Strategies for Decreasing Multidrug Antibiotic Resistance: Role of Ototopical Agents for Treatment of Middle Ear Infections

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Abstract

Change in the susceptibility of bacterial pathogens to antimicrobial agents is constant. The efficacy of a new drug may change as it is used in clinical settings, and resistant bacterial clones result from the encounter of drug and organism. Soon after the introduction of the sulfonamides in the mid-1930s, the first effective agents of the antimicrobial era, resistance of pneumococci and group A streptococci was evident. In each of the following decades, a different problem in multidrug resistance occurred among common bacterial pathogens: β-lactamase–producing staphylococci in the 1950s; highly resistant gram-negative enteric bacteria in the 1960s; β-lactamase–producing *Haemophilus influenzae* and *Moraxella catarrhalis* in the 1970s; and multidrug-resistant pneumococci in the 1980s.

Antimicrobial resistance among respiratory pathogens is now a common clinical problem throughout the world, and its management is a part of routine office practice. Currently in the United States, about 25% of pneumococci are resistant to penicillin, and 25% of *H influenzae* and 90% of *M catarrhalis* produce β-lactamase and would be inactivated by organisms producing the enzyme. The emergence of penicillin and multidrug-resistant pneumococci and β-lactamase–producing strains of *H influenzae* and *M catarrhalis* have special importance for the management of infections of the middle ear.

The widespread use of oral and parenteral antimicrobial drugs for appropriate and inappropriate uses has driven the emergence and spread of resistant organisms. This article discusses current susceptibility patterns of organisms involved in middle ear infections, risk factors associated with development of resistant strains, strategies for limiting the incidence and spread of resistant organisms and, as part of the strategy, use of ototopical rather than systemic antimicrobial drugs for chronic suppurative otitis media (CSOM) and acute otitis media (AOM) in children with tympanostomy tubes. Although many ototopical agents are approved by the Food and Drug Administration for the indication of otitis externa, only ofloxacin otic is approved for treatment of CSOM in patients older than 12 years of age and AOM in children with tympanostomy tubes who are 1 year of age or older.

(Am J Manag Care. 2002;8:S345-S352)

The major bacterial pathogens responsible for the middle ear infections, chronic suppurative otitis media (CSOM) and acute otitis media (AOM) occurring in children with tympanostomy tubes, are those that are derived by contiguous spread from the nasopharynx to the middle ear, such as *Streptococcus pneumoniae*, nontypable *Haemophilus influenzae*, and *Moraxella catarrhalis*, as well as those that enter the middle ear from the external canal through the nonintact tympanic membrane, such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Choice of antimicrobial agents for CSOM or AOM in children with tympanostomy tubes must include drugs with a spectrum of activity covering each of the major pathogens. The susceptibility pattern in the community will determine the initial choice of drug, and the susceptibility pattern of the organism isolated from the site of infection will determine the continued use of the drug or the need to alter the initial choice. The clinical relevance of antibiotic resistance in otolaryngologic infections has been discussed in recent reviews by Barnett and Klein,[1] Klugman,[2] Applebaum,[3] and others. Current information about national patterns of antibiotic resistance can be found on the Web site of the Centers for Disease Control and Prevention (CDC) (www.cdc.gov).

Streptococcus pneumoniae

Clinical resistance of pneumococci to penicillin and other antimicrobial agents is now a problem throughout the world.[2-4] Pneumococcal strains are designated as susceptible and nonsusceptible, including intermediate and resistant, according to the minimum inhibitory concentrations (MICs) of the antimicrobial agent. The MIC is defined as the least amount of drug required to inhibit growth of the organism. The clinical relevance of the MIC lies in comparing the MIC of the strain of bacteria with levels of antibiotic achievable in the appropriate body fluid or tissue. If the concentration achieved at the site of infection exceeds the MIC, the organism is likely to be eradicated and clinical success is achieved. The converse is also true; if the concentration of drug at the site of infection is lower than the MIC of the organism, the organism is likely to persist with continuation of the clinical signs.

