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# Topical Ciprofloxacin/Dexamethasone Otic Suspension Is Superior to Ofloxacin Otic Solution in the Treatment of Children With Acute Otitis Media With Otorrhea Through Tympanostomy Tubes

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**ABSTRACT.** *Objective.* To determine the efficacy and safety of topical ciprofloxacin/dexamethasone otic suspension compared with ofloxacin otic solution in the treatment of acute otitis media with otorrhea through tympanostomy tubes (AOMT) in pediatric patients.

*Methods.* This multicenter, prospective, randomized, observer-masked, parallel-group study was conducted at 39 sites in 599 children aged  $\geq 6$  months to 12 years with an AOMT episode of  $\leq 3$  weeks' duration. The mean age of patients was 2.5 years (standard deviation: 2.37 years). Patients received either ciprofloxacin 0.3%/dexamethasone 0.1% otic suspension 4 drops twice daily for 7 days or ofloxacin 0.3% otic solution 5 drops twice daily for 10 days. Clinical signs and symptoms of AOMT were evaluated at clinic visits on days 1 (baseline), 3 (on therapy), 11 (end of therapy), and 18 (test of cure). A patient diary was used to measure time to cessation of otorrhea. Principal pretherapy pathogens included *Streptococcus pneumoniae* (16.8%), *Staphylococcus aureus* (13.0%), *Pseudomonas aeruginosa* (12.7%), *Haemophilus influenzae* (12.4%), *S epidermidis* (10.2%), and *Moraxella catarrhalis* (4.1%).

*Results.* Ciprofloxacin/dexamethasone is superior to ofloxacin for clinical cure (90% vs 78%) and microbiologic success (92% vs 81.8%) at the test-of-cure visit, produces fewer treatment failures (4.4% vs 14.1%), and results in a shorter median time to cessation of otorrhea (4 days vs 6 days). Ciprofloxacin/dexamethasone treatment is also superior to improvement in clinical response by visit, absence of otorrhea by visit, and reduction of otorrhea volume by visit. Both topical otic preparations are safe and well tolerated in pediatric patients. No change in speech recognition threshold or decrease in hearing from baseline, based on audiometric testing, was noted with either regimen.

*Conclusion.* Topical ciprofloxacin/dexamethasone treatment is superior to topical ofloxacin in the treatment of AOMT. *Pediatrics* 2004;113:e40–e46. URL: <http://www.pediatrics.org/cgi/content/full/113/1/e40>; *ciprofloxacin, dexamethasone, ofloxacin, otorrhea, AOM, tympanostomy tubes.*

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ABBREVIATIONS. AOMT, acute otitis media with otorrhea through tympanostomy tubes; CSOM, chronic suppurative otitis media; TOC, test of cure; ITT, intention-to-treat.

The most common surgery performed in children for treatment of recurrent otitis media with effusion is the insertion of a tympanostomy tube into the eardrum.<sup>1</sup> However, otorrhea is a common complication after their insertion. The vast majority (90%–95%) of cases of acute otitis media with otorrhea through tympanostomy tubes (AOMT) occur in children aged 1 to 12 years, and typically 2 to 6 episodes of AOMT are experienced.<sup>2,3</sup> Topical ciprofloxacin is an effective and safe therapy for AOMT<sup>4,5</sup> and chronic suppurative otitis media (CSOM).<sup>6–8</sup>

Bacteria commonly isolated from patients with AOMT include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*.<sup>3</sup> Because of the inflammatory response induced by these microorganisms, topical corticosteroids have often been given empirically together with topical antibiotics in an effort to reduce the sequelae. Although several studies demonstrated the efficacy and safety of antibiotic-corticosteroid combinations in the treatment or prophylaxis of AOMT,<sup>9–14</sup> definitive evidence of the benefit of adding a topical corticosteroid has not been shown in randomized, controlled trials.

Recently, we reported on the efficacy and safety of a combination of topical dexamethasone 0.1% and ciprofloxacin 0.3% in children with AOMT.<sup>15</sup> Otorrhea resolved more rapidly with the combination preparation than with ciprofloxacin alone and produced significantly greater clinical responses early after completion of a 7-day course of treatment.<sup>15</sup> The present study was designed to evaluate further the efficacy and the safety of the topical ciprofloxacin/dexamethasone combination by comparing it with the related fluoroquinolone ofloxacin administered alone in children with AOMT. Topical ofloxacin was chosen as the comparator for this study because of its reported efficacy and safety in ear infections, including AOMT,<sup>16,17</sup> CSOM,<sup>18</sup> and acute otitis externa.<sup>19</sup>

## METHODS

This study was a randomized, prospective, observer-masked, parallel-group clinical trial comparing ciprofloxacin 0.3%/dexamethasone 0.1% otic suspension to ofloxacin 0.3% otic solution in the treatment of children with AOMT.

methasone 0.1% otic suspension with ofloxacin 0.3% otic solution in children with AOMT conducted at 39 centers in the United States and Canada. The primary objectives were to 1) demonstrate that ciprofloxacin/dexamethasone is at least as effective as ofloxacin for clinical and microbiologic response at the test of cure (TOC) visit and 2) evaluate the safety and efficacy of ciprofloxacin/dexamethasone otic suspension in pediatric patients with AOMT. The study protocol was approved by independent ethics committees/institutional review boards at each investigative site and conducted in accordance with the ethical principles contained in the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all patients before enrollment.

