Single-Dose (30 mg/kg) Azithromycin Compared with 10-Day Amoxicillin/Clavulanate for the Treatment of Uncomplicated Acute Otitis Media: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial

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ABSTRACT

Background: The long half-life of azithromycin allows for single-dose oral therapy for acute otitis media (AOM).

Objective: This study was designed to compare the efficacy and tolerability of single-dose azithromycin with 10-day, twice-daily amoxicillin/clavulanate for the treatment of new-onset, uncomplicated AOM in children.

Methods: Children aged 6 months to 12 years with new-onset AOM were randomly assigned to receive either a single 30-mg/kg dose of azithromycin or standard-dose amoxicillin/clavulanate (45 mg/kg administered BID for 10 days) in a double-blind, double-placebo, multicenter clinical trial. The diagnosis of AOM was based on specific clinical signs and symptoms, and was confirmed by pneumatic otoscopy and acoustic reflectometry (level ≥ 3). Clinical response was assessed on days 12–16 and 28–32.

Results: Mean (SD) age of children receiving azithromycin ($n = 173$) or amoxicillin/clavulanate ($n = 173$) was 2.7 (2.3) years and 3.4 (2.8) years, respectively, with 43% and 36% ≤ 2 years of age. Most (53.2%) of the children were boys, and most (51.2%) were white. Clinical success rates (intent-to-treat) for azithromycin and amoxicillin/clavulanate, respectively, were 87% and 88% (95% CI, -9.2 to 6.5) on day 12–16 and 75% and 75% (95% CI, -10.2 to 10.5) on day 28–32. The incidences of treatment-related adverse events for azithromycin and amoxicillin/clavulanate were 16.8% and 22.5%, respectively. Corresponding rates of diarrhea were 6.4% and 12.7%, respectively. Vomiting, which was generally mild, occurred in 7 children in each group. One azithromycin patient and 5 amoxicillin/

clavulanate patients discontinued treatment because of adverse events. The compliance rate for azithromycin was significantly higher than that for amoxicillin/clavulanate (99% vs 83%; $P < 0.001$).

Conclusions: In this trial comparing the efficacy of single-dose azithromycin (30 mg/kg) with twice-daily amoxicillin/clavulanate (45 mg/kg) for the treatment of new-onset, uncomplicated AOM, no differences were detected between the 2 regimens. Single-dose azithromycin was generally well tolerated and provides an alternative to conventional oral regimens for AOM. (*Curr Ther Res Clin Exp.* 2003;64[Suppl A]:A30–A42) Copyright © 2003 Excerpta Medica, Inc.

Key words: acute otitis media, amoxicillin/clavulanate, azithromycin, short-course therapy.

INTRODUCTION

Antibiotic efficacy, safety, and compliance are primary considerations for selection of an antibiotic to treat acute otitis media (AOM). However, drug palatability and compliance with multiple daily doses over a customary 10-day period can be problematic even under optimal circumstances. Single-dose azithromycin is widely accepted as the standard of care for treatment of certain sexually transmitted diseases in adolescents and adults.¹ Administration of a single dose of antibiotic as a complete course of therapy in the clinic or office setting would ensure total compliance. Intramuscular ceftriaxone (50 mg/kg) is currently used as single-dose therapy for AOM. The efficacy and tolerability of single-dose oral treatment of AOM has not previously been reported with any beta-lactam, sulfonamide, or any other macrolide antibiotic because of the short half-life, the large volume of liquid required, and the high likelihood of gastrointestinal distress.

The pharmacokinetics of azithromycin are characterized by a prolonged half-life and sustained tissue concentrations in a wide range of body sites, including the middle ear. In a study of children with AOM, azithromycin administered as a 10-mg/kg dose on day 1 followed by a 5-mg/kg dose on day 2 achieved total mean peak concentrations in the middle ear of 8.6 and 9.4 µg/mL at 24 and 48 hours after the initial dose, respectively.² These concentrations exceed the minimal inhibitory concentrations (MICs) of the majority of strains of the 3 most common AOM pathogens—*Streptococcus pneumoniae* (MIC₅₀, 0.06 µg/mL; MIC₉₀, 16 µg/mL; 72.3% susceptible), *Haemophilus influenzae* (MIC₉₀, 2 µg/mL; 99.5% susceptible), and *Moraxella catarrhalis* (MIC₉₀, ≤0.12 µg/mL; 99.9% susceptible).^{3,4} These observations have led to consideration of single-dose azithromycin as a novel approach to treating AOM.

