

Topical Ofloxacin Treatment of Otorrhea in Children With Tympanostomy Tubes

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Objective: To determine the safety and efficacy of ofloxacin otic solution in the treatment of acute otorrhea in children with tympanostomy tubes.

Design: Multicenter study with an open-label, prospective ofloxacin arm and retrospective historical and current practice arms.

Setting: Ear, nose, and throat pediatric and general practice clinics and office-based practices.

Subjects: Children younger than 12 years with acute purulent otorrhea of presumed bacterial origin and tympanostomy tubes.

Intervention: Instillation of 0.3% ofloxacin, 0.25 mL, twice daily for 10 days in the prospective arm; review of medical records in the retrospective arms.

Main Outcome Measures: The primary index of clinical efficacy was absence (cure) or presence (failure) of

otorrhea at 10 to 14 days after therapy. The primary index of microbiologic efficacy (in the ofloxacin arm only) was eradication of pathogens isolated at baseline. Safety was evaluated in the ofloxacin arm only.

Results: Significantly more clinically evaluable ofloxacin-treated subjects were cured (84.4%; 119/141) than were historical practice subjects (64.2%; 140/218) ($P \leq .001$) or current practice subjects (70%; 33/47) ($P \leq .03$). All baseline pathogens were eradicated in 103 (96.3%) of 107 microbiologically evaluable ofloxacin subjects. Adverse events considered "possibly" or "probably" treatment related occurred in 29 (12.8%) of 226 ofloxacin-treated subjects.

Conclusion: Ofloxacin is safe and significantly more effective than treatments used in historical or current practice for acute purulent otorrhea in children with tympanostomy tubes.

Arch Otolaryngol Head Neck Surg. 1999;125:537-545

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BY CURRENT estimates, approximately 1 million children undergo tympanostomy tube insertions each year in the United States for the treatment of intractable middle ear effusions or repeated episodes of acute otitis media (AOM).¹ Otorrhea occurs in 21% to 34% of all such children at some time after the tubes are in place.² Unlike patients with AOM and intact tympanic membranes, children with tympanostomy tubes seldom have otalgia, fever, or other systemic signs of AOM without also having infections at other sites. Acute purulent otorrhea (draining ear) is the hallmark of AOM in the presence of tympanostomy tubes.

Not only do the presenting signs and symptoms of AOM differ between patients with and without tympanostomy tubes but there are also significant differences in microbial origin. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are the pathogens most often seen with AOM in children with-

out tubes. In those with perforated membranes, however, one also frequently finds other pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*, which probably gain access to the middle ear through the external auditory canal.^{1,3,4}

There is no standardized treatment for AOM in children with tympanostomy tubes, since the Food and Drug Administration (FDA) has approved no drug for this specific purpose and different specialties have taken different approaches to treatment. Although oral antibiotics are sometimes used, particularly by pediatricians, they have only been demonstrated to be effective in patients with intact membranes and may not be equally effective in children with tympanostomy tubes because of the different spectrum of patho-

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MATERIALS AND METHODS

STUDY DESIGN

This was a multicenter, open-label study of the treatment of AOM in subjects with tympanostomy tubes, with 1 prospective arm (the ofloxacin group) and 2 retrospective arms (the historical practice and current practice arms). The primary end point was the presence or absence of otorrhea 7 to 10 days after completion of a course of treatment.

STUDY POPULATIONS

Subjects in all 3 arms were between 1 and 12 years of age; were premenarchal if female; had patent tympanostomy tubes in the infected ear(s); and had mucopurulent or purulent otorrhea of presumed bacterial origin for less than 3 weeks. The study protocol was approved by the reviewing institutional review board, and only subjects whose parents or guardians had read and signed a written informed consent (and, where appropriate, the California Experimental Subject's Bill of Rights) were included. Exclusion criteria are outlined in **Table 1**.

Data from subjects treated with ofloxacin were acquired prospectively, whereas medical records of subjects who had been treated before initiation of the prospective arm in the same institutions were reviewed to obtain data for the historical practice group. Data for the current practice group were obtained by reviewing records of patients treated at the study centers during the time the prospective ofloxacin arm was ongoing who did not wish to or could not participate in the ofloxacin arm. These patients all met the inclusion and exclusion criteria for the trial.

STUDY MEDICATIONS

In the ofloxacin group, 0.25 mL (5 drops) of 0.3% ofloxacin was instilled twice daily for 10 consecutive days of therapy (20 doses). Thus, each dose contained 0.75 mg of ofloxacin. No adjustments in dose were permitted. During visit 1, a parent or guardian of each subject in the ofloxacin group was taught to instill ofloxacin drops, with the subject recumbent and the head in a lateral decubitus position, letting the drops fall into the auditory canal and pumping the tragus by pressing inward to improve

penetration through the tympanostomy tube into the middle ear. After instillation, the subject was to remain in the lateral decubitus position for approximately 5 minutes. Parents or guardians were to keep the subjects' ears dry for the entire study period. A treatment diary was distributed to each subject's parent or guardian.

The therapy administered to subjects in the historical practice and current practice groups was at the discretion of the treating physician. It did not include ofloxacin otic solution.

CLINICAL EVALUATION

In the ofloxacin group, subjects were evaluated at 4 points in the study: visit 1, the pretreatment or baseline visit, on day 1; visit 2, during therapy, on days 4 through 6; visit 3, after therapy, on days 11 through 13; and visit 4, follow-up evaluation, on days 17 through 20.

