

What is the best antibiotic treatment for meningococcal meningitis under epidemic conditions?

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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 best antibiotic treatment for meningococcal meningitis under epidemic conditions?*

The WHO Pocketbook of Hospital Care for Children recommends the following regimen for the treatment of bacterial meningitis in children: Chloramphenicol and ampicillin or chloramphenicol and penicillin. However resistance to penicillins and chloramphenicol is increasingly seen in many regions amongst *Streptococcus pneumoniae* and *Haemophilus influenzae*. In such circumstances the WHO recommends adherence to local guidelines, which in most cases will include treatment with a 3rd generation cephalosporin - cefotaxime or ceftriaxone. (Pocketbook 6.3, page 149). In epidemics of meningococcal meningitis where resources are limited WHO recommends using oily chloramphenicol (100mg/kg) as a single dose up to a max. of 3g.

INTRODUCTION

This review aims to examine the effective antibiotic treatment options for meningococcal meningitis in children, particularly during meningococcal meningitis epidemics. For the purposes of this review, 'effective' is quantified in terms of mortality rate, rate of CSF sterilisation, the incidence of auditory and neurological sequelae and the incidence of adverse effects. Although there is accumulating evidence that a shorter course of antibiotic therapy may be as effective as the currently recommended 10-day course, it was not within the scope of this review to examine this aspect of therapy.

METHODOLOGY

A search of the literature was conducted using the Cochrane Central Register of Controlled Trials and PubMed Clinical Queries with clinical filters for both 'therapy' and 'specific'. The following limits were applied: humans, English language and children 0-18 years.

The clinical search strategy employed was as follows: meningitis AND (meningococc* OR neisseria meningitidis) AND treatment AND endemic.

The PubMed Clinical Queries search yielded 61 results and Cochrane yielded two. The following trials were manually excluded: three on chemoprophylaxis and eradication of nasopharyngeal carriage, 19 on vaccinations, three including only adults, one including only cases of non-meningococcal meningitis, four pharmacokinetic studies, and one study on the quantification of fever in meningitis, four on short-course versus full-course cephalosporins. Five trials and one Cochrane review that included steroids in the treatment of meningitis were also excluded.

One Cochrane review [1] and 21 trials were therefore eligible for inclusion. Of the 21 trials, two were the same trial published in different journals [2] and one article was describing the results of another of the trials included [3][4]. Two additional trials carried out in developing countries were obtained from the reference lists of these studies [5][6]. Of the 21 trials included, 12 were carried out in developed countries and 9 in developing countries. 3 studies included only participants with meningococcal meningitis [5][7][8] one with meningococcal or pneumococcal [9] and the other 18 included all cases of bacterial or "purulent" meningitis.

RESULTS AND DISCUSSION

All studies reported the following outcomes: mortality, auditory or neurological sequelae, CSF sterility and adverse side effects. The antibiotics included were in the following categories: cephalosporins; chloramphenicol or ampicillin as monotherapy; and combination regimens (chloramphenicol plus ampicillin, chloramphenicol plus benzylpenicillin and sulbactam plus ampicillin); and were compared against each other. All of the included studies were randomised trials. However, these studies varied in terms of sample size adequacy, potential for reproducibility and the quality of data presentation (see Appendix for details of individual studies).

Treatment Outcomes

No significant differences between antibiotic regimens were demonstrated by mortality rates or the incidence of sensorineural sequelae. Only one study, by Peltola et al [10], found a significantly greater probability of bacteriological failures (i.e. recurrent cases of meningitis, recurrent or persisting bacteraemia or positive CSF until day 4 of treatment) with chloramphenicol compared to other antibiotics. Worse outcomes were found in children receiving chloramphenicol compared to those receiving ampicillin ($p < 0.01$), ceftriaxone ($p < 0.01$) and cefotaxime ($p < 0.05$). The treatment was extended or changed the most in the group receiving chloramphenicol.