The objective of the current study was to compare the safety, tolerability, and efficacy of a single dose of azithromycin oral suspension with amoxicillin/clavulanate suspension administered twice daily for 10 days in the treatment of new-onset, uncomplicated AOM in children.

METHODS

Study Design

This study was a double-blind, placebo-controlled, multicenter, randomized clinical trial comparing a single dose of azithromycin oral suspension (30 mg/kg) with amoxicillin/clavulanate oral suspension (45/6.4 mg/kg; “standard-dose” amoxicillin/clavulanate) administered BID for 10 days for the treatment of AOM. Standard-dose amoxicillin/clavulanate was selected as the comparator because our study population comprised children with uncomplicated AOM, and because a standard amoxicillin dose was considered inappropriate for treating uncomplicated AOM at the time the study was initiated.⁵ Each patient received active drug and placebo match for the alternate therapy. The study was conducted at 9 clinical centers in the United States between November 1998 and December 1999. An institutional review board approved the study protocol at each center.

Inclusion/Exclusion Criteria

Children aged 6 months to 12 years, in generally good health, with a diagnosis of new-onset AOM based on specific clinical signs and symptoms, documented by pneumatic otoscopy and spectral gradient acoustic reflectometry (SGAR), were eligible for study entry. An episode of new-onset AOM was characterized by the absence of AOM within the previous 30 days. Evidence of middle-ear effusion (MEE) on clinical examination was documented by at least 2 of the following: decreased or absent tympanic membrane (TM) mobility, yellow/white discoloration of the TM, or purulent opacification of the TM. At least 1 of the following indications of acute inflammation was also required: ear pain, marked TM redness, TM fullness or bulging, or fever $>37.8^{\circ}\text{C}$ within 24 hours of presentation. Written informed consent was obtained from a parent or guardian.

Children who had the following conditions were excluded: weight >40 kg; AOM or any other illness requiring systemic antimicrobial therapy ≤ 30 days before study entry; significant interfering medical conditions, such as gastroenteritis; hypersensitivity to penicillins or macrolides; chronic or persistent otitis media; presence of tympanostomy tubes, cholesteatoma, or perforation of the TM; or prior ear surgery.

Medication Administration

At the baseline visit, medical history was recorded and physical examination and SGAR were performed. Patients were randomly assigned (1:1) to receive either a single dose of azithromycin with amoxicillin/clavulanate placebo administered twice daily for 10 days, or amoxicillin/clavulanate administered twice daily for 10 days with a single dose of azithromycin placebo. Study personnel who dispensed the first dose of study medication and placebo in the office remained blinded to treatment assignment. The parent or guardian was instructed to administer subsequent doses of study medication, starting the evening of enrollment and continuing administration twice a day for a total of 20

doses. Medications were to be refrigerated and administered with food. Each dose of medication administered was to be recorded in a diary, as well as an explanation for any missed doses or adverse events.

Patients were observed for 30 minutes in the office after administration of the first dose of study medication. If vomiting occurred during this half-hour interval, the dose was repeated with the identical initial medication. If the child vomited after the 30-minute period, no redosing occurred and the patient continued with the protocol.

Clinical Evaluation

Follow-up at study day 3–5 was conducted by telephone interview, which reviewed dosing instructions and determined whether the child was responding clinically. If initial symptoms either had not improved or had worsened, an interim visit took place. Clinical response was determined on days 12–16 and 28–32. Clinical response was defined as follows: *cure* = complete resolution of all signs and symptoms, with or without the presence of MEE; *improvement* = partial resolution of signs and symptoms, with or without persistence of MEE, and not requiring additional antibiotics for AOM; *failure* = worsening of signs and/or symptoms of AOM, no response to therapy, or requirement for additional antimicrobial therapy for AOM; *recurrence* = patients previously considered cured or improved on day 12–16 who then developed a recurrence of AOM by day 28–32. Clinical success was defined as cure or improvement. Additional assessments of efficacy at follow-up visits included evaluation of clinical signs and symptoms and administration of a parental questionnaire.

