Potential Role of Fluoroquinolone Therapy in Childhood Otitis Media

Ron Dagan, MD,* Adriano Arguedas, MD,† and Urs B. Schaad, MD‡

Abstract: Increased resistance of pneumococci and other pathogens to available antibiotics raises concerns about bacteriologic and clinical failure in children with acute otitis media. Few therapeutic options exist for patients with recurrent infections or recent treatment failure. The limited experience from the compassionate use of fluoroquinolones in pediatrics and pediatric studies has not been linked unequivocally with arthrotoxicity, the primary safety concern in children. Newer 8-methoxyfluoroquinolones may have a role in selected cases associated with multidrug-resistant pathogens.

Key Words: Fluoroquinolones, pediatrics, otitis media, antimicrobial resistance, gatifloxacin.

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Antimicrobials in Perspective

Acute otitis media (AOM) is the world’s most common bacterial respiratory tract infection in early childhood and the main reason for antimicrobial use in children.¹⁻² Recurrent otitis media (ROM) is defined as ≥3 episodes of AOM in a 6-month period or ≥4 in 12 months, with each episode being fully resolved.³ Recent estimates put the occurrence of ROM in young children at 20 to 30%.⁴ Similar to ROM is nonresponsive AOM or otitis media treatment failure (OMTF), the persistence of symptoms during antimicrobial therapy or a relapse of AOM within 1 month after completion of therapy.⁴⁻⁵ OMTF occurs in ~10% of children with AOM.⁵

AOM is defined by middle ear fluid (MEF) accompanied by signs or symptoms of acute illness, although the latter may be nonspecific.⁶ To prevent overdiagnosis MEF should be documented by pneumatic otoscopy or other techniques such as acoustic reflectometry or tympanometry,²,⁶ with consideration of nonbacterial etiologies. Approximately one-fourth of AOM cases are initially caused exclusively by viruses,⁵ most commonly respiratory syncytial virus, influenza and rhinoviruses, although some patients have a mixed viral-bacterial infection. The frequency of viral infection and the high rate of spontaneous clinical resolution have led to an observational approach in many countries. Although there are a few exceptions,⁷,⁸ the high rate of spontaneous recovery has made a correlation between bacteriologic efficacy and clinical outcome after antimicrobial therapy difficult to establish.⁵,⁹

Because physicians are unable to identify by physical examination alone the patients whose infection will resolve spontaneously, most infants and children worldwide with AOM are treated with antibiotics. Multidrug-resistant pathogens can make some of these infections serious; complications of untreated AOM include meningitis and chronic suppurrative otitis media.¹⁰ Hearing loss and delayed speech development may follow from untreated AOM.⁶ In general antibiotics should be administered if AOM is identified in infants and young children with recurrent infections, in those with structural or immunologic abnormalities and in severely ill children.⁵

In this review we describe the problem of antibiotic resistance in AOM and the limited treatment options available for children with ROM or OMTF caused by multidrug-resistant Streptococcus pneumoniae and beta-lactamase-producing Haemophilus influenzae. The potential role of newer fluoroquinolones in patients with refractory AOM infections is presented, along with initial clinical results with gatifloxacin, an 8-methoxyfluoroquinolone. Clinical implications associated with the expanded use of fluoroquinolones in chil-
dren with AOM are discussed. Finally we review prior experiences with fluoroquinolones in pediatrics, including the absence of arthropotoxicity.

ANTIMICROBIAL RESISTANCE IN OTITIS MEDIA

The predominant pathogens in AOM are *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis* and *Streptococcus pyogenes*, although their relative frequencies have marked geographic variations. Resistant *S. pneumoniae* and β-lactamase-producing *H. influenzae* predominate in ROM and OMTF. *S. pneumoniae* causes 30 to 40% of all AOM cases, and its virulence means that infections caused by pneumococci are least likely to resolve without treatment. Although *M. catarrhalis* is recovered in fewer than 10% of AOM cases, most strains produce β-lactamase.

