Are antibiotics indicated as initial treatment for children with acute otitis media? A meta-analysis

Christopher Del Mar, Paul Glasziou, Mauricio Hayem

Centre for General Practice, University of Queensland Graduate School of Medicine, Brisbane, Australia 4006

Christopher B Del Mar, *professor of general practice*

Paul P Glasziou, *reader*

Mauricio Hayem, *postgraduate student*

Correspondence to: Professor Del Mar.

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Abstract

Objective: To determine the effect of antibiotic treatment for acute otitis media in children.
Design: Systematic search of the medical literature to identify studies that used antibiotics in randomised controlled trials to treat acute otitis media. Studies were examined blind, and the results of those of satisfactory quality of methodology were pooled.
Subjects: Six studies of children aged 7 months to 15 years.
Main outcome measures: Pain, deafness, and other symptoms related to acute otitis media or antibiotic treatment.
Results: 60% of placebo treated children were pain free within 24 hours of presentation, and antibiotics did not influence this. However, at 2-7 days after presentation, by which time only 14% of children in control groups still had pain, early use of antibiotics reduced the risk of pain by 41% (95% confidence interval 14% to 60%). Antibiotics reduced contralateral acute otitis media by 43% (9% to 64%). They seemed to have no influence on subsequent attacks of otitis media or deafness at one month, although there was a trend for improvement of deafness at three months. Antibiotics were associated with a near doubling of the risk of vomiting, diarrhoea, or rashes (odds ratio 1.97 (1.19 to 3.25)).
Conclusions: Early use of antibiotics provides only modest benefit for acute otitis media: to prevent one child from experiencing pain by 2-7 days after presentation, 17 children must be treated with antibiotics early.

Introduction

Acute otitis media is extremely common in children. By the age of 3 months, 10% of children will have suffered at least one episode. The incidence peaks between 6 and 15 months.[1] In Western countries mortality is low, but it may be higher in underdeveloped countries.[2] Complications are now rare in the West, although in 1954 the rate of mastoiditis was 17% in cases of acute otitis media.[3] Symptoms consist mainly of pain and systemic illness, sometimes very distressing, which in 80% of children is limited to 24 hours' duration.[4] The pain is caused by pressure on the tympanic membrane, which can sometimes be seen bulging and inflamed at otoscopic inspection. After the inflammation settles, the consequent deafness left by fluid retained within the middle ear space may take several weeks to resolve.

Considerable attention has been focused on the role of infection in acute otitis media. Several attempts at identifying causative infectious agents have yielded several, the main ones being *Streptococcus*, *Branhamella catarrhalis*, and *Haemophilus* species.[5] Some viruses have been implicated. Twelve different case series failed to identify a causative infectious agent in the middle ear fluid of 28-62% of patients.[5] The details of the pathophysiological process, traditionally described as arising from the increased bacterial load and obstructive elements that occur during an upper respiratory tract infection, may be incompletely understood.

There is wide variation in the use of antibiotics between the doctors of different nations, from as low as 31% of cases of acute otitis media in the Netherlands to as high as 98% in Australia and the United States.[6] We examined the literature by meta-analysis to establish what benefits or harm antibiotics provide for patients with acute otitis media. Because acute otitis media is a disease that remits spontaneously the notion of "cure" is not meaningful. We examined the health outcomes of resolution of symptoms (pain and deafness) and the most commonly reported serious complication (mastoiditis) without reference to signs. While other end points (such as microbiological "cure") may enhance an understanding of the disease process, we regarded them as only of secondary interest in this empirical study of effectiveness.

Methods

Literature search

We manually searched titles in *Index Medicus* from 1958 to 1965 and, by computer, searched Medline and *Current Contents* from 1966 to August 1994 using combinations of "OTITIS MEDIA" and a search strategy previously described for optimally identifying controlled trials.[7] The references of all retrieved studies were searched as well. All identified randomised controlled trials of antimicrobial drugs versus placebo control were included. The data we extracted consisted of severity and duration of pain (midterm and long term), deafness, adverse effects, and recurrent attacks.