Safety Evaluation

Adverse events, either reported by the parent/caregiver or observed by the investigator, were recorded at each study visit. Adverse reactions were assessed for severity (mild, moderate, or severe), relation to study drug, and need for intervention. Collection of information on diarrhea was based on the perception of the parent/caregiver rather than on a strict, protocol-specified definition.

Compliance

Compliance with the first dose of study medication was assured by direct observation by study personnel. Compliance with the remainder of the study regimen was verified by parental diaries, as well as inspection of returned medication bottles at day 12–16.

Statistical analysis

The study was powered to ensure that the lower limit of the 2-sided 95% confidence interval for the true difference in response rates was greater than –15% with a power of 85% to detect equivalence between the 2 drugs. When a satisfactory response rate (cure + improvement) of 80% for amoxicillin/clavulanate and a 25% rate of nonevaluable patients were assumed, 175 patients per treatment group were required.

Two efficacy analyses were conducted; one was a modified intent-to-treat (MITT) analysis, and the other was based on a per-protocol evaluable population. Because a critical aspect of the study was receipt and tolerability of the first antibiotic dose, the MITT population included all patients who had received at least 1 dose of study medication. Patients included in the per-protocol analysis were required to have received at least 80% of the protocol-specified doses of medication (ie, amoxicillin/clavulanate or placebo) and no other concomitant systemic antibiotic therapy, and to have completed study visits within the appropriate time windows (day 12–16 $\pm$ 2 days and day 28–32 $\pm$ 4 days).

Patients who received other systemic antibiotics at any time prior to the day 12–16 visit were classified as failures for each of the subsequent follow-up visits. Patients who received other systemic antibiotics after the day 12–16 visit were classified as recurrences.

The number and percentage of patients were classified as clinical success (cure or improvement) or failure at day 12–16 for each treatment group. At day 28–32, the rate of failures for each treatment group included both the failures at day 12–16 and those children with a recurrence of AOM by day 28–32. Determination of equivalence between the 2 treatment regimens was based on the difference between the percentages of clinical success and the 95% CI of this difference. The 2 regimens were considered equivalent if the 95% CI contained zero and remained within the following prespecified boundaries: $\pm$ 10% when the higher of the 2 cure rates was above 90%, $\pm$ 15% when it was 80% to 90%, and $\pm$ 20% when it was below 80%. Normal approximation to the binomial distribution was used in computing the 95% CI.

Safety Analysis

Treatment-related adverse events were classified according to severity (mild, moderate, or severe) and by the affected body system. Adverse events of unknown relationship to the study drug were included with those considered related to treatment. All patients who received at least 1 dose of study drug were included in the safety analysis. The Fisher exact test was used to compare the incidence of treatment-related adverse events between treatment groups.

RESULTS

Patients

Three hundred fifty children were enrolled and randomly assigned to treatment groups. Four children (2 azithromycin, 2 amoxicillin/clavulanate) were assigned to treatment groups but did not receive treatment (2 withdrew consent, and 2 did not meet entrance criteria). These 4 patients were excluded from all analyses. All efficacy and safety analyses presented are based on the MITT population.

The demographic characteristics of the MITT population are shown by treatment group in [Table I](#). Overall, 40% were ≤ 2 years of age (azithromycin, 43%; amoxicillin/clavulanate, 36%), and 74% were < 60 months; 53.2% were boys, and 51.2% were white. Most (82%) of the children had a history of AOM, ~63% of whom had an episode of AOM before 12 months of age. In the 12 months preceding study entry, 57% of patients had 1 to 3 episodes of AOM and 9% had 4 or more episodes. About 5% of patients had a history of tympanostomy tubes. Approximately one third of the total study population had been treated with antibiotics, usually for AOM, between 30 and 90 days before study entry. The distribution of risk factors across treatment groups was similar.

As seen in [Table II](#), the distribution of clinical signs and symptoms of AOM at baseline across drug treatment groups was similar. At baseline, 27% of study patients had bilateral AOM. All children had clinical evidence signifying an acute infection, as demonstrated by the presence of TM signs at the following rates: decreased or absent mobility, 97%; fullness or bulging, 90%; and marked erythema, 82%. Fever and symptoms of ear pain, including tugging or rubbing, were present in 59% and 77% of children in the azithromycin and amoxicillin/clavulanate groups, respectively.

