

High-Dose Azithromycin versus High-Dose Amoxicillin-Clavulanate for Treatment of Children with Recurrent or Persistent Acute Otitis Media

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Infants and young children, especially those in day care, are at risk for recurrent or persistent acute otitis media (AOM). There are no data on oral alternatives to high-dose amoxicillin-clavulanate for treating AOM in these high-risk patients. In this double-blind, double-dummy multicenter clinical trial, we compared a novel, high-dose azithromycin regimen with high-dose amoxicillin-clavulanate for treatment of children with recurrent or persistent AOM. Three hundred four children were randomized; 300 received either high-dose azithromycin (20 mg/kg of body weight once a day for 3 days) or high-dose amoxicillin-clavulanate (90 mg/kg divided twice a day for 10 days). Tympanocentesis was performed at baseline; clinical response was assessed at day 12 to 16 and day 28 to 32. Two-thirds of patients were aged ≤ 2 years. A history of recurrent, persistent, or recurrent plus persistent AOM was noted in 67, 18, and 14% of patients, respectively. Pathogens were isolated from 163 of 296 intent-to-treat patients (55%). At day 12 to 16, clinical success rates for azithromycin and amoxicillin-clavulanate were comparable for all patients (86 versus 84%, respectively) and for children aged ≤ 2 years (85 versus 79%, respectively). At day 28 to 32, clinical success rates for azithromycin were superior to those for amoxicillin-clavulanate for all patients (72 versus 61%, respectively; $P = 0.047$) and for those aged ≤ 2 years (68 versus 51%, respectively; $P = 0.017$). Per-pathogen clinical efficacy against *Streptococcus pneumoniae* and *Haemophilus influenzae* was comparable between the two regimens. The rates of treatment-related adverse events for azithromycin and amoxicillin-clavulanate were 32 and 42%, respectively ($P = 0.095$). Corresponding compliance rates were 99 and 93%, respectively ($P = 0.018$). These data demonstrate the efficacy and safety of high-dose azithromycin for treating recurrent or persistent AOM.

Acute otitis media (AOM) is an important health problem in early childhood and is the most frequent condition for which antibiotics are prescribed for children in the United States (26, 27). The emergence of drug-resistant *Streptococcus pneumoniae* presents challenges for clinicians who manage children with AOM, and recent consensus recommendations have been developed to address these challenges (15, 23). Amoxicillin, especially at higher doses (80 to 90 mg/kg of body weight/day), is recommended as first-line therapy for children with no recent antimicrobial exposure, and high-dose amoxicillin-clavulanate (90/6.4 mg/kg/day, respectively) is the preferred oral agent for cases of documented treatment failure and for children with recent antimicrobial exposure (15, 23).

Azithromycin, an azalide antibiotic, has a prolonged half-life of 68 h and achieves sustained tissue concentrations in a wide range of body sites, including the middle ear (19, 32). These pharmacokinetic properties allow for once-daily dosing and shorter treatment regimens (18). In a number of AOM treatment trials, azithromycin oral suspension (30-mg/kg total dose) given over 5 days, over 3 days, or as a single dose has demon-

strated clinical efficacy comparable to that of a 10-day regimen of amoxicillin-clavulanate (45/6.4 mg/kg/day, respectively) (1, 2, 4, 17, 25, 28). Of note, in one of the single-dose azithromycin trials, rates of clinical success (cure or improvement) for both azithromycin and amoxicillin-clavulanate tended to be lower among children 2 years of age or younger (4), a group at risk for recurrent episodes of AOM, treatment failure, and infection due to penicillin-resistant *S. pneumoniae* (5, 31). Results from another study comparing 5-day azithromycin (30-mg/kg total dose) with 10-day amoxicillin-clavulanate (45/6.4 mg/kg/day, respectively) differ from those cited above (13). Dagan et al. (13) reported that amoxicillin-clavulanate demonstrated superior bacteriological efficacy against *Haemophilus influenzae* at day 4 to 6 and superior clinical efficacy on day 12 to 14. However, the latter difference was no longer statistically significant at day 22 to 28. All of the above-mentioned trials using the 30-mg/kg azithromycin regimen involved children who had not received antibiotics within 30 days of enrollment, and most of the children did not have a history of recurrent or persistent AOM. Children in these studies would thus be considered to have had uncomplicated AOM (16).

The management of high-risk children with recurrent or persistent AOM is an issue of great importance to clinicians. A recent noncomparative open-label trial demonstrated the effi-

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cacy of a new high-dose formulation of amoxicillin-clavulanate (90/6.4 mg/kg/day, respectively) for the treatment of high-risk children with recurrent AOM (12). At present, there are no published comparative data on oral alternatives to this regimen. In studies of children with streptococcal pharyngitis, a higher, 60-mg/kg total dose of azithromycin given over 3 or 5 days has been shown to be safe and efficacious (8, 33). Additionally, studies in the clinic and in a variety of animal infection models have demonstrated that higher doses of azithromycin achieve enhanced bactericidal activity against *S. pneumoniae*, *H. influenzae*, and *Streptococcus pyogenes* and result in improved eradication of these pathogens (3, 8, 21, 22). Taken together, these data support the hypothesis that a total dose of 60 mg of azithromycin/kg is safe and effective for the treatment of AOM in children at risk for recurrence or treatment failure. We tested this hypothesis in a large, double-blind, double-dummy clinical trial comparing 3-day, high-dose azithromycin with 10-day, high-dose amoxicillin-clavulanate for the treatment of children with recurrent or persistent AOM.

