Paparella II: Section 3: Diseases of the Ear

Part 3: Middle Ear and Mastoid

Chapter 30: Microbial Aspects of Otitis Media

G. Scott Giebink, Paul G. Quie

Otitis media is a major pediatric health problem in both developed and underdeveloped countries. Long-term prospective studies have indicated that approximately 50 per cent of children have an episode of acute otitis media before the age of 1 year, and 70 to 85 per cent of children have at least one episode before starting school. Otitis media is often asymptomatic, especially during the first year of life. Many children with early initial middle ear infections suffer recurring episodes of acute otitis media before starting school. The exact frequency of nonsuppurative otitis media during childhood is not known, although it is common for middle ear effusion to persist in many children for 2 to 4 weeks following a single episode of acute otitis media. Chronic otitis media with effusion is significantly more frequent in children whose first otitis media episode is identified before age 2 months, compared with those who first experience otitis media after 2 months.

Otitis media represents a spectrum of both suppurative and nonsuppurative inflammatory events occurring in the middle ear cleft. Acute (suppurative or purulent) otitis media and chronic nonsuppurative (serous or mucoid) otitis media have been described. Combinations such as mucopurulent and seropurulent otitis media also occur. Clinical and experimental evidence suggests that the spectrum of otitis media encompasses mechanical, microbial, and immunochemical factors. If ventilation of the middle ear cleft is obstructed, either by extrinsic eustachian tube blockage, intrinsic inflamation resulting from microbial infection, or other immunochemical events, middle ear effusion is produced.

Microbial Etiology

In children 1 month of age and older with acute otitis media, *Streptococcus pneumoniae* is cultured from 25 to 50 per cent of middle ear effusions and *Haemophilus influenzae* is found in 15 to 25 per cent. Only a small number of the 83 known pneumococcal serotypes accound for the majority of middle ear infections with the pneumococcus. *H. influenzae* isolates from infected middle ears are rarely (< 5 per cent) type b, most being nontypable, whereas *H. influenzae* isolates in other instances of invasive disease are nearly always type b. *H. influenzae* is found as often in older as in younger children with otitis media, despite early reports that suggested this organism only infected younger children. Less common bacterial pathogens found in infected middle ears include *Branhamella catarrhalis, Staphylococcus aureus* and *epidermidis,* and the Enterobacteriaceae. Rarely, agents such as *Mycobacterium tuberculosis* infect the middle ear. Enterobacteriaceae and staphylococci are important middle ear pathogens in the newborn, particularly those hospitalized for extended periods in neonatal intensive care units. In contrast to these hospitalized neonates, otitis media in young infants outside the hospital is usually caused by pneumococcus and *H. influenzae.* Acute otitis media during the neonatal period, especially in the premature, may be a focus of infection leading to bacteremia and meningitis.

Bacterial pathogens may also contribute to the pathogenesis of chronic, nonsuppurative otitis media. Bacteria have been cultured from 30 to 50 per cent of serous and mucoid middle ear effusions; *H. influenzae*, *S. pneumoniae*, *Staph epidermidis*, and *B. catarrhalis* predominate. Moreover, Gram stain examination of chronic effusion has revealed bacteria, despite sterile cutlures, in 10 to 15 per cent of cases; most of these children have no clinical signs of acute middle ear infection.

Cultures from the nasopharynx correlate poorly with bacterial pathogens recovered from infected middle ears. Although in most instances the pathogen present in the middle ear is also present in the nasopharynx, other potentially pathogenic bacteria commonly colonize the nasopharynx. Thus, upper respiratory cultures do not predict with accuracy the middle ear pathogen causing infection.

Despite the evidence for a bacterial etiology in approximately 70 per cent of cases of acute otitis media, nearly one-third of these middle ear effusions are sterile for aerobic bacteria. Although a few reports suggest that anaerobic bacteria may cause acute otitis media, studies of gas tension in the middle ear show that the middle ear cleft poorly supports anaerobic growth. Viruses and mycoplasma are rarely cultured from middle ear effusions, although many children with acute otitis media have recent or coexistent upper respiratory infection with these agents. Using virus isolation and serologic methods, viral respiratory tract infection has been identified in 25 to 30 per cent of otitis media episodes. Infestions with respiratory syncytial virus, adenoviruses, and influenza viruses impart a greater risk for otitis media thandoes infection with parainfluenza viruses, rhinoviruses, and enteroviruses. Respiratory syncytial virus is the viral agent most frequently isolated from middle ear effusions in acute otitis media.

