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Co-amoxiclav in recurrent acute otitis media: placebo controlled study

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Abstract

***Objective*—To determine the efficacy of co-amoxiclav in children aged 6 months to 12 years with recurrent acute otitis media.**

***Design*—A randomised double blind placebo controlled clinical trial.**

***Setting*—General practice in the Netherlands.**

***Patients*—121 children with recurrent acute otitis media, defined by onset of otalgia and otoscopic signs of middle ear infection within four to 52 weeks after the previous attack. Confirmation of diagnosis and randomisation was done by otolaryngologists.**

***Intervention*—Oral co-amoxiclav or placebo in weight related doses for seven days.**

***Main outcome measure*—An irregular clinical course defined as the presence of otalgia or a body temperature ≥38°C, or both, after three days.**

***Results*—Eleven (16%; 95% confidence interval 9% to 28%) children had an irregular course in the co-amoxiclav group and 10 (19%; 9% to 31%) in the placebo group (difference not significant). Age, dichotomised at 2 years, was the only significant prognostic factor for irregular course of the disease (odds ratio 5·9; 1·8 to 19·1). Among children aged below 2 years, 28% (4/14) in the co-amoxiclav group and 58% (7/12) in the placebo group had irregular courses. For children 2 years and older these percentages were 13% (7/52) and 7% (3/41).**

***Conclusion*—Children with recurrent acute otitis media are at greater risk of an irregular clinical course of the disease than children with a first episode of acute otitis media. Co-amoxiclav has no significant benefit over placebo in treating children over 2 years with acute otitis media.**

Introduction

Acute otitis media is common among children. Cumulative incidences have been reported at 65-93% in children up to the age of 7 years.[1,2] Several therapeutic strategies have been used to prevent complications and enhance recovery, including tympanocentesis, antibiotics, antihistamines, and decongestants. Though placebo controlled trials have not shown a relevant difference in clinical outcome between placebo and antibiotics in children aged 2 years and older,[3] antibiotics are the first choice in medical management in most countries.[4] Without antibiotics an irregular course occurs in less than 5% of patients.[5]

The current policy in the Netherlands is to prescribe oral analgesics and decongestant nose drops for otherwise healthy children aged 2 years and older. Antibiotics are prescribed only when no clinical improvement has occurred after three days. It is questionable, however, whether watchful waiting is acceptable in children with recurrent acute otitis media, in whom a complicated course and sequelae can be expected to be more common.[6] The objective of this study was to establish the efficacy of co-amoxiclav among children aged 6 months to 12 years with recurrent acute otitis media. We included patients younger than 2 years as little research has been conducted in this age group.

Patients and methods

Children were recruited from an urban primary care setting by their general practitioners. They were enrolled if they had a recurrence of acute otitis media characterised by a (sub)acute onset, otalgia, and otoscopic signs of middle ear infection, within four weeks to 12 months of the previous attack. A previous attack of acute otitis media was considered to have occurred if it had been assessed by a doctor and written down in the medical record. Children had to be older than 6 months and younger than 12 years.

Children were excluded if they had taken an antibiotic during the past four weeks; had previously participated in this study; were allergic to penicillin; or had a serious concurrent disease that necessitated treatment with an antibiotic. Informed parental consent was obtained by the general practitioner. The child was referred to one of the otolaryngologists at the three participating hospitals, who repeated the history and examination. He evaluated the diagnosis and checked that all the criteria were met. Thus the reliability of the diagnosis was also checked.

STUDY DESIGN AND TREATMENT

A randomised placebo controlled double blind trial was carried out from September 1986 to April 1990. The protocol was approved by the ethics committee of the University Hospital of Utrecht. Random allocation to treatment was achieved by opening in numerical order a sealed envelope that contained the treatment code. The codes had been linked at random to the envelope numbers by a computer program. Treatment was allocated by the otolaryngologist to ensure that both the child and the general practitioner were blind to treatment. Drugs and placebo were supplied by the specialist and were started immediately after the diagnosis was confirmed. Every child was given paracetamol orally as long as earache was present and oxymetazoline nose drops for one week. The child was given either co-amoxiclav orally or placebo in a weight related dose for seven days (table I). Compliance was determined by inquiry after three and 14 days.