The primary goal of antibiotic therapy for AOM is to achieve clinical cure secondary to eradication of causative pathogens from MEF. Empiric therapy should be selected with knowledge of the local prevalent pathogens and their resistance characteristics, with consideration given to prior antibiotic use. Decreasing susceptibility of *S. pneumoniae* to penicillin and other β-lactams and the growing frequency of β-lactamase production by *H. influenzae* and *M. catarrhalis* have complicated drug selection. Accumulating evidence suggests that resistance to the administered drug correlates with a rising rate of bacteriologic failure and accounts for clinical failure in many patients.

Before the 1990s most strains of pneumococci in the United States were susceptible to penicillin. Recently identified penicillin-resistant strains now demonstrate moderate to high rates of resistance to the macrolides, tetracycline and trimethoprim-sulfamethoxazole (TMP-SMX) as well. Penicillin- or multidrug-resistant *S. pneumoniae* has become prevalent worldwide. In a multinational study of 917 children with AOM, only 70% of pneumococcal MEF isolates were susceptible to penicillin, and nearly one-half of the strains with intermediate or full penicillin resistance were resistant to multiple antimicrobial classes. Resistance to amoxicillin was common among nonpneumococcal organisms (Table 1); 31% of *H. influenzae* isolates produced beta-lactamase, including 47% of those from the United States.

The prevalence and patterns of antimicrobial resistance among pneumococci causing AOM vary among countries. An example of a country with high prevalence of resistance and multidrug resistance is Israel, where nonsusceptibility to penicillin, TMP-SMX and erythromycin and multidrug resistance (three antibiotic classes or more) was observed in 15, 13, 2 and 1%, respectively, in 1992, but increased exponentially to 69, 48, 24 and 23%, respectively, in 2001.

Costa Rica is an example of a country with a relative low resistance rate. However, even in Costa Rica resistance is increasing, consistent with a general trend of decreasing antibiotic susceptibility worldwide. Pneumococcal resistance patterns in Costa Rica were identified by diagnostic tympanocentesis performed in children with acute uncomplicated AOM who participated in drug efficacy studies. Between 1995 and 1997, of 46 *S. pneumoniae* strains isolated from MEF cultures, 9 (20%) demonstrated diminished susceptibility to penicillin: 8 were intermediate (MIC 0.12 to 1 g/ml) and 1 had high level resistance (MIC > 1.2 μg/ml) (Fig. 1). Of 276 MEF isolates obtained from 1999 to 2001 in the same country, 102 were from children with AOM, 98 from those with ROM and 76 from patients with OMTF. *S.

**TABLE 1.** Susceptibility of Isolates from Middle Ear Fluid of 917 Children With AOM in a Multinational Study

<table>
<thead>
<tr>
<th>No. of Susceptible Isolates* / Total No. of Isolates (% of Isolates)</th>
<th>Streptococcus pneumoniae</th>
<th>Haemophilus influenzae</th>
<th>Moraxella catarrhalis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>154/166 (93)¹</td>
<td>45/52 (87)</td>
<td>0/5 (0)</td>
<td>199/223 (89)</td>
</tr>
<tr>
<td>Europe</td>
<td>19/25 (76)</td>
<td>23/31 (74)</td>
<td>0/4 (0)</td>
<td>42/60 (70)</td>
</tr>
<tr>
<td>Israel</td>
<td>70/80 (88)</td>
<td>36/64 (56)</td>
<td>0/27 (0)</td>
<td>106/171 (62)</td>
</tr>
<tr>
<td>United States</td>
<td>243/271 (90)</td>
<td>102/147 (69)</td>
<td>0/36 (0)</td>
<td>345/454 (76)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>155/166 (93)</td>
<td>52/52 (100)</td>
<td>5/5 (100)</td>
<td>212/223 (95)</td>
</tr>
<tr>
<td>Europe</td>
<td>19/25 (76)</td>
<td>31/31 (100)</td>
<td>4/4 (100)</td>
<td>54/60 (90)</td>
</tr>
<tr>
<td>Israel</td>
<td>70/80 (88)</td>
<td>63/64 (98)</td>
<td>27/27 (100)</td>
<td>160/171 (94)</td>
</tr>
<tr>
<td>United States</td>
<td>244/271 (90)</td>
<td>146/147 (99)</td>
<td>36/36 (100)</td>
<td>426/454 (94)</td>
</tr>
</tbody>
</table>

*Isolates not received for testing were *S. pneumoniae* (*n* = 29), *H. influenzae* (*n* = 26) and *M. catarrhalis* (*n* = 14).

