ADJUNCTIVE THERAPY FOR BACTERIAL MENINGITIS

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The overall mortality in bacterial meningitis remains at greater than 10% and has only decreased slightly despite the introduction of antibiotics.[1-3] Furthermore, the morbidity among survivors including long term neurological complications (particularly hearing loss, seizures, mental retardation) remains high (10%-30%).[4-6] New antimicrobials with excellent bactericidal activity and adequate cerebrospinal (CSF) penetration have failed to have a significant impact on the mortality and morbidity of bacterial meningitis; the exception may be the mortality rate among adults with gram-negative bacillary meningitis with the advent of third generation cephalosporins.[7] It is therefore unlikely that further improvements in outcome will come from better bactericidal agents. New treatments based on our understanding of the basic disease mechanisms[8] aimed at reducing the amount of injury to the brain attributable to the host inflammatory response[9, 10] could theoretically improve clinical outcome.

Despite the widespread literature on meningitis, most of the work has been based on experience in children or in animal models. The epidemiology of childhood meningitis differs from that of adult meningitis but it is unlikely that the basic pathophysiology is fundamentally different. Most clinical features of acute bacterial meningitis in adults are similar to those in children. Twenty-seven per cent of adults have initial cranial nerve palsies or focal central nervous system (CNS) findings (beginning within 24 hours of admission) and 23% have seizures during the course of the meningitis.[7, 11]

Bacterial subcapsular components such as lipo-polysaccharide (LPS), and lipoteichoic acids are uncovered by bacterial replication or lysis. When exposed to these compounds, cerebral microvascular endothelial cells and other resident CNS cells (e.g. macrophages and macrophage-like cells such as astrocytes and microglia) produce and release chemotactic factors, vasodilators, and inflammatory mediators. There is now a wealth of evidence to support the role of interleukin 1 (IL-1) and tumour necrosis factor (TNF) alone or together with other mediators in the pathophysiology of bacterial meningitis. There are excellent reviews dealing with this topic.[8, 12] The inflammation results in alteration of blood brain barrier, meningeal inflammation, increased intracranial pressure, and decreased cerebral vascular perfusion.

EFFECTS OF IL-1 AND TNF

TNF is a macrophage-secreted hormone that is released in response to bacterial toxin. Raised levels of TNF are found in the CSF during bacterial meningitis in both mice and humans.[13] TNF induces IL1 release from endothelial cells and macrophages.[14] IL-1 released by astrocytes into brain tissue may contribute to brain gliosis and scar formation.[15] IL-1 increases the concentrations of metabolites of arachidonic acid, prostaglandin E2 and leukotriene B4 that are potent mediators of inflammation.[14] Increases in IL-1 and TNF have been observed in human purulent CSF and their levels may be associated with morbidity and outcome.[16, 17] The morbidity and mortality due to bacterial meningitis are probably related to changes in cerebral blood flow and increases in intracranial pressure.

It may be possible to reduce inflammatory response in the subarachnoid space (SAS) and thus improve the outcome by administering anti-inflammatory agents in conjunction with antibiotics. However, by the time a patient with bacterial meningitis presents for medical attention, it is likely that the inflammatory cascade is well under way and that the administration of appropriate antibiotics will result in the additional release of inflammatory mediators. Dexamethasone seems to decrease the release of various cytokines[18-20] and seems to be the best studied of anti-inflammatory agents.

ANTI-INFLAMMATORY EFFECTS OF STEROIDS

Steroids can inhibit expression of messenger ribonucleic acid (RNA) for TNF and IL-1,[21-23] and the production of prostaglandins and platelet activating factor.[24] They have been shown to reduce vasogenic brain oedema caused by neoplasms of the CNS.[25] They can also inhibit the activity of inducible nitric oxide synthase.[26]

In the rabbit model of pneumococcal meningitis, methylprednisolone decreased meningeal inflammation,[27] CSF outflow resistance[28] and cerebral oedema,[29] and led to a more rapid normalisation of CSF protein concentration, presumably by improving the blood brain barrier permeability. In the rabbit model of *H. influenzae* meningitis, dexamethasone plus ceftriaxone resulted in significant reductions in CSF concentrations of TNF, and the white cell count.[30]