ASSESSMENTS

A history was taken by the general practitioner at the first visit. With regard to potential confounding, attention was paid to raised body temperature, the laterality of the acute otitis media, the onset of the episode, the dates of recurrences of the acute otitis

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TABLE I—*Daily dosage schedules for drugs used in study*

	Age or weight of child	Dose (mg)	No of times a day
Paracetamol (as long as pain is present)	½-1 year	60	3
	1-2 years	60	4
	2-4 years	120	3
	4-7 years	120	4
	7-12years	240	3
Oxymetazoline nose drops	<6 years	2 drops 0·025%	3
	6-12years	2 drops 0·05%	3
Co-amoxiclav (amoxycillin/clavulanate) (for 7 days)	<3 kg	25/6·25	3
	4-6 kg	50/12·5	3
	7-10kg	75/18·75	3
	11-13kg	100/25·0	3
	14-25kg	125/31·25	3
	26-35kg	250/62·5	3

TABLE II—*Age of distribution of all children with acute otitis media and those admitted to trial*

Age	No of patients with reported acute otitis media	No (%) admitted to trial
0	56	5 (9)
1	100	22 (22)
2	102	14 (15)
3	95	18 (19)
4	110	30 (27)
5	69	14 (20)
6	52	11 (21)
7	27	1 (4)
8	29	3 (10)
9	25	1 (4)
10	12	2 (17)
11	7	
≥12	104	
Total	788	121

media, and the drugs taken. The date of this first visit was recorded as well as the child's sex, date of birth, and system of health insurance. If the infant was too young to express verbally the presence of otalgia, pulling at the ear and irritability were interpreted as otalgia. The physical examination included rectal measurement of body temperature and description of the appearance of the tympanic membranes. Signs of inflammation were classified as follows[7]: stage I, redness of the membrane at the periphery and at the malleus, absence of light reflex; stage II, total redness of the tympanic membrane; stage III, bulging of the tympanic membrane.

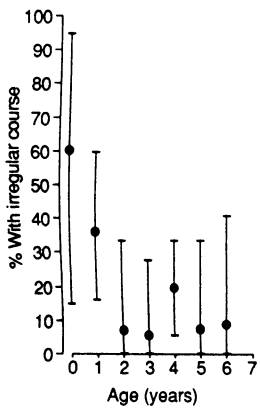
Immediately after this visit the child was seen by the otolaryngologist, who took the history, repeated the physical examination, and confirmed the diagnosis. After three days the general practitioner evaluated the course of the disease by measuring body temperature and noting the presence or absence of otalgia.

The child was seen once more after 14 days by the general practitioner, who recorded the history and physical data and presence of otorrhoea. After one month the child visited the otolaryngologist, who carried out otoscopy, tympanography, and, in children over 3 years, an audiogram. The general practitioner could contact the otolaryngologist at any time to inquire about the given treatment if it was thought necessary. The therapy code could be broken and treatment could be changed. The patient was classified as a treatment failure in this situation. An irregular clinical course of the disease was defined as the presence of otalgia or a body temperature of 38°C or above, or both, after three days.

STATISTICAL METHODS

Differences in proportions of treatment failures in the treatment and placebo groups and 95% confidence intervals were calculated. The χ^2 test with Yates's correction for small numbers was used for comparisons between two proportions. Logistic regression analysis was conducted to estimate the weight of risk factors. The results are expressed in odds ratios with 95% confidence intervals.

In the study protocol we agreed on a minimal relevant difference of 10% with an α of 5% and a power of 80% between the percentages of children with "irregular courses" in the two groups. This is based on the assumption that the percentage of children with irregular courses would be 5% in the group treated with the antibiotics.



Percentage (95% confidence interval) of children with irregular clinical course by age

Results

During 1 October 1986 to 30 April 1990 the participating general practitioners registered 799 patients with acute otitis media. According to the general practitioners, 185 children fulfilled the entry criteria for recurrent acute otitis media. Informed consent was withheld for 54 children, the commonest reason being difficulties in transportation to the hospital. These children were comparable with those in the trial population with regard to age, sex, and date of onset. After investigation by the otolaryngologist one child was diagnosed as having otitis media with effusion, and four with acute otitis media failed one of the eligibility criteria, leaving 126 to enter the study.

