

## Clinical Efficacy of Antimicrobial Drugs for Acute Otitis Media; Randomized Comparative Study of Amoxycillin Versus Other Extended Spectrum Antimicrobials.

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**Objective:** To evaluate the difference in clinical efficacy between Amoxycillin and other broad spectrum antibiotics (Amoxycillin-clavulanate and Cefaclor) in the treatment of acute otitis media (AOM) in infants and children.

**Methods:** One hundred and twenty patients aged 6 months to 5 years with AOM were randomly allocated to 3 treatment groups. Group A was treated with amoxycillin, group B and C randomly treated either with amoxycillin-clavulanate or Cefaclor. AOM was diagnosed on clinical grounds, including proper pneumatic otoscopic examination. Subjects were followed up for one month. Enrolment criteria, exclusion criteria, follow up intervals and compliance monitor were similar in three groups. Clinical response of subjects in all groups was statistically analysed.

**Results:** Overall 67 of 98 (68.4%) subjects were considered cured or improved at 21-30 days post therapy visit. Out of 40 patients treated with amoxycillin, 28 (70%) were considered cured or improved. The same status was noted for 22 of 30 (73%) patients treated with amoxycillin-clavulanate and 17 of 28 (61%) patients treated with Cefaclor. No significant differences were found in the comparative clinical efficacy of anti-microbial agents used. B-lactamase-stable agents did not significantly increase the cure rates of AOM.

**Conclusion:** The empiric selection of an antibiotic for treatment of AOM should be based on the cost effectiveness, safety and tolerability. It was concluded that amoxycillin is the drug of choice for empiric therapy of AOM.

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AOM is the most common childhood illness requiring treatment with antibiotics. There is a great deal of expense involved in outpatient antibiotic therapy for children with otitis media. About 240 million dollars was spent in the United States in 1990 on outpatient antibiotic therapy for children with AOM<sup>1</sup>. Confusion over the optimal management of AOM is apparent from the diverse conclusions expressed in more than 100 published clinical trials<sup>2</sup>. AOM has a multifactorial etiology, but it is extremely difficult to differentiate between bacterial and viral causes on clinical ground<sup>3</sup>.

The question that paediatricians usually have to address is not whether AOM should be treated with an antimicrobial agent, but rather the choice of antimicrobial agent.

Appropriate use of antibiotic is one of the major issues in medicine today. In most countries AOM in

children is treated with antibiotics, however the efficacy of antibiotic use is a controversial issue<sup>4</sup>.

Many experts still recommend amoxycillin for initial empiric treatment of all episodes<sup>2,5,6</sup>, though some limit this to situations where B-lactamase producing organisms are unexpected<sup>7,8</sup>, others suggest initial treatment with B-lactamase stable drug because of increased prevalence of amoxycillin resistant organisms<sup>9</sup>. Some clinicians restrict the use of antimicrobials to children continuing to have symptoms after 24-72 hours<sup>10,11</sup> because of the high rate of spontaneous resolution of acute symptoms.

An excessive use of antimicrobial agents may accelerate the emergence of bacterial resistance which will affect B-lactamase stable drugs. Therefore, our study was planned to assess the comparative efficacy of various broad spectrum antimicrobials versus amoxycillin for the same endpoint.

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## METHODS

This is a prospective randomized study conducted in the Paediatric and Otolaryngology clinics in Prince Rashid Hospital in the north of Jordan from July 1996 to April 1997. Children aged 6 months to 5 years who were diagnosed as having AOM were included in this study. Diagnosis was based on presenting symptoms (fever, irritability and otalgia) which was confirmed by otoscopic findings of a red or yellow tympanic membrane (TM) with absent or diminished mobility.

Exclusion criteria included those who received antibiotic therapy within the previous 7 days, those with upper respiratory tract infection or allergy, who currently had tympanostomy with ventilating tube in place, had history of middle ear surgery, or had perforation of TM or had any condition that might increase susceptibility to OM ie, Down's syndrome, cleft palate, immune deficiency or malabsorption.

Eligible patients were allocated to 3 treatment groups. Group A was given amoxycillin in a daily dosage of 40mg/kg in 3 equal doses for 10 days. The Group B and C were randomly given either amoxycillin-clavulanate at a daily dosage of 40 mg/Kg, depending on amoxycillin content; in 3 equal doses for 10 days; or cefaclor at a dose of 40 mg/Kg/day in 3 divided doses for 10 days. No other medication apart from antipyretics was given.

Follow-up intervals and compliance measures were similar for both groups. Compliance with taking the medication was monitored by measuring the contents of returned medication bottle. Follow-up consisted of examination at 3-5 days after entry and at the end of therapy visit. Patients were re-evaluated 10-14 days and 21-30 days after entering the study. The clinical response at each visit was classified as cure, improvement, failure, or relapse.

Cure was defined as complete resolution of clinical signs and symptoms including otoscopic findings. Improvement was defined as resolution of clinical signs and symptoms except residual middle ear effusion (MEE) suggested by persistent diminished TM mobility. Failure was defined as persistence of clinical signs and symptoms and/or otoscopic findings of TM inflammation including colour and mobility. Relapse was defined as initial clinical improvement of symptoms and otoscopic signs followed by deterioration detected at the 21-30 days follow up visit.

## STATISTICAL ANALYSIS

Clinical response of subjects in all treatment groups was statistically analyzed using Chi-squared test. The level of significance was taken at  $<0.05$ .