Table 1: Description of included studies

Author Date Country	Antibiotics	Sample size	Level of eviden ce	Proportion of meningoco cal cases	Outcomes			
					Mortality	Auditory or Neurologic al Sequelae	CSF Sterilisation	Adverse effects
Barson 1985 USA	Ceftriaxone vs chloramphenicol -ampicillin	50 children	1b ¹	6% (n=3)	No deaths occurred	No significant difference	Sterility at 10.5- 18h: ceftriaxone 67% chloram-amp 60% (p>0.05)	diarrhoea: ceftriaxone 59% chloram-amp 22% (p<0.01)
Congeni 1984 USA	Ceftriaxone vs chloramphenicol -ampicillin	45 children	1b	9% (n=4)	ceftriaxone 2 (9%) chlor-amp 1 (4%) p>0.05	ceftriaxone 13% chlor-amp 22% (p>0.05)	sterility at 24h: ceftriaxone 95% chlor-amp 78% (p>0.05)	transient eosinophilia neutropenia, anaemia or diarrhoea: ceftriaxone 23% chlor-amp 9%
Del Rio 1983 Texas	Ceftriaxone vs chloramphenicol + ampicillin	78 children	1b- ²	11.5% (n=9)	No deaths occurred	ceftriaxone 13% chlor-amp 15% (p>0.05)	Reduced colony count at 4-12h: ceftriaxone 54% chor-amp 49% (p=0.58) All sterile at 24h	diarrhoea: ceftriaxone 41% chor-amp 21% p<0.05
Girgis 1988 Cairo	Ceftriaxone vs chloramphenicol + ampicillin	70 children	1b	38.6% (n=27)	ceftriaxone 6 (17%) chlor-amp 9 (26%) (p>0.05)	No sequelae developed in any surviving patient	CSF sterile in all surviving patients at 6 days	diarrhoea: with ceftriaxone 5.7% chlor-amp 0% (p>0.05)
Hassan 1976 Egypt	Epicillin vs ampicillin	96 adults and children	1b-	78% (n=75)	total deaths 13 (13%) comparable rates between groups (data not presented)	7 day follow up showed comparable rates of good recovery (data not presented)	Response rate non-significantly slower with epicillin (data not presented)	no adverse drug reactions
Jacobs 1985 USA	Cefotaxime vs chloramphenicol -ampicillin	50 children	1b- ²	16% (n=8)	chlor-amp 1 (4%) cefotaxime 0 (0%)	chlor-amp 5 (19%) cefotaxime 5 (22%)	Sterile by day 2: cefotaxime 100% chlor-amp: data not presented	no adverse drug reactions
Manios 1969 Greece	Ampicillin vs combined sulphadimidine- penicillin G	159 children	1b	100% (n=159)	ampicillin 3 (4%) sulph-penG 3 (3.6%) (p>0.05)	ampicillin 1 (1.5%) sulph-penG 3 (3.6%) (p>0.05) No long- term follow-up for sequelae	Time to normal CSF: ampicillin 12.4 days sulph-penG 13.4days CSF sterility: all sterile by 48h	severe drug reaction (thrombocytope nia or haematuria): ampicillin 0 (0%) sulph-penG 3 (3.6%)
Marks 1985 USA	Cefuroxime vs chloramphenicol -ampicillin	107 children	1b	6.5% (n=7)	cefuroxime 1 (2%) chlor-amp 1 (1.8%) (p>0.05)	cefuroxime 5 (10%) chlor-amp 4 (7%) No long- term follow-up for sequelae	sterility at day 2: 100% meningococcal cases No difference between treatment groups (p>0.05)	mild rash or diarrhoea: cefuroxime 4 (8%) chlor-amp 3 (5%)
Nathan 2005 Niger	Ceftriaxone Vs chloramphenicol	308 children	1b- ³	100%	ceftriaxone 6 (4%) chloramph 5 (3%) (p>0.05)	at 72h: ceftriaxone 14 (9%) chloramph 9 (6%) (p>0.05)	not measured in this trial	no adverse effects

