

What is the appropriate antibiotic management of suspected meningitis in a confirmed epidemic of meningococcal disease?

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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 appropriate antibiotic management of suspected meningitis in a confirmed epidemic of meningococcal disease?*

The **WHO Pocketbook of Hospital Care for Children** recommends during a confirmed epidemic of meningococcal meningitis to give oily chloramphenicol (100 mg/kg IM as a single dose up to a maximum of 3 grams). (Pocketbook chapter 6.3, page 149).

Introduction:

In developing countries, the morbidity and mortality from acute bacterial meningitis remains significantly higher than that of industrialized countries. Factors including lack of access to healthcare, unavailability of appropriate antibiotics and other pharmacotherapies, difficulty in obtaining prompt accurate diagnoses, and late patient presentation all contribute to this increased mortality risk. *Neisseria meningitidis* continues to be one of the major pathogens involved in bacterial meningitis in the developing world, with an estimated mortality rate of 20-40% and with 25-50% of survivors suffering neurological sequelae [1-3]. Epidemics of meningococcal meningitis continue to occur in sub-Saharan Africa, the Middle East, and South and East Asia. The 600-km wide "meningitis belt" of sub-Saharan Africa extends from Gambia

and Senegal in the west to Ethiopia and Sudan in the east. In this region, rates of endemic meningococcal disease are 10 to 50 times greater than that found in developed countries, and large epidemics of group A (and sometimes group C) meningococcal meningitis occur every 8 to 14 years [4]. During these epidemics, access to effective, inexpensive, and simple antibiotic regimens is paramount. Long-acting chloramphenicol (oily suspension) has been used successfully for the treatment of meningococcal meningitis [5]; a series of one or two daily intramuscular injections (100 mg/kg) has been the World Health Organization's (WHO) recommended antibiotic regimen for treatment of meningococcal meningitis in the setting of an epidemic in resource-poor areas since 1995 [6]. Prospective [7] and retrospective [8] studies using oily chloramphenicol in meningococcal meningitis have showed case fatality rates varying between 2.2% and 9.1%, which is comparable with other studies in developing countries. With the wider distribution of 3rd generation cephalosporins (primarily, ceftriaxone and cefotaxime) and growing concerns regarding antibiotic-resistance patterns and chloramphenicol availability in the upcoming years, this review intends to examine the evidence behind the WHO recommendation as well as to answer the question "what is the appropriate antibiotic management of suspected meningitis in a confirmed epidemic of meningococcal disease"

Methodology

Search of The Cochrane Library for "meningococcal meningitis" yielded 12 reviews, one of which was relevant to our question [1]. However, the review (published in 2003) did not focus on antibiotic use for meningococcal

meningitis but for all bacterial meningitides (subgroup analysis was performed for *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*), specific trials were rejected if they did not contain a 3rd generation cephalosporin arm, and 16 of the 18 included trials were dated in the 1980's. Therefore, a search of Pubmed for more trials using the search strategy established by Haynes et al "Clinical queries" for therapy questions. Narrow, specific searches for controlled trials in "meningococcal disease in developing countries" or "meningococcal meningitis in developing countries" yielded less than five results. Broad, sensitive searches for "meningococcal epidemic" and "antibiotic AND meningococcal epidemic" yielded 286 and 95 articles, respectively. Each abstract was skimmed for relevance; seven articles were true controlled clinical trials published in 1990 or later. Of these, two were conducted in emergency rooms of developed countries and one was from an unavailable journal. In addition, a detailed review article by Fuller et al. [2] was found which consolidated the finding of all clinical trials prior to 2003 regarding antibiotic treatment for bacterial meningitis in developing countries. This review article encompassed three of the remaining four clinical trials.

Therefore, the results of the Cochrane review [1], the detailed review article by Fuller et al. [2], and the remaining clinical trial by Nathan et al. [9] will be discussed here. Pertinent data from other pivotal studies (pre- and post-1990) will also be discussed.