Table 1 Characteristics of randomised, controlled studies of treatment for acute otitis media in children (antibiotic *v* placebo) eligible for inclusion in meta-analysis

Study	Method	Participants	Interventions	Outcomes	Quality score
Thalin *et al* 1985[13]	Block randomisation controlled by hospital pharmacy; double blind	Swedish children aged 2-15 years; acute otitis media defined clinically	Penicillin 50 mg/kg/day in three doses for 7 days	Examined on days 0, 3-4, 8-10, and 30; audiogram on day 30 and repeated at 2 months if abnormal	11
Burke *et al* 1991[12]	Randomisation by identical number bottles, sealed randomisation code; double blind; intention to treat analysis	English children aged 3 and 10 years with acute earache and at least one abnormal eardrum	Amoxycillin 250 mg thrice daily for 7 days	Symptom diary kept by parents; home visits by researcher at 24 hours and at 5-7 days	10
Van Buchem *et al* 1981[9]	Randomisation by identical bottles; baseline comparability documented; double blind; without intention to treat analysis (31 of 202 patients excluded)	Dutch children aged 2-12 years with acute otitis media defined clinically	Amoxycillin 750 mg/day in three doses for 7 days or myringotomy, or both, in 2×2 factorial design (placebo antibiotic and sham myringotomy for the controls)	Parent report of pain and clinical assessment on days 2, 7, 14, 28, and 56; audiogram at 2 weeks or later; assessed blind	10
Mygind *et al* 1981[15]	Randomisation by coded bottles; documented baseline comparability; double blind; dropouts excluded (9 of 165)	Danish children aged 1-10 years with acute otitis media who had had earache for 1-24 hours	Penicillin-V 55 mg/kg/day in three doses for 7 days	Parents completed score cards for pain and fever each evening; otoscopy at follow up; tympanometry classified blind	9
Kaleida *et al* 1991[14]	Stratified randomisation, method not stated; documented baseline comparability; double blind; intention to treat analysis	American children aged 7 months to 12 years with acute otitis media, (otoscopic middle ear effusion plus general symptoms or signs)	Amoxycillin 40 mg/kg/day in three doses for 14 days	Treatment failure defined by high otalgia score or high fever	8
Halsted *et al* 1968[16]	Randomisation by predetermined code, unknown to physician; blinded using placebo	American children aged 2-66 months; clinical diagnosis of acute otitis media; excluded if evidence of perforated tympanic membrane or if antibiotics used recently	Ampicillin 100 mg/kg/day or phenethicillin 30 mg/kg/day plus sulfisoxazole 150 mg/kg/day	Culture results and clinical improvement, (decreased symptoms and resolution of illness)	5
Howie *et al* 1968[10]	Randomisation controlled by pharmacist; placebo controlled, all treatments given four times daily	American children aged ⩽2.5 years; clinical diagnosis of acute otitis media	One of erythromycin, ampicillin, or triple sulphonamide, and erythromycin	Culture and randomisation compared with culture at 2-5 days; no patient relevant (symptomatic) outcomes	5
Laxdal *et al* 1970[11]	Randomisation claimed but no method stated; not blinded; no placebo	Canadian children with clinical diagnosis of acute otitis media; excluded if evidence of perforated tympanic membrane	Penicillin 250 mg/m^2/day or ampicillin 250 mg/m^2/day in four doses; controls had treatment for symptoms only	Failure was deterioration or no improvement on day 7 based on middle ear inspection	2

Quality assessment

In assessing the quality of the methodology of each study identified, we adapted a protocol described previously to attribute scores[8]: for the manner in which subjects were assigned to treatment or control group; control of selection bias after assignment to treatment (trials analysed on an intention to treat basis were preferred, and where necessary and possible intention to treat analyses were reconstructed); adequacy of blinding; and objectiveness of assessment of the outcome. Scores could range from 0 (worst possible) to 11 (best possible). The method used is available from us. By cutting and pasting, we assessed the studies blind to the authors, institutions, journal, and results of each study. The three of us met to resolve differences in our independent assessments still blind to the identity of each study.