The basis for penicillin resistance is alteration in penicillin-binding proteins in the cell wall of the pneumococcus. Recent surveys of pneumococci obtained from body fluids indicates a national average of about 25% of strains that are not susceptible to penicillin.[4,5] Penicillin-resistant pneumococci are often resistant to other antimicrobial agents with different mechanisms of action. The proportion of trimethoprim-sulfamethoxazole–resistant strains is higher than the proportion of penicillin-resistant strains. Rates of resistance for cephalosporins and macrolides are lower than those for penicillins. Rates of resistance to new quinolones, gatifloxacin, levofloxacin, and ofloxacin, are low, and no pneumococcal strains have been identified that are resistant to vancomycin.

Haemophilus influenzae

The majority of resistance of strains of *H influenzae* to β-lactam agents is caused by plasmid-mediated β-lactamase production. The enzyme β-lactamase hydrolyzes ampicillin, amoxicillin, and penicillin G and V, thereby conferring resistance of the organism to these drugs. The resistance is absolute and not dose dependent; breaking the β-lactam chain renders the susceptible drug inactive. β-Lactamase as a mechanism of resistance for *H influenzae* was first recognized in the 1970s. The rate of resistant strains in the United States has grown steadily and now varies from as low as 15% in some reports to as high as 60% in others.[4,5] Rates of resistance to trimethoprim-sulfamethoxazole, β-lactamase–resistant cephalosporins and quinolones remain low.

Moraxella catarrhalis

Before 1970, virtually all strains of *M catarrhalis* were susceptible to penicillins. Today, β-lactamase production occurs in the majority of strains and is usually in excess of 90%.[5] Most strains of *M catarrhalis* remain susceptible to trimethoprim-sulfamethoxazole, β-lactamase–resistant cephalosporins, and quinolones.

Staphylococcus aureus

During the 1950s and 1960s, a pandemic of multidrug-resistant *S aureus* caused serious life-threatening infections throughout the world. The semisynthetic penicillins, including methicillin, oxacillin, and nafcillin, were first introduced in the 1960s, followed by the β-lactamase–resistant cephalosporins; these new drugs provided effective therapy for the previously resistant infections. Methicillin-resistant *S aureus* (MRSA), which shows cross-resistance to other penicillins and cephalosporins, became a significant problem in hospitals and in occasional community-acquired infections in the 1980s. MRSA is now found throughout the world. Methicillin-resistant staphylococci may carry other resistance determinants, including both chromosomal and plasmid-mediated traits, which may confer resistance to other drugs including aminoglycosides, macrolides, trimethoprim-sulfamethoxazole, and quinolones. MRSA strains are usually susceptible to vancomycin and linezolid.

Pseudomonas aeruginosa

The susceptibility of gram-negative enteric bacilli is variable and unpredictable, and isolates should be tested to determine the optimal choice of antimicrobial agents. The optimal agents for therapy for *P aeruginosa* include the aminoglycosides, ceftazidime, and quinolones.

···RISK FACTORS FOR MULTIDRUG RESISTANCE···

Prior exposure to antibacterial agents, young age, day-care attendance, and hospitalization are risk factors for colonization and infection with resistant pneumococci. The most prominent risk factors are recent use of an antimicrobial agent in the patient and the volume of antimicrobial drug use in the community. Countries with restrictive antibiotic policies have low rates of resistance; the Netherlands has had rates of nonsusceptible strains of pneumococci during the past decade of less than 5%. Countries with few restrictions of antibiotic usage, including over-the-counter availability, have high rates of resistance; Korea, Taiwan, and other Far East nations have had rates of 80% or more.[3] Isolates from mucosal surfaces, including the throat and nasopharynx, yield higher rates of resistance than do isolates from body fluids, such as blood and cerebrospinal fluid. Infection with resistant organisms cannot be distinguished clinically from infection caused by susceptible ones. Additionally, resistant organisms do not appear to be more virulent than those that are not resistant.

···STRATEGIES FOR DECREASING THE INCIDENCE OF MULTIDRUG-RESISTANT BACTERIA···

If the most important risk feature for the increasing incidence of multidrug-resistant bacteria is the volume of antimicrobial drug used, strategies to decrease the incidence of antibiotic-resistant bacteria need to be directed at reducing the volume of oral and parenteral antimicrobial drugs. Systemic antimicrobial agents eradicate or suppress susceptible organisms from the upper respiratory tract, permitting resistant strains to flourish. Because ototopical agents remain localized to the external canal, there is no antimicrobial activity that would alter the microflora in the throat or nasopharynx.