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MATERIALS AND METHODS

Study design and ethics. This was a randomized, double-blind, double-dummy trial involving 13 U.S. and 5 Latin American centers. The trial was conducted from March 2001 to March 2002. The design and conduct of the study were consistent with the 1998 Food and Drug Administration *Guidance for Industry, Acute Otitis Media—Developing Antimicrobial Drugs for Treatment* (7). The Institutional Review Board or Independent Ethics Committee at each center approved the study protocol. Prior to enrollment, written informed consent was obtained from the parent or legal guardian of all participating patients.

Patients. The study population consisted of children between 6 months and 6 years of age with a history of recurrent or persistent AOM, defined as follows: recurrent AOM, ≥ 1 episode within 30 days of enrollment, ≥ 3 episodes within 6 months of enrollment, or ≥ 4 episodes within 12 months of enrollment; persistent AOM, presence of signs and symptoms of AOM after at least 48 h of treatment with a single course of a standard oral agent (other than study drugs). Previous episodes of AOM were diagnosed by the patient's primary care provider and documented in the patient's clinical record. Diagnostic criteria included first the presence of middle ear effusion as evidenced by at least two of the following tympanic membrane findings: (i) decreased or absent mobility documented by pneumatic otoscopy, (ii) yellow or white discoloration, (iii) opacification (other than scarring), and (iv) acute perforation with purulent otorrhea. Second, to be eligible children also were required to have at least one of the following signs of acute inflammation: (i) ear pain, including irritability or tugging or rubbing of the ear, within the previous 24 h; (ii) marked redness of the tympanic membrane; and (iii) fullness or bulging of the tympanic membrane. Exclusion criteria included weight of >25 kg; clinically significant cardiovascular, hepatic, renal, or hematologic disease; AOM requiring hospitalization or intravenous antibiotic therapy; history of hypersensitivity or intolerance to penicillin, penicillin derivatives, or macrolides; treatment with systemic antibiotics for indications other than AOM within 30 days of enrollment; use of any investigational product within 1 month of enrollment; presence of tympanostomy tubes; cholesteatoma; retraction pockets; chronic perforation of the tympanic membrane; or inability to take oral medication.

Treatment. Study drugs were administered in a double-blind, double-dummy fashion, i.e., the treating physician and patient or caregiver were unaware of drug assignment, and each patient received active drug plus a placebo that matched the comparator drug. At the time at which the trial was initiated, high-dose amoxicillin-clavulanate at 90/6.4 mg/kg/day, respectively (Augmentin ES), was not commercially available. We therefore used a high-dose amoxicillin-clavulanate regimen consisting of amoxicillin-clavulanate at 45/6.4 mg/kg/day, respectively, plus additional amoxicillin at 45 mg/kg/day. Patients were randomly assigned to receive either high-dose azithromycin (20 mg/kg once a day for 3 days) plus amoxicillin-clavulanate placebo (divided twice a day [b.i.d.] for 10 days) with additional amoxicillin placebo (divided b.i.d. for 10 days) or azithromycin placebo (once a day for 3 days) plus amoxicillin-clavulanate at 45/6.4 mg/kg/day,

respectively (divided b.i.d. for 10 days), with additional amoxicillin at 45 mg/kg/day (divided b.i.d. for 10 days).

Study procedures. At enrollment-baseline (day 1), medical history, physical examination, and pneumatic otoscopy were performed. Additionally, middle ear fluid was obtained by tympanocentesis before the first dose of study drug was administered. When perforation was present, the exudate was collected with a sterile swab. A telephone follow-up (day 3 to 5) was scheduled to assess safety, compliance, and response to therapy. If the patient's symptoms had not improved, an interim visit was scheduled. At the end of therapy (day 12 to 16), clinical, otoscopic, and safety assessments were repeated, and medication bottles and diaries were collected. At the end-of-study visit (day 28 to 32), clinical, otoscopic, and safety assessments were performed. A repeat tympanocentesis could be performed at any time after treatment, if judged by the investigator to be clinically indicated.

Microbiology. Pathogens from middle ear fluid samples were isolated and identified by the local laboratory. Isolates were then sent to a central laboratory (Covance Central Laboratory Services, Indianapolis, Ind.) for confirmation and susceptibility testing by broth microdilution (29). Isolates considered to be pathogens were *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, and *S. pyogenes*. *H. influenzae* and *M. catarrhalis* were tested for β -lactamase production by the chromogenic nitrocefin test. PCR determination of macrolide resistance mechanisms was performed on all azithromycin-resistant *S. pneumoniae* isolates (34, 36).