## Patients and Medication

A total of 599 children who were aged 6 months to 12 years and had patent tympanostomy tubes and a clinical diagnosis of uncomplicated AOM with otorrhea (drainage visible to the parent or guardian) of  $\leq 3$  weeks' duration in 1 or both ears were enrolled into the study. Patients were randomized to receive either 1) topical ciprofloxacin/dexamethasone otic suspension (Ciprodex; Alcon Research, Ltd, Fort Worth, TX) 4 drops twice daily for 7 days or 2) topical ofloxacin otic solution (Floxin; Daiichi Pharmaceutical Corp, Montvale, NJ) 5 drops twice daily for 10 days. Because of the physical distinction and difference in administration schedules between the 2 treatments, the study was not double blinded, but it was observer masked such that those conducting the clinical observations were unaware of the treatment assignments.

Patients who were not eligible for enrollment included those in whom otorrhea had been present for  $>3$  weeks and those with acute or malignant otitis externa. Key differences between AOM patients who had otorrhea and were enrolled in the study compared with patients who had acute otitis externa and were excluded from the trial included the absence or presence of pain on palpation of the pinna and the degree of edema or erythema present in the external ear canal. Additional exclusions were known or suspected fungal or mycobacterial ear infections, a history of or active viral infection of the tympanic membrane, mastoiditis, or infections requiring systemic antibacterial therapy. Patients were also excluded when there was a requirement for otologic surgery (except that confined to the tympanic membrane) in the previous year or when they presented with or had a history of diabetes, immunosuppressive disorders, acute or chronic renal disease, active hepatitis, chronic nasal obstruction and/or persistent rhinorrhea, complicating structural abnormalities, known or suspected quinolone hypersensitivity, and, in girls, menarche. Patients were not permitted to receive topical (otic or ophthalmic) corticosteroids or antibiotics concurrently or within the preceding 3 days, systemic corticosteroids within the preceding 7 days, inhaled corticosteroids at doses  $\geq 800$   $\mu\text{g}/\text{d}$ , topical antibiotics for skin infections within the preceding 7 days, topical otic analgesics/anesthetics or antiseptic washes, or nonsteroidal anti-inflammatory drugs, with the exception of oral acetaminophen for relief of pain.

Eligible patients were evaluated at 4 scheduled visits: baseline (day 1), on therapy (3 + 2 days), end of therapy (11 + 2 days), and TOC (18 + 3 days). At the baseline visit, a complete clinical assessment was performed. The ear canal first was cleaned of all fluid and debris via suction, and then a culture specimen was obtained from the lumen of the tube under direct microscopic vision, paying particular attention to avoid contamination by contact with the surface of the external auditory canal. Ear cultures were taken in all patients at baseline and were repeated only in patients who were discontinued from the study as a result of treatment failure or adverse events. A specimen was obtained from the lumen of the tympanostomy tube from any patient when the physician declared a "clinical failure," regardless of the visit day. The parents or guardians were instructed in the use of patient diaries and the need for avoiding significant water immersion of the ear(s). At subsequent visits, clinical assessments were repeated to assess responses, patient diaries were reviewed, and adverse events were recorded. Audiologic evaluations, including speech reception threshold, were conducted by certified audiologists in children aged 4 to 12 years at the baseline and TOC visits.