¹ Level of evidence 1b represents an individual randomised controlled trial, with narrow CI and >80% follow-up (Oxford Centre for Evidence-based Medicine, May 2001)

² Trial had no description of randomisation, was not double blinded

Author Date Country	Antibiotics	Sample size	Level of eviden ce	Proportion of meningoco ccal cases	Outcomes			
					Mortality	Auditory or Neurologic al Sequelae	CSF Sterilisation	Adverse effects
Overturf 1977 California	Carbenicillin vs ampicillin	86 (62 children)	1b	8% (n=7 children)	ampicillin 3 (6.5%) carbenicilli n 0 (0%) (p>0.05)	significant sequelae: ampicillin 8 (17%) carbenicilli n 5 (13%) (p>0.05)	sterility at 24h: 100% patients No significant differences between treatment groups	eosinophilia, rash, diarrhoea or fever: carbenicillin 27% ampicillin 17.5%
Pecoul 1991 Mali, Niger	Chloramphenic ol vs Ampicillin	528 children	1b-3	30.5% (n=161)	case fatality rate at day 4: chloram 28% ampicillin 24.5% (95%CI = 0.86-1.52)	deaths or serious sequelae at discharge chloram 45.3% ampicillin 39.1% (95%CI = 0.95-1.42)	not measured in this trial	no adverse effects reported
Peltola 1989 Finland	Chloramphenic ol vs ampicillin vs cefotaxime vs ceftriaxone	197 children	1b	16% (n=32)	chloram 3 (5.6%) ampicillin 1 (2%) cefotaxime 4 (7.8%) ceftriaxone 1 (2%) (not significant)	chloram 2 (3.7%) ampicillin 2 (4.3%) ceftriaxone 8 (16%) (no significant differences)	sterile significantly earlier in Mnc ⁴ meningitis than Hib ⁴ (p<0.01) day 4 sterility all cases except 1 case of Hib treated with chloramphenicol	mild diarrhoea: chloram 9 (17%) ampicillin 7 (15%) cefotaxime 6 (12%) ceftriaxone 19 (38%) significantly increased risk with ceftriaxone (p<0.05)
Rodriguez 1985 Dominican Republic	Ceftazidime vs chloramphenic ol-ampicillin	100 children	2b ⁵	18% (n=14)	ceftazidime 12(20%) chlor-amp 8 (21%)	gross neurologica l sequelae: ceftazidime 2 (5%) chlor-amp 1 (4%)	CSF normalised by end of therapy in all patients ceftazidime 10.2days chor-amp 9.5 days (mean duration)	diarrhoea, reactive arthritis: ceftazidime 2 (3%) diarrhoea, fever, leukopenia+ana emia chlor-amp 3 (8%)
Rodriguez 1986	Sulbactam- ampicillin vs chloramphenic ol-ampicillin	81 children	2b	10% (n=8)	chlor-amp 6(18%) sulbactam- amp 1(3%)	chlor-amp 18% sulbactam- amp 12%	not measured	no significant difference
Rodriguez 1986	Ceftazidime vs chloramphenic ol-ampicillin	100 chilren	1b	18% (n=14)	ceftazidime 12 chlor-amp 8	ceftazidime 5% chlor-amp 4%	not measured	no significant difference
Schaad 1990 Switzerland	Ceftriaxone vs Cefuroxime	106 children	1b	28% (n=30)	no deaths in either group	auditory sequelae at 2 months: ceftriaxone 4% cefuroxime 17% (p=0.052) neurologica l sequelae ceftriaxone 9% cefuroxime 9% (p>0.05) all resolved by10wks	at 18-36h ceftriaxone 52 (98%) cefuroxime 47 (89%) (p=0.11)	reversible biliary pseudolithiasis ceftriaxone 45% cefuroxime 0% (p<0.001) secondary fever due to diarrhoea/reacti ve arthritis/ drug fever higher in cefuroxime (p=0.093)

³ Trial was not blinded⁴ Mnc = meningococcal, Hib = *Haemophilus influenzae* type b⁵ Level of Evidence 2b represents a low quality RCT: no description of randomisation, non-blinded. No statistical analysis of results.