Outcome measures. (i) **Efficacy.** Efficacy was assessed based on an intent-to-treat analysis. Clinically evaluable intent-to-treat patients received at least one dose of study drug and had a diagnosis of AOM at baseline. Microbiologically evaluable intent-to-treat patients included clinical intent-to-treat patients who had a pathogen recovered from middle ear fluid at baseline. The primary efficacy endpoint was the clinical response among clinically evaluable patients at day 28 to 32 (test-of-cure [7]). Secondary endpoints included the clinical response among clinically evaluable patients at day 12 to 16, as well as the clinical response among microbiologically evaluable patients at day 12 to 16 and day 28 to 32. Clinical response was defined as cure (complete resolution of signs and symptoms, with or without the presence of middle ear effusion), improvement (partial resolution of signs and symptoms, with or without the presence of middle ear effusion, and without the need for additional antibiotic therapy for AOM [day 12 to 16 only]), or failure (no change, a worsening of signs or symptoms, or a requirement for additional antibiotic therapy for AOM).

(ii) **Safety and compliance.** Patients who received at least one dose of study drug were included in the safety analysis. Treatment-related adverse events included those judged by the investigator to be related or possibly related to study drug. Diarrhea was not specifically defined in the protocol, and information was collected as presented by parents or caregivers. The severity of adverse events was categorized by the investigator as mild, moderate, or severe. Compliance with the study regimen was verified by parental diaries as well as inspection of returned medication bottles at the day 12 to 16 visit.

Statistical methods. The study was powered to ensure with 80% probability that the lower limit of a two-sided 95% confidence interval (CI) for the true difference in efficacy did not exceed 15%, based on a reference rate for the comparator of 80% at the primary endpoint (day 28 to 32). Allowing for non-evaluability, a total of 150 patients per treatment group were required to protect the power of the study. Fisher's exact test was used to assess differences in categorical variables by treatment group. Ninety-five percent CIs on the difference in the response rate by treatment group were calculated based on the normal approximation to the binomial distribution.

RESULTS

Patients. A total of 304 patients were randomized, and 300 were evaluable for the safety analysis (153 in the azithromycin group and 147 in the amoxicillin-clavulanate group). Four patients were excluded from the clinical intent-to-treat population due to an incorrect baseline diagnosis (three patients) or failure to meet inclusion criteria (one patient), leaving a total of 296 children in the clinical intent-to-treat population (151 in the azithromycin group and 145 in the amoxicillin-clavulanate group). Demographic and clinical characteristics were similar between the two treatment groups (Table 1). Eighty-one percent of the patients had a history of recurrent AOM, while 33% had persistent AOM at the time of enrollment. The pro-

TABLE 1. Demographic and clinical characteristics

Characteristic	Value for patient group:	
	Azithromycin (n = 151)	Amoxicillin-clavulanate (n = 145)
Gender ratio (male/female)	1.3	1.4
Mean age, mo (±SD)	24.6 ± 18.4	25.7 ± 19.7
No. (%) children ≤ 24 mo	98 (65)	93 (64)
Wt, kg (±SD)		
Male	12.8 ± 4	12.5 ± 4
Female	12.2 ± 4.2	13 ± 4.5
No. (%) of siblings with history of AOM	47 (31)	52 (36)
No. (%) attending day care	63 (42)	57 (39)
Prior medical history, no. (%)		
Persistent AOM	35 (23)	20 (14)
Recurrent AOM	101 (66)	99 (67)
Recurrent plus persistent AOM	16 (11)	27 (19)
Age < 6 mo at first AOM episode, no. (%)	59 (39)	68 (47)
Household smoke exposure, no. (%)	48 (32)	29 (20)
Pacifier use, no. (%)	46 (31)	29 (20)

portions of patients from the United States and Latin America were 61 and 39%, respectively. The microbiological intent-to-treat population included 80 azithromycin and 83 amoxicillin-clavulanate patients. The most common reason for exclusion from the microbiological intent-to-treat analysis was lack of a baseline pathogen.

Microbiology. One or more AOM pathogens were recovered from the middle ear fluid of 163 of 296 children (55%) at baseline. The relative frequency of each pathogen was as follows. A total of 67 children (41%) had *H. influenzae*, either alone (n = 62) or with *M. catarrhalis* (n = 5). A total of 65 (40%) had *S. pneumoniae*, either alone (n = 63) or with *M. catarrhalis* (n = 2). Eight children (5%) had both *H. influenzae* and *S. pneumoniae*, two of them with *M. catarrhalis* as well. Thirteen children (8%) had *M. catarrhalis* alone, and 10 (6%) had *S. pyogenes* alone. Of 74 *H. influenzae* isolates, 26 (35%) were β-lactamase positive (one isolate failed to grow on subculture); 22 of 22 *M. catarrhalis* isolates (100%) were β-lactamase positive. Among 22 *M. catarrhalis* isolates, the MICs of azithromycin and amoxicillin-clavulanate at which 90% of the isolates tested were inhibited were 0.12 (range, 0.06 to 0.25) and 0.25 (range, 0.03 to 0.25) μg/ml, respectively. All *H. influenzae* isolates were susceptible to azithromycin (MIC, ≤4 μg/ml) and amoxicillin-clavulanate (MIC, ≤4/2 μg/ml). All *S. pyogenes* isolates were susceptible to azithromycin (MIC, ≤0.5 μg/ml) and penicillin (MIC, ≤0.12 μg/ml) (30).

