

What is the most effective antibiotic regime for chronic suppurative otitis media in children?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at:

http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: What is the most effective antibiotic regime for chronic suppurative otitis media in children?

The WHO Pocketbook of Hospital Care for Children recommends;

- Keep the ear dry by wicking.
- Instill topical antibiotic or antiseptic ear drops (with or without steroids) once daily for 2 weeks.
- Drops containing quinolones (norfloxacin, ofloxacin, ciprofloxacin) are more effective than other antibiotic drops. (pg 163)

INTRODUCTION

Chronic suppurative otitis media (CSOM) is defined as persistent discharge from the ear continuing for over 2 weeks where there is a tympanic membrane perforation (WHO criteria) [1]. It is a serious condition with 65–330 million sufferers, of whom 60% have significant hearing loss. This accounts for a burden of disease of over 2 million DALYs, despite it being preventable [2]. The cases are mainly in children in developing countries, particularly Africa, SE Asia and the West Pacific [2]. Treatment aims to improve hearing levels by eliminating ear discharge in order to promote healing of tympanic perforation. Treatments for CSOM are nothing, dry mopping, topical antiseptics, antibiotics (topical, oral or parenteral) or surgery. However expense of the latter groups limits their use in developing countries. A 2005 Cochrane Review of adult data shows that topical quinolone antibiotics clear aural discharge better than no drug treatment or topical antiseptics in the short-term [3]. This is yet to be researched in children.

METHODOLOGY

The Cochrane Library and Medline databases were searched for systematic reviews and randomised controlled trials.

- A Cochrane search for "otitis media" yielded two systematic reviews on this topic, but they used adult data [3][4]. I therefore copied the Cochrane search strategy from these systematic

reviews, and hand-selected only the results for children. The search yielded 234 clinical trials, where 6 were relevant for the study. [5-10].

- Medline was searched using:
 1. "otitis media" with MeSH suppurative
 2. "paediatrics" with MeSH Child or Child/Preschool or Pediatrics or Infant or Adolescent
 3. "chronic" with MeSH Chronic Disease .
 4. I limited 1 to "humans" and "English language" and ("therapy (sensitivity)" or "therapy (specificity)" or "therapy (optimized)")

This yielded 256 results. After reading abstracts and selected full texts, 12 relevant trials were found, 5 had already been found by the Cochrane search, so 7 were used for the review. [11-17]

Papers were excluded if they used children over 18 years of age or reported ear diseases other than chronic suppurative otitis media (as defined in the introduction) or where there was an additional cholesteatoma. Trials must have used a single antibiotic therapy in at least one of their comparison groups. No combinations of antibiotics must be given to individuals, or additional steroids. Methodological quality of the trials used for conclusions was type 1b according to the criteria of the Oxford Centre for Evidence-Based Medicine [9] (http://www.cebm.net/levels_of_evidence.asp). Due to the small number of trials on children with these criteria, other lower quality trials were included for discussion and comparison.

All trials used resolution of discharge from the ear to assess the short term outcome of drug efficacy.

Studies were divided into groups according to the route of administration of antibiotics (topical, oral and parenteral). Within groups studies varied in that they used different doses and durations of treatments, they were set in different countries (different antibiotic resistance rates) and they used children with different disease severities.

RESULTS

The Cochrane Library and Medline searches came up with 4 studies using topical antibiotics, 2 using oral, 7 using Parenteral (IV and IM routes).
Topical antibiotics

Three RCTs were found [6][9][11], but only one of them compared antibiotics [9]. The other two compared an antibiotic to an antiseptic. The first RCT done in aboriginal Australians in 2003 found that 5 drops twice daily of 0.3% Ciprofloxacin ear drops were significantly more effective than FGD eardrops

