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# Comparative Evaluation of Loracarbef and Amoxicillin-Clavulanate for Acute Otitis Media

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**One hundred five infants and children with acute otitis media were randomized to therapy with loracarbef, an experimental carbacephem antibiotic, or amoxicillin-clavulanate (Augmentin), an approved drug for this disease. Ninety-two were evaluable (46 in each group). Middle ear fluid samples obtained for culture before therapy grew *Haemophilus* spp. in 30% of cases, pneumococci in 29% of cases, and *Moraxella catarrhalis* in 15% of cases. β-Lactamase-producing bacteria were found in 37% of patients. Clinical failure occurred in four loracarbef-treated patients and one amoxicillin-clavulanate-treated patient ($P = 0.361$). Recurrence of acute otitis media was more common in the 2 to 3 weeks after loracarbef treatment (eight patients) than it was after amoxicillin-clavulanate therapy (three patients), but not significantly so ($P = 0.197$). Thus, combined failure and recurrence occurred in 12 loracarbef-treated patients and four amoxicillin-clavulanate-treated patients ($P = 0.052$). Gastrointestinal side effects occurred in 13 loracarbef-treated and 21 amoxicillin-clavulanate-treated patients ($P = 0.13$). Diaper rash was more common with amoxicillin-clavulanate (22 patients) than with loracarbef (10 patients; $P = 0.016$). Satisfactory results were achieved with both antibiotics, and adverse effects, although common, were minor.**

In recent years, several reports of the bacteriology of middle ear effusion in patients with acute otitis media (AOM) have shown increasing numbers of β-lactamase-producing strains of *Haemophilus influenzae* (2, 4, 9). In Dallas, recently, 27% of 120 patients with AOM had β-lactamase-producing bacteria in their middle ear fluid (6). This increasing rate of bacteria that are β-lactamase producers suggests that the new antibiotics with a broader spectrum of activity than that of amoxicillin need to be studied.

Loracarbef is a synthetic, orally administered carbacephem antibiotic that is structurally identical to cefaclor, with the exception of a carbon replacing a sulfur molecule at the 1 position in the dihydrothiazine ring. It has a spectrum of activity against gram-positive and gram-negative organisms that commonly cause otitis media (8). The MICs of loracarbef and cefaclor against common respiratory pathogens are similar, with the exception that loracarbef is more active against *H. influenzae* (MIC for 90% of strains tested, 0.5 mg/liter) than is cefaclor (MIC for 90% of strains tested, 8 mg/liter) (8). The plasma half-life is approximately 0.8 h, and the mean peak concentration in serum after a dose of 15 mg/kg is 18.7 mg/liter (range, 9.9 to 24 mg/liter) (7). Peak concentrations in serum are similar to those found after comparable dosages of cefaclor, but they persist longer after loracarbef, and the area under the time-concentration curve is almost twice as great (7). The objective of this study was to compare the clinical efficacy and safety of loracarbef with those of amoxicillin-clavulanate potassium (Augmentin) in children with AOM.

## MATERIALS AND METHODS

**Patients.** During a 15-month period, children in the pediatric clinic outpatient department at Children's Medical Center, Dallas, who were 6 months of age or older and who had a diagnosis of AOM were eligible for study. Patients were excluded if they had (i) a history of impaired renal function, (ii) a history of allergy to a cephalosporin or penicillin, (iii) spontaneous perforation of the tympanic membrane and drainage for longer than 24 h, (iv) antimicrobial therapy within the preceding 3 days or, (v) an inability to return for follow-up visits. This study was approved by the Institutional Review Board of The University of Texas Southwestern Medical Center, and written informed consent was obtained from the parents of all children studied. A standardized patient history was obtained from each subject before enrollment in the study.

**Diagnosis.** AOM was suspected if there were acute symptoms of otalgia and at least two other symptoms, such as fever, irritability, loss of appetite, simultaneous respiratory tract symptoms, as well as findings on pneumatic otoscopy by the initial examining physician of middle ear effusion with loss of anatomic landmarks, opacity, bulging, and decreased or absent mobility of the tympanic membrane. The diagnosis was confirmed by pneumatic otoscopy performed by the same investigator (V.N.G.) who is a validated otoscopist (sensitivity, 100%; specificity, 93%; tested in 100 ears). Tympanograms were obtained with an electroacoustic impedance bridge (model TA 7A; Teledyne). The diagnosis was confirmed by tympanocentesis. Children with spontaneous perforation of tympanic membranes were included only if the ear had been draining for less than 24 h.