¹Susceptibility breakpoints: ≤ 0.5 μg/ml for *S. pneumoniae*, and ≤ 4 μg/ml for *H. influenzae* and *M. catarrhalis*. Recently set new National Committee for Clinical Laboratory Standards breakpoints classify *S. pneumoniae* isolates with amoxicillin MIC ≤ 2.0 μg/ml as susceptible.

Numbers in parentheses, percent of patients.
pneumoniae accounted for 75, 52 and 41% of these isolates, respectively. Nearly one-half of the isolates associated with failed therapy were strains of H. influenzae (100% β-lactamase-negative). Pneumococcal susceptibility to penicillin continued to decrease in Costa Rica after 1997 (see Fig. 1). Penicillin-intermediate strains increased to 39% of isolates in AOM and were even higher in ROM (60%) and OMTF (57%).

CURRENT TREATMENT GUIDELINES IN AOM

In 1996 the Centers for Disease Control and Prevention convened the Drug Resistant Streptococcus pneumoniae Therapeutic Working Group to establish AOM treatment recommendations (Table 2). In these guidelines amoxicillin was the drug of choice for uncomplicated AOM regardless of the community-wide prevalence of drug-resistant pneumococci or β-lactamase-producing H. influenzae.21 Supporting this recommendation were a long record of safety and effectiveness, efficacy against pneumococci, an excellent pharmacodynamic profile against drug-resistant strains (the time that MEF concentrations exceed MIC90) and a relatively narrow spectrum of activity.

High dose amoxicillin (80 to 90 mg/kg/day) was recommended for patients at high risk of infection with drug-resistant S. pneumoniae, including those <2 years of age, attending day care or with antimicrobial exposure within 3 months.21 Low risk patients could receive 40 to 45 mg/kg/day, a standard dosage. In the event of clinically defined treatment failure, identification of the etiologic agent by tympanocentesis was recommended.21 Failing that, criteria for second line therapy included efficacy against β-lactamase-producing H. influenzae and M. catarrhalis as well as drug-resistant S. pneumoniae, as demonstrated by high dose amoxicillin/clavulanate, cefuroxime axetil and a 3-day regimen of intramuscular ceftriaxone. (The US Food and Drug Administration approval of single dose ceftriaxone for pneumococcal AOM is limited to infections caused by penicillin-susceptible strains.)

IMPACT OF ACTIVE IMMUNIZATION AGAINST PNEUMOCOCCI

Widespread use of pneumococcal conjugate vaccines has the potential to reduce the incidence of drug-resistant pneumococcal infections substantially.22 Five of the seven serotypes included in the licensed seven valent vaccine are frequently penicillin-resistant. Although vaccination protects against serotype-specific AOM in children and reduces carriage of penicillin-resistant pneumococci, overall efficacy may be limited by an increasing number of infections attributed to other serotypes.23,24 Prevention of AOM in children may require a strategy targeting both viral and bacterial pathogens, including H. influenzae and M. catarrhalis.1,24 Nevertheless reducing the burden of pneumonia and invasive pneumococcal infections in infants and children, particularly in developing countries, may be achievable through active immunization.22

TABLE 2. Treatment Recommendations From the Drug-Resistant Streptococcus pneumoniae Therapeutic Working Group for AOM in Children*1

<table>
<thead>
<tr>
<th>Antibiotics in Prior Month</th>
<th>Day 0</th>
<th>Clinically Defined Treatment Failure on Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>High dose or usual dose of amoxicillin*</td>
<td>High dose amoxicillin/clavulanate or cefuroxime axetil or intramuscular ceftriaxone1</td>
</tr>
<tr>
<td>Yes</td>
<td>High dose amoxicillin, amoxicillin/clavulanate or cefuroxime-axetil</td>
<td>Intramuscular ceftriaxone1 or clindamycin1 or tympanocentesis</td>
</tr>
</tbody>
</table>

*High dose amoxicillin, 80 to 90 mg/kg/day; usual dose of amoxicillin, 40 to 45 mg/kg/day, may be used in patients at low risk for infection with drug-resistant S. pneumoniae, including children >2 years old with no antimicrobial exposure in the preceding 3 months and no day-care attendance.