Modeling of otitis media in experimental animals indicates that middle ear inflammation is initially characterized by a serous or purulent effusion. Although not confirmed by studies in patients, it is suspected that functional or mechanical eustachian tube dysfunction, most likely caused by upper respiratory tract viral infection or subtle anatomic abnormalities of the paratubal structures, leads to hyperemia of middle ear subepithelial capillaries, subepithelial space edema, and serous transudation into the middle ear space. It is not clear whether the respiratory tract viruses that seem to trigger these events actually invade the middle ear cleft, directly causing hyperemia and edema, or whether they affect the middle ear by infecting epithelial cells only in the nasopharynx. By mechanisms not yet defined, certain upper respiratory tract bacteria localize and multiply within the middle ear space, causing an influx of polymorphonuclear leukocytes, a release of inflammatory mediators, and the appearance of purulent effusion. These events have been partially characterized following influenza A virus infection in chinchillas colonized with *S. pneumoniae*. It seems likely that the natural history of acute otitis media in humans follows a similar sequence of events.

The middle ear cleft is protected by a distinct, secretory immune system similar to that found in other areas of the upper respiratory tract. Patients with acute otitis media due to pneumococci or *H. influenzae* who develop specific antibody in a middle ear effusion clear bacteria more rapidly than those who do not develop specific antibody. Clearing of bacteria does not appear to be associated with a specific immunoglobulin class, although studies in other areas of the respiratory tract indicate that IgA is the principal immunoglobulin

protecting these mucous membranes.

Certain bacterial products may also play a role in middle ear inflammation and local immunologic responses. Bacterial products that have been implicated include capsular polysaccharide antigens, certain components of the bacterial cell wall, and oxidative and hydrolytic bacterial enzymes.

Antimicrobial Treatment

The goal in managing acute otitis media is to amerliorate symptoms of fever and ear pain, to accelerate resolution of middle ear fluid and accompanying conductive hearing loss, and to minimize recurrence, complications, and sequelae. Since bacteria play an etiologic role in the pathogenesis of acute otitis media, antimicrobial drugs are used commonly to treat this disease. Clinicians in the USA and in most other countries have found that antimicrobial treatment hastens resolution of fever and ear pain and that it reduces suppurative complications. Selection of an appropriate antimicrobial agent requires knowledge of the pathogen and its antimicrobial sensitivity and of the drug's ability to distribute into the middle ear and effusion. Since *S. pneumoniae* and *H. influenzae* represent more than 50 per cent of the bacterial pathogens in acute otitis media, antimicrobial regimens must include drugs effective against these organisms. An increasing proportion of *H. influenza* strains (15 to 30 per cent) are beta-lactamase-producing and, therefore, resistant to ampicillin and amoxicillin. Although *B. catarrhalis* and *Staph aureus* each account for fewer than 10 per cent of cases, a majority of these organisms are also resistant to ampicillin and amoxicillin.

More than 40 clinical trials comparing antimicrobial drug regimens have been reported in the literature; dosage and dosing intervals have been compared in several. In the usual non-neonatal, uncomplicated case of acute otitis, each of the following has been shown to be clinically effective when given for 10 to 14 days: oral ampicillin (50 mg/kg of body weight/24 hours, divided in four doses), amoxicillin (40 mg/kg/24 hours, divided in three doses), amoxicillin combined with the beta-lactamase inhibitor clavulanate (40 and 10 mg/kg/24 hours, divided in three doses), oral trimethoprim and sulfamethoxazole (8 and 40 mg/kg/24 hours, divided in two doses), cefaclor (40 mg/kg/24 hours, divided in three doses), and erythromycin ethylsyccinate and sulfisoxazole (50 and 150 mg/kg/24 hours, divided in four doses). Amoxicillin, an anlogue of ampicillin, has largely replaced ampicillin because amoxicillin is better absorbed and has a longer half-life than ampicillin, permitting administration every 8 hours, but retains the antimicrobial spectrum of ampicillin.