**Diagnostic procedures.** Tympanocentesis was performed before therapy in all children with a diagnosis of AOM with a 3.5-inch (~9 cm), 20-gauge spinal needle attached to a Juhn Tymp-Tap (XO Med, Jacksonville, Fla.) and electric pump suction. Before tympanocentesis, a sample for culture was obtained from the ear canal with a calcium alginate swab after the ear canal was cleaned with 70% alcohol for 1 min and then flushed with acetic acid-alcohol mixture.

Middle ear aspirates were inoculated onto 5% sheep blood and chocolate agar plates and were incubated for 18 to 24 h in 5% $CO_2$. Isolates were identified by standard methods and tested for susceptibility to 30-μg loracarbef disks and 30-μg

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TABLE 1. Demographic and clinical features of children with AOM

| Characteristic | No. (%) | |
|---|---|---|
| | Loracarbef | Amoxicillin-clavulanate |
| Race | | |
| Caucasian | 11 (24) | 10 (22) |
| Black | 23 (50) | 18 (39) |
| Hispanic | 11 (24) | 18 (39) |
| Other | 1 (2) | 0 |
| Sex | | |
| Male | 25 (54) | 27 (59) |
| Female | 21 (46) | 19 (41) |
| Age (mo) | | |
| 6–11 | 9 (20) | 14 (30) |
| 12–23 | 15 (33) | 16 (35) |
| 24–35 | 7 (15) | 8 (17) |
| 30–47 | 7 (15) | 1 (2) |
| 48–59 | 1 (2) | 2 (4) |
| >60 | 7 (15) | 5 (11) |
| Clinical features | | |
| Previous otitis media | | |
| None | 21 (46) | 23 (50) |
| Infrequent | 19 (41) | 16 (35) |
| Frequent[a] | 6 (13) | 7 (15) |
| Laterality of otitis media | | |
| Unilateral | 30 (65) | 27 (59) |
| Bilateral | 16 (35) | 19 (41) |
| Spontaneous rupture of tympanic membrane | 9 (20) | 7 (15) |
| Fever, >38°C | 20 (43) | 18 (39) |
| Otalgia | 35 (76) | 40 (87) |
| Lethargic | 13 (28) | 11 (24) |
| Irritable | 28 (61) | 37 (80) |
| Decreased appetite | 22 (48) | 24 (52) |
| Vomiting | 12 (26) | 13 (28) |
| Diarrhea | 11 (24) | 8 (17) |
| Rhinitis | 42 (91) | 42 (91) |
| Cough | 32 (70) | 35 (76) |

[a] Three or more episodes of otitis media within the previous 6 months.

amoxicillin-clavulanate disks containing 20 μg of amoxicillin and 10 μg of clavulanic acid by the methodology of the National Committee for Clinical Laboratory Standards (5) and by using media appropriate for fastidious organisms. All *Haemophilus*, *Staphylococcus aureus*, and *Moraxella catarrhalis* strains were tested for β-lactamase production on Cefinase disks (BBL, Cockeysville, Md.). Pneumococcal isolates were screened for penicillin resistance with a 1-μg oxacillin disk. MICs and MBCs were determined by a microdilution method (1) by using Mueller-Hinton broth for *S. aureus* and *M. catarrhalis*, Mueller-Hinton broth supplemented to 1% with supplement C (Difco, Detroit, Mich.) for *Haemophilus* strains, and Todd-Hewitt broth supplemented to 2% with sheep blood for *Streptococcus pyogenes* and *Streptococcus pneumoniae*.

All *Haemophilus* isolates were biotyped according to their reactions in media containing indole, urease, and ornithine decarboxylase substrates (3).

Complete blood count with differential counts, urinalysis and serum specimen for creatinine, urea nitrogen, calcium, phosphorus, cholesterol, and liver function tests were obtained at the time of enrollment in the study and at the end of therapy. If there were abnormal values, repeat tests were done until the results were normal.