1Documented efficacy in treatment failures if three daily doses are used.

1Not effective against Haemophilus influenzae or Moraxella catarrhalis.
FAILURE OF ANTIMICROBIAL THERAPY IN ROM OR OMTF

No approved single-agent oral therapy covers all AOM pathogens, although nearly complete coverage is provided by the 3-day intramuscular ceftriaxone regimen and by high dose amoxicillin/clavulanate, the latter being the only antimicrobial agent approved by the US Food and Drug Administration for the treatment of AOM episodes in patients with ROM. Several studies have documented the value of using double tympanocentesis, at enrollment and on Treatment Day 4 or 6, to document early bacteriologic eradication. In these studies bacteriologic failure was defined by positive culture on follow-up tympanocentesis, and clinical failure was defined by no change or worsening in AOM signs and symptoms and a need for additional antibiotics.

In a prospective trial in Israel, 50 culture-positive patients, 3 to 22 months old, were treated with high dose amoxicillin for AOM; 24 patients presented with a first episode. Among 65 pathogens isolated at enrollment, 38 were H. influenzae (13 β-lactamase-positive), and 24 were S. pneumoniae (18 penicillin-non-susceptible). Bacteriologic failure was documented in 14 of 50 children (28%), including 9 with β-lactamase-positive H. influenzae. Three clinical failures occurred, 2 involving enzyme-producing Haemophilus. This overall clinical efficacy suggests that high dose amoxicillin is satisfactory first line therapy for AOM; however, the high bacteriologic failure with β-lactamase-producing H. influenzae warrants consideration of alternative therapy in areas of high prevalence.

In a trial conducted in Israel, the United States, and Central America, high dose amoxicillin/clavulanate 90/6.4 mg/kg/day was administered in 2 divided doses for 10 days to 521 children with AOM. Nearly three-fourths of patients were younger than 2 years; additional risk factors for drug-resistant S. pneumoniae were previous AOM episode (26%), antibiotic therapy within 3 months (50%) and day-care attendance (38%). H. influenzae was isolated from 197 patients, and 37% of the strains produced β-lactamase. Among 154 S. pneumoniae isolates, 28% were fully penicillin resistant (MIC > 2 μg/ml), and 18% were intermediate (MIC 0.12 to 1 μg/ml). A total of 141 pneumococci (92%) were susceptible to amoxicillin/clavulanate at the National Committee for Clinical Laboratory Standards breakpoint of 2 μg/ml.

S. pneumoniae was eradicated in 98% of evaluable children (Table 3), although eradication rates were lower for children with penicillin-resistant isolates (31 of 34, 91%) compared with penicillin-susceptible or -intermediate isolates (88 of 88, 100%; P = 0.02). Resistant pneumococci were likely to be associated with recurrent AOM and previous antibiotic use within 3 months. Eradication of H. influenzae occurred in 94% of evaluable patients (see Table 3), including 89% of those with β-lactamase-positive isolates.

By covering the major AOM pathogens, high dose amoxicillin/clavulanate has proved a useful second line agent for infections unresponsive to the regular dose because of drug-resistant S. pneumoniae. As penicillin-resistance among pneumococci continues to increase and cause ROM or OMTF, however, an increasing percentage of bacteriologic resistance will need to be covered.

### TABLE 3. Bacteriologic Outcome with High Dose Amoxicillin/Clavulanate in Evaluable Children* with AOM Caused by Streptococcus pneumoniae (n = 93), Haemophilus influenzae (n = 51) or Both (n = 32) on Days 4 to 6, Based on MIC of Initial Isolate†