Table 1: Studies including topical antibiotics

	Journal, year author and country	Study type and Evidence Level	Clinical question	No. of children and ages	Definition of cure	Results and time period	Comments and significance
A	<i>Medical journal of Australia</i> , 2003 Couzos, Aboriginal Australia ⁽¹⁴⁾	RCT-community based, multicentre, double-blind 1b	Ciprofloxacin (0.3%) vs FGD eardrops (framycetin 0.5%, gramicidin, dexamethasone) Which is an aminoglycoside	111 Ages 1-14 years	Complete elimination of otorrhoea judged by otoscopy	76.4% cured with CIP 51.8% with FGD after 21 days	P=0.009 Used 5 drops twice daily
B	<i>Tropical Medicine and International Health</i> , 2005, Macfadyen, Kenya ⁽⁵⁾	RCT community based, multicentre, double-blind 1b	Ciprofloxacin (0.3%) vs boric acid (antiseptic)	427 Age 5-15	Resolution of discharge Healing of tympanic membrane, Improved hearing	59% cured with CIP, 32% with antiseptic after 2 weeks. No differences in healing of membrane, hearing levels were improved with CIP.	P<0.001 Fewer adverse events of ear pain, irritation and bleeding with CIP. Used drops twice daily
C	<i>New Zealand Medical Journal</i> , 1986, Eason, Solomon Islands ⁽¹¹⁾	Randomised Controlled Clinical Trial 1b Not blinded	Comparison of 1.No treatment 2.Aural toilet 3.Boric acid 2% 4.Topical Sofradex=aminoglycoside (framycetin 0.5%, gramicidin, dexamethasone) 5.sofradex and IV clindamycin	134 with 184 ears Ages 0-15 (results measured per child not per ear)	Improved ear (healed tympanic membrane, or resolution of discharge without perforation closure)	Improvement occurred in: 18% group 1 50% group 2 64% group 3 58% group 4 43% group 5 After 3-6 weeks Aural toilet was as effective as all other combinations of therapy.	P < 0.01 between all groups and group 1, but insignificant between groups 2-5. Groups 3-5 also performed aural toilet as well as therapy.
D	<i>International Journal of Pediatric Otorrhinolaryngology</i> , 2002, Piet Van Hasselt ⁽¹⁰⁾	Case series Unclassified	Ofloxacin (0.075%) in hydroxypropyl methylcellulose ear drops. No control	83 (115 ears) Ages 0-14	Observed resolution of discharge	73% of ears were dry by day 10 Gave only 3 treatments in total, on day 3, 7 and 10.	Results were per ear, this is biased where bilateral disease occurs. Mixed adult and child data No control

(framycetin 0.5%, gramicidin, dexamethasone)- framycetin is an aminoglycoside. This was judged by complete elimination of otorrhoea on otoscopy. However, there was no difference in hearing levels or healing of perforations between groups. This may reflect the short follow-up of this trial. 21 days follow-up is insufficient to assess long-term outcomes of the antibiotic, yet these outcomes are vital in order to decide whether to invest in a new more expensive treatment regime. The second RCT from Kenya showed that twice daily drops of 0.3% ciprofloxacin was significantly more effective than boric acid (antiseptic) [11]. These results were different to the Australia study as hearing levels were also improved as well as resolution of discharge. This could be due to a smaller number of children in the ciprofloxacin group having continuing discharge, or for another reason. The third RCT from the Solomon Islands 1986 showed that aural toilet was equally as effective as regimes which added boric acid, topical aminoglycoside and/or IV clindamycin to aural cleansing [6]. It therefore concluded there is no advantage to any of these treatments in addition to ear-cleaning. However all regimes were significantly more effective than no treatment. This study did not assess quinolones. The fourth trial was not an RCT but served to suggest a method of making quinolone treatment cheaper by using low dose ofloxacin 0.075%. [5] The trial was flawed as it mixed adult and child data, yet it is included here because "adult" was classed as >14 years

(therefore still including some under 18s) and there were only 7 "adults" compared to 83 children. However, the 73% cure-rate result of this study cannot be relied upon because of this lack of differentiation and the fact there is no control. The use of low-dose quinolones should be researched in further trials, as a lower dose could be equally as effective and would be more affordable.

The Australian and Kenyan RCTs are high quality trials using 111 and 147 children respectively. From this it can be concluded that topical quinolones are the most effective short-term topical treatment for CSOM. Neither of the trials showed evidence of improvement in long term hearing or ear-drum perforation closure. Long term follow up is needed before proposing to change the recommended CSOM treatment regime to one involving a costly quinolone antibiotic. The study from the Solomon islands has a high quality method but an large flaw in that half the participants are an unreliable population as they participated in regular sea-water swimming (as admitted by 87% of the parents). Water entry into the middle ear is known to exacerbate otorrhoea [6]. Any treatment given to these children may have been diluted or ineffective due to lack of penetration, which may account for why all topical treatments had equal results. No conclusions can therefore be drawn about

Table 2: Oral Antibiotics

	Journal, year author and country	Study type and Evidence Level	Clinical question	No. of children and ages	Definition of cure	Results and time period	Comments and significance
E	<i>East African Medical Journal</i> 2006 Minja, Tanzania ⁽¹⁵⁾	RCT- community based, multicentre 1b	Comparison of 1.Dry mopping 2.Dry mopping and boric acid 3.Dry mopping and oral amoxicillin (dose adjusted to body weight) for first 10 days of trial	328 Age 5-17 years	Complete elimination of otorrhoea and improvement in hearing	Cure occurred in: 31% of group 1 54% of group 2 56% of group 3. after 3 months. Hearing thresholds were the same or better in groups 2 and 3.	P=0.82 between group 2 and 3 on last visit. Children were from comparable districts, no contact between schools having different treatments
F	<i>The Pediatric Infectious Disease Journal</i> , 1992, Lang ,Israel ⁽¹⁷⁾	Case series unclassified	Ciprofloxacin 30mg/kg/day	21 Age 1-15 years	Complete resolution of discharge,	18/21 = 86% cured after 21 days	Had all previously failed conventional antibiotic therapy, no control, small study

the efficacy of aminoglycoside ear drops compared to antiseptics.