Statistical analysis

We performed χ^2 tests for heterogeneity of the odds ratio for all analyses. These showed no significant heterogeneity. We used the Peto method to calculate combined estimates for a fixed effects model for the odds ratio and performed a *z* test of significance. All calculations were done with REVMAN 2.0 (Update Software, 1995).

Results

Eight trials were eligible for inclusion in our review of antibiotics against placebo. One had a factorial design (treatment by myringotomy, antibiotics, both, or neither), of which we used only the antibiotic and placebo arms.[9] One study did not report on empirically relevant, patient centred outcomes.[10] Another reported only recurrences.[11] Thus, only six studies of children aged 7 months to 15 years were available for analysis. Studies allowed for children in the trials who were not doing well to be removed and treated with antibiotic after the code was broken. This occurred at different rates (14%,[12] 8%,[13] and 7%[14]).

The methodological quality of the six selected studies was good (see table 1). Five used a blinded randomisation and outcome assessment. Two failed to include all children in follow up assessments, although data were missing for less than 10%.

Figure 1 shows the outcomes of the studies. About 60% of placebo treated children were pain free within 24 hours of presentation, and antibiotic treatments did not influence this. However, at two to seven days after presentation, antibiotics reduced pain in the remaining children by 41% (95% confidence interval 14% to 60%). They similarly reduced the risk of developing contralateral acute otitis media by 43% (9% to 64%), and they showed trends for reducing perforations of the tympanic membrane. Antibiotics seemed to have no influence on subsequent attacks of otitis media or deafness at one month (as estimated from tympanometry), although there was a trend for a benefit at three months. They were associated with a near doubling of the risk of problems commonly associated with antibiotics including vomiting, diarrhoea, and rashes (odds ratio 1.97 (1.19 to 3.25)).

Discussion

The number of well conducted studies is small for such a common condition.[17] As all were conducted in Western countries, the results may not be generaliseable to Third World communities, where the far greater risk of serious suppurative complications may support the

early use of antibiotics.[2] There seems to be a deficiency of research on this subject.

Implications of analysis

Several matters must be considered when deciding the implications of our findings. Initial use of antibiotics will reduce pain, and contralateral otitis media, by a relative reduction of about 40%. However, there is benefit only for those 14% of patients whose pain has not spontaneously resolved within 24 hours of presentation. This is equivalent to an absolute benefit of 5.6% fewer children experiencing pain by two to seven days after presentation. Thus, 17 children must be treated at first presentation to prevent one child experiencing pain after two to seven days, which is of the same order as a previous meta-analysis of the subject.[4] Many children suffering contralateral otitis media will be counted among those with persistent ear pain. It is not surprising antibiotics provide no pain relief within the first 24 hours when you consider the steps required for obtaining, ingesting, and absorbing antibiotics and for starting antibiotic activity.

Looking for subgroups of children with otitis media who would benefit from antibiotics might be a useful aspect of research. Knowing which children are going to suffer an illness extending beyond one day would enable doctors to select and treat only those who would benefit. Although we found some evidence of prolonged symptoms with placebo treatment among young children, those with previous episodes of otitis media, and those with bilateral acute otitis media, the differences were small.[12]