<table>
<thead>
<tr>
<th>MIC (μg/ml)</th>
<th>Penicillin†</th>
<th>Amoxicillin/clavulanate†</th>
<th>H. influenzae (amoxicillin/clavulanate)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.25</td>
<td>83/83</td>
<td>85/85</td>
<td>5/5</td>
</tr>
<tr>
<td>0.5</td>
<td>4/4</td>
<td>3/3</td>
<td>51/52</td>
</tr>
<tr>
<td>1</td>
<td>1/1</td>
<td>3/3</td>
<td>19/22</td>
</tr>
<tr>
<td>2</td>
<td>19/20</td>
<td>22/24</td>
<td>2/3</td>
</tr>
<tr>
<td>4</td>
<td>12/14</td>
<td>3/4</td>
<td>1/1</td>
</tr>
<tr>
<td>8</td>
<td>0/0</td>
<td>3/3</td>
<td>0/0</td>
</tr>
<tr>
<td>Not tested</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>All</td>
<td>122/125 (98)</td>
<td>122/125 (98)</td>
<td>78/83 (94)</td>
</tr>
</tbody>
</table>

*There were no failure in nonevaluable children. Of those with S. pneumoniae infections, 13 had isolates that were penicillin-susceptible (S), 4 were penicillin-intermediate (I) and 7 were penicillin-resistant (R).

†Breakpoints: S. pneumoniae penicillin S/I/R, ≤0.06/0.12–1/≥2 μg/ml; S. pneumoniae amoxicillin/clavulanate S/I/R, ≤2/4–8 μg/ml; H. influenzae amoxicillin/clavulanate S/I/R, ≤4–8 μg/ml.

‡Numbers in parentheses, percent of patients.
failures is expected. Among 34 penicillin-resistant pneumococci isolated from 125 evaluable patients, 14 strains had penicillin MICs of 4 μg/ml, a level of resistance at which the best oral therapy currently available may fail (see Table 3).

Several studies in which clinical outcome was used rather than bacteriologic outcome suggest the potential benefits of cefprozil\(^2^6\) and high dose azithromycin (20 mg/kg/day for 3 days)\(^2^7\) for treatment of ROM and OMTF. Studies with bacteriologic outcome are needed to confirm these findings, because the sample sizes were too small to draw definitive conclusions.

Pneumococcal MEF isolates from children with recurrent or nonresponsive AOM clearly demonstrate increasing resistance to penicillin and other agents. In a retrospective Israeli survey,\(^1\) 876 \textit{S. pneumoniae} isolates were obtained from patients with AOM between September 1997 and March 1999. Susceptibility to penicillin (MIC < 0.12 μg/ml) was 56% among children not receiving antibiotics in the previous 3 months, 48% in those treated 2 to 3 months before the sample was collected, 33% in those treated during the previous month but not when the sample was obtained and 19% in patients still receiving antibiotics (nonresponsive AOM group) (Fig. 2). One-fourth of pneumococci isolated during antibiotic therapy were fully resistant to penicillin (MIC > 1.0 μg/ml).

**ROLE OF COLONIZATION IN RESISTANCE**

Nasopharyngeal carriage of bacterial pathogens increases during acute viral respiratory infection.\(^2^9\) The main source of \textit{S. pneumoniae} causing infection in infants and young children is the nasopharynx, and pneumococci can spread to adjacent mucosal tissues, causing AOM or other respiratory tract infections. Antibiotic use has been linked to nasopharyngeal carriage of increasingly resistant \textit{S. pneumoniae},\(^2^9\) which can be transmitted to close contacts, especially among infants and young children in day care.

Colonization can predispose patients to new infections with more resistant organisms. A prospective study evaluated bacteriologic eradication from both the nasopharynx and MEF by azithromycin, amoxicillin/clavulanate or TMP-SMX.\(^3^0\) In 19 (16%) of 119 MEF culture-positive children, susceptible organisms (\textit{S. pneumoniae}, \textit{H. influenzae} or both) were present before therapy whereas a resistant pneumococcus was identified in the nasopharynx after start of therapy. Susceptible MEF pathogens were replaced by the resistant \textit{S. pneumoniae} strain within a few days after treatment began in 9 of these 19 patients.

In another study of children with ROM and OMTF in Israel, 63% had nasopharyngeal carriage of \textit{S. pneumoniae} at the start of treatment; nonsusceptibility to penicillin, TMP-SMX and erythromycin was found in 87, 64 and 18% of isolates, respectively.\(^3^1\) Carriage rates dropped by the end of treatment but rose to 84% 22 to 30 days after treatment. This recolonization was associated with a drop in nonsusceptibility to penicillin (63%), TMP-SMX (48%) and erythromycin (13%).