Results

The Cochrane review (2003) was a meta-analysis of eighteen trials with 993 participants, comparing 3rd generation cephalosporins versus conventional treatment for treating acute bacterial meningitis. Conventional treatment was defined as penicillin or ampicillin alone, ampicillin-chloramphenicol, penicillin-chloramphenicol, or chloramphenicol alone. Primary outcomes evaluated were death, severe sensorineural deafness, and other disabling sequelae; these were also combined into a composite outcome "treatment failure" by the review authors. Secondary outcomes included antibiotic side-effects, duration of CSF culture positivity, and duration of coma. Subgroup analysis was performed for three causative organisms (*S. pneumoniae*, *H. influenzae*, and *N. meningitidis*)

and for developed versus developing countries. Risk difference (RD) was used to summarize results since relative risk could not always be calculated. All included trials were level of evidence 1b with varying levels of adherence to strict methodological criteria (i.e., randomisation, blinding, completeness of follow-up, intention-to-treat analysis).

Although "conventional treatment" included the antibiotic combinations listed above, none of the 18 trials had "chloramphenicol alone" as a treatment arm. Overall, there were no statistically significant differences in the risk of death (38 [7.6%] of 503 cephalosporin group vs. 38 [7.8%] of 490 conventional group; RD, -1%; 95% confidence interval [CI], -4% to +3%), risk of sensorineural deafness (19 [7.7%] of 247 cephalosporin group vs. 29 [11.4%] of 254 conventional group; RD, -4%; 95% CI, -9% to +1%), and risk of treatment failure (48 [9.5%] of 503 cephalosporin group vs. 53 [10.8%] of 490 conventional group; RD, -2%; 95% CI, -5% to +2%).

Subgroup analyses by causative organism did not reveal any statistical differences between the difference antibiotic regimens, though power was inadequate and only the result for death could be calculated. For *N. meningitidis*, there was no statistically significant difference in risk of death (two [2.4%] of 84 cephalosporin group vs. four [4.7%] of 85 conventional group; RD, -2%; 95% CI, -11% to +7%).

A developing country was the setting for nine of the 18 included trials. Subgroup analysis of this data also showed no statistical difference in the primary outcomes: risk of death (31 [12.4%] of 249 cephalosporin group vs. 31 [13.2%] of 234 conventional group; RD, -2%; 95% CI, -8% to +4%), risk of sensorineural deafness (two [3.6%] of 55 cephalosporin group vs. three [4.5%] of 66 conventional group; RD, -1%; 95% CI, -9% to +8%), and risk of treatment failure (33 [13.2%] of 249 cephalosporin group vs. 34 [14.5%] of 234 conventional group; RD, -2%; 95% CI, -8% to +4%).

In their discussion, the authors note one study (Peltola, 1989) [10] - the most methodologically sound of the 18 included trials - which demonstrated that those who received chloramphenicol-only had a worse outcome than those receiving 3rd generation cephalosporins. This study will be discussed in more detail below. The article by Fuller et al. [2] is a comprehensive review of the evidence of the most appropriate use of antibiotics, particularly chloramphenicol and 3rd generation cephalosporins, in the

treatment of bacterial meningitis among children in developing countries. Although the article is directed towards the pediatric population, some of the referenced trials/studies included both children and adults in their study populations. Unlike the Cochrane review, this article initially compares the efficacy of chloramphenicol alone versus its use in combination with penicillin/ampicillin. It then addresses the efficacy of chloramphenicol compared to 3rd generation cephalosporins (like the Cochrane review but not in meta-analysis form), and compares the different drug administration routes of chloramphenicol.

Comparing chloramphenicol alone to chloramphenicol with penicillin/ampicillin, six papers were found but only three were prospective, randomised controlled trials (level of evidence 1b) [11, 12]. All three studies showed no significant difference in mortality or severe neurological sequelae between chloramphenicol alone versus chloramphenicol plus penicillin/ampicillin. Two of the studies used small study populations and were probably inadequately powered to show small outcome differences (large risk for type II errors). Also, there were differences in drug schedule and mode of administration between each of the studies. Lastly, the study periods of all three predated 1990.

