In Vitro Activities of Levofloxacin and Comparable Agents against Middle Ear Fluid, Nasopharyngeal, and Oropharyngeal Pathogens Obtained from Costa Rican Children with Recurrent Otitis Media or Failing Other Antibiotic Therapy

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Otitis media (OM) is the most common cause for outpatient consultation for children and one of the most common causes of antimicrobial usage in pediatrics (9). In recent years, there has been concern regarding the increment of bacterial resistance to commonly used antibiotics among pathogens isolated from the middle ear fluid (MEF), nasopharynaxes, and oropharynaxes of children with upper respiratory tract infections (2, 3, 11). Therapeutic options for children with resistant Streptococcus pneumoniae and Haemophilus influenzae are limited (1, 7).

The new fluoroquinolones have excellent in vitro activities against respiratory isolates that are resistant to current first- and second-line antibiotics (4, 6, 8, 12, 14), and recent clinical trials have suggested a potential role of these agents in the treatment of selected children with OM (5, 10).

As part of a clinical trial, Costa Rican children, 3 months to 48 months old, with OM and no history of conjugate S. pneumoniae vaccine usage from whom baseline MEF, nasopharyngeal, and oropharyngeal samples were obtained were considered candidates for this analysis. Patients also had to evidence of recurrent OM or OM failure or two of any of the following risk factors: an age of ≤24 months, occurrence of the first OM episode at ≥6 months of age, day care attendance, frequent contact with children ≤8 years of age, or antimicrobial exposure in the previous 3 months. Recurrent OM was defined as a history of three or more OM episodes in the previous 6 months or four or more episodes in the previous 12 months. OM failure was defined as persistent signs and symptoms of OM after 48 h of appropriate antimicrobial therapy or an OM episode occurring within 7 days of the last dose of an antibiotic prescribed for a previous otitis media episode (1, 2, 5, 7, 10).

The original study protocol was approved by the Institutional Review Board of the Universidad de Ciencias Médicas de Centro América. Informed consent was obtained from the parents of each study participant before inclusion in the study.

Diagnostic tympanocentesis was performed according to our standard procedures (3) for all patients who had intact tympanic membranes. For patients with a perforated tympanic membrane, a deep aspiration of the MEF was attempted. Nasopharyngeal and oropharyngeal samples were obtained before antimicrobial therapy began by means of deep insertion of nasopharyngeal and oropharyngeal swabs (Copan Diagnostics Inc., Corona, CA) before antimicrobial therapy began. Samples were transferred to the local research laboratory for processing according to our standard procedures (2, 3).

MICs were determined by Etest (epsilometer; AB Brodsk, Solna, Sweden) for penicillin, amoxicillin, cefuroxime, ceftriaxone, and levofloxacin, and the interpretation of results was performed according to NCCLS recommendations (13). In the case of trimethoprim-sulfamethoxazole (TMP-SMX), disk diffusion testing was performed and interpreted by following NCCLS recommendations (13).

Between May 2003 and February 2004, samples were obtained from 298 patients. The mean age of study participants was 19.6 months (range, 3 to 48 months), and 199 (67%) patients were less than 24 months old. MEF pathogen distributions were as follows: 74 S. pneumoniae, 84 H. influenzae, 19 Moraxella catarrhalis, and 11 Streptococcus pyogenes isolates. Beta-lactamase production was observed in 7 (8.3%) H. influenzae strains and 19 (100%) M. catarrhalis strains. The antibacterial activities of the various agents evaluated are depicted in Table 1.

Among the S. pneumoniae isolates obtained, the prevalences of strains that were susceptible, intermediate, and resistant to the indicated drugs were as follows: to penicillin, 85.1%, 6.7%, and 8.1%, respectively; to cefuroxime, 91.8%, 2.7%, and 5.4%, respectively; to ceftriaxone, 97.2%, 2.7%, and 0%, respectively; and to TMP-SMX, 14.8%, 22.9%, and 62%, respectively. To amoxicillin and levofloxacin, 100% of the isolates were susceptible. Among the strains that were intermediate (five isolates)
or resistant (six isolates) to penicillin, 100% were susceptible to levofloxacin.

Among the *H. influenzae* isolates tested, the corresponding percentages of strains that were susceptible, intermediate, and resistant to the indicated drugs were as follows: to amoxicillin, 75%, 14.2%, and 10.7%, respectively; to cefuroxime, 95.2%, 4.7%, and 0%, respectively; and to TMP-SMX, 41.5%, 12.9%, and 45.4%, respectively. To ceftriaxone and levofloxacin, 100% of the strains were susceptible. All the *S. pyogenes* isolates were susceptible to penicillin, cefuroxime, and ceftriaxone; however, 81.8% and 18.2% of the isolates were susceptible and intermediate, respectively, to levofloxacin.

A total of 344 pretherapy nasopharyngeal and/or oropharyngeal pathogens were isolated: 161 *S. pneumoniae*, 125 *H. influenzae*, 46 *M. catarrhalis*, and 12 *S. pyogenes* isolates. Beta-lactamase production was observed in 9 (7.2%) *H. influenzae* strains and 46 (100%) *M. catarrhalis* strains. The antibacterial activities of the various agents evaluated are depicted in Table 2.

Among the *S. pneumoniae* strains, the prevalences of strains that were susceptible, intermediate, and resistant to the indicated agents were as follows: to penicillin, 80.7%, 14%, and 4.6%, respectively; to cefuroxime, 91.8%, 4%, and 3%, respectively; to ceftriaxone, 97.6%, 2.4%, and 0%, respectively; and to TMP-SMX, 13.6%, 16.8%, and 69.4%, respectively. To amoxicillin and levofloxacin, 100% of the strains were susceptible. Among the strains that were intermediate (23 isolates) or resistant (7 isolates) to penicillin, 100% were susceptible to levofloxacin.

Among the *H. influenzae* isolates, the percentages of strains that were susceptible, intermediate, and resistant to the indicated agents were as follows: to amoxicillin, 78.6%, 5.9%, and 15.3%, respectively; to cefuroxime, 92.5%, 4.7%, and 0%, respectively; and to TMP-SMX, 41.5%, 12.9%, and 45.4%, respectively. To ceftriaxone and levofloxacin, 100% of the strains were susceptible. Among the *S. pyogenes* isolates tested, all the isolates were susceptible to penicillin, amoxicillin, cefuroxime, ceftriaxone, and levofloxacin.

Levofloxacin activities against MEF, nasopharyngeal, and oropharyngeal isolates that were nonsusceptible to two or more antimicrobial classes are noted in Table 3. Levofloxacin was 100% active against these resistant pathogens.

Although the current antimicrobial recommendations apply to most of the patients with OM, there is a group of children that may present with multidrug-resistant pathogens and for whom a third-line antimicrobial alternative may be needed (2, 3, 7). The percentage of resistant pathogens obtained in our study population was lower than anticipated; however, the overall activity of levofloxacin was excellent against *S. pneumoniae* and *H. influenzae*, including those isolates resistant to other commonly used agents (6, 8, 12, 15).
If, based on the results from controlled clinical trials and safety information, fluoroquinolones are approved for use in pediatric patients with recurrent OM or OM failures, baseline information about the susceptibility pattern to fluoroquinolones will be needed together with a continuous microbiological surveillance program.

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REFERENCES