The nonsusceptible strains of \textit{S. pneumoniae}, still carried in the nasopharynx of more than one-half of the treated children, could result in new bouts of ROM or be passed to other children, resulting in AOM\(^3^2\); appropriate antibiotics would be necessary to treat these cases.

**POTENTIAL ROLE OF FLUOROQUINOLONES IN ROM**

Few therapeutic options exist for children with ROM or OMTF because of multidrug-resistant \textit{S. pneumoniae} and \(\beta\)-lactamase-producing \textit{H. influenzae}. Because oral cephalosporins and macrolides are generally ineffective against penicillin-nonsusceptible \textit{S. pneumoniae}, intramuscular ceftriaxone or high dose amoxicillin/clavulanate are the only viable options today.\(^15,3^3\) \textit{S. pneumoniae} may eventually develop resistance to these agents. Moreover, the 1-day ceftriaxone regimen fails to eradicate penicillin-nonsusceptible \textit{S. pneumoniae} from MEF.\(^3^4\)

The 8-methoxyfluoroquinolones gatifloxacin and moxifloxacin have good in vitro activity against the predominant Gram-negative pathogens (including \textit{H. influenzae} and \textit{M. catarrhalis}) in community-acquired respiratory tract infections.\(^3^5\) The methoxy group at the C-8 position confers enhanced activity against the DNA gyrase of Gram-positive bacteria, especially \textit{S. pneumoniae}.\(^3^6\) Several experimental studies have demonstrated that these 8-methoxyfluoroquinolones...
Fluoroquinolones in Pediatrics

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Fluoroquinolones may have a lower propensity to select for resistant S. pneumoniae than do ciprofloxacin, levofloxacin and other older fluoroquinolones.

Initial Fluoroquinolone Experience in AOM. Gatifloxacin, which was approved in the United States in 1999 for use in adults, is effective and well-tolerated for treatment of community-acquired respiratory tract infections such as pneumonia, acute exacerbations of chronic bronchitis and acute bacterial rhinosinusitis. In results from Phase II trials in carefully selected children with AOM, gatifloxacin was clinically effective and eradicated infecting pathogens. Two non-comparative trials evaluated gatifloxacin oral suspension, 10 mg/kg once daily for 10 days, in children ≥6 months of age with recurrent/nonresponsive AOM defined as ≥3 documented episodes within the past 6 months or ≥4 episodes within 12 months (ROM) or failure of therapy within 14 days of enrollment (OMTF).

In one trial of 254 patients, pretreatment tympanocentesis was mandatory unless MEF was available through a new perforation. Bacteriologic response in patients with a pretreatment pathogen was based on a second tympanocentesis, if performed, or was presumptively based on the patient’s clinical response. Nasopharyngeal cultures were obtained before and after treatment. Cure rate in evaluable patients with baseline MEF pathogens was 86% and was similar among ROM or OMTF patients. In patients with S. pneumoniae in MEF, clinical cure was 84%. Pneumococci were isolated from one-third of pretreatment nasopharyngeal cultures; the eradication rate posttreatment was 55%. Penicillin susceptibility had no effect on outcome, and no selection of resistance to gatifloxacin was observed. Clinical recurrence was reported in 24 patients, although repeat tympanocentesis was not performed.

In a second trial that enrolled 160 patients, most children (81%) had recurrent AOM accompanied by a recent treatment failure. MEF cultures were obtained through tympanocentesis performed pretreatment and after 4 to 6 days of therapy. Bacteriologic success was defined by negative culture results during treatment. Additional cultures were obtained if clinical relapse occurred. A total of 121 pathogens were isolated in 89 microbiologically evaluable patients; identified were 74 H. influenzae, 36 S. pneumoniae, 9 M. catarrhalis and 2 S. pyogenes. Nearly three-fourths of the pneumococci were not susceptible to penicillin (15 fully resistant), although all were susceptible to gatifloxacin, as were all H. influenzae isolates. Bacteriologic success was achieved in 96% of patients, with eradication of all but 3 of the initial pathogens. Among 114 patients clinically evaluable at the end of treatment, 103 (90%) were cured or improved, including 21 of 23 with AOM caused by penicillin-nonsusceptible S. pneumoniae.