The author's literature search then yielded 15 prospective, randomised controlled trials addressing the comparison between chloramphenicol-based regimens and 3rd generation cephalosporins; seven were undertaken in developing countries. Chloramphenicol was combined with penicillin or ampicillin in all of the studies, though one (Peltola) [10] also had a chloramphenicol-only treatment arm. All of the articles used death and major neurological sequelae as primary outcomes. Of these 15 articles, 12 reported statistically similar results between chloramphenicol-based regimens and 3rd generation cephalosporins. Two remaining articles had significant methodologic flaws, and the article by Peltola [10] (as stated above) demonstrated a disadvantage in using chloramphenicol alone (see below for details).

The studies summarized in this review varied in their duration, dosage, and mode of antibiotic administration. The authors note that all the published randomized controlled trials of oily chloramphenicol have been comparisons with sub-optimal regimens of another antibiotic (5 days intramuscular penicillin, 8 days intravenous

ampicillin, 2 days intramuscular ceftriaxone) [5]. All of these studies were also limited by small sample sizes and were inadequately powered, and the study periods in all but one predated 1990; per the authors, these aspects may limit their current generalizability.

The trial by Nathan et al. [9] is directly applicable to our clinical question, and compares the efficacy of single-dose ceftriaxone to single-dose oily chloramphenicol during a meningococcal meningitis outbreak in March-April 2003 in eastern Niger. 510 persons with suspected disease were recruited from eight peripheral health centers and one regional hospital and randomised to receive either ceftriaxone or chloramphenicol. Blinding was not possible due to the different appearance of the antibiotic vials. Primary outcome was treatment failure (death or clinical failure) at 72 hours. Secondary endpoints were death, clinical failure (i.e., lack of improvement or worsening neurological status, persistent fever or seizures), and neurological sequelae at 72 hours. Longer follow-up was not feasible in the acute phase of the epidemic setting. Statistical analysis was performed on both an intention-to-treat (individuals with suspected disease) and a per-protocol (individuals with confirmed meningococcal meningitis) basis.

In the intention-to-treat analysis, there were no statistically significant differences in primary nor secondary outcomes between the two treatment arms: treatment failure (22 [9%] of 256 chloramphenicol vs. 22 [9%] of 247 ceftriaxone; RD, +0.3%; 90% CI, -3.8% to +4.5%); death (12 [5%] of 256 chloramphenicol vs. 14 [6%] of 247 ceftriaxone; RD, +1.0%; 90% CI, -2.3% to +3.8%); and neurological sequelae (13 [5%] of 244 chloramphenicol vs. 16 [7%] of 234 ceftriaxone; RD, +1.6%; 90% CI, -2.1% to +5.1%). In the per-protocol analysis, 489 of 503 participants (7 were lost to follow-up) underwent lumbar puncture, and 356 (43%) were diagnosed with meningitis. The causative agent was *N. meningitidis* in 349 (98%), *S. pneumoniae* in 4 (1%), and *H. influenzae* in 3 (1%). Again, among those with confirmed meningococcal disease, there were no differences in primary or secondary outcomes between the two treatment arms.

These results are further supported by data from another unpublished randomized controlled trial (F Varaine, unpublished data) [13] cited by Fuller et al. [2], comparing daily chloramphenicol in oil for two days with two days of daily intramuscular ceftriaxone. This trial showed similar case fatality rates at 72 hours for those who received chloramphenicol.

Two specific issues require further clarification in this evidence-based review: whether chloramphenicol alone is adequate treatment for *N. meningitidis*, and whether chloramphenicol alone is effective treatment for non-meningococcal meningitis. The following four studies, all of which are included in the review by Fuller et al., (Peltola [10], Shann [11], Pecoul [14], and Kumar [12]) provide some insight into these issues.

In multicenter study by Peltola et al. [10], 220 children with bacterial meningitis were randomised to receive 7 days of chloramphenicol, ampicillin (initially with chloramphenicol), cefotaxime, or ceftriaxone. Of the 200 children included in the final analysis, there were no significant differences in mortality rate, sequelae, or overall clinical recovery. More specifically, there were no outcome differences amongst those with *N. meningitidis* meningitis. There were 4 recurrences (length of treatment failures), all in the chloramphenicol group, and all were non-meningococcal (3 *H. influenzae*, 1 *S. pneumoniae*).