Selection of one regimen versus another may be influenced by host factors, characteristics of the drug, and response to treatment. For example, middle ear effusions of hospitalized neonates with acute otitis media yield gram-negative enteric bacilli in 20 per cent of cases; middle ear paracentesis for culture is usually indicated in these cases to guide antimicrobial drug selection. Cases of acute otitis media complicated by mastoiditis usually require surgical intervention and parenteral antibiotic treatment. Patients allergic to penicillins should be treated with trimethoprim and sulfisoxazole, or erythromycin and sulfisoxazole. Likewise, patients allergic to sulfonamides should receive one of the non-sulfonamide-containing regimens. A known medical condition may govern medical selection - eg, a non-sulfonamide drug in a patient with glucose-6-phosphate dehydrogenase deficiency.

Characteristics of the drug, such as spectrum of activity, pharmacokinetics, bactericidal activity, toxicity, and cost, are also considerations in selection. In most studies, 90 per cent or more of the bacteria isolated from effusions are inhibited in vitro by achievable serum concentrations of each of these drug regiments; that is, they are "sensitive" to the drug(s). There are, however, antibiotic-resistant middle ear bacteria reported in most studies. In addition to amoxicillin-resistant *H. influenzae* and *B. catarrhalis*, cefaclor-resistant *H. influenzae* have been reported. Moreover, the effectiveness of trimethoprim and sulfamethoxazole in acute otitis media due to *Streptococcus pyogenes* is uncertain. Ampicillin-resistant and ampicillin-sensitive strains of *H. influenzae* have been equally susceptible in vitro to trimethoprim and sulfamethoxazole, cefaclor, and amoxicillin and calvulanate.

The study of antimicrobial dose and blood and tissue concentrations is central to understanding and improving the treatment of otitis media. The kinetic principles that govern antimicrobial diffusion into the middle ear have just begun to be evaluated in models of otitis media. If concentrations of antimicrobials reaching the infected ear space are below the minimum inhibitory concentration for the infecting organisms, treatment failures or chronic otitis media may result. Preliminary studies indicate that the distribution of antimicrobial agents from blood into the middle ear cavity may depend on the permeability of blood vessels and other inflammatory tissue reactions in the middle ear cavity. The degree of inflammatory changes differs in different types of otitis media.

Administration of antimicrobials to children with acute otitis media has been associated with very few adverse reactions. Toxicity, nonetheless, is a consideration in drug selection. Skin rashes and gastrointestinal tract upset are the most frequent side effects of all six regimens discussed previously. Maculopapular eruptions seem to occur equally often with all six. Rare, severe reactions have occurred with administration of sulfonamides, including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, and blood dyscrasias; these drugs should be discontinued at first appearance of a skin rash or sign of adverse reaction. Increased risks of erythema multiforme, serum sickness-like reactions, and urticaria have been reported with cefaclor, compared with amoxicillin. Erythromycin causes abdominal cramping and vomiting in as many as 40 per cent of children.

Convenience of administration (eg, twice daily dosing of trimethoprim and sulfamethoxazole) and cost are additional factors in drug selection. Amoxicillin and trimethoprim-sulfamethoxazole are least expensive, whereas the other regimens are considerably more expensive.

It is difficult to evaluate antibacterial efficacy after treatment of acute otitis media, and the randomized, controlled trial has become the established method for evaluating therapeutic efficacy. This design has the ability to prevent bias and give accurate results, but the trial must be generalizable to clinical situations. Recent reports indicate that measurement of clinical outcome may not reflect bacteriologic efficacy. For example, three trials using a bacteriologic outcome found cefaclor to be less efficacious than comparative agents.