Forty-seven percent of *S. pneumoniae* isolates (34 of 73) were penicillin nonsusceptible; of these, 25% (18 of 73) were intermediate (MIC, 0.12 to 1 μg/ml) and 22% (16 of 73) were resistant (MIC, ≥2 μg/ml). Among the 34 penicillin-nonsusceptible pneumococci, 17 (50%) remained susceptible to

TABLE 2. Clinical response, intent-to-treat population

Study visit and population	No. with clinical success ^{a/} total (%)		P	95% CI of difference
	Azithromycin (n = 151)	Amoxicillin-clavulanate (n = 145)		
Day 12 to 16				
All patients	128/149 ^b (86)	122/145 (84)	0.744	-6.4, 10.0
Patients ≤2 yr	82/96 (85)	73/92 (79)	0.339	-4.9, 17.0
Day 28 to 32				
All patients	107/148 ^c (72)	88/144 ^d (61)	0.047	0.4, 22.0
Patients ≤2 yr	65/95 (68)	46/91 (51)	0.017	3.9, 31.8

^a Clinical success, cure or improvement on day 12 to 16 and cure on day 28 to 32.

^b Two patients had no assessment at this visit.

^c Three patients had no assessment at this visit.

^d One patients had no assessment at this visit.

azithromycin (MIC, ≤0.5 μg/ml). Among the 39 penicillin-susceptible isolates, 3 (8%) were azithromycin resistant (all three were clindamycin susceptible). Twenty-seven percent of *S. pneumoniae* isolates (20 of 73) were azithromycin resistant (MIC, ≥2.0 μg/ml); none were azithromycin intermediate (MIC, 1 μg/ml). Seventeen of the 20 azithromycin-resistant isolates (85%) were clindamycin susceptible (MIC, ≤0.25 μg/ml). Of the 17 azithromycin-resistant and clindamycin-susceptible isolates, 16 were *mefA* positive and *ermB* negative, while 1 was *mefA* negative, *ermB* negative, and *ermA*(TR) positive. The azithromycin MIC for this latter isolate was 2 μg/ml, and the isolate was susceptible to amoxicillin-clavulanate (MIC, ≤0.03 μg/ml).

Efficacy. Clinical success rates for the intent-to-treat population are shown in Table 2. At day 12 to 16, rates of clinical success (cure or improvement) for all patients, and for those ≤2 years of age, were comparable between the two treatment groups. At day 28 to 32, the clinical efficacy of azithromycin was superior to that of amoxicillin-clavulanate for both age groups.

In a separate analysis of children with persistent AOM, clinical success rates for azithromycin and amoxicillin-clavulanate at day 12 to 16 were 85% (28 of 33) and 90% (17 of 19), respectively (P = 1.000; 95% CI of the difference, -23.5, 14.2). Corresponding clinical success rates at day 28 to 32 were 79% (26 of 33) and 74% (14 of 19), respectively (P = 0.739; 95% CI of the difference, -19.7, 29.9).

Among children with a history of recurrent AOM, clinical success rates for azithromycin and amoxicillin-clavulanate at day 12 to 16 were 87% (87 of 100) and 87% (86 of 99), respectively (P = 1.000; 95% CI of the difference, -9.3, 9.5). Corresponding clinical success rates at day 28 to 32 were 72% (71 of 99) and 60% (59 of 98), respectively (P = 0.099; 95% CI of the difference, -1.7, 24.7).

Efficacy data for microbiologically evaluable children are presented in Table 3. Clinical success rates for the two regimens did not differ significantly among all patients and among those infected with either *S. pneumoniae* (with or without *M. catarrhalis*) or *H. influenzae* (with or without *M. catarrhalis*). The numbers of children infected with both *S. pneumoniae* and *H. influenzae*, or with *M. catarrhalis* or *S. pyogenes* alone, were too small for meaningful analysis of results.

