

## The comparison of single-dose ceftriaxone, five-day azithromycin, and ten-day amoxicillin/clavulanate for the treatment of children with acute otitis media

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**SUMMARY:** Biner B, Çeltik C, Öner N, Küçükuğurluoğlu Y, Güzel A, Yıldırım Ç, Adalı MK. The comparison of single-dose ceftriaxone, five-day azithromycin, and ten-day amoxicillin/clavulanate for the treatment of children with acute otitis media. Turk J Pediatr 2007; 49: 390-396.

The aim of the study was to evaluate the efficacy of short-course antimicrobial therapies [single intramuscular dose of ceftriaxone (50 mg/kg, not exceeding 1 g), 5 days of azithromycin (10 mg/kg on day 1, then 5 mg/kg daily on days 2-5) and the traditional 10-day course of amoxicillin/clavulanate (90/6.4 mg/kg/day in 2 doses)] in children with acute otitis media (AOM). The study was conducted as a prospective, comparative, open randomized trial between February 2001 and April 2003, and 104 children were enrolled, with a mean age of 3.8 (2.3) years.

The clinical and otoscopic assessments of the children were made on days 0, 3, 11 and 30 after admission, and tympanometry was performed on day 30. The patients were diagnosed and followed with a scoring system. Clinical success was achieved in 29/34 patients (85.3%) in the ceftriaxone group, 27/31 patients (87.1%) in the azithromycin group and 34/39 children (87.2%) in the amoxicillin/clavulanate group. The rate of persistence of middle-ear fluid did not differ between the three groups ( $p>0.05$ ). During the one-month period, no recurrent case was observed. The most common drug-related adverse effects were associated with the gastrointestinal system.

In conclusion, for the treatment of children with AOM, the clinical success of single-dose intramuscular ceftriaxone and of five-day azithromycin treatments was comparable to that of the traditional 10-day therapy with high-dose amoxicillin/clavulanate.

*Key words:* acute otitis media, azithromycin, ceftriaxone, amoxicillin/clavulanate.

Acute otitis media (AOM) is one of the most prevalent bacterial infections of early childhood, and the most common indication for which antibiotics are prescribed<sup>1</sup>. By the age of three years, 50-85% of children have been diagnosed with AOM that required treatment with antibiotics<sup>2</sup>. The most common pathogens associated with AOM are *Streptococcus pneumoniae* (40%-50%), nontypeable *Haemophilus influenzae* (30%-40%) and *Moraxella catarrhalis* (10%-15%)<sup>3</sup>.

Although a traditional 10-day course of amoxicillin is the recommended first-line therapy<sup>4</sup>, the management of AOM remains unsettled and controversial. There is a high rate

of spontaneous recovery from AOM whereas untreated AOM can lead to serious suppurative complications, such as acute mastoiditis, meningitis and facial paralysis<sup>5</sup>. The duration of therapy for AOM has recently been evaluated and short-course antibiotic therapy ( $\leq 5$  days) has been reported to improve adherence and may reduce secondary bacterial resistance<sup>6</sup>. Single-dose intramuscular ceftriaxone (CFX), peroral azithromycin (AZT) (single dose, 3 or 5 days), and amoxicillin/clavulanate (AMX/CVA) (5 days) have been used successfully<sup>6-8</sup>. For the treatment of AOM in children, the first single-dose regimen approved by the U.S. Food and Drug Administration (FDA) was for

intramuscular CFX and it is currently in use in Europe as three intramuscular doses administered over three days<sup>9</sup>. AZT, with a prolonged half-life of 68 h and achieving sustained concentrations in the middle ear, allows for once-daily dosing and shorter treatment regimens<sup>10</sup>.

The aim of study was to compare the effectiveness and the safety profiles of a single intramuscular dose of CFX, and five-day AZT, which are short-course therapies, to 10-day AMX/CVA, which has become the standard therapy in children with AOM.

## Material and Methods

### *Subjects and Study Design*

The study was approved by the Faculty Ethics Committee. Prior to enrolment, written informed consent was obtained from the parents of the children. A total of 104 children aged 6 months to 10 years who were newly diagnosed with AOM in the Departments of Pediatrics and Otorhinolaryngology were enrolled in the study during two winter seasons, starting in November and ending in April, in 2001/2002 and 2002/2003.