## RESULTS

### Clinical outcomes

One hundred and twenty children with AOM were enrolled in this clinical trial, 22 children were excluded from the analysis as they failed to return for the post therapy visits. Forty children were treated with amoxycillin, 28 with cefaclor and 30 with amoxycillin-clavulanate. Overall 67 of 98 (68.4%) subjects were considered cured or improved at the 21-30 days post therapy visit; 28 of 40 (70%) with amoxycillin, 17 of 28 (61%) with Cefaclor and 22 of 30 (73%) with amoxycillin-clavulanate. The differences in outcome between the three groups were not statistically significant ( $P=0.5$ ) (Table 1).

Table 1. Clinical results of all treatment groups

Treatment	Total number	Cured/ improved	Failure	Relapse
Amoxycillin	40	28(70%)	8(20%)	4(10%)
Amoxycillin-Clavulanate	30	22(73%)	6(20%)	2(7%)
Cefaclor	28	17(61%)	10(36%)	1(3%)

Chi-squared test. Chi-square = 3.3 df = 4  $P = 0.5$

Compliance with taking the medication was considered equivalent for all treatment groups; in as much as greater than 80% of the medication was used.

### Demographic characteristics

The differences between the treatment groups were not statistically significant with respect to age ( $P = 0.8$ ), and sex ( $P = 0.6$ ). There were 58 males and 43 females (Tables 2 & 3).

Table 2. Population characteristics (Age)

Age	Amoxycillin	Amoxycillin Clavulanate	Cefaclor	Total
6-23	25	18	15	58
24-60	15	12	13	40

Chi-squared test. Chi-square = 0.6 df = 2  $P = 0.8$



Table 3. **Population characteristics (Sex)**

Sex	Amoxycillin	Amoxycillin Clavulanate	Cefaclor	Total
Male	21	16	15	58
Female	19	14	13	40

Chi-squared test. Chi-square 1.1 df = 2 P = 0.6

Table 4 showed that the majority of patients (76.5 %) in all groups had duration of symptoms less than 2 days. However the difference was not statistically significant (P=0.7).

Table 4. **Duration of symptoms**

	Amoxycillin	Amoxycillin Clavulanate	Cefaclor	Total
<2 days	32	23	20	75
>3 days	8	7	8	23

Chi-squared test. Chi-square = 0.7 df = 2 P = 0.7

## DISCUSSION

AOM is one of the most frequent causes of physician visits by children. About 62% of children (1 year of age) have had an episode of AOM. This increased to 80% of children by 3 years of age<sup>12</sup>. Diversion regarding the optimal management of AOM was reported in many clinical trials; certain percentage of patients with AOM showed spontaneous cure without the use of antibiotics, this percentage reached as high as 88% in one study<sup>12</sup>. On the other hand, complications occurred in 3-20% of cases with AOM who were treated without antibiotics<sup>12</sup>. Variation in the use of antibiotics between the doctors of different nations was reported from as low as 31 % of cases of AOM in Netherlands to as high as 98% in Australia and United States<sup>13</sup>. Many doctors and their patients may be disinclined to use antibiotics at first presentation of AOM for so little benefit. Von Buchen et al<sup>14</sup> found only 3% (136/4860) of children with AOM who were treated with no antibiotic therapy suffered a severe course of the illness. Two of children developed mastoiditis, but this settled uneventfully after treatment with amoxycillin<sup>14</sup>. Most of general practitioners still seldom use antibiotics to treat AOM and mastoiditis remained rare<sup>15</sup>.

Almost all studies were conducted in western countries, so these results may not be generalised to third world countries, where the far greater risk of serious

suppurative complications may support early use of antibiotics for treatment of AOM<sup>16</sup>. So what is the optimal antibiotic to be used? Our clinical trial came to answer this question and support the other clinical trials done in other parts of the world. In Jordan there has been an increased empiric use of extended spectrum antibiotics for treatment of AOM, that might increase emergence of bacterial resistance and interfere with the normal host immune response to infection and hence contribute to early re-infection.

Our study showed no statistically significant difference in clinical response to amoxycillin, amoxycillin-clavulanate and Cefaclor. Amoxycillin-clavulanate was not found to be superior to amoxycillin in treating AOM probably due to low prevalence of the pathogens being beta- lactamase producing.

Amoxycillin has safety and clinical efficacy comparable to those of more expensive agents such as amoxycillin-clavulanate and the cephalosporins<sup>17</sup>. However early relief of symptoms is unaffected by choice of drug<sup>18</sup>.

Hueston et al<sup>19</sup>, was concordant with our conclusion when he reported that for an AOM episode treatment, first line antibiotics (amoxycillin, ampicillin, penicillin, or sulfamethaxazole-trimethoprim) are just as effective as broad-spectrum, more expensive second line antibiotics.

Perry et al<sup>20</sup> also concluded that amoxycillin should remain the drug of choice for treatment of AOM with efficacy reaching 91% compared with Cefaclor with an efficacy of 97%.

Scholz et al<sup>21</sup>, from Germany found that treatment of AOM was successful in 96% of the amoxycillin treated patients and amoxycillin can be administered at 50 mg/ kg/day in a convenient twice - daily dosage schedule. On the other hand Subba et al<sup>22</sup> from India showed that amoxycillin-clavulanate was significantly more effective clinically than Cefaclor in the treatment of AOM in children, a result which differs from our conclusion.

## CONCLUSION

The diverse conclusions may be explained by the different local epidemiology of different countries. Amoxycillin still remains the antibiotic of empiric treatment of AOM primarily guided by cost, safety and tolerability.



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