**Treatment.** Subjects were assigned, according to a randomized list, to receive either loracarbef, 30 mg/kg of body weight per day in two divided doses, or amoxicillin-clavulanate, 40 mg/kg/day in three divided doses. (Each patient received two bottles of medication labeled A and B. The B bottle was for the midday dose. In those taking loracarbef, the B bottle contained placebo.) The maximum daily doses of loracarbef and amoxicillin-clavulanate were 750 and 1,000 mg, respectively, for children weighing 25 kg or more. Both drugs were given as suspension formulations. The duration of treatment was 10 days. Parents were requested not to give antihistamines or decongestants to the children, but acetaminophen was permitted.

**Follow-up evaluation.** The patients were evaluated at the beginning of the study and again after 3 to 5 days of treatment, within 72 h of completion of therapy, and 10 to 16 days after completion of therapy. At the time of return visits, the answers to standard questions concerning the course of illness and drug effects were obtained and pneumatic otoscopy and tympanometry were performed. Clinical or symptomatic responses of the patients were based on the following definitions: cure, elimination of symptoms and signs of infection; improvement, substantial but incomplete resolution of signs and symptoms of infection; recurrence, recurrence of symptoms and signs of AOM within the follow-up period after completion of treatment; failure, signs and symptoms did not subside or improve substantially during therapy. Persistent effusion was considered to be present when signs and symptoms of acute infection had resolved

TABLE 2. Bacteriology of middle ear fluid

| Organism | No. of patients[a] | | | | | |
|---|---|---|---|---|---|---|
| | Loracarbef group | | | Amoxicillin-clavulanate group | | |
| | T | D | D/T | T | D | D/T |
| *Streptococcus pneumoniae* | 2 | | 2 | 10 | | |
| *Haemophilus influenzae* | 7 | | | 10 | 1 | |
| *Moraxella catarrhalis* | 3 | | | 4 | | |
| *Haemophilus parainfluenzae* | 1 | | | 1 | | |
| Group A streptococcus | 1 | 1 | | | | |
| *Staphylococcus aureus* | | 2 | | | 2 | 1 |
| *Streptococcus pneumoniae* and *Haemophilus influenzae* | 2 | | | 1 | | 1 |
| *Streptococcus pneumoniae* and *Moraxella catarrhalis* | 3 | | | 1 | | |
| *Haemophilus influenzae* and *Moraxella catarrhalis* | 1 | | | 1 | | |
| *Haemophilus influenzae* and *Staphylococcus aureus* | | | | 1 | | |
| *Streptococcus pneumoniae* and *Staphylococcus aureus* | 1 | 1 | | | 1 | 1 |
| *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* | 1 | | | | | |
| Nonpathogens | 6 | 3 | | 5 | | |
| No growth | 9 | | | 5 | | |

[a] T, Tympanocentesis fluid; D, drainage fluid; D/T, one ear drainage fluid and the other ear tympanocentesis fluid.

TABLE 3. Bacteriology of middle ear effusions in 35 patients with bilateral ear disease

| Culture results | No. (%) |
|---|---|
| Concordant | |
| Same bacterial type in both ears | 9 (26) |
| Sterile in both ears | 3 (9) |
| Partially concordant, same bacterial type in both ears plus additional type in one ear | 7 (20) |
| Discordant | |
| Different bacterial type in both ears | 4 (11) |
| Growth in one ear and sterile in other | 12 (34) |

and there was middle ear effusion documented by otoscopic examination and tympanometry. Patients considered treatment failures and those with recurrent disease were treated with cefaclor, and further follow-up was by the original referring physician. Tympanocentesis was done, when permitted, in patients considered failures, relapses, or recurrences. Compliance with the treatment was monitored during the first follow-up visit by a urine test for the presence of antimicrobial activity. At the end of therapy, the remaining medicine was measured. Patients who missed three or more doses of medication were excluded from the analysis of efficacy.

**Statistical analysis.** Fisher exact tests (two-tailed) were used for comparisons of treatment responses and adverse events.

## RESULTS

**Patient population.** One hundred five children (ages, 6 months to 11 years) were enrolled in the study. Thirteen cases were excluded from efficacy evaluation. The reasons for exclusion in the loracarbef group were failure to return (five patients), poor compliance (one patient), and abdominal pain on day 2 (one patient). In the amoxicillin-clavulanate-treated group, the reasons were no return (two patients), vomiting on days 3, 3, and 5 (three patients), and poor compliance (one patient).