Baseline evaluations performed at visit 1 included a medical history and complete physical examination. At visit 2, a physical examination was performed, focusing on the skin, head and neck, ears, eyes, nose, throat, mouth, lymph nodes, and vital signs. At visit 3, the baseline physical examination was repeated and changes from baseline were noted. At visit 4, the focused physical examination of visit 2 was repeated. All subjects rated as clinical failures had visit 3 procedures performed and did not return for visit 4 evaluation.

At each visit, an investigator evaluated the clinical status of both ears for characteristics of otorrhea (absent, serous, mucopurulent, or purulent), otorrhea odor (absent or present), and degree of granulation tissue (absent, mild, moderate, or severe) and rated each with a relative numerical score. The more severely affected ear—or the right ear if both were equally affected—was designated the “target ear.” At each visit, signs of otorrhea were recorded and evaluated as representing cure (resolution of otorrhea), improvement (visits 2 and 3 only—decrease in volume of otorrhea), no change (visits 2 and 3 only—no difference from baseline otorrhea), or failure (presence of otorrhea).

The overall clinical responses were classified as cure (resolution of otorrhea: “dry ear”) or failure (presence of otorrhea: “not dry ear”). At visits 2 and 3, treatment diary entries were reviewed for treatment compliance and for parent's or guardian's degree of satisfaction with the treatment.

For analysis, subjects in the ofloxacin arm were considered clinically evaluable if they received at least 75% but not more than 120% of the 10-day treatment. Subjects were

gens commonly found when tubes are in place.^{1,5} No oral agent currently approved by the FDA for pediatric use is effective against *P aeruginosa*, and other approved agents have variable activity against *S aureus*, penicillin- and trimethoprim-sulfamethoxazole-resistant *S pneumoniae*, and β -lactamase-producing strains of *M catarrhalis* and *H influenzae*.²⁻⁴ Children who receive tympanostomy tubes for recurrent AOM have typically been treated with multiple courses of oral antibiotics and therefore may be more likely to harbor resistant organisms.⁶⁻⁸

Otolaryngologists have often opted to treat these children with a variety of ototopical or ophthalmic agents containing 1 or more antibiotics with or without corticosteroids. Neither the safety nor the efficacy of these agents has been proven when they are applied topically

in patients with otitis media who have tympanostomy tubes in the infected ears. Introduction of aminoglycoside-containing solutions to the middle ear is particularly worrisome, since these agents are known to produce ototoxic effects when administered by this route in animal models⁹ and are used topically in clinical practice to purposely induce vestibular injury, as in the case of Meniere disease.¹⁰

Ofloxacin is a broad-spectrum antibiotic of the fluoroquinolone class, which acts by inhibiting DNA-gyrase. It is available in the United States for systemic treatment of a wide variety of infections. Its coverage includes the organisms most commonly associated with AOM in the presence of an intact tympanic membrane (*S pneumoniae*, regardless of susceptibility to penicillin,

not included in the clinically evaluable population if they failed to comply with the study protocol, violated the inclusion or exclusion criteria, took any prohibited concomitant therapy, or experienced an adverse event necessitating early withdrawal. Subjects were likewise excluded from analysis if a subject with unilateral infection at baseline subsequently developed infection in the contralateral ear.

Medical records of patients in the historical practice and current practice groups were reviewed to determine whether the patients could be classified as "cure" or "failure." If the records contained insufficient information to make this evaluation, subjects were considered not clinically evaluable.

MICROBIOLOGIC AND OVERALL CLINICAL AND MICROBIOLOGIC EVALUATION

Microbiologic efficacy was evaluated by subject and pathogen for all pathogens isolated at baseline in subjects from the ofloxacin group. At baseline and when otorrhea was present at any visit, a specimen was taken from the lumen of the tympanostomy tube for bacterial and fungal cultures and Gram stain. Specimens from both ears were evaluated for all subjects with bilateral otorrhea. Aerobic, fungal, and mycobacterial cultures were performed.

Bacteria with the potential to cause otitis media, with a growth index of 2+ or greater, were considered valid pathogens. Regardless of growth index, isolates of *H influenza*, *M catarrhalis*, and *S pneumoniae* were considered valid pathogens because they are highly associated with otitis media and are not known to colonize the normal external auditory canal. The organisms listed in **Table 2** were not considered valid bacterial pathogens, regardless of growth index.

Susceptibilities of each pathogen were determined in accordance with guidelines of the National Committee for Clinical Laboratory Standards. The minimum inhibitory concentrations (MICs) of ofloxacin, amoxicillin-clavulanic acid, amoxicillin, cefaclor, trimethoprim-sulfamethoxazole, erythromycin, penicillin, and clindamycin were determined for pathogens isolated throughout the study. In addition, disk susceptibility for ofloxacin was performed on the same isolates. β -Lactamase testing by the chromogenic cephalosporin method was performed on all isolates of *H influenzae* and *M catarrhalis*.

Subjects were considered not evaluable for microbiologic response under any of the following conditions: (1)

not evaluable for clinical efficacy analysis; (2) no valid pathogen isolated at baseline; (3) no culture performed when culture source was present; (4) inappropriate culture submitted (ie, culture submitted when no source to culture was reported); or (5) no source to culture (ie, no exudate or secretion) or no pathogen isolated but a worsening of other clinical signs or symptoms relative to the baseline condition.

Overall clinical and microbiologic success was defined as either complete eradication of baseline pathogens, as documented by cultures taken at visit 4, or presumed eradication, based on sustained clinical cure without a second culture at visit 4 in the absence of a pathogen source. All other subjects evaluable for microbiologic efficacy and not classified as successes were considered clinical failures.