Clinical Response

MITT and per-protocol analyses of clinical response yielded similar results. Of 346 children in the MITT population, 321 were evaluable at day 12–16 and 305 at day 28–32. At day 12–16, both drugs were comparably efficacious, with clinical success rates of 87% and 88% in azithromycin-treated and amoxicillin/clavulanate-treated children, respectively ([Table III](#)). Clinical success rates at day 28–32 were also comparable (75% in each group). Six children in each group who were considered cured or improved at day 12–16 subsequently developed a

Table I. Demographic characteristics of the modified intent-to-treat population.

Characteristic	Azithromycin (n = 173)	Amoxicillin/Clavulanate (n = 173)
Age, y		
Mean (SD)	2.7 (2.3)	3.4 (2.8)
Range	0.5–10.6	0.5–12.3
Sex, no. (%)		
Male	92 (53.2)	92 (53.2)
Female	81 (46.8)	81 (46.8)
Race, no. (%)		
White	87 (50.3)	90 (52.0)
Black	54 (31.2)	60 (34.7)
Hispanic	28 (16.2)	23 (13.3)
Other	4 (2.3)	0 (0.0)

Table II. Clinical signs and symptoms of acute otitis media at baseline.

Sign/Symptom	Azithromycin (n = 173)	Amoxicillin/Clavulanate (n = 173)
Decreased/absent mobility	171 (99)	165 (95)
Fullness/bulging	155 (90)	155 (90)
Marked redness	148 (86)	137 (79)
Opacification	145 (84)	145 (84)
Ear pain	130 (75)	135 (78)
Yellow/white discoloration	120 (69)	116 (67)
Fever	100 (58)	104 (60)
Air-fluid level	88 (51)	84 (49)

recurrence of AOM by day 28–32. At both visits, clinical success rates for children ≤ 2 years were similar for the 2 treatment groups. However, at both days 12–16 and 28–32, clinical success rates for the younger age group were lower than those for children >2 years.

Compliance

The rate of compliance for children in the azithromycin group was significantly higher than that for the amoxicillin/clavulanate group (99% and 83%, respectively; $P < 0.001$).

Safety and Tolerability

Treatment-related adverse events occurred in 16.8% of azithromycin-treated children and 22.5% of amoxicillin/clavulanate-treated children. In both treatment groups, the most common events were gastrointestinal. Rates of

Table III. Number(%) of patients with clinical success* (modified intent-to-treat population).

	Azithromycin (n = 173)	Amoxicillin/Clavulanate (n = 173)	95% CI
Day 12–16			
All patients	139/160 (87)	142/161 (88)	–9.2 to 6.5
Age >2 y	86/92 (93)	97/105 (92)	–7.1 to 9.3
Age ≤ 2 y	53/68 (78)	45/56 (80)	–18.0 to 13.7
Day 28–32			
All patients	114/151 (75)	116/154 (75)	–10.2 to 10.5
Age >2 y	73/87 (84)	86/101 (85)	–12.7 to 10.3
Age ≤ 2 y	41/64 (64)	30/53 (57)	–12.2 to 27.1

*Cure or improvement.

treatment-related adverse events (>1 symptom may have occurred in the same patient) were similar for azithromycin- and amoxicillin/clavulanate-treated patients, respectively: diarrhea, 6.4% versus 12.7%; vomiting, 4.0% versus 4.0%; abdominal pain, 1.2% versus 1.2%; nausea, 1.7% versus 1.2%; fungal dermatitis, 0.6% versus 1.7%; and generalized rash, 1.7% versus 5.2%. None of the differences reached statistical significance. One child in the azithromycin group withdrew because of severe diarrhea. Five patients in the amoxicillin/clavulanate group withdrew because of moderate (1) or severe (1) rash, and moderate to severe vomiting and/or diarrhea (3). A 28-month-old boy who received azithromycin was hospitalized for diarrhea and vomiting on study day 4. Rotavirus infection was confirmed by enzyme-linked immunosorbent assay on the stool. The gastroenteritis was not considered drug related and resolved on study day 5.