## Efficacy Assessment

Three primary efficacy variables were selected for evaluation at the test of cure (TOC) visit. 1) Clinical response to therapy (patients who were rated as cured/resolved by the investigator) based on a 4-point scale (0, cured/resolved; 1, improved; 2, not changed; 3, worsened compared with the baseline visit). An overall clinical response of cured/resolved was defined as the absence of otorrhea at the TOC visit. Improved was defined as a significant improvement in clinical signs or symptoms compared with the baseline (day 1) visit. 2) Microbiologic response (success or failure) in patients with positive pretherapy cultures. In the event of a clinical failure (and the taking of an additional ear specimen for culture), there were several possible microbiologic outcomes: a) "microbiologic failure" as a result of the persistence of pretherapy pathogen(s), b) "microbiologic failure" as a result of superinfection (if a new pathogen was recovered during therapy), and c) "microbiologic failure" as a result of reinfection (if a new pathogen was recovered after the end of therapy). 3) Treatment failure rate based on the number of patients who were discontinued from the study because they did not respond to assigned therapy. Secondary efficacy variables included time to cessation of otorrhea as recorded twice daily in the patient's diary (0, absent; 1, present) and as assessed by the physician at each study visit (0, absent; 1, present); physicians' assessment of clinical response on a 4-point scale (0, cured/resolved; 1, improved; 2, no change; 3, worsened) by visit; and otic discharge volume (0, absent; 1, scant; 2, moderate; 3, severe) at each visit. Scant discharge was defined as a little fluid (serous, mucoid, or mucopurulent) accumulating in the anterior sulcus but the tube was still clearly visible in its entirety. Moderate discharge was defined as the anterior sulcus being full and the fluid comes to or nearly to the edge of the tympanostomy tube. Part of the tympanostomy tube may be covered with fluid. Copious discharge was defined as not being able to see the tube until fluid was aspirated from the ear canal. Fluid often recurs during the course of the examination, even after it has been suctioned.

## Safety Assessment

The safety evaluation was conducted on all patients who were randomized into the trial and received at least 1 dose of study drug. The safety analysis was based on the extent of exposure to the study drug, adverse events, and audiometry examination. The occurrence of adverse effects was assessed at each study visit and via questioning of parents or guardians during daily telephone calls relating to completion of the patient diaries. All adverse events were recorded in the patients' case report forms. Patients who experienced adverse events that, in the opinion of the investigator, presented a significant risk to their safety or well-being were withdrawn from the study. Data from the exit audiometry examinations were evaluated to determine whether any clinically significant decrease in hearing had occurred.

## Statistical Analysis

The primary statistical objective was to demonstrate that ciprofloxacin/dexamethasone was at least as effective (noninferior) as ofloxacin treatment in clinical and microbiologic response at the TOC visit. Two-sided 95% confidence intervals for the difference in proportions between the 2 treatment groups were constructed. Noninferiority was demonstrated for both variables, and the confidence interval constructed around these differences did not include 0. This result enabled statistical testing for superiority, using  $\chi^2$  tests of independence. For analysis of secondary variables, the number and proportion of patients per response in each treatment group was presented and assessed using LSMEANS (Mixed Model Analysis of Variance) or the  $\chi^2$  test as appropriate. The log-rank test (Kaplan-Meier survival analysis) was conducted to compare median time to cessation of otorrhea between the 2 treatments.

## Data Sets Analyzed

A total of 599 patients (297 in the ciprofloxacin/dexamethasone group and 302 in the ofloxacin group) were randomized to treatment and assessable for the intention-to-treat (ITT) analysis. Of these, 424 (208 in the ciprofloxacin/dexamethasone group and 216 in the ofloxacin group) were included in the modified ITT analyses in that they had received treatment, had met inclusion/exclu-

**TABLE 1.** Baseline Characteristics of the ITT Group

| Characteristic   | Ciprofloxacin/<br>Dexamethasone<br>(N = 297) | Ofloxacin<br>(N = 302) |
|------------------|--|------------------------|
| Age group        |  |                        |
| 1–23 mo          | 146 (49.2%)                                  | 148 (49.0%)            |
| 2–11 y           | 148 (49.8%)                                  | 154 (51.0%)            |
| 12–17 y          | 3 (1.0%)*                                    | 0 (0%)                 |
| Sex              |  |                        |
| Male             | 172 (57.9%)                                  | 201 (66.6%)            |
| Female           | 125 (42.1%)                                  | 101 (33.4%)            |
| Race             |  |                        |
| White            | 242 (81.5%)                                  | 244 (80.8%)            |
| Black            | 16 (5.4%)                                    | 17 (5.6%)              |
| Asian            | 0 (0%)                                       | 3 (1.0%)               |
| Hispanic         | 26 (8.8%)                                    | 28 (9.3%)              |
| Other            | 13 (4.4%)                                    | 10 (3.3%)              |
| Affected ear     |  |                        |
| Right only       | 122 (41.1%)                                  | 125 (41.4%)            |
| Left only        | 114 (38.4%)                                  | 100 (33.1%)            |
| Both             | 61 (20.5%)                                   | 77 (25.5%)             |
| Discharge volume |  |                        |
| Scant            | 34 (11.4%)                                   | 27 (9.0%)              |
| Moderate         | 146 (49.2%)                                  | 155 (51.3%)            |
| Copious          | 117 (39.4%)                                  | 120 (39.7%)            |

\* Three children aged 12 years were enrolled in the ciprofloxacin/dexamethasone group

sion criteria at baseline, and had a positive culture for bacteria on day 1. The modified per protocol data set composed a total of 357 patients (182 in the ciprofloxacin/dexamethasone group and 175 in the ofloxacin group) who received drug treatment, met inclu-

sion/exclusion criteria at baseline, were culture positive, and presented at all scheduled study visits.