Of the children randomly allocated to treatment, 70 received co-amoxiclav and 56 received placebo. Data on five children could not be analysed as their registration forms were lost; three of these children had received antibiotic and two placebo. The 121 evaluable patients had an age distribution similar to that of the total population with acute otitis media (p=0·192) (table II). The low percentage of children younger than one year admitted to the trial compared with the other age groups is due to our selection criteria for recurrence and age. The treatment and placebo groups did not differ with regard to age, sex, insurance, laterality of the acute otitis media, season of onset, temperature at onset, localisation of earache at enrolment, and number of previous episodes (table III). None of the differences in the values of the variables exceeded the significance level of p=0·05.

All children reported taking the prescribed antibiotic or placebo during the required seven days. In one child the treatment code was broken before the first outcome assessment after three days because of the development of a pneumonia. This child, who had been in the antibiotic group, was classified as having had an irregular course. There was no difference between the treatment and placebo groups with respect to the clinical course after three days (table IV). Irregular clinical course was associated with younger age (figure).

Only age and laterality of the acute otitis media seemed to have a prognostic value with respect to the

TABLE III—*Characteristics of children with recurrent acute otitis media. Figures are numbers (percentages) unless otherwise stated*

	Co-amoxiclav group (n=67)	Placebo group (n=54)
Mean (range) age (years)	3·9 (0·7-10·2)	4·1 (1·1-10·2)
No (%) of boys	36 (54)	29 (54)
Sickfund:private insurance	1·9	2·1
Unilateral:bilateral acute otitis media*	1·14	2·06
Season of onset:		
September-March	50 (75)	40 (74)
April-August	17 (25)	14 (26)
Body temperature at enrolment:		
<38°C	45 (67)	36 (67)
≥38°C	22 (33)	18 (33)
Earache at enrolment:		
Unilateral	53 (79)	48 (89)
Bilateral	14 (21)	6 (11)
Previous episodes:		
1	41 (61)	32 (59)
2	19 (28)	15 (28)
≥3	7 (10)	7 (13)

*Diagnosis of otolaryngologist.

TABLE IV—*Clinical course in children with recurrent acute otitis media after three days*

Treatment group	No (%) with regular course	No (%) with irregular course	95% Confidence interval (%)
Co-amoxiclav (n=67)	56 (84)	11 (16)	9 to 28
Placebo (n=54)	44 (81)	10 (19)	9 to 31
All patients (n=121)	100 (83)	21 (17)	11 to 25

χ^2=0·092, p=0·381; difference in percentages of irregular courses between co-amoxiclav and placebo groups=2% (95% confidence interval −11·5 to 15·7).

TABLE V—*Prognostic factors for an irregular clinical course in children with recurrent otitis media*

Prognostic factor	Odds ratio (95% confidence interval)	Adjusted odds ratio* (95% confidence interval)
<2 *v* ≥2 years	5·8 (2·1 to 15·8)	5·9 (1·8 to 19·1)
Bilateral *v* unilateral otitis media	2·7 (1·0 to 7·2)	1·6 (0·4 to 7·7)
≥38°C *v* <38°C	1·7 (0·6 to 4·5)	1·2 (0·4 to 3·7)
Winter *v* summer	1·6 (0·5 to 5·1)	2·0 (0·5 to 7·9)
>1 *v* >1 previous attacks	1·2 (0·7 to 1·9)	1·1 (0·6 to 1·9)
Boys *v* girls	1·1 (0·4 to 2·7)	1·1 (0·4 to 3·5)

*Adjusted by logistic regression.

course of the disease (table V). After multivariate logistic regression only age dichotomised at 2 years was a relevant prognostic factor for the course of the disease (table V). Irregular courses occurred in 11 (41%; 95% confidence interval 22% to 61%) children younger than 2 years and in 10 (11%; 5% to 19%) children aged 2 years and older. The probability of an irregular course in children younger than 2 years was 5·9 times greater than in children 2 years and older.