Encourage Judicious Use of Antimicrobial Agents

The CDC and the American Academy of Pediatrics (AAP) developed programs in 1998 to promote the judicious use of antimicrobial agents. The goal of the programs is to reduce the inappropriate use of antimicrobial agents, such as for viral upper respiratory tract infections that resolve spontaneously and do not benefit from an antibacterial drug. Because otitis media is the leading diagnosis identified for use of antimicrobial agents in children, this disease has been the focus of attention to limit antimicrobial agents. Representatives of the CDC and the AAP outlined principles for the judicious use of antimicrobial agents for management of otitis media.[6] These principles are as follows:

- Episodes of otitis media should be classified as AOM or otitis media with effusion (OME).
- Antimicrobials are indicated for treatment of AOM. This diagnosis requires documented middle ear effusion and signs or symptoms of acute local or systemic illness.
- Antimicrobials are not indicated for initial treatment of OME. OME may persist for weeks to months after every episode of AOM and does not require retreatment.
- Antimicrobial prophylaxis should be used for carefully selected patients, including those with 3 or more documented episodes of AOM over 6 months or 4 or more episodes over 12 months.

Physician and Parent Education

The CDC and the AAP have distributed

educational materials to physicians about the need to reduce the volume of antibiotics because of concern for the increasing incidence of multidrug-resistant bacterial pathogens.[6] Use of antibiotics needs to be curtailed for diseases likely to be caused by viruses, such as colds or bronchitis, and for signs likely associated with respiratory viruses, such as rhinorrhea and cough. Because physicians report that their choice for or against use of antimicrobial agents is influenced by the expectations of parents, the educational program includes materials for patients to identify the reasons to choose or withhold antimicrobial agents.

Vaccines

Conjugate* H influenzae *type b Vaccine. If vaccines are capable of reducing the incidence of disease, they can also be expected to reduce the volume of antimicrobial agents that would be used for those diseases. Although the conjugate *H influenzae* type b vaccine has been successful in limiting the incidence of invasive diseases, such as sepsis and meningitis, this vaccination has had little effect on the incidence of AOM because the strains of *H influenzae* causing AOM are most often nontypable; only a small proportion are due to type b.

Conjugate Pneumococcal Vaccine. The conjugate pneumococcal vaccine has the potential to reduce the incidence of AOM substantially because pneumococcus is the major pathogen of AOM. Similar to the conjugate *H influenzae* type b vaccine, the conjugate pneumococcal vaccine was effective in reducing the incidence of invasive disease.[7] However, data available from trials in Northern California[7] and Finland[8] indicate a more modest effect on the incidence of AOM; each study identified a decrease in episodes of AOM of 7%. Microbiologic data from the Finnish trial identified an increased number of episodes of AOM caused by nonvaccine serotypes in children who received the pneumococcal vaccine compared with those children who received the control vaccine.[8] These results suggest the possibility of decreased carriage and AOM caused by vaccine serotypes, with replacement by nonvaccine serotypes in the nasopharyngeal flora as the cause of AOM in vaccinated children.

Influenza Virus Vaccines. Influenza virus vaccines have been found to be successful in reducing the incidence of AOM as a complication of influenza virus infection. Influenza virus vaccine resulted in a reduction in cases of influenza A as well as a 36% decline in AOM in children attending a day-care center.[9] The introduction of a live, attenuated, cold-adapted intranasal influenza vaccine resulted in a similar reduction (30%) in episodes of febrile otitis media.[10] These results and other epidemiologic data indicating the value of annual influenza virus immunization programs for infants have encouraged physicians to promote immunization of infants 6 to 24 months of age.