Acute otitis media was diagnosed by the presence of the characteristic otoscopic findings, and children were enrolled within 48 h of the onset of one or more acute symptoms such as fever (axillary:  $>38^{\circ}\text{C}$ ), ear pain/tugging of the ear and irritability/sleep disturbance. Diagnostic otoscopic findings were defined as erythema and/or cloudy appearance, and/or bulging of tympanic membrane. These findings were verified by two experienced pediatricians and two otorhinolaryngologists.

Exclusion criteria included a history of AOM during the preceding month, antibiotic use during the previous two weeks,  $\geq 4$  episodes of AOM in the past 12 months, spontaneous perforation of the tympanic membrane or presence of tympanostomy tubes, and hypersensitivity to penicillins, macrolides or cephalosporins. Moreover, patients with craniofacial anomalies, Down syndrome, immunodeficiency, use of immunosuppressive medications or another concurrent acute disease were also excluded from the study.

### *Therapy Regimens and Assessment*

This was an open-label, single-center, randomized study. Children with AOM were prospectively enrolled in the study and each

patient was allocated to receive either a single-dose intramuscular CFX (50 mg/kg, not exceeding 1 g), or AZT suspension (10 mg/kg on day 1, then 5 mg/kg daily on days 2 through 5) or AMX/CVA suspension (90/6.4 mg/kg per day in 2 divided doses) for 10 days. If the patient vomited within the first 30 minutes of ingestion of the suspension, dosing was repeated. In addition, all children received adequate analgesic and antipyretic as paracetamol (10-15 mg/kg per dose).

### *Follow-up Observations*

At entry and at follow-up visits, history and examination findings were recorded on a standardized form. Patients were assessed on days 3, 11 and 30 after commencement of treatment. The evaluation consisted of an interval history including questions about possible side effects and adherence to therapy and also of otoscopy performance. Severity of symptoms and tympanic membrane changes were assessed according to a scoring system modified from the clinical otitis score published by Dagan et al.<sup>11</sup>. Tympanometry was performed on day 30 after initiation of therapy by the same audiologist who was blinded to group assignment, symptoms and otoscopy findings. Tympanometry was not applied to the patients with tympanic membrane perforation. Tympanogram curves with a peak pressure at  $-99$  to  $+200$  mm H<sub>2</sub>O were defined as type A; curves with a peak of  $-100$  to  $-300$  mm H<sub>2</sub>O as type C; and flat curves as type B. Middle ear fluid was diagnosed when tympanometry revealed type B tympanogram. Diagnostic tympanocentesis was not performed.

### *Clinical Scoring System*

The symptoms and otoscopic findings were evaluated according to a scoring system (Table I). Fever and ear pain/irritability were evaluated as symptoms and erythema and bulging/air-fluid level as features of tympanic membrane, grading each parameter from none (0) to severe (3), and perforation had a grade of (4). Reference photographs of tympanic membrane appearances corresponding to relevant scores were used for standardization. The maximum achievable symptom and tympanic membrane scores were 5 and 7, respectively. If the sum of the clinical and otoscopic scores was "zero", this condition was

**Table I.** Clinical and Otosopic Scoring System for Assessment of Acute Otitis Media (AOM)

Clinical assessment	Point	Otosopic assessment	Point
Fever		Erythema	
Absent	0	Absent	0
Mild (37.5-38.5°C)	1	Mild	1
Severe(>38.5°C)	2	Moderate	2
		Severe	3
Otalgia/Irritability		Bulging/air-fluid level	
Absent	0	Absent	0
Mild	1	Mild	1
Moderate	2	Moderate	2
Severe	3	Severe	3
		Perforation	4

defined as success. Otherwise, if total of clinical and otoscopic scores was 0-3 points or  $\geq 4$  points, those conditions were accepted as improvement or failure, respectively. Cumulative clinical resolution was defined as the sum of clinical success and improvement and if they remained totally resolved through day 11. When the result was failure for any treatment regimen on day 3, the therapy regimen was changed to intramuscular CFX (50 mg/kg, maximum dose 1 g, daily for 3 days). The patients who were evaluated as treatment failure on day 3 were also assessed on days 11 and 30 but they were not included in day 11 and 30 statistical analysis. Recurrence was defined as the reappearance of symptoms on days 12-30 after their initial resolution.