## RESULTS

### Demographics

Study demographics for all 599 patients enrolled are summarized in Table 1. The mean age of all patients in the ITT data set was 2.45 years (standard deviation: 2.37 years), with a range from 6 months to 12 years. No statistically significant differences were identified between the 2 groups with respect to age, ethnicity, affected ear(s), or discharge volume. There was a difference in baseline sex, with more boys than girls randomized in both treatment groups. This imbalance was exaggerated in the ofloxacin group (67% compared with 58%;  $P = .0291$ ). However, this sex difference did not affect the outcomes of the study and is likely a spurious result that arose because of the many baseline tests that were performed. The treatment group difference in the distribution of boys and girls randomized was not seen in any of the other data sets that were analyzed for this study.

### Clinical Efficacy

Ciprofloxacin/dexamethasone treatment (90%) was superior to ofloxacin treatment (78%) for the primary efficacy variable of clinical cure at the TOC visit ( $P = .0025$ ; Table 2). There were significantly

**TABLE 2.** Clinical Efficacy

| Efficacy Variable                    | Ciprofloxacin/<br>Dexamethasone | Ofloxacin      | P Value |
|--------------------------------------|---------------------------------|----------------|---------|
| Primary efficacy                     | N = 80 (MPP)                    | N = 170 (MPP)  |         |
| Clinical cure at TOC                 | 162 (90.0%)                     | 133 (78.2%)    | .0025†  |
| Micro eradication at TOC             | 165 (92.0%)                     | 139 (81.8%)    | .0061†  |
| Treatment failures                   | 8 (4.4%)                        | 24 (14.1%)     | .0017‡  |
| Secondary efficacy                   | N = 207 (MITT)                  | N = 216 (MITT) |         |
| Median time to cessation of otorrhea | 4.0 d                           | 6.0 d          | .0209§  |
| Physicians' assessment of response   |                                 |                |         |
| Day 3                                |                                 |                |         |
| Cured                                | 64 (30.9%)                      | 38 (17.6%)     | <.0001  |
| Improved                             | 130 (62.8%)                     | 134 (62.0%)    |         |
| Unchanged                            | 9 (4.4%)                        | 35 (16.2%)     |         |
| Worsened                             | 4 (1.9%)                        | 9 (4.2%)       |         |
| Day 11*                              |                                 |                |         |
| Cured                                | 174 (84.1%)                     | 136 (63.0%)    | <.0001  |
| Improved                             | 25 (12.1%)                      | 58 (26.9%)     |         |
| Unchanged                            | 4 (1.9%)                        | 12 (5.6%)      |         |
| Worsened                             | 4 (1.9%)                        | 10 (4.6%)      |         |
| Day 18†                              |                                 |                |         |
| Cured                                | 174 (84.1%)                     | 153 (70.8%)    | .0023   |
| Improved                             | 20 (9.7%)                       | 38 (17.6%)     |         |
| Unchanged                            | 6 (2.9%)                        | 12 (5.7%)      |         |
| Worsened                             | 7 (3.4%)                        | 13 (6.0%)      |         |
| Absence of otorrhea                  |                                 |                |         |
| Day 3                                | 67 (32.2%)                      | 40 (18.5%)     | .0012‡  |
| Day 11                               | 176 (84.6%)                     | 137 (63.4%)    | <.0001‡ |
| Day 18*                              | 176 (85.0%)                     | 153 (70.8%)    | .0004‡  |
| Reduction of otorrhea volume         |                                 |                |         |
| Day 3*                               | 66 (31.9%)                      | 39 (18.1%)     | <.0001‡ |
| Day 11*                              | 175 (84.5%)                     | 136 (63.0%)    | <.0001‡ |
| Day 18†                              | 175 (85.0%)                     | 153 (70.8%)    | .0003‡  |

MPP indicates modified per protocol; MITT, modified ITT; CI, confidence interval; LS, least square.