···USE OF OTOTOPICAL AGENTS FOR MIDDLE EAR INFECTIONS···

Although ototopical agents have been documented for various illnesses since 1500 BC, only in recent years have these products been evaluated in studies of appropriate design and adequate sample size for middle ear infections. A large number of ototopical agents are available. In addition to the agents noted in the **Table**, ophthalmic preparations have been used, off-label, as otic agents. All of the ototopical agents listed in the Table are effective to varying degrees for management of otitis externa, but only one, ofloxacin otic, has been approved for the middle ear infections CSOM and AOM in patients with tympanostomy tubes. Although ototopical ciprofloxacin has been evaluated and found to be effective for CSOM[11] and for AOM in patients with tympanostomy tubes,[12] ototopical ciprofloxacin has not been approved by the Food and Drug Administration for these indications. Because of the safety profile from clinical trials, ofloxacin is the only otic agent approved for use in children with a nonintact tympanic membrane.

Table. Current Status of Ototopical Agents

	Approved for Use by FDA		
	OE	**AOM With TT**	**CSOM**
Cipro HC (suspension)	Yes	_____	_____
Coly-Mycin S (neomycin and colistin with hydrocortisone)	Yes	_____	_____
Cortane B (same as Zoto HC but in aqueous solution)	Yes	_____	_____
Cortisporin (neomycin and polymyxin B sulfate with hydrocortisone)	Yes	_____	_____
Cortisporin TC (same as Cortisporin + thonzonium bromide)	Yes	_____	_____
Domeboro (aluminum acetate-acetic acid, higher pH than acetic acid)	Yes	_____	_____
Floxin otic (ofloxacin otic solution)	Yes	Yes	Yes
Otocort (same ingredients as Cortisporin)	Yes	_____	_____
Pediotic (less acidic but same ingredients as Cortisporin and more viscous)	Yes	_____	_____
Vosol HC (hydrocortisone and acetic acid solution)	Yes	_____	_____
Vosol (plain) (acetic acid only used prophylactically)	Yes	_____	_____
Zoto HC (chloroxylenol, pramoxine hydrochloride, hydrocortisone)	Yes	_____	_____

OE indicates otitis externa; AOM with TT, acute otitis media with tympanostomy tubes; CSOM, chronic suppurative otitis media; FDA, Food and Drug Administration.

···CHRONIC SUPPURATIVE OTITIS MEDIA···

Definition, Pathogenesis, and Microbiology

CSOM is defined by chronic infection in the middle ear and mastoid and a nonintact tympanic membrane (chronic perforation or tympanostomy tube). Otorrhea may or may not be present.[13] CSOM is a major health problem throughout the world but is of particular concern in developing countries. The bacterial pathogens associated with CSOM are derived from episodes of AOM (*S pneumoniae*, *H influenzae*, and *M catarrhalis*) or from organisms resident in the external canal that gain entry into the middle ear space through the tympanic membrane perforation (*P aeruginosa* and *S aureus*).

Management

The management of CSOM, in the absence of cholesteatoma, has included ototopical medications and oral or parenteral antimicrobial agents. In addition to the use of the antimicrobial agent, meticulous aural cleansing, which consists of aspirating the purulent material and debris from the external canal, enhances the effectiveness of the antibiotic treatment. Cultures of the purulent material is helpful in identifying the most effective antimicrobial agents. The culture is obtained during visualization of the tympanic membrane through the perforation or tympanostomy tube; a swab placed blindly in the external canal is likely to yield ambiguous culture results.

Ofloxacin was an attractive candidate for use as an ototopical agent because of its safety and its spectrum of antibacterial

activity that includes the major bacterial pathogens of CSOM. Agro et al conducted a multicenter open-label trial to determine the clinical and microbiologic efficacy of ofloxacin otic solution in the treatment of patients 12 years of age and older with CSOM.[14] The primary clinical end point was cure (dry ear) or failure (persistent otorrhea). The primary microbiologic end point was eradication of baseline pathogens. Ofloxacin otic resulted in a 91% cure rate and was effective in eradicating the bacterial pathogens from the otorrhea fluid, including all 40 isolates of *S aureus* and all 39 isolates of *P aeruginosa*.