POTENTIAL DRAWBACKS WITH STEROIDS

It is possible that the anti-inflammatory properties of corticosteroids may adversely affect the outcome of bacterial meningitis by mending the disruption in the blood brain barrier leading to reduced CSF penetration and hence reduced CSF levels of antimicrobial agents. In the rabbit model of pneumococcal meningitis, concomitant administration of methylprednisolone reduced ampicillin penetration into CSF and in the rabbit model of *E. coli* meningitis, methylprednisolone reduced gentamicin CSF penetration. However, CSF concentration of both antibiotics exceeded the minimum bactericidal concentration and bacterial killing *in vivo* was not affected.[31] Furthermore, Rodriguez and colleagues showed that dexamethasone did not affect CSF penetration of ampicillin, cefotaxime, or cefuroxime in infant rat model of *H. influenzae* meningitis.[32] In an experimental model of pneumococcal meningitis, concomitant administration of dexamethasone has been demonstrated to reduce entry of vancomycin into CSF and to reduce the rate of bactericidal killing. Neither rifampicin nor ceftriaxone was affected by

dexamethasone in this model. Finally, in a model of highly penicillin-resistant strain of *S. pneumoniae*, dexamethasone adversely affected the rate of bactericidal activity of combination ceftriaxone and vancomycin.[33]

In a single study of 11 children with bacterial meningitis treated with dexamethasone and ceftriaxone, there was no significant difference in the CSF levels of ceftriaxone when compared to those reported for children not treated with dexamethasone.[34] There is therefore some animal evidence to support the view that corticosteroids may reduce the CSF penetration of antimicrobials and, more importantly, this effect is likely to be very significant when treating patients with penicillin resistant pneumococcal meningitis.

TABLE 1

Study	No. of children/ adults	% of isolates HI SP NM	Antibiotic	Results	Comments
Lebel *et al.* 1988[35]	100/0	77 10 7	Cefuroxime	More rapid improvement in CSF indices and temperature. Hearing loss reduced.	No change in neurologic impairment and mortality.
Lebel *et al.* 1988[35]	100/0	77 7 10	Ceftriaxone	More rapid improvement in CSF indices and temperature.	No effect on hearing, neurological impairment or mortality.
Lebel *et al.* 1989[36]	60/0	75 15 7	Cefuroxime	Improvement in CSF glucose.	No effect on hearing, neurological impairment or mortality.
Girgis *et al.* 1989[37]	282/147	13 25 62	Ampicillin + Chloramphenicol	No difference in CSF indices. Reduced mortality and incidence of sensorineural deafness but only in pneumococcal meningitis.	The ampicillin dose was low (160 mg/kg/day); a high proportion of patients (60%) were comatose on admission and had suboptimal care and it was not clear if the chloramphenicol was stopped once *S pneumoniae* was identified. Antibiotics and dexamethasone were administered by IM route.
Odio *et al.* 1991[38]	101/0	78 8 2	Cefotaxime	Improvement in CSF glucose. Decreased frequency of one or more neurological sequelae and trend in reduction in hearing impairment.	Dexamethasone 0.4 mg/kg BD for two days.
Schaad *et al.* 1993[39]	115/0	58 10 24	Ceftriaxone	Improvement in CSF glucose. Reduction in one or more neurological or audiological sequelae at 15 months.	
Kilpi *et al.* 1995[40]	122/0	53 10 33	Ceftriaxone	No difference in CSF indices. No difference in outcome.	32 patients received dexamethasone, 30 oral glycerol only, 34 dexamethasone plus glycerol, and 26 placebo.
Wald *et al.* 1995[41]	143/0	59 23 17	Ceftriaxone	No difference in clinical outcome.	Dexamethasone given within four hours of antibiotics. Auditory Brain Stem Responses used to assess hearing impairment.
Kanra *et al.* 1995[42]	56/0	0 100 0	Ampicillin + Sulbactam	No difference in CSF indices.	Improvement in frequency of hearing impairment. No data on antimicrobial resistance.

PROBLEMS IN EVALUATING PUBLISHED CLINICAL TRIALS

There are three main variables that can affect the outcome of various trials evaluating the use of corticosteroids as adjunctive therapy in the management of bacterial meningitis: timing of administration of corticosteroids, dose and duration of corticosteroids, and finally the choice of antibiotics. The results of some of the well designed studies are shown in Table 1.