Cost is an important factor when deciding on a new treatment regime. Ciprofloxacin is more expensive than both FGD and antiseptic, and also requires more health workers to deliver the intensive regime required. A careful cost/benefit analysis is needed before any change is recommended.

CSOM is not a particularly severe clinical problem in the short term, as discharge is uncomfortable but not disabling. However, long term CSOM can cause serious hearing problems and permanent ear drum damage. These trials are therefore very limited in that they don't assess long term hearing and ear drum perforation closure, as these are the serious issues that need addressing.

It would also be worth experimenting to see if a less intensive ciprofloxacin regime could still produce better results than FGD, as a less intensive regime would be more feasible in developing countries.

From these trials ciprofloxacin addresses the problems of frequency of CSOM infection and the discharge and pain that it causes. It has not been shown to benefit long-term hearing and therefore does not have a proven cost/benefit advantage. Long term follow up is needed.

Oral antibiotics

There were 2 trials included, but only one RCT. This high quality RCT from Tanzania 2006 showed that there was no significant advantage in adding oral amoxicillin (dose adjusted for body weight) to a regime of aural cleansing and topical boric acid. [10] The second study from Israel 1992 shows an 86% cure rate after 21 days with oral ciprofloxacin 30mg/kg/day. However, there is no control so this study is unreliable [12]. There is therefore little evidence to support funding oral antibiotics for first line treatment of CSOM in children of developing countries, especially as it has been already concluded above that topical quinolones are more effective than topical boric acid ear drops. Oral antibiotics have not been adequately tested on children. More trials need to be done, especially as an oral regime may result in better compliance in a developing country setting, as no training or special equipment is required to administer the drug.

Parenteral antibiotics

There were 7 trials included but only two are RCTs from which reliable results can be drawn. An RCT from Israel 1990

compared IV mezlocillin, IV ceftazidime and no antibiotic treatment, where all groups received suction and debridement of the ear (cleaning). Results were that IV antibiotics ceftazidime and mezlocillin are more effective than no antibiotic treatment for CSOM, and are both equally effective [7]. A second RCT from Israel 2000 compares IV ceftazidime with IV aztreonam, finding them equally effective (p value insignificant) [8]. However these RCTs only used 48 and 30 children respectively and only used children that had failed previous antibiotic therapy and that had already been found to have *Pseudomonas aeruginosa* infection. The treatment is therefore only testing for efficacy against these bacteria in these groups of children. They are also both set in Israel which is a developed country [18]. This makes the data less reliable for a conclusion on treatment in developing countries, as antibiotic resistance may be different in Israel. The other five studies serve only to back up that ceftazidime has indeed been shown to be effective in some cases.

The result of this is to say that there is no strong evidence to fund IV antibiotics as primary treatment for CSOM in children in developing countries. It is worth realising that subjects who go to hospital are generally more severely ill, or have not responded to other treatments. Considering this, there may be some role for IV ceftazidime or aztreonam for in-hospital care where previous courses of topical and oral antibiotics have failed and/or in *Pseudomonas aeruginosa* infections. This would need further trials in children.

DISCUSSION

The conclusion that topical quinolones are the most effective short-term treatment for CSOM in children supports the Cochrane Review findings for adults on this same topic [3].

However, both this and the Cochrane review concentrate on efficacy of antibiotics as measured by cure- rate of acute episodes of ear discharge. This information is important for reducing the duration of discharge and the associated hearing loss during each acute bout of otorrhoea due to CSOM. However, the long-term benefit of reducing acute episodes of purulent discharge is not documented. CSOM is a chronic condition which may last years, and is associated with chronic perforation of the ear drum, changes in hearing levels and repeated episodes of ear discharge. Even where ears heal spontaneously there may be impaired hearing with abnormal ear structures. Prevention of CSOM is therefore the long term goal, but effective treatment is needed to alter the course of the disease. In order to be an effective treatment for CSOM the treatment must be shown to (1) reduce the frequency and duration of the bouts of discharge and associated hearing loss (2) hasten the permanent healing of