Clinical features and demographic characteristics of 92 evaluable patients (127 ears) are summarized in Table 1. There were 46 patients in each treatment group. Of the 92 patients, 54 (59%) were younger than 2 years of age, 52 (57%) were male, and 48 (52%) had a history of one or more ear infections before enrollment in the study. Spontaneous perforation of the tympanic membrane with drainage occurred in 16 (17%) cases. There were no significant differences between the two treatment groups in any of the features listed in Table 1. More than 90% of the patients had associated rhinorrhea. A history of fever was recorded in 63 (68%) patients, but was present in only 38 of 92 patients (41%) at the time of examination. Sixteen (17%) children had a fever of 39°C or above. The pretreatment mean leukocyte counts were 13,600 and 13,800/mm$^3$ in the loracarbef- and amoxicillin-clavulanate-treated groups, respectively.

**Microbiology.** The culture results are summarized in Table 2. *Haemophilus* spp., alone or in combination with other pathogens, were present in 28 patients (30%), pneumococci were present in 27 patients (29%), and *M. catarrhalis* was present in 14 patients (15%). There were two patients with *Haemophilus parainfluenzae* infections, and the remainder of *Haemophilus* isolates were nontypeable *H. influenzae*. Fourteen patients (15%) had sterile cultures. The organisms designated nonpathogens were coagulase-negative staphylococci ($n$ = 6), diphtheroids ($n$ = 5), viridans group streptococci ($n$ = 2), and *Gafkya* sp. ($n$ = 1). Ear canal culture samples from children with intact tympanic membranes were sterile, except for two patients with coagulase-negative staphylococci.

The concordance of bacterial cultures in 35 patients with bilateral disease is presented in Table 3. Only 35% were fully concordant.

Of 16 *M. catarrhalis* strains, 15 (94%) were β-lactamase producers, as were 17 (50%) of 34 *Haemophilus* isolates. Of the 92 patients, 26 (28%) were infected with β-lactamase-producing *Haemophilus* spp. or *M. catarrhalis*, or both. Added to those with *S. aureus* infections, there were 34 patients (37%) with β-lactamase-producing organisms.

One pneumococcal isolate was relatively resistant to penicillin G, with an MIC of 0.125 mg/liter. The MIC of loracarbef for that strain was 4 mg/liter; for the other pneumococcal strains, loracarbef MICs were 2 mg/liter or less.

Results of tests of pathogen susceptibilities to loracarbef and amoxicillin-clavulanate are presented in Table 4. Loracarbef was less active against the gram-positive organisms.

**Clinical responses.** Five patients were clinical failures (Table 5). Reinfection within 30 days of enrollment into the study occurred in 11 cases, 8 in the loracarbef-treated group and 3 in the amoxicillin-clavulanate-treated group ($P$ = 0.197). These new episodes of AOM occurred within 18 days after the end of therapy in both loracarbef- and amoxicillin-clavulanate-treated patients. Retap was done in one amoxicillin-clavulanate-treated patient 18 days after stopping therapy. At the time of initial diagnosis, the culture had pneumococci and *S. aureus*; at the time of recurrence, the culture grew *S. aureus*. Tympanocentesis was done at the time of reinfection in two loracarbef-treated patients 12 and 18 days after stopping therapy. Both had had pneumococcal

TABLE 4. In vitro susceptibility testing results

| Organism[a] | No. of strains | MIC (mg/liter) | | | |
|---|---|---|---|---|---|
| | | Loracarbef | | Amoxicillin-clavulanate | |
| | | 50%[b] | Range | 50% | Range |
| *Streptococcus pneumoniae* | 45 | 2 | 1–4 | 0.016 | ≤0.004–0.125 |
| *Haemophilus influenzae*, B+ | 16 | 1 | 0.5–4 | 0.5 | 0.25–2 |
| *Haemophilus influenzae*, B− | 20 | 1 | 0.5–2 | 0.5 | 0.25–1 |
| *Moraxella catarrhalis*, B+ | 17 | 1 | 0.25–2 | 0.125 | <0.016–0.25 |
| *Staphylococcus aureus*, B+ | 14 | 2 | 2–16 | 0.5 | 0.125–1 |

[a] B+ or B−, β-lactamase positive or negative.
[b] 50%, MIC for 50% of isolates tested.