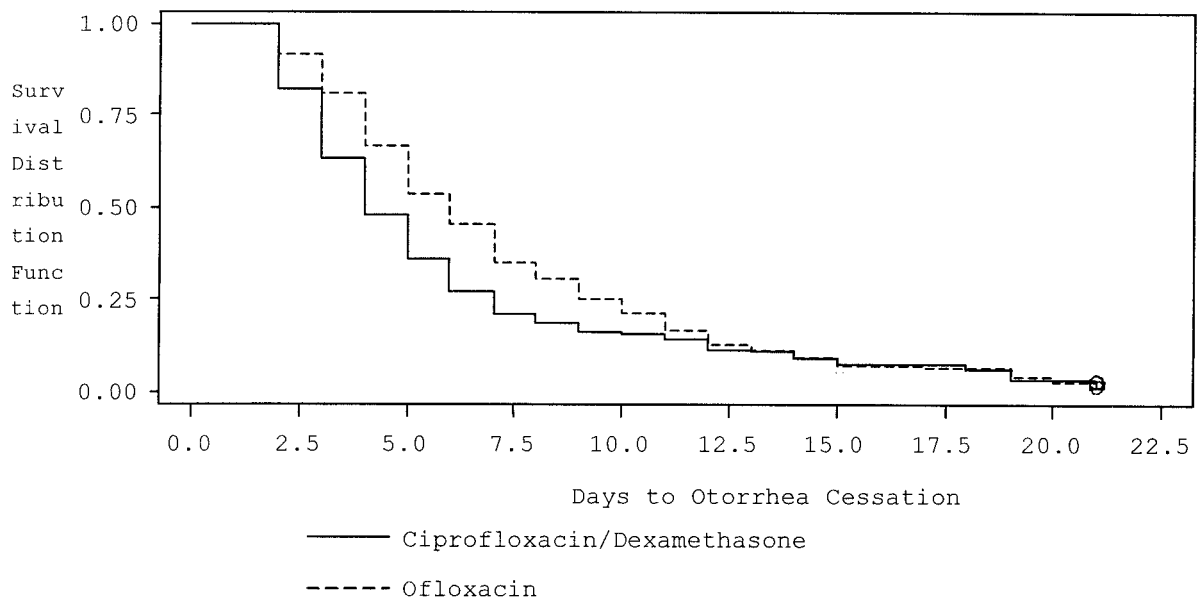
\* Data missing in 1 patient who received ciprofloxacin/dexamethasone.

† Data missing in 2 patients who received ciprofloxacin/dexamethasone.

‡  $\chi^2$  test of independence (Fisher's exact test when  $n < 5$ ).

§ Log-rank test (Kaplan-Meier survival analysis).

|| Treatment difference from LS means (mixed model analysis of variance).



**Fig 1.** Kaplan-Meier survival plot of days to cessation of otorrhea (modified ITT data set) for ciprofloxacin/dexamethasone compared with ofloxacin treatment in AOMT patients.

fewer treatment failures in patients who were treated with ciprofloxacin/dexamethasone (4%) compared with ofloxacin (14%;  $P = .0017$ ). There is a significant difference in favor of ciprofloxacin/dexamethasone (4 days) compared with ofloxacin (6 days) in the median time to cessation of otorrhea, indicating earlier resolution of AOMT in patients who were treated with the antibiotic/steroid combination compared with the single agent fluoroquinolone (Table 2, Fig 1). This difference (2 days) in favor of ciprofloxacin/dexamethasone over ofloxacin is considered to be clinically meaningful because it represents a 33% improvement in clinical response and was obtained using considerably less drug (56 drops compared with 100 drops) for a shorter time (7 days compared with 10 days). The finding is confirmed by data obtained in the physicians' assessment of clinical response at each visit, which showed significantly greater cure rates with ciprofloxacin/dexamethasone at days 3 ( $P < .0001$ ), 11 ( $P < .0001$ ), and 18 ( $P = .0023$ ; Table 2). Similar findings are also evident for the proportion of patients in whom otorrhea and otic discharge were absent at each visit (Table 2).

#### Microbiologic Efficacy

Pretherapy pathogens that were present at the baseline examination are listed in Table 3. The eradication rates of pretherapy organisms after treatment with ciprofloxacin/dexamethasone or ofloxacin are summarized in Table 4 for bacterial species with 5 or more reported cases. These data show that substantially similar rates for microbiologic success by species are obtained for either treatment. However, we note there are significantly fewer treatment failures reported for ciprofloxacin/dexamethasone compared with ofloxacin therapy. In terms of overall response, treatment with ciprofloxacin/dexamethasone was superior to ofloxacin for microbiologic eradication at the TOC visit (92% and 82%, respec-

tively;  $P = .0061$ ; Table 2). Therefore, microbiologic success favors ciprofloxacin over ofloxacin in treating AOMT infections in pediatric patients.

#### Adverse Events

The safety of ciprofloxacin/dexamethasone and ofloxacin was evaluated in 599 pediatric patients who had AOMT and were randomized to treatment and received study drug. Overall, the adverse-event profiles of ciprofloxacin/dexamethasone and ofloxacin are similar. Ciprofloxacin/dexamethasone or ofloxacin administered twice daily in the affected ears is safe and well tolerated in pediatric patients with AOMT. No serious treatment-related adverse events were reported during the study. Fewer patient discontinuations as a result of adverse events were noted in the ciprofloxacin/dexamethasone group (32 patients) compared with ofloxacin (46 patients).