Oral antibiotics that are approved to treat AOM may be effective if the bacterium is susceptible, but because the infection often includes *P aeruginosa*, no currently available oral antimicrobial agents for children are active against all pathogens. If the patient with CSOM has signs of extension to the mastoid or fails on treatment with ototopical agents and aural cleansing, the patient should be considered for a parenteral antibiotic directed at the pathogens identified by culture. When *Pseudomonas* species are isolated, agents such as ticarcillin, piperacillin, or ceftazidime are usually effective. When patients fail medical therapy, surgery on the middle ear and mastoid (ie, tympanomastoidectomy) may be required to eradicate the infection.

Acute Otitis Media in Patients With Tympanostomy Tubes

The procedure for placement of tympanostomy tubes is common, with approximately 600 000 procedures performed annually.[15] Tympanostomy tubes are effective in children with recurrent AOM or persistent middle ear effusion because they serve to aerate the middle ear, drain middle ear secretions, equilibrate ambient and middle ear pressure, and result in return to a healthy middle ear mucosa. Tubes are designed to remain in place for at least a year; in a study of Pittsburgh children, tubes remained in place from 19 days to 38.5 months.[16]

Although the patient with tympanostomy tubes does not endure the pain of AOM because the fluid egresses through the tube, AOM is still seen in these patients as infection and inflammation of the mucosal lining of the middle ear and is represented clinically as otorrhea. Tube otorrhea is a common and often recurrent problem in young children. In the study of Pittsburgh children, the mean number of episodes per child was 0.79 in the first 6 months following tube placement; 1.5 episodes in the first 12 months; and 2.17 episodes in the first 18 months.[16] The mean duration of tube otorrhea was 16 days. The major bacterial pathogens isolated from otorrhea in patients with AOM and tympanostomy tubes include the middle ear pathogens (*S pneumoniae*, *H influenzae* and *M catarrhalis*) and pathogens derived from the skin flora of the external canal (*P aeruginosa* and *S aureus*).

In prior years, children with tympanostomy tubes who had episodes of AOM were treated with systemic antimicrobial agents, the same array of drugs used for AOM in the patient with intact tympanic membranes. If the AOM could be treated safely and effectively without use of a systemic antimicrobial agent, the selective pressure for development of resistant strains would likely be reduced. Goldblatt and colleagues evaluated the safety and efficacy of ofloxacin otic and the orally administered drug, amoxicillin-clavulanate.[17] The investigators designed a multicenter, randomized, evaluator-blind study involving 240 patients 1 to 12 years of age with AOM and tympanostomy tubes. Patients were treated for 10 days with either oral amoxicillin-clavulanate 40 mg/kg/day in 3 doses or 5 ofloxacin drops twice daily applied directly to the ear canal. The authors identified equivalent clinical efficacy (**Figure 1**) for the ototopical and oral antimicrobial agents; the ototopical agent was microbiologically equivalent (**Figure 2**) to the oral agent against infections caused by the *Pneumococcus* species, *H influenzae*, and *M catarrhalis* but was more effective against strains of *S aureus* and *P aeruginosa*.

Clinical Implications of Ofloxacin Otic for Management of Middle Ear Infections

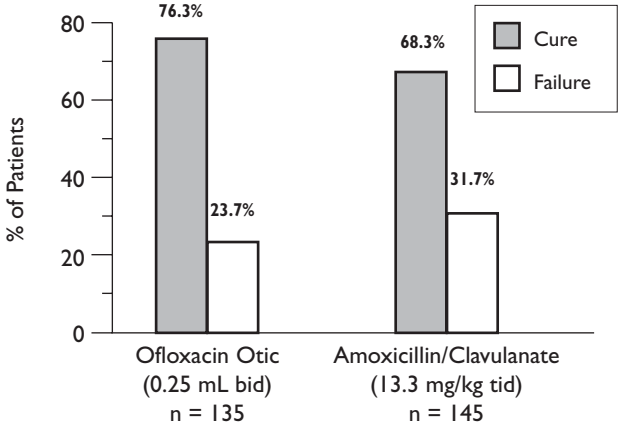
If children who have tympanostomy tubes inserted have more than 1 episode

of AOM in the year after the procedure and approximately 600 000 procedures are performed annually with tubes staying in place for approximately 1 year after insertion, a logical assumption would be that at least 600 000 courses of an antimicrobial agent are likely to be administered for AOM in these children. An oral or systemic antimicrobial agent is likely to result in alteration of the upper respiratory flora with possible selection of resistant strains. An ototopical agent that remains in the external canal and middle ear is not likely to alter the flora in the upper respiratory tract. If the ototopical agent is found to be comparable in safety and efficacy to the systemically administered agent, the advantage in decreasing the selective pressure on the nasopharyngeal microflora in patients could be achieved.