EVALUATION OF ADVERSE EVENTS

Safety evaluations were conducted on the entire intent-to-treat population of the ofloxacin arm, each of whom received at least 1 dose of ofloxacin. Subjects were observed, parents and guardians were questioned, and daily treatment diaries were reviewed at visits 2, 3, and 4 for any adverse events. All adverse events, regardless of whether considered drug related, were recorded. An investigator determined the relationship of each adverse event to administration of the study drug. Parent or guardian satisfaction ratings of ofloxacin treatment were gathered from the daily treatment diaries at visits 2 and 3.

STATISTICAL METHODS

Differences among treatment groups with respect to continuous variables such as age were analyzed using 1-way analysis of variance from the SAS PROC GLM (SAS Institute Inc, Cary, NC) test procedure. Mean statistics were given and frequency counts presented for remaining continuous and categorical variables, respectively. Comparisons among treatment groups of age group, sex, and summarized clinical responses were analyzed using the χ^2 test from the SAS PROC FREQ (SAS Institute Inc) test procedure. The paired *t* test was used to examine changes from baseline and subsequent visits in mean scores for the signs and symptoms of otorrhea. The Stuart-Maxwell test was used to analyze shifts from baseline for the number of subjects with each clinical sign and symptom score.

and *H influenzae* and *M catarrhalis*, regardless of β -lactamase status) and AOM in the face of a tympanostomy tube (*P aeruginosa* and *S aureus*). Systemic use of ofloxacin has been limited in children because of the observation that quinolones, when administered systemically, may have an adverse effect on the development of weight-bearing joints in juvenile animals.

A new topical otic formulation of ofloxacin was designed to provide high local levels of ofloxacin in the middle ear. Minimal systemic levels were anticipated after otic administration, since the total administered dose is very low (1.5 mg/d per ear) and maximum serum levels after administration to adults with tympanostomy tubes are in the nanogram range.¹¹ This minimizes the risk of adverse events generally associated with systemic ad-

ministration of quinolones. Ofloxacin has near neutral pH and was shown in an animal study to not irritate the middle ear mucosa or cause ototoxic effects at the concentration studied (0.5%).⁹

Because no topical agent was approved for use in treating middle ear infections at the time this study was designed, the ofloxacin arm was conducted as an open-label trial. Furthermore, relatively few data were available in the medical literature for predicting expected cure rates with commonly used therapies. A retrospective review of records from historical and concurrent clinical practices was performed to give perspective on cure rates achieved with regimens that had been used in clinical practice in the settings where the open trial was conducted.

Table 1. Criteria for Exclusion From the Study

Prior medical history
In the target ear
Otorrhea for ≥ 3 weeks
Otologic surgery other than tympanostomy tube placement in previous year
History of cholesteatoma or mastoid surgery
Use of antiseptic otic washes (acetic acid, boric acid, etc) within 5 days before study entry (ofloxacin group only)
In general
Exposure to any investigational agent within 90 days before study entry
Current medical history
In the target ear
Visible drainage surrounding the tympanostomy tube and no drainage through the lumen of the tube (ofloxacin group only)
Known or suspected mycobacterial infection
Known fungal infection without other identifiable pathogens
Known or suspected cholesteatoma
In general
Condition or disease, such as chronic sinusitis or otitis external, that could interfere with evaluation of study drugs
Known (positive rapid streptococcus test result from oropharynx) or suspected (fever, pharyngitis, etc) middle ear infection caused by group A streptococci (ofloxacin group only)
Requirement for systemic antibiotic therapy for other infections (due to fever, pharyngitis, etc), as judged by the investigator (except the current practice group)
Current chemotherapy for cancer
Concurrent disease not stable for at least 2 weeks
Known allergy to quinolones or the preservative benzalkonium chloride (ofloxacin group only)
Known immunocompromise or positive HIV serologic test result (HIV testing was not required)*
Known acute or chronic renal insufficiency or hepatitis
High likelihood of death during study (ofloxacin group only)
Prior or current use of an antibiotic (ofloxacin group only)
Received 1 of the following systemic antibiotics within 24 hours of enrollment:
Ampicillin
Amoxicillin
Amoxicillin clavulanate
Cefaclor
Chloramphenicol palmitate
Dicloxacillin
Erythromycin
Penicillin V potassium
Received 1 of the following systemic antibiotics within 72 hours of enrollment:
Cefixime
Ciprofloxacin
Doxycycline
Minocycline
Tetracycline
Trimethoprim-sulfamethoxazole
Received any other systemic or topical antibiotic within 7 days of enrollment, except topical antibiotics taken for acne in a stable dose on a long-term basis for at least 7 days before study entry
Other (ofloxacin group only)
Required informed consent papers (approved by the reviewing institutional review board) not signed by the subject's parent or guardian
Parent or guardian not considered reliable or capable of complying with administration of medication as instructed, with scheduled appointments, or other aspects of the study protocol
Subject related to investigator or other study site personnel

* HIV indicates human immunodeficiency virus.