In a prospective multicenter study by Shann et al. [11] from 1985, 367 children from Papua New Guinea with CSF findings indicative of bacterial meningitis were randomised to receive either chloramphenicol alone versus chloramphenicol plus penicillin. There was no overall difference in rates of mortality (26% chloramphenicol alone vs. 27% chloramphenicol plus penicillin) or poor outcome (38% chloramphenicol alone vs. 40% chloramphenicol plus penicillin), and no difference in poor outcome rate amongst those with *N. meningitidis* (33% for both treatment groups). The rate of poor outcomes differed between treatment groups in those with *S. pneumoniae* (45% chloramphenicol alone vs. 56% chloramphenicol plus penicillin) and *H. influenzae* (49% chloramphenicol alone vs. 39% chloramphenicol plus penicillin). This is the largest study to date comparing chloramphenicol alone to other treatment regimens. However, it is quite dated and is inadequately powered to perform definitive subgroup analysis for the individual causative organisms.

Pecoul et al. [14] compares daily oily chloramphenicol to 8 days of intravenous ampicillin in the treatment of bacterial meningitis amongst patients in Mali and Nigeria. Overall, there was no significant difference in case-fatality rate (28% for chloramphenicol vs. 24.5% for ampicillin; relative risk, 1.14; 95% CI, 0.86 to 1.52). The case fatality rates were 13% for *N. meningitidis*, 36% for *H. influenzae* meningitis

and 67% for pneumococcal meningitis. The study reported organism-specific case fatality rates for all treatments combined, but did not report organism-specific case fatality rates for each antibiotic. In their review, the authors in Fuller et al. [2] state that “despite having fewer patients with pneumococcal meningitis (the group with the poorest outcomes), the chloramphenicol arm had higher case fatality rates and rates of treatment failure, with results that approached, but did not reach, significance”, and caution that the use of oily chloramphenicol for non-meningococcal meningitis has yielded poorer results.

Lastly, Kumar and Verma [12] studied of the effectiveness of chloramphenicol alone versus chloramphenicol plus penicillin among 70 children aged >3 months with bacterial meningitis, and demonstrated no significant differences between the two treatment regimens. Treatment failure occurred in 9% of the chloramphenicol group vs. 12.1% in the chloramphenicol plus penicillin group ($p>0.05$). This study had a small sample size, and organism-specific outcomes were not reported.

In summary of these 4 studies, it appears that chloramphenicol alone is adequate in treatment for meningococcal meningitis. However, there is substantially more doubt whether chloramphenicol alone is effective treatment of non-meningococcal meningitis.

Discussion

Overall, both the Cochrane meta-analysis and the comprehensive review of the evidence by Fuller et al. demonstrate that there are no significant differences between chloramphenicol-based regimens and 3rd generation cephalosporins in the treatment of acute bacterial meningitis. However, for the purpose of our initial clinical question, all but one of the included studies does not have a chloramphenicol-only arm. Fuller et al. goes on to review the evidence (including the trials by Shann [11] and Kumar [12]) between chloramphenicol alone versus chloramphenicol with penicillin or ampicillin, and concludes that there are no significant overall outcome differences. In contrast, a larger investigation by Peltola [10] concluded that chloramphenicol alone should never be used in the setting of acute bacterial meningitis. Again, these studies were mostly carried out prior to 1990 and many did not have adequate power to demonstrate small outcome differences.

These data are very useful in the setting of acute bacterial meningitis. However, their application towards our initial clinical question is limited for two reasons. First, these studies consider all bacterial causes of meningitis rather than meningococcal meningitis specifically; there was significant difficulty finding articles that pertained specifically to meningococcus. *S. pneumoniae* and *H. influenzae* demonstrate very different antibiotic resistance patterns to each other and to *N. meningitidis*; substantial resistance to chloramphenicol has been increasingly reported for these two organisms over the last decade. *N. meningitidis* resistance to chloramphenicol has only rarely been documented [15] and recent microbiological analyses of strains from Africa show no evidence of resistance [14, 16, 17]. Secondly, the studies were not conducted in the setting of a meningococcal epidemic, during which the pre-test probability for meningococcus as the causative agent of meningitis is exponentially higher than in the non-epidemic setting.

A few studies have yielded important epidemiologic data regarding the usual causative organisms of suspected meningitis in the setting of a meningococcal epidemic. During the meningitis epidemic investigated by Nathan et al. [9], the causative agent was *N. meningitidis* in 349 (98%), *S. pneumoniae* in 4 (1%), and *H. influenzae* in 3 (1%). In another meningococcal outbreak in Jos, Nigeria in 1996, 70 (80%) of 87 CSF samples collected from children were positive for *N. meningitidis*, implying that 20% were caused by other organisms [17]. Lastly, Campagne et al. [18,19] performed a revealing epidemiologic survey of the causative organisms for bacterial meningitis in Niamey, Niger (within the African meningitis belt) from 1981 to 1996. This time period included three epidemic years as well as inter-epidemic years. The survey demonstrated that the causative agent was *N. meningitidis* in 57.7% of cases, *S. pneumoniae* in 13.2%, and *H. influenzae* in 9.5%. More importantly, among children less than one year of age, *H. influenzae* and *S. pneumoniae* were the main causes of meningitis (35.1% and 26.3% of cases, respectively); 17.6% of cases were caused by *N. meningitidis*. This applied to both epidemic and inter-epidemic years. These epidemiologic differences must be taken into account when formulating the diagnostic and treatment guidelines.

In general, the article by Nathan et al. [9] is the most applicable to our initial clinical question regarding the most appropriate antibiotic

management of suspected meningitis in the setting of a confirmed meningococcal epidemic. It was performed during a recent meningococcal epidemic in a developing country, and is methodologically sound and adequately powered. It demonstrated that single-dose ceftriaxone was equally as effective as single-dose chloramphenicol in treating meningococcal disease during an epidemic. Carrying out both an intention-to-treat and per-protocol analysis was very important to this study. In an outbreak setting with limited laboratory and diagnostic capabilities, the intention-to-treat scenario is most realistic, though valuable insight was gained from the latter (per-protocol) analysis. The very similar outcomes between both analyses reassures us that during a meningococcal epidemic, the inability to culture every patient does not thwart appropriate treatment. A lumbar puncture in every patient may not be necessary, though the authors do advise that other diagnoses be considered if there is no clinical improvement within a reasonable period of time.

Summary

In the non-epidemic setting, during which there is a higher likelihood of having meningitis caused by other organisms such as *S. pneumoniae* or *H. influenzae*, a lumbar puncture is warranted and antibiotic coverage with chloramphenicol plus penicillin/ampicillin or a 3rd generation cephalosporin (according to the WHO guidelines for acute bacterial meningitis) is appropriate and supported by the above evidence.

In the event of a confirmed meningococcal epidemic, during which the likelihood of meningococcus being the causative agent of meningitis is significantly high (using clinical signs, such as the presence of petechiae or purpura, may help support this diagnosis), single-dose oily chloramphenicol remains an effective and reasonable method of treating meningococcal disease, especially in areas where resources are limited. Single-dose ceftriaxone is a fast, simple, increasingly inexpensive and available alternative treatment. However, even in the setting of a confirmed meningococcal epidemic, greater caution must be taken with those children less than one year of age since this age group is more likely to have meningitis caused by *H. influenzae* or *S. pneumoniae*; a lumbar puncture and broader antibiotic coverage would be justified.

Further trials are definitely needed that address meningococcal disease specifically, especially in outbreak settings among resource-poor countries.

Editor's note

It should be noted that all the RCT's were done before 1990. Since then resistance amongst CSF isolates amongst *Haem. Infl.* and *Strep.* have increased markedly globally. In those countries where the rates of resistance to chloramphenicol of CSF isolates of *S. pneumoniae* or *H. influenzae* are 'high', the WHO recommends a change in the standard treatment of meningitis from chloramphenicol and penicillin to a third-generation cephalosporin.

Although there are few randomised, controlled trials to inform policy decisions on appropriate antibiotics, there are many epidemiological and antimicrobial susceptibility studies published since 1990.

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