···CONCLUSION···

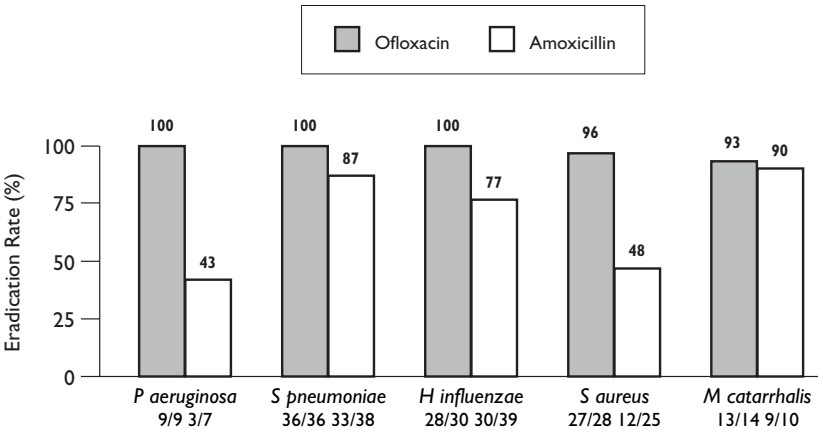
Multidrug-resistant bacteria have been and will continue to be a concern for management of respiratory infectious diseases, particularly multidrug-resistant pneumococci and β-lactamase–producing strains of *H influenzae*. Multidrug-resistant pneumococci are of particular concern because of the prevalence of pneumococci in local infections, such as otitis media and pneumonia, as well as invasive infections, such as bacteremia and meningitis. Risk features for multidrug-resistant bacteria include prior antimicrobial use, recent hospitalization, young age, and day-care attendance. The most important determinants for occurrence of resistant strains appear to be the prior use of antimicrobial agent in the patient and the volume of use of antimicrobial agents in the community. Strategies for reducing the incidence of multidrug-resist-

Figure 1. Clinical Efficacy of Ofloxacin Otic or Oral Amoxicillin/Clavulanate for Acute Otitis Media in Patients With Tympanostomy Tubes



Source: Adapted with permission from *Int J Pediatr Otorhinolaryngol* 1998;46:91-101.

Figure 2. Microbiologic Efficacy of Ofloxacin Otic or Oral Amoxicillin/Clavulanate for Acute Otitis Media in Patients With Tympanostomy Tubes



Source: Adapted with permission from *Int J Pediatr Otorhinolaryngol.* 1998;46:91-101.

ant strains focus on reducing the volume of antimicrobial drug by encouraging judicious use of antimicrobial agents, parent and physician education about appropriate use of antimicrobial agents, and use of conjugate pneumococcal and influenza virus vaccines. Use of the ototopical agent ofloxacin in place of oral or parenteral antibiotics for patients with CSOM and patients with AOM and tympanostomy tubes will reduce the use of systemic antimicrobial agents, thus decreasing the risk of development of resistant strains for the patient and the community. Ofloxacin has a spectrum of activity that includes all of the major pathogens associated with CSOM as well as AOM in patients with tympanostomy tubes, including bacteria from the nasopharynx (such as *S pneumoniae*, *H influenzae*, and *M catarrhalis*) and organisms acquired from the external canal (such as *P aeruginosa* and *S aureus*). The rate of pneumococci resistant to quinolones in the United States remains low. Trials involving use of ofloxacin otic solution show a high rate of cure without affecting resident flora of the upper respiratory tract, thus not providing selective pressure for development of resistant bacteria in the upper respiratory tract. The topical medication is delivered directly to the site of infection in the external and middle ear spaces and is not absorbed into the systemic circulation.[18] Clinical efficacy for otic disease is maximized without affecting resident flora of the upper respiratory tract. Because there is no systemic absorption of the otic antibiotic there is no selective pressure for development.

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