Overall there were 31 episodes of recurrent AOM in patients with bacteriologic eradication of MEF pathogens on Days 4 to 6. Among the 27 patients in whom tympanocentesis was performed, 16 episodes were new infections, 4 were culture-negative and 7 were true relapses established by pulsed field gel electrophoresis (3 S. pneumoniae, 3 H. influenzae, 1 M. catarrhalis). No resistance to gatifloxacin was observed among the pneumococci isolated during therapy or the 3-week follow-up period after completion of treatment, although MICs were not reported.

Fluoroquinolones and Resistance. The increasing empiric use of fluoroquinolones in adults with respiratory tract infections parallels the rise in resistance to traditional antimicrobials. Data from the SENTRY program indicate generally low rates of fluoroquinolone resistance among recent S. pneumoniae isolates, including penicillin-resistant strains.

In a Canadian study increasing pneumococcal resistance to ciprofloxacin was accompanied by reduced susceptibility to the newer 8-methoxyfluoroquinolones as well.

High level resistance to levofloxacin has increased among penicillin-resistant isolates; in one study 2.8% were resistant. A pattern of point mutations in genes coding DNA gyrase and topoisomerase IV, the bacterial targets of fluoroquinolones, was demonstrated recently among 30 levofloxacin-resistant pneumococci isolated in the United States and Canada. Multidrug resistance was prevalent, with 4 strains fully resistant to penicillin, 9 to ceftriaxone and 5 to erythromycin. Eight isolates were susceptible to moxifloxacin; the remainder showed intermediate resistance. (Gatifloxacin was not tested in that study.) Failure of empirical therapy with oral levofloxacin in patients with community-acquired pneumococcal pneumonia has been reported, including patients with no history of prior fluoroquinolone use in whom resistance developed during treatment. Non-respiratory tract pathogens have reduced susceptibility to fluoroquinolones, including SENTRY isolates of staphylococci and multidrug-resistant Gram-negative enteric bacteria causing skin and soft tissue infections in hospitalized patients.

Emergence of S. pneumoniae with reduced susceptibility to fluoroquinolones has been described worldwide. The fluoroquinolones gatifloxacin, gemifloxacin, levofloxacin and moxifloxacin are recommended for initial empiric therapy for selected outpatients with community-acquired pneumonia in the most recent guidelines from the Infectious Diseases Society of America. These guidelines caution, however, that continued misuse and overuse of fluoroquinolones may cause their demise as useful antibiotics within 5 or 10 years. Few therapeutic options are available for patients with invasive infections attributable to pneumococci that are resistant to fluoroquinolones as well as other agents.

Widespread pediatric use of fluoroquinolones could accelerate emergence of pneumococcal resistance, given that
nasopharyngeal colonization with high density populations of pneumococci occurs more often in children than in adults. Therefore pediatric use of fluoroquinolones should be cautious and restricted to AOM patients who lack other therapeutic options.

SAFETY OF FLUOROQUINOLONES IN PEDIATRICS

Fluoroquinolones are generally well-tolerated; the most frequent adverse events in adults have been gastrointestinal disturbances, dizziness, headache and skin reactions. Fluoroquinolone-induced toxic cartilage reactions in the weight-bearing joints of juvenile animals (demonstrated with all tested quinolones and fluoroquinolones) has led to concern that similar adverse events might result from their use in children.

This concern prompted the contraindication of fluoroquinolones in children, growing adolescents, pregnant women and new mothers who are lactating. This section will discuss fluoroquinolone-induced arthrotoxicity in animals and its possible mechanisms and review pediatric experiences with fluoroquinolones, including the absence of arthrotoxicity.

Quinolone Arthropathy in Animals. Fluid-filled blisters, fissures and erosions typically occur in juvenile animals after quinolone administration. Electron microscopy reveals chondrocyte necrosis and mitochondrial swelling, followed by disruption of the extracellular matrix. Animals demonstrate limping and swelling characteristic of an acute arthritis. Although lameness may resolve with continued treatment, structural changes in affected cartilage do not completely disappear.