The effect of the treatment was stratified for children below 2 years and 2 years and older (table VI). The differences in the percentages of irregular courses for the two age categories were not significant.

TABLE VI—*Clinical course after three days stratified by age*

	<2 years		≥2 years	
	Co-amoxiclav	Placebo	Co-amoxiclav	Placebo
No (%) with:				
Regular course	11 (73)	5 (42)	45 (87)	39 (93)
Irregular course	4 (27)	7 (58)*	7 (13)	3 (7)†
Difference in % with irregular course (95% confidence interval)	−31 (−67 to 4)		6 (−6 to 18)	

*$\chi^2=1{\cdot}613$, p=0·102. †$\chi^2=0{\cdot}424$, p=0·257.

Discussion

We expected a greater risk of an irregular course of acute otitis media in children with a recurrent attack. In our total study population 17% (95% confidence interval 11% to 25%) of children did not recover clinically within three days. Comparisons of these results with those of other studies indicate the value of the characteristic recurrence as a predictive factor. In our patients aged 2 years and older who received placebo the percentage with an irregular course was 7·1%. Van Buchem *et al* found the percentage with an irregular course to be 2·7% in untreated children of similar age with a first as well as with a recurrent acute otitis media episode.[5] Their conclusion that a history of previous attacks does not influence the course of the acute otitis media does not agree with our findings.

The percentage of irregular courses was 58% in children aged 6 months to 2 years who received placebo. Engelhard *et al* report an irregular course of 23·1% with regard to fever and 28·1% with regard to pain in patients aged 3-12 months with a first or a recurrent acute otitis media.[8] Children with recurrent acute otitis media should be given special attention because of the increased risk of an irregular course.

The age, sex, season of onset, bilaterality of the acute otitis media, temperature, and earache at enrolment in our study population are similar to those in other studies.[9] The internal validity was also high with no differences between the two treatment groups. We could not analyse data on five children because information was lost, but the reason for loss was independent of the treatment. The child who withdrew from the study was analysed as a treatment failure according to the intention to treat principle.

ANTIBIOTIC TREATMENT

We found no difference between co-amoxiclav and placebo with regard to the resolution of the acute otitis media. These results correspond with the findings of the few reliable placebo controlled clinical trials conducted since 1965. No difference was found in the failure rate of clinical recovery between 62 children aged 2-66 months treated with ampicillin and 27 given a placebo (Fisher's exact test: p=0·353).[10] Howie and Ploussard reported that symptoms and fever had resolved within 4 days in all children in the placebo and antibiotic groups.[11] Van Buchem *et al* concluded that antibiotics were needed for children with an irregular course or complications or in children with a persistent otorrhea after two weeks.[3] Mygind *et al* studied 149 children aged 1-10 years and found no difference between an antibiotic and placebo,[12] and Engelhard *et al* found that most of their patients improved clinically irrespective of the therapeutic approach.[8]

PROGNOSTIC FACTORS

Some investigators studied the prognostic value of several factors with regard to the course of the disease. Age seems to be important: the younger the child the larger the probability of developing an irregular clinical course irrespective of the treatment.[13-16] The course of the disease is independent of the season.[15 17] The initial presence of a red or bulging eardrum does not influence the course of otitis media.[3] Our results suggest that only age has an independent prognostic value. The difference in the percentage with an irregular course between the co-amoxiclav and placebo groups was −31% in children aged less than 2 years and 6% in children aged 2 years or older, although these differences were not significant.

The most striking result of this study is that even in a population of children aged 6 months to 12 years prone to otitis media the natural course of the clinical improvement is not different from the course when co-amoxiclav is prescribed. In children aged less than 2 years the non-significant result might be due to the low power alone. As the result was near to significance, and taking into consideration the clinical relevance of the difference of irregular courses in 31% of children, we recommend that antibiotics be given to children younger than 2 years with recurrent acute otitis media. Further research is needed with larger numbers of patients to confirm this strategy. In children aged 2 years and older with recurrent acute otitis media antibiotics do not affect the short term course.

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