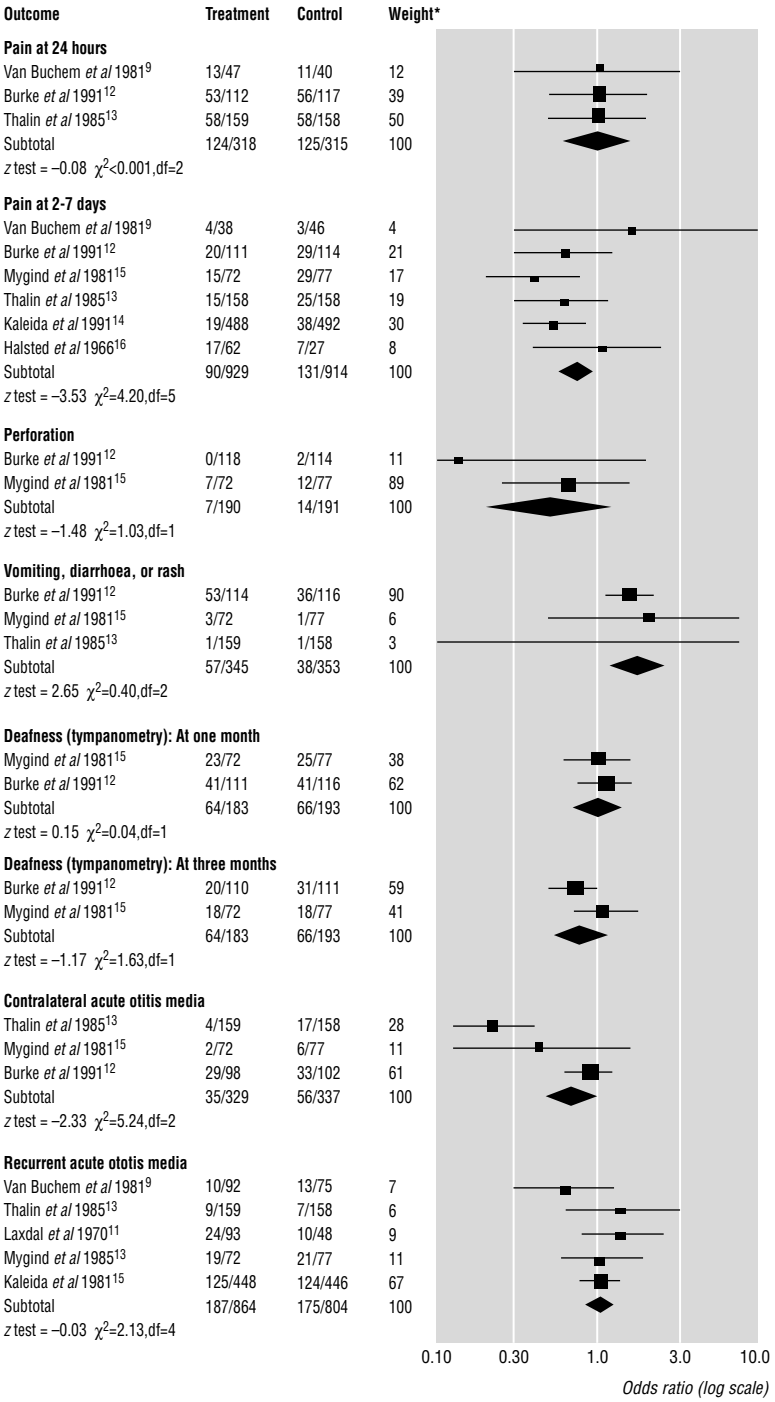
Antibiotics seem to have little effect on deafness, particularly deafness that is not prolonged. This is surprising in view of a recent report that antibiotics may assist in managing glue ear.[18]

Implications of not using antibiotics

What are the likely consequences of not using antibiotics? For 17 months, 60 general practitioners in the Netherlands used nose drops and analgesia alone for initial treatment of acute otitis media in all children aged 2-12 years. Only 3% (136/4860) of these children suffered a severe course of the illness (that is, child still ill after 3-4 days or ear discharge for more than 14 days).[19] This proportion is far smaller than the results for the control groups in this meta-analysis would suggest. Two of the children developed mastoiditis, but this settled uneventfully after treatment with amoxycillin.[19] Subsequent follow up of