### Statistical Methods

According to applied therapy regimens, three groups were formed. Kolmogorov-Smirnov and Shapiro-Wilk tests were applied to evaluate homogeneity of the variances. Kruskal-Wallis test and one-way-ANOVA were used for the nonhomogeneous and homogeneous mean values, respectively. As post hoc tests, Mann-Whitney U and Tukey test were applied.

Differences between groups with respect to categorical data (success, failure, etc.) were assessed by chi-square tests. Data were shown as mean, standard deviation (SD) [minimum-maximum value] or n (%). Statistical tests were based on a level of significance of  $p < 0.05$ .

### Results

A total of 104 children ranging in age from 6 months to 10 years with a mean (SD) of 3.8 (2.3) years were evaluated. There were 53 males and 51 females; 34 were treated with CFX, 31 with AZT and 39 with AMX/CVA.

According to age distribution and gender, no significant difference was determined among the groups ( $p > 0.05$ ). There was also no statistically significant difference in the severity of the initial clinical and otoscopic findings assessed by the scoring system between the three treatment groups ( $p > 0.05$ ) (Table II).

### Clinical Outcome

Clinical outcome of the 104 eligible patients is presented in Table III. According to assessment of clinical and otoscopic scores on day 3, 14 patients were regarded as failure. On

**Table II.** Admission Data of 104 Children Randomized to Receive CFX, AZT or AMX/CVA

	CFX n=34	AZT n=31	AMX/CVA n=39	P
Age (years)*	3.5 (2.4) [0.5-9]	4.5 (2.2) [0.5-10]	3.6 (2.3) [0.5-10]	NS
Gender (male)**	18 (52.9)	13 (41.9)	22 (56.4)	NS
Initial clinical score*	3.8 (0.9) [2-5]	3.7 (0.6) [3-5]	3.9 (0.7) [3-5]	NS
Initial otoscopic score*	1.2 (0.7) [1-3]	1.1 (0.4) [1-3]	1.3 (0.7) [1-3]	NS
Initial total score*	7.2 (0.7) [6-9]	7.0 (0.4) [6-9]	7.3 (0.8) [6-9]	NS

\* Mean (SD) [range]. \*\* n(%).

NS: Not significant. CTX: Ceftriaxone. AZT: Azithromycin. AMX-CVA: Amoxicillin/clavulanate.

**Table III.** Efficacy of Therapy Regimens (Day 3 After Initiation of Therapy)

	Treatment results				
	n	Success	Improvement	Cum. clinical resolution	Failure
CTX	34	22 (64.7)	7 (20.6)	29 (85.3)	5 (14.6)
AZT	31	22 (71.0)	5 (16.1)	27 (87.1)	4 (12.9)
AMX-CVA	39	29 (74.4)	5 (12.8)	34 (87.2)	5 (12.8)
P values		NS	NS	NS	NS

Values are shown as n (%). NS: Not significant. Cum: Cumulative.  
 CTX: Ceftriaxone. AZT: Azithromycin. AMX-CVA: Amoxicillin/clavulanate.

day 3, 29/34 (85.3%) children in the CFX group had clinical resolution [success (22) or improved (7)], and 5 (14.6%) failed; 27/31 (87.1%) in the AZT group had clinical resolution [success (22) or improved (5)] and 4 (12.9%) failed; and 34/39 (87.2%) in the AMX/CVA group had clinical resolution [success (29) or improved (5)] and 5 (12.8%) failed. The clinical and otoscopy scores declined similarly in the three groups on days 3 and 11. There were no statistically significant differences in the mean clinical and otoscopic scores assessed on day 3 and 11 between the groups ( $p > 0.05$ ) (Figs. 1, 2).

Tympanic membrane perforation developed in two cases, one from the AZT and one from the AMX/CVA group. Therapy regimens of 14 children with treatment failure, including those with tympanic membrane perforation, were changed on day 3 to intramuscular ceftriaxone (50 mg/kg daily for 3 days).

Follow-up data on day 30 for the persistence of middle ear fluid by type B tympanograms was defined in 16/90 (17.8%) patients by tympanometry. Otitis media with effusion (OME) was defined in 5/29 cases (17.2%) in CFX, 6/27 cases (22.2%) in AZT, and 5/34 cases (14.7%) in AMX/CVA treatment groups.

