antimicrobial has no influence on the culture results; 5) that the recovery of any bacterial pathogens from middle ear exudate, irrespective of their concentration, is indicative of inadequate antibacterial efficacy; 6) that whatever the antimicrobial drug used, the rate of bacterial killing is a consistent indicator of eventual antibacterial efficacy; and 7) that performing tympanocentesis twice within 6 days does not affect clinical outcomes favorably, and, therefore, does not obscure differences in such outcomes that might otherwise have been observable. None of these assumptions has, to my knowledge, been tested.

Currently, some experts favor a trial design that would involve relatively small numbers of subjects and would require both initial and repeat tympanocentesis routinely. Others, however, favor a design that would involve, in combination with in vitro studies of efficacy of the drugs in question, somewhat larger numbers of subjects, stratification by initial clinical severity, outcome measures that include otoscopic findings as well as symptomatic response, and repeat tympanocentesis only in subjects with clinically defined treatment failure (M. L. Cohen, MD, personal communication, July 1997; letter to FDA).

Even if it becomes established that early bacteriologic response is, in fact, a more sensitive index of antibacterial efficacy than either early or later clinical response, one might then reasonably ask whether it is preferable, in the interest of restricting sample size, to subject all projected patients in a trial to a second tympanocentesis on day 3 to day 5, even though by then most will have become asymptomatic, or whether it would be preferable to enroll a larger number of subjects, all of whom would undergo initial tympanocentesis but few of whom would undergo repeat tympanocentesis because few would have an unfavorable clinical course. The issue involves both practical and ethical considerations.

Plainly, the reports over the past half-century in Pediatrics involving tympanocentesis have laid crucial groundwork not only for rational antimicrobial treatment of AOM, but also for continuing efforts by otitis media researchers in this complex era of evolving antimicrobial resistance.

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