TABLE 3. Clinical response, microbiologically evaluable intent-to-treat population

Baseline pathogen	No. with clinical success ^a /total (%)							
	Day 12 to 16				Day 28 to 32			
	Azithromycin	Amoxicillin-clavulanate	<i>P</i>	95% CI of difference	Azithromycin	Amoxicillin-clavulanate	<i>P</i>	95% CI of difference
All patients	63/80 (79)	67/83 (81)	0.846	-14.3, 10.4	49/78 (63)	47/82 (57)	0.521	-9.7, 20.7
<i>S. pneumoniae</i> ^b	22/26 (85)	31/39 (80)	0.749	-13.7, 23.9	17/26 (65)	26/39 (67)	1.000	-24.8, 22.2
<i>H. influenzae</i> ^c	24/36 (67)	25/31 (81)	0.271	-34.7, 6.8	17/36 (47)	16/31 (52)	0.808	-28.4, 19.6
<i>S. pneumoniae</i> and <i>H. influenzae</i> ^d	4/4 (100)	3/4 (75)	ND ^e		4/4 (100)	1/3 (33)	ND	
<i>M. catarrhalis</i> alone	7/8 (88)	4/5 (80)	ND		7/8 (88)	2/5 (40)	ND	
<i>S. pyogenes</i> alone	6/6 (100)	4/4 (100)	ND		4/4 (100)	2/4 (50)	ND	

^a Clinical success, cure or improvement at day 12 to 16 and cure at day 28 to 32.

^b *S. pneumoniae* alone or with *M. catarrhalis*.

^c *H. influenzae* alone or with *M. catarrhalis*.

^d *S. pneumoniae* and *H. influenzae*, with or without *M. catarrhalis*.

^e ND, not done (not calculated because numbers of children were insufficient for statistical analysis).

Among the 33 microbiologically evaluable patients classified as clinical failures at day 12 to 16, 8 underwent a repeat (follow-up) tympanocentesis between days 4 and 15 (two azithromycin patients and six amoxicillin-clavulanate patients). The results are presented in Table 4. Serotyping was not performed to assess whether baseline and follow-up isolates were the same. However, when MICs and β -lactamase results were compared, patients E, F, and G appeared to have a recurrence of the initial infection, while the follow-up isolates from patients B and H most likely represent a new infection with a different pathogen.

Among the 64 microbiologically evaluable patients classified as clinical failures at day 28 to 32, 7 underwent a follow-up tympanocentesis between days 26 and 33 (four azithromycin patients and three amoxicillin-clavulanate patients). The results are shown in Table 5. A comparison of MICs and β -lac-

tamase results between baseline and follow-up isolates suggested that patients J and N had a recurrence of the initial infection. The follow-up isolate from patient K may represent a new infection with a different pathogen; however, selection of a resistant strain during azithromycin therapy cannot be ruled out.

For patients infected with *S. pneumoniae* at baseline, clinical efficacy was analyzed according to the azithromycin MIC (Table 6). Among children with azithromycin-susceptible isolates, outcomes were similar between the two treatment groups. However, the numbers of children with azithromycin-resistant isolates were too small for meaningful analysis of results. Similarly, an analysis of *S. pneumoniae*-infected patients stratified by the penicillin MIC demonstrated comparable clinical success rates between the two treatment regimens (Table 7). Of note, high-dose amoxicillin-clavulanate is approved for treat-

TABLE 4. Results of follow-up tympanocenteses among patients classified as clinical failures at day 12 to 16 (microbiologically evaluable intent-to-treat population)

Treatment group	Patient	Baseline pathogen	Pathogen recovered at follow-up	Comments
Azithromycin	A	<i>H. influenzae</i>	No growth	
	B	<i>H. influenzae</i>	<i>H. influenzae</i>	Baseline isolate, β -lactamase positive; follow-up isolate, β -lactamase negative
Amoxicillin-clavulanate	C	<i>S. pneumoniae</i>	No growth	
	D	<i>S. pneumoniae</i>	No growth	
	E	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>	Penicillin MIC at both baseline and follow-up, 0.25 μ g/ml
	F	<i>H. influenzae</i>	<i>H. influenzae</i>	Amoxicillin MIC at baseline and follow-up, 2 and 1 μ g/ml, respectively. Both isolates were β -lactamase negative
	G	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>	Penicillin MIC at both baseline and follow-up, 2 μ g/ml
	H	<i>H. influenzae</i>	<i>H. influenzae</i>	Amoxicillin MIC at baseline and follow-up, 2 and >64 μ g/ml, respectively. Baseline isolate, β -lactamase negative; follow-up isolate, β -lactamase positive
		<i>S. pneumoniae</i> <i>M. catarrhalis</i>		

TABLE 5. Results of repeat and/or follow-up tympanocenteses among patients classified as clinical failures at day 28 to 32 (microbiologically evaluable intent-to-treat population)

Treatment group	Patient	Baseline pathogen	Pathogen recovered at follow-up	Comments
Azithromycin	I	<i>S. pneumoniae</i>	No growth	Azithromycin MIC at baseline and follow-up, 1 and 2 µg/ml, respectively. Both isolates were β-lactamase positive Azithromycin MIC at baseline and follow-up, 0.12 and 8 µg/ml, respectively
	J	<i>H. influenzae</i>	<i>H. influenzae</i>	
	K	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>	
	L	<i>H. influenzae</i>	<i>M. catarrhalis</i>	
Amoxicillin-clavulanate	M	<i>H. influenzae</i>	No growth	Amoxicillin MIC at both baseline and follow-up, 0.5 µg/ml. Both isolates were β-lactamase negative
	N	<i>H. influenzae</i>	<i>H. influenzae</i>	
	O	<i>S. pneumoniae</i>	<i>H. influenzae</i>	