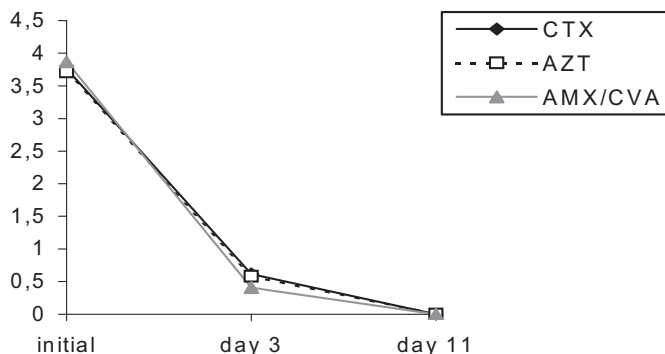


Fig. 1. The mean clinical scores of the patients with acute otitis media;  $p > 0.05$ .

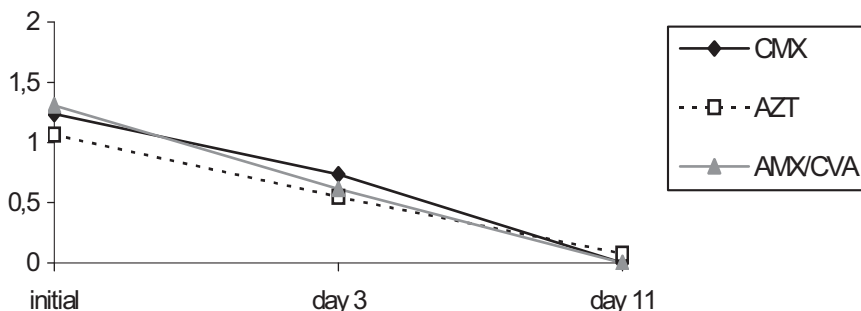


Fig. 2. The mean otoscopic scores of the patients with acute otitis media;  $p > 0.05$ .

With respect to the development of OME, there was no statistically significant difference among groups ( $p>0.05$ ). Recurrence did not occur during the one-month period.

### Side Effects

The observed side effects were not severe and were mainly directed to the gastrointestinal system. Diarrhea was observed in 2 CTX (5.8%), in 2 AZT (6.4%) and in 3 AMX/CVA patients (7.6%) ( $p>0.05$ ), and vomiting in 1 patient in each of the oral treatment groups. These side effects did not necessitate any changes in study medications. None of the children complained of persistent pain or of a local complication at the injection site.

### Discussion

Evaluation of the efficacy of antimicrobial agents for treatment of AOM is complicated by the problems in the clinical diagnosis of AOM, especially in young children, and differences in the definition of outcome measures, a high rate of spontaneous recovery, and the necessity for large sample sizes in clinical studies.

In our study with limited sample size, outcomes of the three treatment groups based on the scoring system were comparable: 85.2%, 87.1% and 87.2% for CTX, AZT and AMX/CVA treatment groups, respectively. The scoring system including both clinical and otoscopic assessment was useful especially for precise diagnosis and follow-up. It has been estimated that AOM is diagnosed correctly in approximately 50% of infants and young children<sup>12</sup>. Furthermore, AOM may be overdiagnosed in more than 30% of children<sup>13</sup>. A scoring system combining clinical criteria of fever, ear pain/irritability and otoscopic findings of erythema, bulging/air-fluid level may improve diagnostic accuracy. Diagnostic accuracy, especially differentiation of AOM from OME, is of primary importance since the latter needs no antibiotic treatment. When OME is mistakenly identified as AOM, antibacterial agents may be prescribed unnecessarily<sup>14</sup>. A similar scoring system has been used in a recent study to determine the severity of disease<sup>15</sup>.