Adverse events in the overall safety population all were nonserious with the exception of 3 reports unrelated to treatment (abdominal pain, pneumonia, and cellulitis). In general, adverse events were generally mild to moderate, usually resolved with or without treatment, and generally did not interrupt patient continuation in the study. Similar types of related otic and nonotic adverse events were noted in pediatric patients who were treated in both treatment groups (Table 5). No clinically relevant or statistically significant differences in mean change of speech recognition threshold from baseline or decrease in hearing from baseline were observed after treatment with either ciprofloxacin/dexamethasone or ofloxacin, based on bone and air conduction audiometry.

#### DISCUSSION

Both ciprofloxacin and ofloxacin, when used alone as topical otic preparations, are effective for the treat-

**TABLE 3.** Baseline Pretherapy Isolates

|   | Total Pretherapy Isolates | Single Isolate Count |
|---|---------------------------|----------------------|
| Total Isolates All Categories                   | 748                       | 395                  |
| <i>Staphylococcus</i>                           |                           |                      |
| <i>S aureus</i>                                 | 97                        | 62                   |
| <i>S capitis</i>                                | 1                         | 1                    |
| <i>S capitis</i> subsp. <i>capitis</i>          | 1                         | 1                    |
| <i>S capitis</i> subsp. <i>ureolyticus</i>      | 6                         | 5                    |
| <i>S caprae</i>                                 | 5                         | 1                    |
| <i>S cohnii</i>                                 | 1                         | 1                    |
| <i>S epidermidis</i>                            | 76                        | 40                   |
| <i>S haemolyticus</i>                           | 5                         | 4                    |
| <i>S hominis</i> subsp. <i>hominis</i>          | 2                         | 1                    |
| <i>S hominis</i> subsp. <i>novobiosepticus</i>  | 1                         | 0                    |
| <i>S lugdunensis</i>                            | 1                         | 1                    |
| <i>S pasteurii</i>                              | 1                         | 0                    |
| <i>S simulans</i>                               | 5                         | 4                    |
| <i>S warneri</i>                                | 6                         | 3                    |
| Group total                                     | 208                       | 124                  |
| Group percentage                                | 27.8                      | 31.4                 |
| <i>Micrococcaceae</i>                           |                           |                      |
| <i>Kocuria kristinae</i>                        | 1                         | 0                    |
| Group total                                     | 1                         | 0                    |
| Group percentage                                | 0.13%                     | 0%                   |
| <i>Coryneform bacteria</i>                      |                           |                      |
| <i>C amycolatum</i>                             | 4                         | 3                    |
| <i>C propinquum</i>                             | 3                         | 2                    |
| <i>C pseudodiphtheriticum</i>                   | 5                         | 3                    |
| <i>Corynebacterium</i> sp. nov.                 | 1                         | 0                    |
| <i>C striatum</i>                               | 4                         | 1                    |
| <i>Turicella otitidis</i>                       | 1                         | 0                    |
| Group total                                     | 18                        | 9                    |
| Group percentage                                | 2.4%                      | 2.3%                 |
| <i>Streptococcus</i> and <i>Enterococcus</i>    |                           |                      |
| <i>E faecalis</i>                               | 5                         | 1                    |
| <i>S agalactiae</i>                             | 2                         | 0                    |
| <i>S constellatus</i>                           | 1                         | 0                    |
| <i>S dysgalactiae</i> subsp. <i>equisimilis</i> | 1                         | 0                    |
| <i>S gordonii</i>                               | 1                         | 0                    |
| <i>S mitis</i>                                  | 5                         | 1                    |
| <i>S mitis</i> subsp. nov.                      | 1                         | 0                    |
| <i>S oralis</i> subsp. nov.                     | 2                         | 0                    |
| <i>S pneumoniae</i>                             | 126                       | 82                   |
| <i>S pyogenes</i>                               | 15                        | 11                   |
| <i>S salivarius</i>                             | 1                         | 0                    |
| <i>S sanguis</i>                                | 1                         | 0                    |
| <i>S viridans</i> group                         | 5                         | 0                    |
| Group total                                     | 166                       | 95                   |
| Group percentage                                | 22.2%                     | 24.1%                |