Table 2. Organisms Not Considered Pathogens Regardless of Growth Index

<i>Acinetobacter</i> species
<i>Aerococcus</i> species
<i>Agrobacterium radiobacter</i>
<i>Alcaligenes denitrificans</i>
<i>Alternaria</i> species
<i>Aspergillus flavus</i> , <i>A fumigatus</i> , <i>A glaucus</i> , <i>A niger</i> , <i>A terreus</i> , <i>A versicolor</i>
<i>Bacillus</i> species
<i>Bipolaris</i> species
<i>Candida albicans</i> , <i>C glabrata</i> , <i>C guilliermondia</i> , <i>C humicola</i> , <i>C lusitaniae</i> , <i>C parapsilosis</i> , <i>C paratropicalis</i> , <i>C tropicalis</i>
Coagulase-negative: <i>Staphylococcus</i> species
<i>Corynebacterium</i> species
<i>Eikenella corrodens</i>
<i>Enterococcus avium</i>
Fungus; sterile hyphae
<i>Fusobacterium necrophorum</i>
<i>Haemophilus parainfluenzae</i>
<i>Lactobacillus</i> species
<i>Micrococcus</i> species
<i>Neisseria subflava</i>
<i>Pasteurella multocida</i>
<i>Penicillium</i> species
<i>Peptostreptococcus anaerobius</i> , <i>micros</i>
<i>Prevotella loeschii</i>
<i>Staphylococcus S auricularis</i> , <i>S epidermidis</i> , <i>S haemolyticus</i> , <i>S hominis</i> , <i>S simulans</i> , <i>S agalactiae</i> , <i>S equi</i> , <i>S equismilis</i> , <i>S pyogenes</i> , <i>S sangius II</i> , <i>S viridans</i>
<i>Streptomyces</i> species
<i>Synecephalastrum</i> species
<i>Trichosporon pullulans</i>
Yeast

RESULTS

A total of 226 subjects were enrolled in the ofloxacin group, 309 subjects in the historical practice group, and 68 in the current practice group (at 24 centers). Eighty-three subjects in the ofloxacin group were excluded from the clinically evaluable population, chiefly for violations of protocol or exclusion criteria, leaving 143 clinically evaluable subjects. Thirty-seven clinically evaluable subjects were excluded from the microbiologically evaluable population, primarily because of no baseline pathogen, leaving 107 microbiologically evaluable subjects. Reasons for exclusion from evaluable populations are summarized in **Table 3**. Of those qualified for the historical practice group, 218 had follow-up outcomes in their records. Follow-up outcomes were recorded for 47 subjects in the current practice group. Subject enrollment and evaluable populations are listed in **Table 4**.

Demographic characteristics of the ofloxacin group were similar to those of the other 2 treatment groups with respect to age and sex. The mean age in the ofloxacin group was 3.6 years. In each study population, there were more male subjects than female subjects. In the ofloxacin group, AOM infections were mainly unilateral (81%) at baseline. Demographic and baseline characteristics of clinically evaluable ofloxacin-treated subjects are given in **Table 5**. The numbers of organisms and valid pathogens isolated at baseline from otorrhea specimens of

Table 3. Reasons for Exclusion of Ofloxacin-Treated Subjects From Evaluable Populations

Reason for Exclusion	No. (%) of Subjects
Total Intent-to-Treat Population	226
Excluded From Clinically Evaluable Population	83 (37)
Took prohibited medication	15 (7)
Group A streptococci found*	12 (5)
Did not meet inclusion and exclusion criteria	11 (5)
Postbaseline bilateral infection	11 (5)
Protocol noncompliance	10 (4)
Fungus found	5 (2)
Discontinued for other reason	15 (6)
Lost to follow-up	4 (2)
Total Clinically Evaluable Population	143 (63)
Excluded From Microbiologically Evaluable Population	36 (16)
No valid baseline pathogen	28 (12)
Out of visit 3 window†	4 (2)
Source present but culture not done	3 (1)
No culture source but symptoms persist	1 (0.4)
Total Microbiologically Evaluable Population	107 (47)

*Subjects in whom group A streptococci were cultured were excluded because they might require systemic antibiotic therapy.

†Visit 3 window is from 8 hours after last dose to day 16.

microbiologically evaluable ofloxacin-treated subjects are summarized in **Table 6**.

CLINICAL RESPONSE

At visit 3, significant improvement ($P < .001$) in mean baseline scores for otorrhea characteristics and otorrhea odor was experienced by 95% and 98%, respectively, of subjects in the ofloxacin group ($n = 142$). A clinical cure was achieved by 93.1% of 130 ofloxacin-treated subjects evaluated at visit 4. Clinical responses to ofloxacin at each visit after initiation of therapy are listed in **Table 7**.

An overall clinical cure ("dry ear") was achieved by 84.6% of 143 clinically evaluable subjects in the ofloxacin group. Of the 218 subjects in the historical practice group with a follow-up visit, 64.2% achieved a clinical cure. Of the 47 subjects in the current practice group with a follow-up visit, 70% had a clinical cure. Incidence of cure was significantly higher in the ofloxacin group than in either the historical practice ($P < .001$) or the current practice ($P = .03$) groups. The overall clinical responses by treatment group are listed in **Table 8**.

For the ofloxacin group intent-to-treat population ($n = 226$), most subjects' parents or guardians were either "satisfied" or "very satisfied" with treatment at visits 2 (85.0%) and 3 (80.0%). Incidence of either "dissatisfied" or "very dissatisfied" was 4.4% at visit 2 and 8.0% at visit 3.

MICROBIOLOGIC RESPONSE

A total of 107 subjects in the ofloxacin group were microbiologically evaluable. No microbiologic evaluations were conducted for subjects in the retrospective arms of the study. Demographic characteristics of the microbiologically evaluable subjects were similar to those of the clinically evaluable subjects with respect to age and sex.

Table 4. Subject Enrollment and Evaluable Populations

	Ofloxacin	Historical Practice	Current Practice
Enrolled/intent-to-treat	226	309	68
Clinical evaluation			
Follow-up outcome in record	...	218	48
Clinically evaluable	143	218	47
Microbiologically evaluable	107

*Ellipses indicate not applicable.