ing AOM due to certain penicillin-nonsusceptible pneumococci (MIC, 0.1 to 2 µg/ml; Augmentin ES600 [amoxicillin-clavulanate potassium] package insert; GlaxoSmithKline, 2002). As shown in Table 7, the numbers of children with pneumococci for which penicillin MICs were between 0.1 and 2 µg/ml were small; nevertheless, outcomes in the high-dose azithromycin group were similar to those in the comparator group. In an additional analysis of the data from Table 7, we attempted to determine whether penicillin and macrolide cross-resistance affected outcomes among azithromycin-treated patients. Interpretation of the results was again limited by the small numbers of azithromycin-treated children with penicillin-nonsusceptible isolates; however, the findings are as follows: (i) among the children with penicillin-susceptible pneumococci, all 17 isolates were azithromycin susceptible; (ii) of the five children infected with penicillin-intermediate pneumococci, four had azithromycin-susceptible isolates while one had an azithromycin-resistant isolate; this latter child was classified as a clinical failure at both study visits; (iii) of the eight children infected with penicillin-resistant pneumococci (MIC, 2 to 4 µg/ml), seven had isolates that were azithromycin resistant, while one had an isolate that was susceptible to azithromycin; this latter child was classified as a clinical success at both study visits.

Compliance. Compliance with at least 80% of the prescribed regimen was significantly higher in the azithromycin group than in the amoxicillin-clavulanate group (99 and 93%, respectively; *P* = 0.018).

Safety. Rates of treatment-related adverse events in the azithromycin and amoxicillin-clavulanate groups were 32 and 42%, respectively (*P* = 0.095). None of these were considered serious. Treatment-related adverse events occurring at a frequency of ≥2% are listed in Table 8. The incidence of diarrhea was significantly higher in the amoxicillin-clavulanate group than in the azithromycin group (*P* = 0.045). Patients who discontinued treatment due to adverse events included one azithromycin patient (diarrhea) and three amoxicillin-clavulanate patients (one with diarrhea, one with vomiting, and one with rash). All of these adverse events resolved upon discontinuation of study drug.

DISCUSSION

Although several attempts have been made to generate definitive and broad recommendations for the treatment of AOM in children, much debate still exists about this topic. Recent consensus recommendations have suggested that high-dose amoxicillin-clavulanate (90/6.4 mg/kg/day, respectively) is the

TABLE 6. Clinical response of azithromycin- and amoxicillin-clavulanate-treated patients infected with *S. pneumoniae*, stratified by azithromycin MIC

Azithromycin MIC ^b (µg/ml)	No. with clinical success/total ^a (%)			
	Day 12 to 16 (cure or improvement)		Day 28 to 32 (cure)	
	Azithromycin	Amoxicillin-clavulanate	Azithromycin	Amoxicillin-clavulanate
≤0.5	21/22 (96)	25/31 (81)	18/22 (82)	20/30 ^d (67)
1	— ^c	—	—	—
2–32	4/7 (57)	8/10 ^e (80)	2/7 (29)	6/10 (60)
≥64	1/1 ^f	1/2 ^g (50)	1/1	1/2 (50)

^a Number of children with either *S. pneumoniae* or *S. pneumoniae* plus *H. influenzae* (with or without *M. catarrhalis*) at baseline.
^b Susceptible; ≤0.5 µg/ml, intermediate, 1 µg/ml; resistant, ≥2 µg/ml.
^c —, no isolates.
^d One child did not return for the day 28 to 32 visit.
^e One child who was a clinical success at both visits had a baseline isolate that was azithromycin resistant (MIC, = 2 µg/ml), clindamycin susceptible, *mefA* negative, *ermB* negative, and *ermA*(TR) positive.
^f For the isolate from this child, the azithromycin MIC was >512 µg/ml, and the isolate was clindamycin resistant, *mefA* negative, and *ermB* positive.
^g Of the two children with azithromycin-resistant isolates, one was a clinical success at both visits (baseline isolate, clindamycin resistant, *mefA* negative, and *ermB* positive) and the other was a clinical failure at both visits (baseline isolate; clindamycin resistant, *mefA* positive, and *ermB* positive).

TABLE 7. Clinical response of azithromycin- and amoxicillin-clavulanate-treated patients infected with *S. pneumoniae*, stratified by penicillin MIC

Penicillin MIC ^a (μg/ml)	No. with clinical success/total ^b (%)			
	Day 12 to 16 (cure or improvement)		Day 28 to 32 (cure)	
	Azithromycin	Amoxicillin-clavulanate	Azithromycin	Amoxicillin-clavulanate
≤0.06	16/17 (94)	18/22 (82)	13/17 (77)	15/22 (68)
0.12–1	4/5 (80)	11/13 (85)	4/5 (80)	9/12 (75) ^c
2	6/7 (86)	4/6 (67)	4/7 (57)	2/6 (33)
4	0/1	1/2 (50)	0/1	1/2 (50)

^a Susceptible, ≤0.06 μg/ml; intermediate, 0.12–1 μg/ml; resistant, ≥2 μg/ml.