Author Date Country	Antibiotics	Sample size	Level of eviden ce	Proportion of meningoco ccal cases	Outcomes			
					Mortality	Auditory or Neurologic al Sequelae	CSF Sterilisation	Adverse effects
Scholz 1998 Germany	Ceftriaxone vs cefotaxime	82 children	1b	50% (n=41)	no deaths in either group	ceftriaxone 13.7% cefotaxime 23.6%	at 24h: ceftriaxone 44 (10 0%) cefotaxime 37 (97%)	diarrhoea: ceftriaxone 13.6% cefotaxime 7.9% subclinical pseudolithiasis: ceftriaxone 12 (27%)
Shann 1985 Papua New Guinea	Chloramphenic olvs chloramphenic ol + ampicillin	367 children	1b	4% (n=15)	chlor 48 (26%) chlor-amp 49 (27%) (p>0.05)	brain damaged at discharge: chlor 10 (5%) chlor-amp 20 (11%) no long- term follow-up	not measured	not measured
Tuncer 1988 Turkey	Ceftriaxone vs penicillin G	42 children	1b-2	67% (n=28) with meningococ cal meningitis (remainder with meningococ c-aemia)	ceftriaxone 1 (5%) penicillinG 2 (9%)	not measured	all patients had sterile CSF by day 3 of therapy (data not presented)	increased incidence of necrotic skin lesions due to increased time of IV administration and slower mobilisation in penicillin G group (p<0.05) (data not presented)
Wells 1984 USA	Ceftriaxone vs chloramphenic ol-ampicillin	30 children	1b	10% (n=3)	chlor-amp 1 (5.5%) ceftriaxone 0 (0%)	chlor-amp 5 (28%) ceftriaxone 2 (17%)	all cases had sterile CSF by 24-48h of treatment	acute tubular necrosis: chlor-amp 1 (5.5%)
Whittle 1973 Nigeria	Chloramphenic ol vs penicillin	123 children	2b	100% (n=123)	chlor 2 (3%) penicillin 1 (1.7%)	at discharge: chloram 5 (7.7%) penicillin 8 (13.8%)	not measured	not measured
Section 1.01 Systematic Review								
Prasad 2005 (Cochrane Collaboration)	Cefotaxime or Ceftriaxone Vs Penicillin or chloramphenic ol or ampicillin + chloramphenic ol	993 patient s from 18 trials	1a ⁶	Not quantified.	No significant difference Risk of death -1% with cephalospo rins CI= -4% to +3%	No significant difference Risk of deafness is -4% with cephalospo rins CI= -9% to +4%	Significantly decreased risk of (-6%) CSF culture positivity at 10-48h with 3 rd generation cephalosporins 95%CI= -11-0%	Significantly increased risk (+8%) of diarrhoea with a cephalosporin 95%CI=3-13%

⁶ Level of Evidence 1a represents a systematic review of randomised controlled trials

However, these results reflect the poorer efficacy of chloramphenicol against *S. pneumoniae* and *H. influenzae* type b, and not against *N. meningitidis* where it was found to be as efficacious.

Overall, the speed of CSF sterilisation in bacterial meningitis was found to be quicker among patients receiving cephalosporins [1][10][11][12]. However, several studies comparing chloramphenicol-ampicillin therapy to a cephalosporin showed no significant difference in the speed of CSF sterilisation [13][14][15], with sterilisation occurring in all cases irrespective of the antibiotic received by day 1 [12], day 2 [15][16] and day 3 [7] of therapy, or by completion of treatment [2][14].