Adjunctive Treatment

In the pre-antibiotic era, myringotomy was an established treatment for acute otitis media. Introduction of sulfonamides and penicillin lead to gradual disappearance of this

treatment modality. The value of myringotomy in addition to antimicrobial treatment has been examined. A randomized, controlled trial showed that myringotomy plus antibiotic treatment produced greater pain relief during the first 8 hours than antibiotic treatment alone, but only in the small group of patients who had severe earache initially; there were no differences in clinical response rates at 2 weeks and at 1, 2, and 3 months. Most clinicians reserve myringotomy only for the patient who has appreciable earache or persistent fever after 48 hours of antimicrobial treatment; in these cases, paracentesis and effusion culture is also indicated to guide antimicrobial drug selection. There is no information on the value of myringotomy in hastening middle ear fluid resolution in cases of acute otitis media also treated with an antibiotic. Since the presence of an effusion alone after treatment does not constitute a clinical failure, therapeutic myringotomy in an attempt to hasten fluid resolution is not indicated.

Oral decongestant and antihistamine treatment does not hasten clinical resolution of acute otitis media when combined as adjunctive therapy with an oral antibiotic, although these drugs may benefit nasal congestion. In some patients the use of decongestants may slow resolution of middle ear fluid. Moreover, oral decongestant treatment does not hasten the resolution of middle ear fluid that persists after antibiotic treatment of the initial acute otitis media episode.

Treatment Failure and Recurrent Acute Otitis Media

Most children with acute otitis media are improved after 2 to 3 days of antimicrobial therapy, but some remain ill. Failure appears to be more common in children younger than 3 years of age, in those with more than five previous otitis media episodes, with mucoid or serous effusion, and with bilateral otitis media. Among children unresponsive to initial antimicrobial treatment, aspiration of middle ear fluid will yield a bacteria resistant to initial therapy in approximately one-fourth of cases; bacteria sensitive to initial therapy are present in about one-fourth, and the effusion is sterile in about one-half. Children with resistant bacteria are clinically indistinguishable from children with sterile effusion or sensitive bacteria in the effusion. Therefore, changing antimicrobial therapy during treatment is not usually necessary, and tympanocentesis is advised to determine effusion microbiology if a change in therapy is being considered.

Recurrences of acute otitis media are particularly frustrating to physicians and parents. In a recent study, 35 per cent of 103 children had a recurrent acute otitis media episode within 30 days after the initial episode; 21 per cent had a new effusion, and 14 per cent had persistent effusion with new symptoms. Early recurrence was more likely in children with several recent episodes of otitis media. The bacteriology of the effusion at initial and recurrent episodes was similar; that is, relapse was not more frequent with certain initial bacterial infections. The incidence of beta-lactamase-producing organisms was also similar at both episodes, indicating that initial treatment did not select resistant bacteria. Reinfection with a new organism was four times more common than was bacteriologic relapse with the same organism. Therefore, in the absence of an effusion culture, physicians should not assume that early recurrent acute otitis media is the result of treatment failure of the initial episode.

Preventing Acute Otitis Media

Antimicrobial prophylaxis given to children with a history of recurrent acute otitis media and chronic otitis media with effusion significantly reduces the occurrence of acute otitis media episodes. Chronically administered sulfisoxazole (75 to 100 mg/kg/24 hours divided in two doses) or sulfamethoxazole (40 to 50 mg/kg/24 hours in a single dose) is generally administered for a period of several months, especially during the winter respiratory tract illness season. With chronic administration of sulfonamides, it is important to monitor for hematopoietic and dermatologic adverse effects; leukopenia or skin rash should lead to prompt discontinuance of the drug. Intermittent sulfonamide administration during episodes of symptomatic upper respiratory tract infection may be as effective as chronic administration in preventing acute otitis media. Continuously administered ampicillin was also effective in reducing the frequency of acute otitis media.

Active immunization against the bacteria that cause acute purulent otitis media will most likely also be effective in preventing the acute disease. A polyvalent pneumococcal capsular polysaccharide vaccine was effective in reducing the frequency of pneumococcal otitis media caused by pneumococcal serotypes represented in the vaccine, but only for those serotypes that were immunogenic in young children.

Unfortunately, pneumococcal polysaccharides are not very immunogenic in children less than 2 years of age, during the years when prophylaxis is most necessary. Thus, a vaccine prophylaxis of pneumococcal otitis media must await a more immunogenic vaccine. Recent vaccine research with type b *H. influenzae* indicates that infants show an immune response to the capsular polysaccharide of this organism when it is coupled to a protein carrier. Such a strategy may prove effective in developing vaccines against pneumococcal and nonencapsulated (nontypable) *H. influenzae.*