Table 5. Demographic and Baseline Characteristics of Clinically Evaluable Subjects

Characteristics	Ofloxacin (n = 143)	Historical Practice (n = 309)	Current Practice (n = 68)
Age, y			
Mean \pm SD	3.6 \pm 2.7	3.6 \pm 2.5	3.7 \pm 2.5
<2, No. (%)	51 (36)	104 (34)	24 (36)
2-12, No. (%)	92 (64)	205 (66)	43 (64)
Sex, No. (%)			
Male	89 (62)	175 (57)	45 (67)
Female	54 (38)	134 (43)	22 (33)
Race/ethnic origin, No. (%)			
White	117 (82)
Black	12 (9)
Hispanic	8 (6)
Other	6 (4)
Duration of tube, mean, d			
Placement	307.3
Drainage	4.7

*Ellipses indicate not applicable.

Table 6. Baseline Microbiology of Microbiologically Evaluable Subjects in the Ofloxacin Group

No. of Isolates	Incidence in Subjects, No. (%) (n = 107)
Organisms	
1	38 (36)
2	32 (30)
3	27 (25)
≥ 4	10 (9)
Valid pathogens	
1	67 (63)
2	28 (26)
≥ 3	12 (11)

Characteristics of pathogens isolated at baseline in microbiologically evaluable subjects are reported in **Table 9**. Distribution of target-ear baseline pathogens according to subjects' ages is outlined in **Table 10**.

Eradication of baseline pathogens occurred in 96.3% ($n = 107$) of microbiologically evaluable subjects in the ofloxacin group. *Pseudomonas aeruginosa* persisted in 2 microbiologically evaluable subjects, *S pneumoniae* persisted in 1 subject, and a superinfection—eradication of baseline pathogens with the presence of a new pathogen (*P aeruginosa*)—occurred in 1 subject.

Table 7. Clinical Responses in Clinically Evaluable Ofloxacin Group*

Visit	Response	Incidence, No. (%)
2	Clinical improvement	127 (90.7)
	No clinical change	12 (8.6)
	Clinical failure	1 (0.7)
	Total No. of subjects	140
3	Clinical improvement	128 (90.1)
	No clinical change	1 (0.7)
	Clinical failure	13 (9.2)
	Total No. of subjects	142 (100)
4	Clinical cure	121 (93.1)
	Clinical failure	9 (6.9)
	Total No. of subjects	130 (100)
Overall	Cure (dry ear)	121 (84.6)
	Failure (not dry ear)	22 (15.4)
	Total No. of subjects	143 (100)

*Subjects could be clinically evaluable without visit 2. Subjects in whom treatment failed at visit 2 or visit 3 had procedures performed and did not return for visit 4.

Table 8. Overall Clinical Response by Treatment Group

	No. (%)		P
	Cure/ Dry Ear	Failure/ Not Dry Ear	
Ofloxacin group (n = 141)	119 (84)	22 (16)	<.001
Historical practice (n = 218)	140 (64)	78 (36)	
Current practice (n = 47)	33 (70)	14 (30)	

One hundred sixty isolates of 17 valid pathogenic species were cultured from baseline otorrhea specimens from microbiologically evaluable subjects in the ofloxacin group. The most common valid pathogens (and number of isolates) isolated at baseline were *P aeruginosa* (34), *H influenzae* (30), *S pneumoniae* (29), *S aureus* (26), and *M catarrhalis* (15).

Of the 160 valid pathogens isolated at visit 1, 156 were sensitive to ofloxacin. Two isolates had intermediate sensitivity (*P aeruginosa* and *Enterococcus faecium*), 1 was resistant to ofloxacin (*P aeruginosa*), and 1 acquired resistance to ofloxacin (*P aeruginosa*). Of these 4 isolates, only 1 with intermediate sensitivity (*E faecium*) was among the 20 isolated from subjects who experienced an overall clinical failure. Pathogen eradication was achieved for all but 2 (*P aeruginosa* and *S pneumoniae*) of the other 19 pathogens that were sensitive to ofloxacin and isolated from subjects who experienced an overall clinical failure.

Forty percent of the baseline *H influenzae* and 93% of *M catarrhalis* isolates in the microbiologically evaluable population were shown to produce β -lactamase. Incidence of clinical cure was 92% and 80% in subjects infected with a β -lactamase-producing isolate of *H influenzae* and *M catarrhalis*, respectively.

Ten percent (n = 3) of the baseline *S pneumoniae* isolates were highly resistant to penicillin (MIC ≥ 4), 21% (n = 6) were intermediately sensitive to penicillin, and 28% (n = 8) were resistant to trimethoprim-sulfamethoxazole. Two of the 3 subjects infected with a highly penicillin-

Table 9. Characteristics of Pathogens Isolated at Baseline

Condition	Count, No. (%) (n = 160)
Susceptibility to ofloxacin	
Sensitive	156 (97.5)
Intermediate*	2 (1.3)
Resistant†	1 (0.7)
Acquired resistance†	1 (0.7)
Production of β -lactamase	
<i>Haemophilus influenzae</i> (n = 30)	12 (40)
<i>Moraxella catarrhalis</i> (n = 15)	14 (93)
Susceptibility to penicillin <i>Streptococcus pneumoniae</i> (n = 29)	
Sensitive (minimum inhibitory concentration ≤ 0.12 μ g/mL)	20 (69)
Intermediate	6 (21)
Resistant (minimum inhibitory concentration ≥ 4 μ g/mL)	3 (10)
Susceptibility to trimethoprim-sulfamethoxazole <i>S pneumoniae</i> (n = 29)	
Sensitive (minimum inhibitory concentration $\leq 2/38$ μ g/mL)	16 (55)
Intermediate	5 (17)
Resistant (minimum inhibitory concentration $\geq 8/152$ μ g/mL)	8 (28)

**Pseudomonas aeruginosa*, *Enterococcus faecium*.

†*Pseudomonas aeruginosa*.

resistant isolate were clinically cured, all 6 subjects with an isolate intermediately sensitive to penicillin were clinically cured, and 7 of the 8 infected with a trimethoprim-sulfamethoxazole-resistant isolate were clinically cured.