^b Number of children with either *S. pneumoniae* or *S. pneumoniae* plus *H. influenzae* (with or without *M. catarrhalis*) at baseline.

^c One child did not return for the day 28 to 32 visit.

preferred choice for second-line treatment of children who have failed first-line therapy for AOM and for those who present with a new infection and have received antibiotics within the past month (23). These recommendations are based on (i) pharmacokinetic and pharmacodynamic data (9, 10), (ii) results of a recent double tympanocentesis (“double-tap”) study (13), and (iii) the concept that the addition of clavulanate to amoxicillin will uniformly inactivate β-lactamase produced by strains of *H. influenzae* and *M. catarrhalis*. Azithromycin is suggested as an alternative only for children “with a true allergy to β-lactam antibiotics.” This is due to a perceived lack of efficacy against *H. influenzae* in the above-mentioned double-tap study, in which a per-protocol analysis suggested superior microbiological efficacy at day 4 to 6 for amoxicillin-clavulanate compared with azithromycin and superior clinical success at day 12 to 14 among patients who were microbiological cures (13). In the present trial, we aimed to ascertain if these recommendations were sound.

The patients in this trial were similar clinically and demographically to those in the high-dose amoxicillin-clavulanate study by Dagan and colleagues (12), with two exceptions: our population included children with persistent AOM, i.e., those who were failing prior therapy for AOM for at least 48 h, and in our study the mean age was 25 months, compared with 18.6 months in the previous study (12). We noted a slight predominance of *H. influenzae* in our patients with recurrent or persistent AOM. Dagan et al. (12, 13) also reported a higher incidence of *H. influenzae* in their studies of children with recurrent disease. Our 55% culture positivity rate was lower than the 68% reported by Dagan and associates (12). This may reflect suppression of bacterial growth by prior therapy among

our patients who had persistent disease. Alternatively, site-to-site variability in processing middle ear fluid specimens for culture could also account for the difference.

The primary endpoint (test-of-cure) in this trial was the clinical response among clinically evaluable patients at day 28 to 32 (7). At that visit, the clinical success rate in the azithromycin group was superior to that in the amoxicillin-clavulanate group. Given the long half-life of azithromycin, this finding may represent prevention of recurrence of the initial infection or protection against a new infection. Of note, the appropriateness of the day 28 to 32 test-of-cure has recently been questioned. It is currently thought that the end-of-treatment endpoint better reflects the ability of an antibacterial to clear the infection (11). In the present trial, outcomes for azithromycin- and amoxicillin-clavulanate-treated patients were comparable at the end-of-treatment (day 12 to 16) endpoint.

S. pneumoniae generally is considered the most important pathogen in AOM, in that pneumococcal AOM is least likely to resolve spontaneously and most likely to be associated with suppurative complications (20, 26). Increasing rates of penicillin and macrolide resistance in *S. pneumoniae*, and the association between resistance and treatment failure, continue to drive treatment recommendations (15, 23). The 47% rate of penicillin nonsusceptibility in our trial is similar to that in a recent U.S. survey (14) and in a study of children with recurrent AOM (12). It is interesting that 50% of the penicillin-nonsusceptible pneumococci in our study remained susceptible to azithromycin.

High-dose amoxicillin-clavulanate is indicated for the treatment of children with recurrent or persistent AOM due to *S. pneumoniae* including certain penicillin-resistant strains (penicillin MIC, ≤2 μg/ml). When we analyzed efficacy in children with pneumococci for which penicillin MICs were between 0.1 and 2 μg/ml, clinical success for high-dose azithromycin was comparable to that for amoxicillin-clavulanate at both day 12 to 16 and day 28 to 32. These results, and the fact that half of the penicillin-nonsusceptible pneumococci in this trial were azithromycin susceptible, support consideration of high-dose azithromycin for treating AOM in settings where penicillin resistance is a concern.

The 27% rate of azithromycin nonsusceptibility among pneumococci in our study is similar to that reported by Doern and associates (14) and somewhat higher than that seen in the study by Dagan et al. (12). The most common mechanism of macrolide resistance in the United States is mediated by an

TABLE 8. Treatment-related adverse events occurring at a frequency of ≥2%

Adverse event	No. (%) for group	
	Azithromycin (n = 153)	Amoxicillin-clavulanate (n = 147)
Diarrhea	30 (19.6)	44 (29.9) ^a
Vomiting	8 (5.2)	12 (8.2)
Abdominal pain	6 (3.9)	3 (2.0)
Rash	5 (3.3)	7 (4.8)
Anorexia	5 (3.3)	4 (2.7)
Dermatitis	1 (0.7)	3 (2.0)

^a P = 0.045.