The increasing resistance rate of pneumococci to penicillin and beta-lactamase-producing *H. influenzae* and *M. catarrhalis* raises difficulties in the choice of appropriate therapy

for AOM. Because of its low cost and relative safety, AMX is still considered first-line therapy in major guidelines<sup>14</sup>. However, AMX cannot cover beta-lactamase-producing *H. influenzae* and *M. catarrhalis*. For the presence of beta-lactamase-producing pathogens, CVA has been added to AMX (AMX/CVA). Traditional dose of AMX was 45 mg/kg/day when used alone or in combination with CVA. However, when administered at 45/6.4mg/kg/day, AMX/CVA achieves suboptimal eradication rates (62%) for *H. influenzae*<sup>16</sup>. The efficacy of high-dose AMX (90 mg/kg/d) or AMX/CVA (90/6.4 mg/kg/d) is considered appropriate for treating AOM due to possible coverage of some penicillin-resistant pneumococci. In recent studies with high-dose AMX/CVA, eradication rates improved to 90%<sup>17</sup>. In Turkey, approximately 40% of pneumococci are penicillin-resistant and one-fifth of resistant isolates have exhibited high level of penicillin resistance since 2000<sup>18</sup>. Taking this into consideration, we also used the currently recommended dose of AMX/CVA, and a clinical success of 87.2% was achieved.

In the treatment of AOM, CFX has been reserved for patients failing oral therapy or those with severe disease<sup>4</sup>. Although CFX is not "first-line" therapy for AOM, its usefulness in geographic areas with high penicillin resistance and in persistent infections presumed to be secondary to resistant organisms can be considered<sup>9</sup>. CFX has a good antibacterial activity against most pathogens causing AOM and reaches 10% of its serum concentration in the middle-ear fluid. Yet, this exceeds the minimum inhibitory concentrations (MIC) of the typical AOM pathogens for approximately 56 hours after a single intramuscular injection of 50 mg/kg<sup>19</sup>. Parenteral antibiotic treatment, especially if it is a single dose, provides advantages for children who might refuse to take or vomit oral medications and for families who might have compliance problems. In our study, the clinical resolution rate for the CFX group (85.3%) is comparable to reported rates in previous trials<sup>20,21</sup>. Although a single injection of intramuscular CFX is approved for the treatment of AOM, it is recommended as daily injections on three consecutive days for patients in whom initial therapy with high-dose AMX ( $\pm$ CVA) is unsuccessful<sup>4,22</sup>. In our study, 14 children with treatment failure were treated with three doses of CFX. Five children in the

CFX group with failure on day 3 received two additional doses. However, CFX should not be recommended for routine therapy for AOM because this may enhance resistance to this potent antibiotic and interfere with its use in serious and life-threatening infections<sup>20</sup>.

In the present study, clinical success with AZT (87.1%) was similar to other comparative antibiotics ( $p < 0.05$ ). Because of its pharmacokinetic properties, AZT was used in short-course trials with clinical efficacy comparable to 10-day treatments<sup>23</sup>. Except for a recent comparative study of AMX/CVA versus AZT, no difference in clinical success of antibiotics has been verified. In that trial, Hoberman et al.<sup>17</sup> compared high dosage AMX/CVA with five days of AZT, and achieved clinical success rates of 90.5% and 80.9%, respectively ( $p < 0.01$ ). Furthermore, single-dose AZT trials for uncomplicated AOM and high-dose AZT (20 mg/kg/day for 3 days) treatment regimens for recurrent or persistent AOM were reported to have successful outcomes<sup>24,25</sup>.

The present study design has some limitations: it was an open, not placebo-controlled study, and middle ear cultures were not obtained. Finally, given the small sample size, this study was not powered to be categorized as a clinically important efficacy study. Diagnostic tympanocentesis was not performed for ethical reasons because it is not necessary for uncomplicated AOM<sup>26</sup>.

Our results support the findings of other studies that shorter treatments may be comparable to the traditional 10 days of antibiotic therapy. It has been reported that many parents only continue antibiotic therapy until symptoms resolve or by an additional one or two days<sup>27</sup>. As improved treatment adherence in AOM may result in improved outcomes because of less treatment failures and recurrent disease, this would lead to better economic outcomes. Hence, duration of treatment, compliance and cost are important issues in the empiric antibiotic selection for AOM.

In conclusion, single-dose intramuscular CFX, or five-day AZT, which are short-course treatments, have comparable clinical outcome to 10-day AMX/CVA. In addition, three doses of intramuscular CFX in case of treatment failure after 72 hours of an oral antibiotic is an effective therapy. However, single-dose CFX

should not be a routine treatment but reserved for severe cases or when compliance to oral treatment is not possible.

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