International Child Health Review Collaboration

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. 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 sequlae 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 penicillinresistant 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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