**TABLE 3.** Continued

|  | Total Pretherapy Isolates | Single Isolate Count |
|--|---------------------------|----------------------|
| <i>Bacillus</i>  |                           |                      |
| <i>B cereus</i>  | 2                         | 2                    |
| <i>B circulans</i>   | 1                         | 1                    |
| <i>B thuringiensis</i>                                       | 1                         | 1                    |
| Group total  | 4                         | 4                    |
| Group percentage   | 0.5%                      | 1.0%                 |
| <i>Pseudomonas aeruginosa</i>                                |                           |                      |
| <i>P aeruginosa</i>  | 95                        | 47                   |
| Group total  | 95                        | 47                   |
| Group percentage   | 12.7%                     | 11.9%                |
| Other Pseudomonads   |                           |                      |
| <i>P "otitidis"</i>  | 3                         | 3                    |
| <i>P orzyihabitans</i>                                       | 1                         | 0                    |
| <i>Pseudomonas</i> sp. nov.                                  | 3                         | 1                    |
| Group total  | 7                         | 4                    |
| Group percentage   | 0.9%                      | 1.0%                 |
| Enterobacteriaceae and Vibrionaceae                          |                           |                      |
| <i>Aeromonas caviae</i>                                      |                           |                      |
| <i>Citrobacter freundii</i>                                  | 1                         | 0                    |
| <i>Enterobacter cloacae</i>                                  | 2                         | 0                    |
| <i>Enterobacter hormaechei</i>                               | 1                         | 0                    |
| <i>Enterobacter hormaechei</i> subsp. nov.                   | 3                         | 2                    |
| <i>Enterobacteriaceae</i> genus nov.                         | 2                         | 0                    |
| <i>Escherichia coli</i>                                      | 10                        | 5                    |
| <i>Klebsiella oxytoca</i>                                    | 5                         | 2                    |
| <i>Klebsiella pneumoniae</i>                                 | 7                         | 0                    |
| <i>Leclercia adecarboxylata</i>                              | 1                         | 0                    |
| <i>Proteus mirabilis</i>                                     | 1                         | 0                    |
| <i>Proteus penneri</i>                                       | 1                         | 0                    |
| <i>Serratia liquefaciens</i>                                 | 1                         | 0                    |
| <i>Serratia marcescens</i>                                   | 7                         | 2                    |
| Group total  | 43                        | 11                   |
| Group percentage   | 5.8%                      | 2.8%                 |
| Nonfermentative Gram-Negative Bacteria                       |                           |                      |
| <i>Achromobacter ruhlandii</i> subsp. nov.                   | 1                         | 0                    |
| <i>Achromobacter</i> sp. nov.                                | 1                         | 1                    |
| <i>Achromobacter xylosoxidans</i> subsp. <i>xylosoxidans</i> | 3                         | 2                    |
| <i>Acinetobacter baumannii</i>                               | 4                         | 0                    |
| <i>Acinetobacter genospecies 3</i>                           | 7                         | 2                    |
| <i>Acinetobacter ursingii</i>                                | 1                         | 0                    |
| <i>Ochrobactrum anthropi</i>                                 | 2                         | 0                    |
| <i>Stenotrophomonas maltophilia</i>                          | 5                         | 2                    |
| Group total  | 24                        | 7                    |
| Group percentage   | 3.2%                      | 1.8%                 |
| Other Gram-Negative Bacteria                                 |                           |                      |
| <i>Haemophilus "alconae"</i>                                 | 13                        | 10                   |
| <i>Haemophilus "alconae"</i> subsp.                          | 1                         | 1                    |

ment of AOMT in children, with no apparent risk of ototoxicity with either agent.<sup>4,5,16,17</sup> The present study shows that the addition of the corticosteroid dexamethasone to the fluoroquinolone ciprofloxacin achieves superior rates of clinical cure and microbiologic success, results in fewer treatment failures, and provides earlier resolution of AOMT compared with treatment with the single-agent fluoroquinolone ofloxacin. In this regard, the findings confirm our earlier clinical report of ciprofloxacin/dexamethasone versus ciprofloxacin<sup>15</sup> and in experimental animal studies showing that antibiotic/dexamethasone combinations are more effective than antibiotic therapy alone in resolving otorrhea in a primate model of CSOM<sup>14</sup> and in reducing and preventing persistent middle ear mucosal changes in rats with experimental AOM.<sup>20</sup>

In the current AOMT study in children aged  $\geq 6$  months to 12 years, we show that a 7-day course of

ciprofloxacin/dexamethasone (4 drops twice daily, 56 total drops) with less total drug administered is superior to a 10-day course of ofloxacin (5 drops twice daily, 100 total drops) for clinical cure, microbial eradication, and treatment failures. Physicians' assessment of clinical response at each visit showed significantly greater cure rates with ciprofloxacin/dexamethasone at days 3, 11, and 18 (Table 2) compared with the single agent ofloxacin. In addition, ciprofloxacin/dexamethasone treatment results in a clinically significant earlier resolution of AOMT of 2 days. This finding is especially relevant because it provides a substantial advantage to the parent or caregiver of the AOMT patient by allowing an earlier return to normal activities, child care, or school. Economic benefit can be expected from caregivers' being able to return to work earlier.