Probable treatment-related vomiting was reported in 7 patients (4%) in each treatment group. Among patients treated with azithromycin, 6 of the episodes were considered to be mild and 1 was moderate. In 5 patients, vomiting resolved without intervention. The other 2 patients were redosed without further vomiting. In 6 patients, vomiting occurred only on study day 1; the other patient had continued vomiting on study day 2. All patients assigned to the azithromycin group who developed vomiting had a clinical response of cure at days 12–16 and 28–32. Among patients randomized to amoxicillin/clavulanate, 4 had mild vomiting and 3 had moderate vomiting. These patients required the following interventions: none (4), study drug stopped temporarily (1), treatment discontinued (1), and dose repeated without incident (1). Timing of vomiting for amoxicillin/clavulanate patients ranged from study day 1 to 9. Six of 7 patients with vomiting had a successful clinical response at day 12–16, and 1 patient had a recurrence at day 28–32.

DISCUSSION

In this double-blind, placebo-controlled trial comparing the efficacy of single-dose azithromycin with 10 days of twice-daily, standard-dose amoxicillin/clavulanate for the treatment of new-onset AOM, no differences were detected between the 2 regimens. The azithromycin regimen was well tolerated.

This trial excluded children with persistent AOM, as well as those who had received antibiotics within 30 days of enrollment. Thus, children in our study population would be considered to have had uncomplicated AOM.⁶ Recommendations by the CDC working group on drug-resistant *Streptococcus pneumoniae*⁷ emphasize that amoxicillin should remain the initial antibiotic choice for uncomplicated AOM. However, the single-dose azithromycin regimen may be particularly suitable as a first-line alternative to amoxicillin when treating children with penicillin hypersensitivity or moderate diarrhea. In addition, this simple one-dose regimen might be useful for treating obstreperous toddlers or children in families who are traveling. For children failing first-line therapy or those

experiencing recurrent episodes of AOM, the recommended treatment is high-dose amoxicillin/clavulanate (90/6.4 mg/kg daily).⁷

The mean age of our study population was somewhat older than that in recent tympanocentesis trials. Children ≤ 2 years comprised 40% of the study population, an age group most likely to be affected by AOM and to fail therapy.⁸⁻¹⁰ Of note, in both the azithromycin and amoxicillin/clavulanate groups, clinical success rates for children ≤ 2 years were lower than those for children > 2 years.

Single-dose azithromycin has not been studied formally in high-risk children with recurrent or persistent AOM, a population that seems to harbor particularly resistant strains of bacteria.^{11,12} However, a new high-dose azithromycin regimen (20 mg/kg daily for 3 days) was studied recently in children with recurrent or persistent disease.¹³ This high-dose regimen demonstrated efficacy comparable to that of 10-day, high-dose amoxicillin/clavulanate (45 mg/kg administered BID).

This study has several important strengths, as well as limitations. The double-blind, placebo-controlled design of this trial conducted by a limited number of experienced investigators minimized bias in diagnosis, treatment assignment, and outcome determination. However, because tympanocentesis was not performed, the "Pollyanna phenomenon" of overly optimistic cure rates, as espoused by Marchant et al,¹⁴ must be considered. Nonetheless, the 95% CI for clinical success at days 12-16 and 28-32 were within conservative a priori designated ranges (day 12-16: 95% CI, -9.2 to 6.5; day 28-32: -10.2 to 10.5). Also, because tympanocentesis was not performed in this trial, confirmation of bacterial etiology was not possible. However, a recent noncomparative study of single-dose azithromycin in children with bacteriologically confirmed AOM demonstrated clinical success rates of 86% and 81% at days 12 and 24-28, respectively.¹⁵ Nearly all of the children enrolled in this clinical trial had significant signs and symptoms of AOM, as evidenced by the high prevalence of fullness or bulging of the TM and marked TM redness. Although fever is commonly caused by viral infection, it was present in almost 60% of children as well, possibly signifying more symptomatic AOM. Adherence to required study visits was high, with 93% of all patients seen at the day 12-16 visit and 88% of all patients retained throughout the 30-day follow-up visit.