efflux pump encoded by the *mefA* gene, which results in an increase in the MIC to a range of 2 to 32 $\mu\text{g/ml}$ (MIC at which 90% of the isolates tested are inhibited, 8 to 16 $\mu\text{g/ml}$). In our study, 16 of 20 (80%) azithromycin-resistant pneumococci were *mefA* strains. High-level azithromycin resistance (MIC, $\geq 64 \mu\text{g/ml}$), mediated by the *ermB* gene, was noted in 15% (3 of 20) of azithromycin-resistant isolates and in only 4% (3 of 73) of all pneumococci isolated at baseline. These results agree with those of Hyde and colleagues (24), who noted that the frequency of *ermB* strains in the United States during the 1990s remained stable at 3 to 4%, while *mefA*-mediated resistance increased over the same period. One azithromycin-resistant *S. pneumoniae* isolate in this study was *mefA* negative, *ermB* negative, and *ermA*(TR) positive by PCR analysis. This unusual genotype previously has been seen only in Greece (35). The organism was susceptible to amoxicillin-clavulanate (MIC, $\leq 0.03 \mu\text{g/ml}$) and clindamycin (MIC, 0.25 $\mu\text{g/ml}$), and the azithromycin MIC for it was 2 $\mu\text{g/ml}$. The patient from whom this strain was recovered at baseline was in the amoxicillin-clavulanate treatment group and was judged to be a clinical cure at both day 12 to 16 and day 28 to 32.

There are few published data on the efficacy of azithromycin in AOM due to *mefA* strains of *S. pneumoniae*. In a recent study of standard-dose azithromycin (30 mg/kg) administered as a single dose, Dunne and associates (17) reported clinical success among six of seven children infected with *mefA* pneumococci. In the present trial, clinical success was noted in only four of seven (day 12 to 16) and two of seven (day 28 to 32) children infected with *mefA* strains. Given these limited data from small numbers of children, additional studies are needed to assess the efficacy of azithromycin in AOM caused by pneumococci with mid-level, efflux-mediated resistance.

Clinical success rates among children with *H. influenzae* (alone and with *M. catarrhalis*) were somewhat higher for amoxicillin-clavulanate than for azithromycin at day 12 to 16. However, the difference did not reach statistical significance. Additionally, among the small number of children infected with both *H. influenzae* and *S. pneumoniae*, clinical success was comparable for the two groups. Although a previous report demonstrated superior clinical efficacy for amoxicillin-clavulanate compared with azithromycin against *H. influenzae* at day 12 to 14, that study compared the standard amoxicillin-clavulanate formulation with the standard 30-mg/kg regimen of azithromycin (13).

A potential limitation of the design of this trial is the lack of a third, standard azithromycin (30-mg/kg) treatment arm, which would have allowed us to determine whether high-dose azithromycin is superior to the 30-mg/kg dose. Although this approach is conceptually attractive, when studying a new AOM treatment regimen it is standard practice to use a comparator whose efficacy for the specific study population has been established. A noninferiority study design is usually employed in such trials because of the limited feasibility of conducting very large superiority trials, especially those involving tympanocentesis.

In a recent report, Block and colleagues (6) highlighted the difficulty of predicting which pathogens are responsible for an episode of recurrent AOM in a child who fails treatment with aminopenicillins. The authors also discussed the need for invasive procedures to diagnose, and broader-spectrum and/or

parenteral antibiotics to treat, patients who experience reinfection shortly after completing antibiotic treatment. Eighty-one percent of the patients in our study had a history of recurrent AOM. The efficacy of high-dose azithromycin demonstrated here supports the use of this regimen for treating children with recurrent disease. Additionally, one-third of the children in our trial had persistent AOM, a group excluded from the study by Dagan et al. (12). Among these patients, azithromycin and amoxicillin-clavulanate achieved comparable rates of clinical success, suggesting that high-dose azithromycin may also be a reasonable alternative for treating children with persistent AOM.

Compliance with therapy was significantly better for the azithromycin regimen. Both regimens were well tolerated, and only four patients discontinued therapy due to adverse events (one in the azithromycin group and three in the amoxicillin-clavulanate group). As expected, diarrhea was noted significantly more often in the amoxicillin-clavulanate group than in the azithromycin group. However, the incidence of diarrhea for both regimens was markedly higher than in previous studies (12, 33). This may be due to the fact that collection of information on diarrhea was based on the perception of the parent or caregiver, rather than on a strict, protocol-specified definition.

In summary, the results of this large, rigorously designed and analyzed study demonstrate the efficacy and safety of a new, 3-day, high-dose azithromycin regimen for the treatment of children with recurrent or persistent AOM. The overall clinical efficacy of high-dose azithromycin was comparable to that of high-dose amoxicillin-clavulanate at day 12 to 16 and was superior at day 28 to 32. Clinical efficacy among microbiologically evaluable patients was also comparable, including patients infected with penicillin-nonsusceptible pneumococci for which MICs were between 0.1 and 2 $\mu\text{g/ml}$. These data support consideration of high-dose azithromycin as an option for treating AOM in children who have failed first-line therapy or who experience recurrent episodes of AOM.

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