The data presented in the current study demon-

**TABLE 4.** Microbiologic Response Rates by Pathogen of MPP Subjects at TOC Visit

| Pathogen               |                                   | Ciprodex Success |       | Floxin Success |       |
|------------------------|-----------------------------------|------------------|-------|----------------|-------|
|                        |                                   | N                | %     | N              | %     |
| Aerobic, Gram-positive | <i>Staphylococcus aureus</i>      | 32               | 91.4  | 30             | 93.8  |
|                        | <i>Staphylococcus epidermidis</i> | 28               | 93.3  | 20             | 95.2  |
|                        | <i>Streptococcus pneumoniae</i>   | 22               | 95.7  | 32             | 88.9  |
| Aerobic, Gram-negative | <i>Pseudomonas aeruginosa</i>     | 36               | 97.3  | 23             | 95.8  |
|                        | <i>Haemophilus influenzae</i>     | 19               | 90.5  | 24             | 92.3  |
|                        | <i>Moraxella catarrhalis</i>      | 6                | 85.7  | 7              | 87.5  |
|                        | <i>Haemophilus "alconae"</i>      | 4                | 100.0 | 2              | 100.0 |
|                        | <i>Escherichia coli</i>           | 4                | 100.0 | 0              | 0     |

**TABLE 5.** Therapy-Related Adverse Events: ITT Group

| Adverse Event              | Ciprofloxacin/<br>Dexamethasone<br>(N = 297) | Ofloxacin<br>(N = 302) |
|----------------------------|--|------------------------|
| Otic events                |  |                        |
| Pain ear                   | 7 (2.4%)                                     | 9 (3.0%)               |
| Discomfort ear*            | 10 (3.4%)                                    | 3 (1.0%)               |
| Precipitate ear†           | 2 (0.7%)                                     | 3 (1.0%)               |
| Tympanostomy tube blockage | 1 (0.3%)                                     | 0 (0.0%)               |
| Tinnitus                   | 1 (0.3%)                                     | 0 (0.0%)               |
| Infection super ear        | 0 (0.0%)                                     | 2 (0.7%)               |
| Irritation ear             | 0 (0.0%)                                     | 2 (0.7%)               |
| Pruritus ear               | 0 (0.0%)                                     | 2 (0.7%)               |
| Ear debris                 | 0 (0.0%)                                     | 1 (0.3%)               |
| Edema eardrum              | 0 (0.0%)                                     | 1 (0.3%)               |
| Hyperemia eardrum          | 0 (0.0%)                                     | 1 (0.3%)               |
| Nonotic events             |  |                        |
| Headache                   | 0 (0.0%)                                     | 1 (0.3%)               |
| Monilia oral               | 1 (0.3%)                                     | 1 (0.3%)               |
| Diarrhea                   | 0 (0.0%)                                     | 1 (0.3%)               |
| Irritability               | 2 (0.7%)                                     | 0 (0.0%)               |
| Dizziness                  | 1 (0.3%)                                     | 0 (0.0%)               |
| Crying                     | 0 (0.0%)                                     | 1 (0.3%)               |
| Cough                      | 0 (0.0%)                                     | 1 (0.3%)               |
| Erythema                   | 1 (0.3%)                                     | 0 (0.0%)               |
| Taste perversion           | 1 (0.3%)                                     | 3 (1.0%)               |

\* One patient receiving ciprofloxacin/dexamethasone and 1 patient receiving ofloxacin discontinued from the study as a result of a therapy-related event.

† Precipitate ear was described as study drug residue.

strate that ciprofloxacin/dexamethasone is clinically and microbiologically superior to ofloxacin. A review of the published clinical study of the efficacy of ofloxacin in AOMT patients tends to corroborate this conclusion. In a prospective, randomized, controlled trial comparing topical otic ofloxacin with oral amoxicillin/clavulanate potassium, no difference was noted between the 2 treatments for overall clinical cure or improvement by visit.<sup>16</sup> Clinical cure rate at the TOC visit was 89% for both treatments. Overall clinical/microbiologic eradication was also not significantly different, 77% for ofloxacin and 67% for amoxicillin/clavulanate.<sup>16</sup> Our study results for ofloxacin demonstrated similar outcomes for clinical cure (78%) and microbiologic eradication (82%) compared with 90% and 92%, respectively, for ciprofloxacin/dexamethasone treatment.

### CONCLUSIONS

Topical ciprofloxacin/dexamethasone treatment is superior to topical ofloxacin in clinical cure and microbiologic eradication, results in fewer treatment failures, provides earlier resolution of AOMT, and

gives a significantly better overall therapeutic response. Topical administration of the antibiotic/corticosteroid combination represents a significant clinical advantage over single-agent antibiotic therapy and can be expected to result in important medical and economic benefits.

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# Topical Ciprofloxacin/Dexamethasone Otic Suspension Is Superior to Ofloxacin Otic Solution in the Treatment of Children With Acute Otitis Media With Otorrhea Through Tympanostomy Tubes

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