Two isolates of *P aeruginosa* and 1 isolate of *S pneumoniae* persisted in otorrhea specimens from the target ear of subjects at visit 4. All 157 other baseline isolates were eradicated at visit 4 by ofloxacin therapy. The correlation of clinical cure with pathogen eradication is presented by pathogen in **Table 11** and by subject in **Table 12**.

OVERALL CLINICAL AND MICROBIOLOGIC EVALUATION

Eradication of all baseline pathogens was achieved in 103 (96.3%) of 107 microbiologically evaluable subjects, 92 of whom had complete resolution of otorrhea. In the microbiologically evaluable population, therefore, the incidence of overall clinical and microbiologic success was 86.0% (92/107).

The 4 subjects with overall clinical and microbiologic failure had the following combined microbiologic-clinical responses at the follow-up visit: 1 subject had persistence of a baseline pathogen at visit 3 but absence of otorrhea at visit 4, 2 subjects had persistence of a baseline pathogen and presence of otorrhea, and 1 subject had a superinfection and presence of otorrhea.

INCIDENCE OF ADVERSE EVENTS

Approximately half the subjects (53.1%) in the ofloxacin arm experienced at least 1 adverse event during the study, most commonly rhinitis, fever, vomiting, cough-

Table 10. Distribution of Baseline Target-Ear Pathogens by Age of Subject

Organisms	Age, y							Total
	≤1	2	3	4	5	6	>6	
<i>Haemophilus influenzae</i>	16	8	4	0	1	1	0	30
<i>Moraxella catarrhalis</i>	8	4	3	0	0	0	0	15
<i>Pseudomonas aeruginosa</i>	5	7	5	4	5	1	7	34
<i>Staphylococcus aureus</i>	4	2	4	3	2	2	9	26
<i>Streptococcus pneumoniae</i>	12	8	5	0	3	1	0	29
All others	7	5	3	3	2	6	0	26
Total	52	34	24	10	13	11	16	160

ing, and rash. Most of these events were mild or moderate in severity and unrelated to the study medication. Only 7 subjects (3%) experienced adverse events characterized by investigators as severe, and only 1 such event, vomiting, was reported in more than 1 subject. Six subjects stopped taking study medication because of adverse events, including pharyngitis, bronchitis, fever, pain, paraesthesia, and otitis externa, but none of these was treatment related. Subjects were required to stop taking study medication if they experienced an adverse event that necessitated administration of another antimicrobial agent.

Twenty-nine subjects (12.8%) experienced adverse events that investigators determined to be either possibly or probably related to the study drug, most of which were mild to moderate in severity. Only 3 subjects (1%) experienced treatment-related adverse events considered severe by investigators—halitosis, taste distortion, and rash. All possible and probable treatment-related adverse events that occurred in more than 1 subject are listed in **Table 13**.

There were no clinically significant changes in subjects' vital signs during the study or any deaths within a month's observation period following the study.

COMMENT

This study compared outcomes in prospectively treated subjects receiving ofloxacin with those recorded in retrospectively reviewed records of a historically treated group and a current group of subjects not participating in the prospective arm of the trial.

A study design using historical and standard practice controls was chosen because there were no antimicrobial eardrops available that had been approved for use by the FDA. This consideration, coupled with ethical concerns about using aminoglycosides topically in the ear with an attendant risk of ototoxic effects, eventuated in the final study design.

Analysis of the overall clinical response of clinically evaluable ofloxacin-treated subjects demonstrated that 0.25 mL of ofloxacin twice daily was more effective in treating the signs and symptoms of AOM in children with tympanostomy tubes than either historical practice or current practice treatments.

The outcome of dry ear at follow-up was used to compare clinical efficacy among the 3 treatment arms. Significantly more clinically evaluable subjects treated with ofloxa-

Table 11. Microbiologic and Clinical Response by Pathogen

Pathogen (Isolates)	Microbiologic Response, %		Clinical Response, %	
	Eradication	Persistence	Cure	Failure
<i>Pseudomonas aeruginosa</i> (n = 34)	94 (n = 32)	6 (n = 2)	88 (n = 30)	12 (n = 4)
<i>Haemophilus influenzae</i> (n = 30)	100 (n = 30)	0	83 (n = 25)	17 (n = 5)
<i>Streptococcus pneumoniae</i> (n = 29)	97 (n = 28)	3 (n = 1)	83 (n = 24)	17 (n = 5)
<i>Staphylococcus aureus</i> (n = 26)	100 (n = 26)	0	96 (n = 25)	4 (n = 1)
<i>Moraxella catarrhalis</i> (n = 15)	100 (n = 15)	0	87 (n = 13)	13 (n = 2)

cin had achieved dry ear at follow-up (84.4%; 119/141) than had historical practice subjects (64.2%; 140/218) ($P < .001$) or current practice subjects (70%; 33/47) ($P < .03$).

The current practice arm had relatively few subjects because most patients seen during the prospective enrollment period chose to enter the prospective arm. Moreover, only records of patients seen during the period of the prospective study (about 20 months) were eligible for the current practice arm, whereas records for the historical practice arm could be searched retrospectively for up to 4 years.

Only historical practice and current subjects whose medical records contained information about treatment outcomes were considered clinically evaluable and were analyzed (Table 8). To avoid bias (subjects more likely to return if outcomes were poor), 2 attempts were made to contact subjects with record of treatment outcome in order to obtain their recollection of outcome. If a subject could not be reached, outcome was assumed to be failure. If a subject could not remember the outcome, it was assumed to be dry ear. Fifty-three of 91 historical practice subjects and 17 of 20 current practice subjects without recorded follow-up were successfully contacted, and all contacted except 2 (both historical practice) remembered outcomes. Analysis of subjects with and without recorded follow-up demonstrated that 60.5% of historical practice and 70.6% of current practice subjects had an outcome of dry ear. Thus, including the best available outcome data on subjects with no record of follow-up does not substantively alter the conclusions of the trial.

Table 12. Microbiologic and Clinical Response by Subject (Ofloxacin Arm)

Visit	Clinical Response	Microbiologic Response, No. of Subjects			Total No. of Subjects
		Eradication	Persistence	Superinfection	
3	Improvement	96	1	0	97
	No change	1	0	0	1
	Failure	5	2	1	8
	Total	102	3	1	106
4	Cure	93	0	0	93
	Failure	6	0	0	6
	Total	99	0	0	99
Overall	Clinical cure	92	1	0	93
	Clinical failure	11	2	1	14
	Total	103	3	1	107

Table 13. Treatment-Related Adverse Events Occurring in 2 or More Subjects (Ofloxacin Arm)

Event	Total No. (%)
Auditory	
Earache	5 (2)
Otorrhagia	3 (1)
Tinnitus	2 (1)
Special senses	
Taste distortion	5 (2)
Skin	
Rash	3 (1)
Whole body	
Fever	2 (1)
Nervous system	
Paresthesia	2 (1)

Overall, ofloxacin eradicated pathogenic organisms related to acute purulent otorrhea in 96.3% of microbiologically evaluable subjects. The most frequently isolated pathogens were *P aeruginosa* (34 isolates), *H influenzae* (30 isolates), *S pneumoniae* (29 isolates), *S aureus* (26 isolates), and *M catarrhalis* (15 isolates). This reflects the dual pathogenesis of AOM in children with tympanostomy tubes, with pathogens entering the middle ear both from the external auditory canal and from the pharynx via the eustachian tube.

Otic preparations have traditionally been formulated as very acidic solutions and suspensions.¹² Acidic solutions are known to inhibit the survival and growth of *P aeruginosa* and fungi. In the current trial, however, at near-neutral pH, ofloxacin was effective in eradicating *P aeruginosa* in 94% of subjects. Fungus was isolated in only 2%, thus proving to be an unusual organism in this setting. Whether these fungi were pathogens or mere colonizers remains unclear, although the fact that no patient required antifungal therapy argues that they were colonizers. There is no rationale, therefore, for subjecting patients to the burning and discomfort—and the attendant risk of decreased compliance—that result from the use of acidic ototopical agents.

This study also demonstrates that the pathogens associated with this disease vary with age of the patient. While *S aureus* and *P aeruginosa* occur in all age groups, infection with *H influenzae*, *M catarrhalis*, and *S pneumoniae* are unusual after the age of 3 years.

Topical administration of ofloxacin is likely to result in extremely high levels of drug at the site of infection, which may contribute to the high eradication rates and low observed incidence of treatment-emergent resistance in this study. One pathogen, a *P aeruginosa* isolate that was initially intermediate in susceptibility (MIC 4 µg/mL of ofloxacin), acquired resistance (MIC 8 µg/mL of ofloxacin). Since a 2-fold increase in MIC is within the range of error for serial 2-fold dilution methods, it is unclear whether this observed change represents a real change in MIC or a true incident of acquired resistance.

Others have substantiated the finding that topical medications do not lead to resistance. In 1982, the FDA said it was “unaware of any evidence that . . . topical antibiotics . . . have led to an increase in infection in the general population by resistant organisms. . . . The agency believes that if the development were a problem . . . it would have been known by now.”¹³ Furthermore, Dohar et al¹⁴ showed in a prospective study that nearly all aural isolates of *P aeruginosa* were sensitive to polymyxin B, despite its presence in a mixture of bacitracin zinc, hydrocortisone, neomycin sulfate, and polymyxin B sulfate (Cortisporin; Burroughs Wellcome, Triangle Park, NC), which has been used widely since the 1970s. Therefore, resistance concerns that have emerged with respect to the use of fluoroquinolones systematically do not apply to their use topically, provided effective topical delivery of the drug is achieved to the target organ.

Incidence of penicillin-resistant and trimethoprim-sulfamethoxazole-resistant *S pneumoniae* and that of β-lactamase-positive *H influenzae* and *M catarrhalis* confirm that this study population was infected with pathogens that probably would be resistant to many commonly used systemic antibiotics. Of the 160 baseline pathogens identified in the microbiologically evaluable population, 156 (97.5%) were susceptible to ofloxacin.

Clinical cure was achieved in 3 of the 4 subjects infected with pathogens of intermediate sensitivity or resistance to ofloxacin. Only 1 subject, who was infected with the pathogen *E faecium* with intermediate susceptibility to ofloxacin, experienced a clinical failure. Since this clinical failure was not predicted by in vitro susceptibility and resistance patterns, clearly other factors must have been responsible.

There was a low incidence of treatment-related adverse events, and these events were generally mild. Only

3 subjects (1%) experienced a treatment-related adverse event that was considered severe (halitosis, altered taste perception, and rash). The efficacy and safety results of this trial support the assertion that topical administration of this broadly effective antibiotic results in excellent clinical and microbiologic outcomes with few systemic toxic effects.

The management of otorrhea in children with indwelling tympanostomy tubes presents a dilemma for pediatricians and other specialists. As reported in this and other studies,¹⁵⁻¹⁷ *P aeruginosa* is the most frequently isolated etiologic agent in otorrhea in children with tympanostomy tubes and is common in all age groups. Systemic antibiotics that possess activity against *P aeruginosa*, notably members of the fluoroquinolone class, are not approved for use in children in the United States. Although ototopical therapy for these patients is appealing, otic solutions containing aminoglycosides may lead to ototoxic effects when used in patients with nonintact tympanic membranes. Ototoxic effects due to aminoglycoside-containing solutions administered to the middle ear have been reported in animal studies and are suspected to occur after ototopical therapy in humans with perforated tympanic membranes.^{18,19}

The results of this study show that 0.3% ofloxacin otic solution provides a safe and effective therapy for children with tympanostomy tubes and AOM. It was significantly more effective than treatments used in the historical practice group. Cultured otorrhea specimens demonstrated that ofloxacin has excellent coverage in vitro and in vivo against pathogens commonly encountered in children with AOM and more commonly associated with otitis externa. Study results also show that 0.3% ofloxacin can be instilled twice daily without frequent or serious adverse events.

Because the total daily dose of ofloxacin administered is only 1.5 mg, systemic toxic effects associated with quinolone use were considered unlikely and were not observed in this study. Thus, topical therapy with ofloxacin otic solution makes the antibacterial spectrum of a quinolone available to children with this disorder without the associated risks.

In light of currently available therapies and the clinical performance of this agent, ofloxacin otic solution would seem to offer a safe and effective new option for the treatment of AOM in children with tympanostomy tubes.

Accepted for publication December 7, 1998.

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REFERENCES

1. Nelson JD. Chronic suppurative otitis media. *Pediatr Infect Dis J*. 1988;7:446-448.
2. Force RW, Hart MC, Plummer SA, et al. Topical ciprofloxacin for otorrhea after tympanostomy tube placement. *Arch Otolaryngol Head Neck Surg*. 1995;121:880-884.
3. Cantor RM. Otitis externa and otitis media: a new look at old problems. *Emerg Med Clin North Am*. 1995;13:445-455.
4. Dohar JE, Kenna MA, Wadowsky RM. Therapeutic implications in the treatment of aural *Pseudomonas* infections based on in vitro susceptibility patterns. *Arch Otolaryngol Head Neck Surg*. 1995;121:1022-1025.
5. Supiyaphun P, Chochoipanichnon L, Tonsakulrungruang K, et al. The treatment of chronic suppurative otitis media and otitis externa with 0.3 percent ofloxacin otic solution: a clinico-microbiologic study. *J Med Assoc Thai*. 1995;78:18-21.
6. McCracken GH. Emergence of resistant *Streptococcus pneumoniae*: a problem in pediatrics. *Pediatr Infect Dis J*. 1995;14:424-428.
7. Leibovitz E, Raiz S, Piglansky L, et al. Resistance pattern of middle ear fluid isolates in acute otitis media recently treated with antibiotics. *Pediatr Infect Dis J*. 1995;14:463-469.
8. Rodriguez WJ, Schwartz RH, Thorne MM. Increasing incidence of penicillin- and ampicillin-resistant middle ear pathogens. *Pediatr Infect Dis J*. 1995;14:1075-1078.
9. Barlow DW, Duckert LG, Krieg CS, Gates GA. Ototoxicity of topical antimicrobial agents. *Acta Otolaryngol (Stockh)*. 1995;115:231-235.
10. Monsell EM, Cass SP, Rybak LP. Therapeutic use of aminoglycosides in Meniere's disease. *Otolaryngol Clin North Am*. 1993;26:737-746.
11. Ohyama M, Furuta S, Ueno K, et al. Ofloxacin otic solution in patients with otitis media. *Arch Otolaryngol Head Neck Surg*. 1999;125:337-340.
12. *Cortisporin Otic Solution and Cortisporin Otic Suspension: Material Safety Data Sheet*. Bristol, Tenn: Monarch Pharmaceuticals Inc; 1998.
13. Langford JH, Benrimoj SI. Clinical rationale for topical antimicrobial preparations. *J Antimicrob Chemother*. 1996;37:399-402.
14. Dohar JE, Kenna MA, Wadowsky RM. In vitro susceptibility of aural isolates of *Pseudomonas aeruginosa* to commonly used ototopical antibiotics. *Am J Otol*. 1996;17:207-209.
15. Schneider ML. Bacteriology of otorrhea from tympanostomy tubes. *Arch Otolaryngol Head Neck Surg*. 1989;115:1225-1226.
16. Brook I, Yocum P, Shah K. Aerobic and anaerobic bacteriology of otorrhea associated with tympanostomy tubes in children. *Acta Otolaryngol (Stockh)*. 1998;118:206-210.
17. Kenna MA, Bluestone CD. Microbiology of chronic suppurative otitis media in children. *Pediatr Infect Dis*. 1986;5:223-225.
18. Hui Y, Park A, Crysdale WS, et al. Ototoxicity from ototopical aminoglycosides. *J Otolaryngol*. 1997;26:53-56.
19. Wong DLH, Rutka JA. Do aminoglycoside otic preparations cause ototoxicity in the presence of tympanic membrane perforations? *Otolaryngol Head Neck Surg*. 1997;116:404-410.