Delayed CSF sterilisation can lead to an increased incidence of sensorineural sequelae and is potentially a problem in pneumococcal and *Haemophilus meningitis* in the setting of antibiotic resistance, inferior antibiotics [17] or delayed presentation. Generally, meningococcal meningitis responds quickly to antibiotic therapy compared to other forms of bacterial meningitis, as reflected by the speed of CSF sterilisation in meningococcal cases [7][9][10] and the lower incidence of sequelae compared to non-meningococcal cases. Peltola et al showed that the CSF became sterile earlier in cases of meningococcal meningitis compared to cases of *Haemophilus meningitis* ($p < 0.01$), and that 100% of meningococcal cases had sterile CSF at 24 hours, irrespective of the antibiotic therapy received [10]. In addition, Tuncer et al showed that all 28 children with meningococcal meningitis had sterile CSF by day 3 of therapy, with either ceftriaxone or benzylpenicillin therapy [7].

There were no severe side effects associated with any of the antibiotics included in these studies. The only side effects reported were mild, self-limiting or were relieved on cessation of therapy. Cephalosporins, particularly ceftriaxone, was associated with a significantly increased risk of diarrhoea compared to other antibiotics [1][10][12]. One study showed a significantly greater occurrence of diarrhoea in patients being treated with ceftriaxone compared to cefotaxime [10]. In all cases diarrhoea was mild and self-limiting, and did not necessitate a change in treatment. The only other significant side-effect was found with the occurrence of reversible biliary pseudolithiasis (i.e. gall stones) in 46% of children treated with ceftriaxone [17]. Three of the 53 children treated with ceftriaxone had symptoms that were severe enough to require a change in treatment. However, all cases resolved when treatment was stopped, or after being switched to an alternative antibiotic. Only two trials actively screened for the presence of gallstones [17][18].

Resistance

Among the 26 trials and one systematic review included in this study, there were no reported cases of meningococcal resistance to any antibiotic. Although no cases of penicillin-resistant or chloramphenicol-resistant meningococci have been reported, there remains the possibility that this may occur in the future [19]. In the event of resistance emerging, these results support treatment with a 3rd generation cephalosporin.

Cost

In countries where meningococcal meningitis is endemic, the efficacy and availability of chloramphenicol in the treatment of meningococcal meningitis, far outweighs the small risk of adverse effects. In 1998, oily chloramphenicol costed US \$13 per adult treatment on average, compared with \$30 for 10 days of

ampicillin or \$100 for 5 days of ceftriaxone [20]. However, drug costs and availability is a complex and ever changing issue. More recently, the cost of generic ceftriaxone has fallen rapidly since patent rights for this drug have expired in most countries. A study conducted in Niger in 2005 on the treatment of meningococcal meningitis estimated that the average treatment cost per patient was US \$4-6 for oily chloramphenicol compared to only \$2-3 for intramuscular ceftriaxone [5].

SUMMARY

For a child with confirmed or suspected meningococcal meningitis, there is no significant difference between the outcome of treatment with either a cephalosporin, chloramphenicol, ampicillin or penicillin monotherapy, or with a combined regimen of chloramphenicol and ampicillin, in terms of mortality, the incidence of auditory or neurological sequelae, rate of CSF sterilisation or risk of significant adverse side-effects.

The results of this study are therefore in alignment with the WHO recommendations for the treatment of meningococcal meningitis with a combination regimen of either chloramphenicol-ampicillin or chloramphenicol-benzylpenicillin. Where resistance has emerged, treatment should be substituted with a 3rd generation cephalosporin which has remained effective against all known strains of bacterial meningitis.

The trials included in this review represent a range of antibiotics, doses, routes of administration and duration of treatment. It has therefore not been within the scope of this review to determine the most effective dosage and duration of therapy for the treatment of meningococcal meningitis.

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