Key messages

- There is wide variation in the use of antibiotics for early treatment of acute otitis media in children, and we examined the literature by meta-analysis to establish what benefits or harm antibiotics provide
- Antibiotics did not influence resolution of pain within 24 hours of presentation, though at 2-7 days after presentation, by which time only 14% of children in control groups still had pain, early use of antibiotics reduced the risk of pain by about 40%
- Antibiotics also reduced contralateral acute otitis media but seemed to have little influence on subsequent attacks of otitis media or deafness
- Antibiotics were associated with a near doubling of the risk of vomiting, diarrhoea, or rashes
- Early use of antibiotics provides only modest benefit for acute otitis media: to prevent one child from experiencing pain by 2-7 days after presentation, 17 children must be treated with antibiotics early



* The contribution of each study to the combined estimate of the odds ratio

Fig 1 Odds ratios of various outcomes among children with acute otitis media who were treated with antibiotics or placebo

these general practitioners indicated that most still seldom used antibiotics to treat otitis media and that mastoiditis remained rare.[20]

Conclusions

Many doctors and their patients may be disinclined to use antibiotics at first presentation of otitis media for so little benefit. Others may regard any potential benefit as worth the inconvenience of purchasing and administering the drugs and the risk of their (usually) minor complications. Perhaps the best approach is to regard antibiotics as an optional treatment for early acute otitis media, together with adequate analgesia, that doctors should discuss openly with their patients. In future, studying what influences doctors' decisions whether to use antibiotics might be more fruitful than undertaking more trials of the treatment itself.

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Population based study of use of anticoagulants among patients with atrial fibrillation in the community

Mark Sudlow, Helen Rodgers, Rose Anne Kenny, Richard Thomson

Several randomised controlled trials have shown that warfarin treatment for patients with atrial fibrillation substantially reduces their risk of stroke.[1] Studies have found low treatment rates among patients with atrial fibrillation in hospital[2] and in primary care,[3] but these have been limited by their reliance on identifying patients with atrial fibrillation from coding of records and prescription of antiarrhythmic drugs. We report the use of warfarin among patients with atrial fibrillation in a community survey.

Concern has been expressed about the high rates of exclusion of subjects from randomised trials of warfarin treatment. It has been suggested that the use of similar exclusions in clinical practice would greatly reduce the number of patients eligible for treatment,[4] which might explain the low treatment rates. We therefore applied exclusion criteria similar to one of these trials[5] to our subjects.

Subjects, methods, and results

As part of a study of atrial fibrillation in the community, we took an age and sex stratified random sample of patients aged 65 and over registered with 10 contiguous general practices in Northumberland, which covered one market town, one industrial town, a dormitory town, and the mining villages and farming communities around them. We invited subjects to attend for electrocardiography, measurement of blood pressure, and completion of a questionnaire including information on contraindications to anticoagulation. We also recorded their current medication.

We identified subjects with atrial fibrillation or flutter from their electrocardiograms, took blood samples, and reviewed patients' medical notes. We sent questionnaires to the subjects' general practitioners asking about their patient's ability to comply with treatment. We derived contraindications to warfarin treatment from the exclusion criteria for the stroke prevention in atrial fibrillation trial[5]:

- Self reported history of vomiting blood, rectal blood loss, or haematuria in the six months before the study; alcohol consumption over 28 units in the past week; three or more falls in the past year; and daily use of non-steroidal anti-inflammatory drugs other than aspirin (when questionnaire data were missing we scrutinised medical records for a history of

Departments of Medicine and Epidemiology and Public Health, The Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne NE2 4HH
Mark Sudlow, *MRC training fellow in health services research*
Helen Rodgers, *senior lecturer in stroke medicine and services*
Department of Medicine, The Medical School
Rose Anne Kenny, *professor of geriatric medicine*

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Department of Epidemiology and Public Health, The Medical School

Richard Thomson, *senior lecturer in epidemiology and public health*

Correspondence to: Dr Sudlow.

recent bleeding, excessive alcohol consumption, or falls)

- General practitioner's report of inability to comply with warfarin treatment (when general practitioners did not respond we used a test of ability—subjects failed if they could not read the label on a bottle of warfarin, extract a single tablet, or pick a specified dose after the strength and colour coding of warfarin tablets had been explained)
- Haemoglobin concentration <100 g/l, platelet count $<100\times10^9$/l, prothrombin time >15.1 s, and creatinine concentration >300 µmol/l (when subjects refused to give a blood sample we scrutinised medical records for a current diagnosis of liver disease or anaemia)
- Uncontrolled hypertension at the initial visit—blood pressure $>180/100$.