Mechanisms of Arthropathy. Specific mechanisms responsible for quinolone arthropathy have not been elucidated, but inhibition of mitochondrial DNA replication has been proposed. A more recent explanation involves chelation of magnesium ions, which alters the function of chondrocyte surface integrin receptors. Whether the primary site of quinolone effects is in chondrocytes or in the matrix remains unknown.

Studies in Pediatric Patients. Since the mid-1980s many children have received fluoroquinolones, mainly ciprofloxacin, on a compassionate use basis as the only oral antimicrobial therapy available for difficult infections caused by multidrug-resistant organisms. These have included Pseudomonas aeruginosa infections in patients with cystic fibrosis, complicated urinary tract infections and enteric infections in developing countries. Published data suggest that prolonged therapy has been well-tolerated by pediatric patients, with no unequivocal evidence of arthropathy, bone abnormalities or other serious adverse events.

Efforts to detect arthropathy in pediatric patients treated with quinolones have included histopathologic analysis, magnetic resonance imaging (MRI) and sonography. MRI detects cartilage lesions in animals with quinolone arthropathy and has the sensitivity to detect comparable lesions in humans. Ultrasound examination of knee or hip joints allows identification of articular effusion, measurement of synovial thickness and assessment of cartilage surface and thickness.

Animal data have shown that postmortem morphologic studies represent the most sensitive way to detect or rule out cartilage damage. One of the authors (UBS) described such observations in two female patients, 7 and 13 years of age, with advanced cystic fibrosis who had died of combined respiratory and cardiac failure. During their last 3 years of life, both children had received multiple courses of oral ciprofloxacin for treatment of bronchopulmonary exacerbations caused by P. aeruginosa. Clinical examinations, laboratory studies of bone metabolism and MRI scans of the left knees had never indicated any pathologic joint changes. At postmortem examination of the left knee, light and electron microscopic studies (Figs. 3 and 4) revealed normal cartilage in each patient.

In a study of cystic fibrosis patients, 13 prepubertal (6 to 13 years of age) and 5 postpubertal (14 to 24 years of age) patients who were receiving 3-month courses of oral ciprofloxacin therapy were monitored for joint damage. Radio logic and MRI studies performed at the start and end of treatment and again 4 to 6 months later revealed no abnormalities. Serial MRI scans of the left knees demonstrated no joint effusion and intact 2-layer appearance of cartilage.

Recently a retrospective, observational study compared the risk of tendon or joint disorders from selected fluoroquinolones (ofloxacin, levofloxacin, ciprofloxacin) with that from azithromycin, a drug not known to affect cartilage or tendons in humans or animals. Information was obtained

FIGURE 3. Light micrograph of tibial articular cartilage section stained with hematoxylin and eosin from a patient (postmortem) with normal findings who received oral ciprofloxacin intermittently (total exposure, 9 months) during 3 years preceding death.
from a validated research database that encompassed 13 affiliated health plans across the United States and included more than 6000 patients <19 years of age at the time of drug prescription. The incidence of verified tendon or joint disorders within 60 days of fluoroquinolone administration was <1%, equivalent to that with azithromycin.

In summary, cartilage toxicity with fluoroquinolones is a laboratory phenomenon in juvenile animals, and no arthropathy has been unequivocally documented in the large numbers of children treated with these agents. Nevertheless expectant observation is warranted for any new quinolone use in pediatrics.

CONCLUSIONS

Further discussion and subsequent refinement of therapeutic approaches may prove beneficial in guiding physicians treating patients with AOM. For ROM or OMTF unresponsive to other antimicrobial therapy, fluoroquinolones appear to fill an unmet need. They are active in vitro against resistant strains and, in their limited role in pediatric compassionate use, have not been associated with any arthropathy, the primary safety concern in children. In view of the risk for rapid emergence of pneumococcal resistance, use of fluoroquinolones only in carefully selected pediatric patients is appropriate. The combined efforts of experts in microbiology and infectious diseases, regulatory authorities and pharmaceutical manufacturers as well as postmarketing surveillance will be required to provide rational guidelines to clinicians who may consider fluoroquinolones for children with refractory AOM.

REFERENCES


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