Table 3: Parenteral antibiotics

	Journal, year, author and country	Study type and Evidence Level	Clinical question	No. of children and ages	Definition of cure	Results and time period	Comments and significance
G	<i>Journal of Pediatrics</i> , 1990 Fliss, Israel ⁽¹²⁾	RCT prospective study 1b	1. mezlocillin vs 2. ceftazidime vs 3. no antibiotics All groups received suction and debridement of the ear	48 (72 ears) ages 3 months - 16 years	Complete elimination of otorrhoea	100% cured in groups 1 and 2, 8% cured in group 3. Patients were treated until 3 days after discharge stopped (up to 18 days)	P<0.01 between group 1 and the other groups
H	<i>Scandinavian Journal of Infectious Disease</i> , 2000, Somekh, Israel ⁽¹³⁾	RCT Prospective open 1b	IV Ceftazidime vs IV aztreonam	30-(15 in each group) age 1-12	Complete resolution of discharge	84.6% with ceftazidime, 67% with aztreonam	P value not significant
I	<i>Pediatric Infectious Disease Journal</i> , 1994, Arguedas, Costa Rica ⁽¹⁸⁾	Open, non-comparative trial unclassified	IV ceftazidime vs oxacillin vs both antibiotics	186 Age 2 months - 18 years	Resolution of discharge within 2 weeks.	130/139 = 94% cured on ceftazidime, 28/28 cured on oxacillin, 14/14 cured on both. Patients were treated until 3 days after discharge stopped or up to 14 days	Not random allocation of antibiotic. Not treated for same amount of time. No control
J	<i>The Pediatric Infectious Disease Journal</i> , 1993, Arguedas, Costa Rica ⁽¹⁹⁾	Open, prospective, non-comparative study unclassified	IV ceftazidime	40 Age 4 -141 months	Complete resolution of discharge	92.5% cured during first hospitalisation (up to 21 days treatment)	Not treated for same amount of time. No control
K	<i>The Pediatric Infectious Disease Journal</i> 1993, Dagan, Israel ⁽²⁰⁾	Open, prospective, non-comparative study. unclassified	IV or IM ceftazidime	37 Age 6 months-16 years	Complete resolution of discharge	100% cured. Patients were treated until 3 days after discharge stopped or up to 21 days	Not treated for same amount of time. No control
L	<i>Journal of Antimicrobial Chemotherapy</i> 1983, Lautala, Finland ⁽²¹⁾	Case series unclassified	IM ceftazidime	17 age 5 months -3 years	Complete resolution of discharge	11/17 cured (these were the 11 with <i>P. aeruginosa</i> isolated) Treated up until cure or maximum 12 days	The only cures were children with <i>P. aeruginosa</i> . 2 patients had severe disabilities, 2 had facial abnormalities No control. Very small study
M	<i>Journal of Chemotherapy</i> 2000, Esposito, Italy ⁽²²⁾	Case series unclassified	IM ceftazidime	52 Age 6 - 11 years	Complete resolution of discharge	67.3% cured, treated for 7-10 days	No control. Not treated for same amount of time

the eardrum so as to prevent complications and the social stigma of the purulent discharge and (3) minimise the effects of acute and long-term hearing loss. The trials in this review only really cover the first of those criteria. Further trials need to assess long-term healing of the ear drum, long-term levels of hearing loss, side effects of medication, causative bacteria in different regions, feasibility of dosing regimes, other long-term outcomes, CSOM discharge recurrence rate and cost/benefit analysis before a drug treatment is fully evaluated and conclusions drawn. Further trials could also research whether the frequency and duration of acute episodes of discharge alter the natural history of CSOM or influence the ultimate hearing levels.

SUMMARY

Topical quinolones are the most effective short-term treatment covered by the literature for children with CSOM. They are

significantly more effective than topical antiseptic treatment and topical aminoglycosides. However, this treatment is expensive and there is not much child data on the subject. More trials need to be done into the efficacy of low dose quinolones, as this treatment is cheaper so would be more attainable for developing countries. Long term outcomes on hearing and tympanic membrane perforation healing are also crucial in performing a cost/benefit analysis. As time goes on the cost of quinolones is likely to drop [11], but in the meanwhile countries should consider stocking this valuable treatment for a very common and potentially serious preventable health problem. There is no evidence to stock oral antibiotics as first line treatment over topical treatments, as oral amoxicillin is equal in efficacy to topical antiseptic. IV antibiotics are also not proven to be effective for first-line treatment, but further trials may show their suitability in hospital or where other therapies have failed.

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