The response rate to the survey was 77% (1530/1990), and 100 subjects had atrial fibrillation. Of the subjects for whom notes were available, atrial fibrillation was recorded before the study in the notes of 76% (71/93). We excluded nine subjects—notes could not be traced for seven and for three there was inadequate information to exclude contraindications. Table 1 summarises the results.

Table 1 Details of warfarin treatment for 100 subjects aged ≥65 with atrial fibrillation (values are numbers (percentages (95% confidence interval of percentage)) unless stated otherwise)

	Age (years)	
	65-74 (n=21)	≥75 (n=79)
No of subjects excluding those without available medical records or adequate information about contraindications to treatment	18	73
Subjects who were treated with warfarin	8/18 (44 (22 to 69))	8/73 (11 (5 to 20))
Subjects without contraindications to treatment:	12/18 (67 (41 to 87))	44/73 (60 (48 to 72))
Who were treated with warfarin	4/12 (33 (10 to 65))	6/44 (14 (5 to 27))
No of subjects without contraindications whose atrial fibrillation was known to their general practitioner:	8	32
Who were treated with warfarin	4/8 (50 (16 to 84))	6/32 (19 (7 to 36))

Comment

In our study about half of the patients aged 65-74 with atrial fibrillation were treated with warfarin. A much lower proportion of those aged over 74 were treated (see table). These low rates can be explained only partially by the presence of contraindications or because subjects were not previously identified by their general practitioner as having atrial fibrillation. It is possible that factors beyond those we considered as contraindications deterred doctors from using warfarin, but the criteria we used cover accepted medical contraindications to warfarin, including poor compliance and falls. If adequate services were available then it should be possible to safely give anticoagulant drugs to most patients without such contraindications. Since treatment is of such benefit and need so widespread, there is an imperative to improve and expand the current use of warfarin.

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An influential doctor

Doctors should be walking question marks

He is dead now. He looked close to it the few times I saw him 30 years ago. A small, wizened man, rendered kyphotic with age. Besuited, but dapper and with spit and polish black shoes, overlarge for his diminutive frame, he conducted his ward rounds slowly and methodically. He was a consultant in a small hospital, and there was just him, the ward sister, a houseman, and me, the medical student. And yet if I had to put my clinical training in a nutshell it would be that one ward round, in that small country hospital with that little, misshapen man.

Those great teaching hospital professors, even the knighted, never left such a mark. We cogitated long over each patient but particularly so over a man with peripheral vascular disease, whose toes were exhibiting dry gangrene, and contemplated the few options before amputation. This was long before the days of revascularisation. I was asked why the patient should be kept warm and the afflicted limb kept cool, with a fan if necessary. I didn't know, and had never really bothered to think. Perhaps, the consultant sensed a certain lack of inquisitiveness for he looked at me, a gaze lifted to make up for our height difference, and, raising his left index finger emphatically, said, "Doctors should be walking question marks." The houseman, on my other side and hidden from the chief's sight, could barely contain himself at the image and dug me in the ribs. It took every effort of will I could muster not to betray his mirth, for the consultant still held me in his gaze, long enough for me to see beyond the caricature in silhouette of a slow marching animated query sign to the essential truth.

I have often wondered if the houseman, who bruised my ribs, ever saw it. It is a most treasured piece of advice from one at the end of his medical vocation to one on its threshold. I now see that old man in my mind's eye, not just as bowed with age, but with the stigma of wisdom.

Ian D Conacher, *consultant anaesthetist, Newcastle upon Tyne*

We welcome filler articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk.