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EVIDENCE-BASED REVIEW

Treatment of bacterial meningitis: An overview of Cochrane systematic reviews

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KEYWORDS
Meningitis;
Treatment;
Systematic reviews;
Overview

Summary

Background: Acute bacterial meningitis (ABM) is a rapidly developing acute inflammation of leptomeninges and underlying subarachnoid cerebrospinal fluid (CSF). ABM is caused by bacteria and has a case fatality rate of 20–30%. Most prevalent causes of ABM are *Neisseria meningitis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. The aim of this paper is to summarize the main findings from Cochrane systematic reviews that have considered the evidence for treatments of ABM.

Methods: We searched the Cochrane Library (issue 1, 2007) for relevant reviews using 'meningitis' as a search term. The titles of all the search results were examined to select reviews on treatment of ABM. The full text of each of the selected reviews was studied to summarize the evidence available in Cochrane systematic reviews.

Results: We found three Cochrane reviews that focused specifically on the treatment of ABM, addressing empiric antibiotic therapy, fluid therapy and effects of adjuvant corticosteroids respectively. No statistically significant difference was found between third generation cephalosporins and conventional antibiotics in the combined endpoint of death or deafness (risk difference (RD) −1%, 95% CI −4% to +2%). However, culture positivity of CSF at 10–48 h was significantly higher in the conventional antibiotic group and diarrhoea was significantly more common in the cephalosporin group. When third generation cephalosporins are not available, ampicillin–chloramphenicol combination may be used as an alternative empiric treatment, however both resistance pattern as well as availability should be considered while prescribing empiric therapy of community acquired ABM. The fluid therapy review found too few studies to provide any robust conclusion. In settings with high mortality rates and where patients present late, use of intravenous maintenance fluids seems preferable to a restricted fluid intake. The efficacy of adjuvant corticosteroids varied between high- and low-income countries suggesting greater mortality reduction in high-income countries (RR 0.74, 95% CI 0.52–1.05) than in low-income countries (RR 0.87, 95% CI 0.72–1.05) and a beneficial effect on severe hearing loss in high-income countries (RR 0.32, 95% CI 0.18–0.57), whereas, sparse data in low-income countries (RR 1.04, 95% CI 0.66–1.63). A four-day regimen of dexamethasone should be given

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preferably before or with the first dose of antibiotics for cases of ABM from high-income countries.
Conclusion: In presence of sensitive organisms, third generation cephalosporins and conventional antibiotics lead to similar outcomes. More studies are needed to determine the antimicrobial resistance pattern against various antibiotics in rural and remote areas of developing as well as developed countries. To assess the effectiveness of either restricting or maintenance fluids in populations where patients present early and on death and disability when mortality rates are low, large trials should be conducted. More trials are needed to assess the use of adjuvant dexamethasone for ABM in low-income countries.

Background

Acute bacterial meningitis (ABM) is rapidly developing inflammation of leptomeninges (pia-arachnoid) caused by pyogenic bacteria. *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* account for most cases of ABM. Despite advances in our knowledge of pathophysiology of meningitis, antibiotic therapy and improved critical care, ABM is associated with a case fatality rate of almost 20—30%, especially in developing countries.[1] An additional 5—40% cases have only partial recovery with disability sequelae.[1] Effective treatment strategies are required to reduce the mortality and morbidity associated with ABM.

In this paper, we review the available evidence on measures for treating ABM. We will restrict ourselves to interventions that have been subject of Cochrane systematic reviews, as these reviews make systematic attempts to synthesize high quality evidence from randomized-controlled trials (RCTs) and may be considered at the top of hierarchy of levels of evidence.

Methods

In January 2007, we searched the Cochrane Library (issue 1, 2007) for relevant reviews using 'meningitis' as a search term. The titles of all the search results were examined to select reviews on treatment of ABM. The full text of each of the selected reviews was printed out and studied.

Results

The initial search yielded 127 hits. After examining the titles, we selected three reviews as relevant to the topic; all the three were focused on treatment of ABM. Table 1 provides a brief summary of these reviews. For each selected review, we provide below the details of methods and results.

Methods common to all reviews

The three included Cochrane reviews were conducted after searching the literature in various databases, mainly MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (central). In addition, reviewers used other strategies to find relevant studies. The strategies included searching specialized databases within the Cochrane Collaboration, such as the Cochrane Airways Group Trials Register or Cochrane Infectious Diseases Group Trial Register, checking references of relevant articles and writing to authors for additional studies.

More than one reviewer independently assessed eligibility of the studies for their review, assessed their methodological quality, and extracted the data. All reviewers used the Cochrane Collaboration software Revman to synthesize their data.

Cochrane review on third generation cephalosporins versus conventional antibiotics for treating acute bacterial meningitis (ABM)

Empirical therapy of suspected ABM is driven by likely pathogens, local antibiotic resistance patterns and availability of medicines. While many physicians continue to use conventional antibiotics (benzylpenicillin, or ampicillin, with or without chloramphenicol), others have started using third generation cephalosporins. It is unclear whether there is difference between the cephalosporins or conventional antibiotics in terms of clinical outcomes. The objective of the review was to compare the effectiveness and safety of the third generation cephalosporins with conventional treatment, i.e. penicillin/ampicillin—chloramphenicol in patients with community-acquired acute bacterial meningitis.

The last search of the literature was carried out in November 2006. The authors selected RCTs comparing third generation cephalosporins with conventional antibiotics in patients with community acquired ABM. The RCTs included children as well as adults. Ceftriaxone (16 trials) or cefotaxime (two) or ceftazidime (one) were compared with penicillin alone, ampicillin—chloramphenicol combination, penicillin—chloramphenicol combination or chloramphenicol alone. Death, severe sensorineural deafness, culture positivity of CSF after 10—48 h and adverse effects of the drugs were the outcome measures.

Nineteen trials with 1496 participants were included in the analysis. Ten trials were contributed by developing countries and nine trials by developed countries. The reports did not have sufficient details to permit adequate assessment of methodological quality. No statistically significant difference was found between third generation cephalosporins and conventional antibiotics in the incidence of deaths (risk difference [RD] 0%, 95% confidence interval (95% CI) −3% to +2%), sensorineural deafness (RD −4%, 95% CI −9% to +1%), combined endpoint of death or deafness (RD −1%, 95% CI −4% to +2%), skin rash (RD −1%, 95% CI −4% to +2%). However, culture positivity of CSF at

Table 1 Summary of Cochrane Reviews.

Topic of Cochrane Review	Most recent search	No. of RCTS included	Author's conclusions
Third generation cephalosporins versus conventional antibiotics for treating acute bacterial meningitis[2]	2006	19	No clinically important difference between the use of cefotaxime and conventional antibiotics. Ampicillin—chloramphenicol combination may be used as an alternative when third generation cephalosporins are not available.
Fluid therapy for acute bacterial meningitis[3]	2005	3	In settings with high mortality rates and where patients present late, intravenous maintenance fluids are preferred to restricted intake, in the first 48 h. Insufficient evidence in case of lower mortality rates and when children present early.
Corticosteroids for acute bacterial meningitis[4]	2006	20	Adjuvant corticosteroids are beneficial in treatment of acute bacterial meningitis in children as well as in adults in high-income countries.

10—48 h was significantly higher in the conventional antibiotic group and occurrence of diarrhoeas was significantly more common in the cephalosporin group. The results of analysis according to the causative organism did not reveal any difference between the two regimens, though the organism-specific data were sparse and power for analysis with respect to each organism was inadequate.

The authors conclude that there was no clinically important difference between ceftriaxone or cefotaxime versus conventional antibiotics. However, they point out that the resistance pattern has changed since the publication of trials; most of which were conducted in the 1980s. Both resistance pattern as well as availability should be considered while prescribing empiric therapy for community acquired ABM.

Cochrane review on fluid therapy for acute bacterial meningitis

Hyponatraemia is present in over 50% of children with meningitis at the time of admission. It is associated with adverse neurodevelopmental outcomes.[5,6] Opinion varies on whether the hyponatraemia is due to dehydration or inappropriate ADH secretion. Accordingly, there is controversy about whether to restrict fluid or to give intravenous maintenance fluid in early stages of ABM in children.

The objective of this review was to compare the effects of administration of restricted-versus full-maintenance fluid volume in the initial 72 h after presentation, on death and neurological sequelae.

The last search of the literature was carried out in March 2005. The authors included only RCTs. They intended to include all age groups of patients but the included studies had only children as subjects.

Only three trials were found eligible. The largest of the three trials was conducted in Papua New Guinea (Duke, 2002) in settings with high mortality rates.[7] The Cochrane review with 415 children included in the analysis, found no statistically significant difference between full maintenance fluid and restricted-fluid groups for deaths (risk ratio (RR) 0.82, 95% CI 0.53—1.27); for acute severe neurological sequelae (RR 0.67, 95% CI 0.41—1.08); and for mild to moderate sequelae (RR 1.24, 95% CI 0.58—2.65). However, all the 95% CIs were wide and did not exclude a clinically important difference. There was statistically significant difference in favour of the maintenance-fluid group, in regard to spasticity (RR 0.50, 95% CI 0.27—0.93), seizures at both 72 h (RR 0.59, 95% CI 0.42—0.83) and 14 days (RR 0.19, 95% CI 0.04—0.88), and chronic severe neurological sequelae at 3 months follow up (RR 0.42, 95% CI 0.20—0.89).

The authors conclude that there is some evidence to support the use of intravenous full maintenance fluid, in preference to restricted fluid, in the first 48 h in children in developing country settings (where patients present late and mortality rates are high). However, there is insufficient evidence to guide practice in settings where children present early and mortality rates are low.

Cochrane review on corticosteroids for acute bacterial meningitis

ABM remains a disease with high mortality and morbidity despite advances in antibiotic therapy and critical care. The severity of CSF inflammatory response correlates well with outcomes[1,8,9] Corticosteroids are known to reduce this inflammation, and hence may improve the outcome. The objective of this Cochrane review was to evaluate the effects of adjuvant corticosteroids on mortality, severe hearing loss and neurological sequelae; in the treatment of children and adults with ABM.

The last search of the literature was carried out in June 2006. The authors included randomized-controlled trials in all age groups with any corticosteroid. Twenty trials involving 2750 patients were included. Dexamethasone was used in 17 of 20 studies. Overall, adjuvant corticosteroids were associated with lower case fatality (RR 0.83, 95% CI 0.71—0.99) and lower rates of both hearing loss (RR 0.65, 95% CI 0.47—0.91) and long-term neurological sequelae (RR 0.67, 95% CI 0.45—1.00). However, efficacy of corticosteroids varied between high- and low-income countries suggesting greater mortality reduction in high-income countries 0.74 (95% CI 0.52—1.05) than in low-income countries 0.87 (95% CI 0.72—1.05). Further, in case of severe hearing loss, corticosteroids had protective effect in high-income countries (RR 0.32, 95% CI 0.18—0.57), whereas, no beneficial effect was seen in low-income countries (RR 1.04, 95% CI 0.66—1.63).

The mortality rates were similar with administration of corticosteroids before or with the first dose of antibiotics (RR 0.84. 95% CI 0.70—1.02) as well as after the first dose of antibiotics (RR 0.80, 95% CI 0.70—1.02).

The results were similar across all causative organisms. The authors conclude that in high-income countries, the use of corticosteroids has beneficial effects showing lower case fatality in adults with acute bacterial meningitis (RR 0.57, 95% CI 0.40—0.81) and in children with ABM, (RR 0.99, 95% CI 0.81—1.20). Further, corticosteroids have beneficial effects on short-term sequelae in adults (RR 0.57, 95% CI 0.40—0.81) and prevention of hearing loss in children (RR 0.61, 95% CI 0.44—0.86). It is recommended that dexamethasone should be given to all patients, children as well as adults with ABM in high-income countries, irrespective of bacterial aetiology and should be initiated before or with the first dose of antibiotics.

Discussion

The mainstay of treatment of ABM is antibiotics. The antibiotic has to be started empirically because culture and sensitivity reports take 24—48 h.

Recent reviews and textbooks recommend use of combination of vancomycin and ceftriaxone[10—14] instead of ceftriaxone alone; while many resource-constrained countries still use conventional antibiotics. The RCT by Nathan et al.[15] suggests that efficacy of single dose treatment with ceftriaxone is not inferior to that of oily chloramphenicol for epidemic meningococcal meningitis. The Cochrane review by Prasad et al.[2] provides strong evidence that the two are of nearly equivalent efficacy, and adopting ceftriaxone or cefotaxime is completely justified. The trial report by Nathan et al.,[15] further strengthens the case for ceftriaxone as initial empiric therapy.

Regarding recommendation to combine vancomycin with ceftriaxone, there is no RCT comparing the combination with ceftriaxone alone, but there is evidence that ceftriaxone resistance is more prevalent amongst penicillin-resistant *S. pneumoniae* isolates, whereas little or no resistance was detected to vancomycin (0% intermediate and resistance).[16] Microbiology experts recommend that when more than 3% of cultures show resistance to an antibiotic, another antibiotic should be added.

A critical question is: what evidence do we need to recommend an empiric antibiotic or combination of antibiotics? Should it be only the evidence of sensitivity or resistance in laboratory isolates for CSF; or should it also require RCTs to make evidence-based recommendation. It seems logical to use combination when resistance is detected in laboratories and the resistance correlates with unfavorable outcome in the patients. To demand RCTs in this situation may entail avoidable risks to human life, but at least there should be local evidence of resistance and documented correlation with outcome. However, it is quite legitimate to ask evidence from RCTs considering that all RCTs involving serious illness are associated with risk of death and/or disability. The only difference may be that in meningitis, we deal with a clearly identifiable cause and laboratories provide reliable evidence of how the organisms might respond to the intervention.

Undoubtedly, when there is no unacceptably high frequency of resistance, then adoption of a new antibiotic requires evidence from RCTs comparing old and new antibiotic regimens such as vancomycin plus ceftriaxone versus ceftriaxone alone. There are no Cochrane reviews of such RCTs, and there is a need to do this if they exist. Probably, the new antibiotics become standard therapies soon after the first or second RCTs and reviewers may not find it worthwhile to conduct the reviews on widely accepted interventions. Yet, these reviews may be important as they provide insights not available from single RCTs.

Fluid therapy is an important issue in the treatment of bacterial meningitis, especially in children. The three studies included in the Cochrane review on the topic have been conducted in developing countries, where patients often reach late and have dehydration. This may be the reason why maintenance therapy is associated with better outcome than fluid restriction. Though the authors presented completely separate analysis for deaths, mild/moderate and severe neurological sequelae, assessed within four weeks (short-term), we think this may be misleading. An intervention that causes more deaths may leave less people with sequelae and hence may appear better when sequelae are analyzed alone. For a valid perspective, analysis of combined outcome of death and sequelae is necessary. We performed this and obtained a combined risk ratio of 0.72 (95% CI 0.48—1.07). Although not statistically significant, it shows a moderately strong trend in favour of maintenance fluid. In the light of statistically significant findings for other outcomes, such as reduced spasticity, seizures and long-term neurological sequelae, maintenance fluid therapy should be used. There are two caveats: one, whether the results apply to developed countries is difficult to assess, as clinical outcomes are available for only two studies conducted in developing countries (Papua New Guinea and India). Second, the findings cannot be described as robust because the total number of patients in the Cochrane review is only 415. For both these reasons, more studies are indicated, particularly from developed countries. Until contrary results appear in the literature, a safe recommendation may be to use maintenance fluid therapy in patients with acute bacterial meningitis.

The burden of mortality and morbidity due to ABM continues to remain high despite antibiotics. Adjuvant therapies are necessary to reduce the burden. As inflammation and its effects form the principal pathophysiological basis for the adverse outcomes associated with meningitis, corticosteroids have the potential to improve outcome through their well established anti-inflammatory effects. On the basis of evidence from the Cochrane review, corticosteroids are effective adjuvants and are recommended to be given before or with the first dose of antibiotics. The efficacy of corticosteroids varies between high-income and low-income countries and is more in case of high-income countries. Possible reasons for the variation may include: better infrastructure in high income countries, which allows for early administration of both antibiotics and corticosteroids; difficulty in differential diagnosis between bacterial and tubercular meningitis, and associated malnutrition in low-income countries which may accentuate the harms with corticosteroids; late diagnosis (where children present late) is also responsible for low efficacy of corticosteroids as adjuvants. It is unlikely that any genetic or pathophysiologic basis explains the difference. Other

potential adjuvants such as non-steroidal anti-inflammatory agents have not yet been the subject of a systematic review. There may not be many RCTs of non-steroidal anti-inflammatory agents yet but still a systematic review may identify issues that need to be addressed for further RCTs.

Besides those indicated above, other potential targets for treatment of bacterial meningitis include agents inhibiting cytokines, anti-inflammatory cytokines like IL-10 or TGF-beta, targeted inhibition of NF-kB signaling pathway regulating cytokines, anti-leukocyte agents, and vascular endothelium growth factor acting on the blood-brain barrier. If some of these strategies could stop the progression of pathophysiologic cascade, they may potentially improve the neurological outcome and advance our ability to effectively treat patients with acute bacterial meningitis. The role of prophylactic and routine use of anticonvulsants in all patients or specific groups, such as children or those with pneumoccocal disease, is also unclear and needs to be addressed in future studies.

Conclusions

Cochrane systematic review suggests that third generation cephalosporins, usually ceftriaxone, and ampicillin—chloramphenicol combinations are equivalent alternatives to start initial empiric treatments in acute bacterial meningitis to conventional therapies. In settings with high mortality rates and where patients present late, intravenous maintenance fluids are preferred to a restricted fluid intake in the first 48 h. Adjuvant corticosteroids are beneficial in treatment of acute bacterial meningitis in adults and in children from high-income countries with good access to services. Yet to be established is efficacy of this approach in developing countries. Based on studies in the Cochrane systematic review, the reviewers recommended a four-day regimen of dexamethasone, given preferably before or with the first dose of antibiotics, in all age groups.

Meta-analysis of individual patient data would be required to define the reasons for differing outcomes in high- versus low-income countries.

Practice points

- Ampicillin—chloramphenicol combination may still be used as an initial empiric treatment in acute bacterial meningitis when third generation cephalosporins are not available and the locally isolated bacteria do not show significant resistance.
- Intravenous maintenance fluids are preferred to restricted fluid intake in the first 48 h, in settings with high mortality rates and where patients present late.
- Adjuvant Corticosteroids are beneficial in treatment of acute bacterial meningitis in children as well as adults from high-income countries with good access to services. Therefore a four-day regimen of dexamethasone can be given preferably before or with the first dose of antibiotics, in high-income countries.

Research directions

- Studies are needed to determine the antimicrobial resistance pattern against various antibiotics in rural and remote areas of developing as well as developed countries. More studies are needed to evaluate whether newer recommended regimens are superior to those already in practice.
- Large trials are needed to assess the effectiveness of either restricting or maintenance fluids in populations where patients present early and mortality rates are low.
- RCTs are required for evaluating corticosteroids in neonatal meningitis. Trials are needed to assess the use of adjuvant dexamethasone in adults with ABM in low-income countries. A meta-analysis of individual patient data is needed to define the reasons for differing outcomes in high- versus low-income countries.

Conflict of interest

The authors have no conflict of interest to declare.

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