The clinical success rates in this study are consistent with data from earlier AOM trials that compared the standard 5-day azithromycin regimen with thrice-daily amoxicillin/clavulanate.^{16,17} However, our results do not agree with those from a trial of bacteriologic efficacy by Dagan and colleagues,¹⁸ comparing 5-day azithromycin (10 mg/kg on day 1 followed by 5 mg/kg on day 2-5) with 10-day amoxicillin/clavulanate (45 mg/kg administered BID). Their study involved tympanocentesis at baseline and day 4-6. At day 4-6, amoxicillin/clavulanate demonstrated significantly higher bacteriologic eradication rates, overall and for *H influenzae*. At day 12-14, greater clinical success was reported with amoxicillin/clavulanate, overall and in patients with *H influenzae*. The study by Dagan et al¹⁸ differs from ours in its single-blind design, younger mean age of patients

(~16 months), predominance of *H influenzae*, and high proportion (>50%) of patients from a single, non-US site. These factors may explain, at least in part, the differences observed.

Only 1 other antibiotic has been studied as single-dose therapy for AOM. Green and Rothrock¹⁹ conducted a double-blind, nontympanocentesis trial in 233 children with new-onset AOM. They found single-dose intramuscular ceftriaxone was as effective as oral amoxicillin administered for 10 days. The authors noted the distinct advantages of single-dose therapy, focusing on compliance, observed completion of the course of therapy, and relief of the parental burden of multiple daily doses. They also concluded that a single dose of intramuscular ceftriaxone should be limited to selected clinical situations. Barnett et al²⁰ also demonstrated equivalence between IM ceftriaxone and 10 days of trimethoprim-sulfamethoxazole. However, when a single dose of ceftriaxone was compared with amoxicillin/clavulanate in another nontympanocentesis trial similar to ours, ceftriaxone was significantly less effective.²¹ Bauchner et al,²² in an unblinded trial, reported that parents preferred a single injection of ceftriaxone over 10 days of oral antibiotic therapy for AOM. However, the preference of the child in any of the preceding ceftriaxone studies was not assessed.

The bactericidal activity of azithromycin, as well as the dose-dependent nature of its bactericidal effect, have been demonstrated in a variety of animal infection models, including *Spneumoniae* and *H influenzae* middle-ear infection in gerbils,²³ viridans streptococcal endocarditis in rats, and mouse models of pneumococcal pneumonia and *Streptococcus pyogenes* soft-tissue infection.²⁴ Using a chinchilla model of AOM, Babl and colleagues²⁵ have also reported that higher doses of azithromycin achieve enhanced killing of *H influenzae*, with improved sterilization of the middle ear. This relationship between higher dose and better killing suggests that a single, large dose of azithromycin may be preferable to divided daily doses.²⁶ Results from a gerbil model of *H influenzae* AOM provide support for this concept. Girard et al²⁷ recently reported that administration of azithromycin as a single dose achieves a significantly greater reduction in bacterial load and earlier sterilization of the middle ear than the same dose divided over 2 or 3 days. Additional studies are needed to assess the pharmacokinetics of single-dose azithromycin in the middle ear of children.

Consumption of the volume necessary for an entire treatment course as a single dose of azithromycin was quite well tolerated and acceptable. In fact, a single dose of 30 mg/kg using the 200 mg/5 mL formulation only requires the ingestion of 7.5, 15, and 22.5 mL in a 10-, 20-, and 30-kg child, respectively. Both antibiotics were associated with vomiting in an equivalent small number of children. As expected, nearly all cases of vomiting in the azithromycin group occurred on the first day, whereas vomiting with amoxicillin/clavulanate occurred over 9 days. Only 2 of 7 children required a repeat dose of azithromycin, and a successful clinical outcome was observed in each of the patients who vomited. The 12.7% rate of drug-related diarrhea (similar to that in other studies^{9,28}) in children treated with a twice-daily formulation of amoxicillin/clavulanate was twice that of azithromycin.

As expected, the compliance rate was significantly higher for azithromycin than for the comparator. The gastrointestinal tolerability, simplicity, and palatability²⁹ of single-dose azithromycin should lead to a notably high compliance rate. This may be particularly useful in clinic settings and emergency departments, where compliance may be in doubt and directly observed therapy becomes a viable option.

CONCLUSIONS

In this non-tympanocentesis trial comparing the efficacy of single-dose azithromycin (30 mg/kg) with 10 days of twice-daily, standard-dose amoxicillin/clavulanate for treatment of new-onset, uncomplicated AOM, no differences were detected between the 2 regimens. Single-dose azithromycin was well tolerated and represents an alternative to conventional 5- or 10-day antibiotic regimens for new-onset AOM.

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