TABLE 5. Outcomes of 92 evaluable patients enrolled in the study

| Outcome | No. (%) | | P value |
|---|---|---|---|
| | Loracarbef | Amoxicillin-clavulanate | |
| Failure | 4 (9) | 1 (2) | 0.361 |
| Recurrence | 8 (17) | 3 (7) | 0.197 |
| Middle ear effusion at days 10 to 14 | 23 (50) | 28 (61) | NS[a] |
| Middle ear effusion at day 28 | 9 (20) | 14 (30) | NS |

[a] NS, Not significant.

infection initially, and pneumococci were cultured from middle ear fluid at the time of the new episode of AOM. The rates of persistent middle ear effusion were similar in both treatment groups.

Total treatment failure and recurrences were more common with loracarbef therapy (12 patients) than with amoxicillin-clavulanate therapy (4 patients) ($P = 0.052$).

Details about the patients who were declared clinical failures or who had relapses after initial improvement are presented in Table 6. One patient in each group had persistence of an initial pathogen, as determined by repeat culture of middle ear fluid, but three patients (two treated with loracarbef and one treated with amoxicillin-clavulanate) had sterile middle ear fluid, despite persisting symptoms. The remaining patients were considered cured after 10 days of therapy.

**Adverse reactions.** As mentioned above, three patients in the amoxicillin-clavulanate treatment group and one patient in the loracarbef treatment group were removed from the study because of gastrointestinal side effects. Loose stools and vomiting were common in the 92 evaluable patients (Table 7). They occurred in 13 children (28%) in the loracarbef-treated group and in 21 children (46%) in the amoxicillin-clavulanate-treated group ($P = 0.13$). Diaper rash was significantly more common in amoxicillin-clavulanate-treated children ($P = 0.016$).

TABLE 7. Adverse reactions attributed to drug

| Reaction | No. (%) | | P value |
|---|---|---|---|
| | Loracarbef | Amoxicillin-clavulanate | |
| Loose stools | 11 (24) | 16 (35) | |
| Vomiting | 1 (2) | 3 (7) | 0.13 |
| Diarrhea and vomiting | 1 (2) | 2 (4) | |
| Diaper rash | 10 (22) | 22 (48) | 0.016 |

Five patients in each group had mildly elevated aspartate aminotransferase values, and one patient in each group developed eosinophilia. One loracarbef-treated patient had an increase in blood urea nitrogen, and one amoxicillin-clavulanate-treated patient had an increase in alkaline phosphatase into the abnormal range. All values returned to normal after treatment on subsequent testing.

## DISCUSSION

The clinical responses of patients with AOM were essentially the same with loracarbef or amoxicillin-clavulanate therapy. Amoxicillin-clavulanate-treated patients were more likely to have diaper rash. They also had more gastrointestinal side effects, but that difference did not achieve statistical significance. The parents of four patients (one treated with loracarbef and three treated with amoxicillin-clavulanate) stopped the medication because of gastrointestinal side effects and were excluded from the efficacy analysis. In the patients who continued the medication despite these side

TABLE 6. Treatment failures and relapses within 3 days of the end of therapy

| Patient (age, characteristic[a]) | Diagnosis[b] | Initial middle ear fluid[c] | Findings at follow-up |
|---|---|---|---|
| Loracarbef therapy group | | | |
| 9 mo, W/M | BOM | L, pneumococcus and *Staphylococcus aureus*; R, *Staphylococcus aureus* | Day 8, fever, vomiting, and diarrhea; seen in clinic; diagnosis BOM, medication changed |
| 14 mo, B/F | BOM | L, *H. influenzae* (β-lactamase positive); R, no growth | Day 9, fever, ear pain, irritable; retap L, no growth |
| 5 yr, LA/M | Bilateral drainage | L, pneumococcus and *Staphylococcus aureus*; R, pneumococcus | Persistent drainage of right ear with initial improvement but worsening ear pain; day 6; repeat culture, no growth |
| 9 mo, B/F | LOM | *Moraxella catarrhalis* and coagulase-negative staphylococcus | Day 4, persistent drainage; culture *Moraxella catarrhalis* and coagulase-negative staphylococcus; day 10, fever, ear pain |
| Amoxicillin-clavulanate therapy group | | | |
| 11 mo, W/F | BOM | *Haemophilus influenzae* (β-lactamase positive), both ears | Day 10, persistent symptoms; refused ear taps |
| 8 mo, B/F | LOM, right ear drainage | L, pneumococcus and *Staphylococcus aureus*; R, pneumococcus | Day 13, purulent drainage (R), *Staphylococcus aureus* |
| 14 mo, LA/M | BOM | L, *Haemophilus influenzae* (β-lactamase negative); R, no growth | Day 4, drainage both ears; culture, no growth; day 10, severe otalgia, irritable; retap R, no growth |

[a] W/M, White male; B/F, black female; LA/M, Hispanic male; W/F, white female.
[b] BOM, Bilateral otitis media; LOM, left otitis media.
[c] L, Left; R, right.

effects, the loose stools and vomiting were mild and tolerated by the parents.

Recurrent episodes of AOM occurred more often in patients treated with loracarbef, but the difference was not significant. In three patients with recurrence for whom tympanocentesis was repeated 12 to 18 days after stopping therapy, the bacterial genera and species that were recovered were the same as those that had been present at the time of the initial illness, so it is possible that they represented delayed relapses of the initial infection.

With one exception, all *S. aureus* isolates were from patients with spontaneous perforation. This is similar to our experience in a previous study (2). Because *S. aureus* is rarely recovered from middle ear fluid behind an intact membrane in patients with AOM, it suggests that the patients who had spontaneous perforation within 24 h of the first examination might have had infection and drainage for longer than the parents suspected. Because of the frequency of *S. aureus* infection in such patients, amoxicillin would not be a suitable drug for empiric initial therapy.

The frequency of β-lactamase-producing *Haemophilus* and *Moraxella* strains in patients with AOM was similar in this study to that in our previous study involving comparable patient populations (2). Almost all *Moraxella* isolates and half of the *Haemophilus* isolates in this study were resistant to amoxicillin, the most commonly prescribed antibiotic for treatment of AOM. Several β-lactamase-resistant antibiotics (ampicillin-clavulanate, cefaclor, cefixime, erythromycin-sulfisoxazole, and trimethoprim-sulfamethoxazole) have been tested in clinical trials of AOM and have been found to be effective. It appears that loracarbef can be added to that list. The greater in vitro activity against *Haemophilus* strains and the greater bioavailability of loracarbef than of cefaclor may be an advantage.

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## REFERENCES

1. **Barry, A. L.** 1986. The antimicrobic susceptibility test: principles and practices, p. 95. Lea & Febiger, Philadelphia.
2. **Hendrickse, W. A., H. Kusmiesz, S. Shelton, and J. D. Nelson.** 1988. Five vs. ten days of therapy for acute otitis media. Pediatr. Infect. Dis. J. **7**:14–23.
3. **Kilian, M.** 1985. *Haemophilus*, p. 387–393. *In* E. H. Lennette, A. Balows, W. J. Hausler, Jr., and H. J. Shadomy (ed.), Manual of clinical microbiology, 4th ed. American Society for Microbiology, Washington, D.C.
4. **Kovatch, A. L., E. R. Wald, and R. H. Michaels.** 1983. Beta-lactamase-producing *Branhamella catarrhalis* causing otitis media in children. J. Pediatr. **102**:261–264.
5. **National Committee for Clinical Laboratory Standards.** 1984. Performance standards for antimicrobial disk susceptibility tests, 3rd ed. Approved standard M2-A3. National Committee for Clinical Laboratory Standards, Villanova, Pa.
6. **Nelson, J. D.** 1990. Emergence of *Branhamella catarrhalis* as a major cause of acute otitis media in Dallas, Texas. Ann. Otol. Rhinol. Laryngol. **99**(Suppl. 149):41–42.
7. **Nelson, J. D., S. Shelton, and H. Kusmiesz.** 1988. Pharmacokinetics of LY163892 in infants and children. Antimicrob. Agents Chemother. **32**:1738–1739.
8. **Shelton, S., and J. D. Nelson.** 1988. In vitro susceptibilities of common pediatric pathogens to LY163892. Antimicrob. Agents Chemother. **32**:268–270.
9. **Shurin, P. A., C. D. Marchant, C. H. Kim, G. F. Van Hare, C. E. Johnson, M. A. Tutihase, and L. J. Knapp.** 1983. Emergence of beta-lactamase-producing strains of *Branhamella catarrhalis* as important agents of acute otitis media. Pediatr. Infect. Dis. **2**:34–38.