A recent meta-analysis of randomised clinical trials of dexamethasone in bacterial meningitis was conducted by McIntyre *et al.*[43] In *H. influenzae* meningitis, dexamethasone reduced severe hearing loss overall (combined Odds Ratio (OR) 0.31; 95% confidence interval (CI) 0.14-0.69, and this was irrespective of the timing of administration of dexamethasone before or with antibiotics) or of the type of antibiotics used (cefuroxime or other). In the case of pneumococcal meningitis, however, only studies in which dexamethasone was given early suggested protection. This was significant for severe hearing loss and approached significance for any neurological or hearing deficit (see Table 2).

For all organisms combined, the pooled OR suggested protection against neurological deficits other than hearing loss but was not statistically significant. There was no difference in outcome between studies using two days versus four days of dexamethasone and the incidence of gastrointestinal bleeding was less in the two days treatment compared to the four days treatment (0.5% in controls, 0.8% with two days of treatment, 3.0% with four days of treatment).

ARGUMENTS IN FAVOUR OF USING STEROIDS IN ADULT MENINGITIS

Since inflammatory processes thought to occur in children with bacterial meningitis are likely to occur in adults as well, it would be reasonable to assume that anti-inflammatory therapy with steroids would be similarly effective in each age group.

Clinical trials suggest strongly that dexamethasone reduces the incidence of long term neurological sequelae in children[44] including one paediatric trial restricted to children with pneumococcal meningitis.[42] Pneumococcal meningitis is the second most common cause of community-acquired bacterial meningitis in adults in most countries. Dexamethasone is effective in animal models of pneumococcal meningitis in reducing the patho-physiological consequences of SAS inflammation.[45, 46] In the study by Girgis *et al.*, only 147 subjects (34%) were 13 years or older. Sixty-two per cent of the cases were caused by *N. meningitidis*, 25% by *S. pneumoniae* and 13% *H. Influenzae*. The difference in deafness in the subgroup of 106 patients with pneumococcal meningitis was 0 in the dexamethasone group versus 12.5 % in the control group ($p<0.05$). Dexamethasone was also associated with reduced overall mortality compared with placebo: 13.5% versus 40.7% ($P<0.002$). However, this was not stratified according to age group.[37]

For pneumococcal meningitis the administration of Dexamethasone has to be *before* or *with* the antibiotics.[43]

Dexamethasone therapy for approximately 48 hours had no apparent adverse effects on the clinical course or incidence of complications in patients with aseptic meningitis.[47] However, it is unknown whether such therapy would have adversely affected the outcome of meningitis caused by *Herpes simplex* or other less frequently encountered viral pathogens of the central nervous system. Clearly, additional studies are required before we can conclude that the administration of steroids is not detrimental to patients with aseptic meningitis.

ARGUMENTS AGAINST USE OF STEROIDS IN ADULT BACTERIAL MENINGITIS

There are no clinical trials that have examined the use of dexamethasone as adjunctive therapy in the management of adult bacterial meningitis. The question is whether we can extrapolate from studies conducted in children, bearing in mind the marked differences in microbial aetiology, and accompanying co-morbidity. The main concern would be the effect of dexamethasone on the penetration of vancomycin into the CSF, particularly in areas where there is a high incidence of penicillin resistant pneumococci. Dexamethasone decreases the penetration of vancomycin into CSF. For example, in one study penetration decreased from 1.4 to 0.36 microg/ml. In areas of high resistance, it is advisable to add rifampicin, or vancomycin until cephalosporin sensitivity is ascertained. The addition of rifampicin to vancomycin and dexamethasone restores bactericidal activity despite the presence of dexamethasone.

There is no information on the efficacy of dexamethasone in treating meningococcal meningitis because complication rate is less than 10% and clinical trials to evaluate its potential benefit will need to be very large.

SHOULD STEROIDS BE USED?

On the basis of evidence presented, the decision to use steroids in adult community-acquired meningitis will

TABLE 2

		Dexamethasone	Control	OR (95% CI)
H. Influenzae	Early Dexa	4/75	7/79	0.53 (0.14-1.94)
	Late Dexa	4/185	20/164	
S. Pneumoniae	Early Dexa	1/52	9/51	0.09 (0.00-0.71)
	Late Dexa	6/29	8/46	1.24 (0.30-4.70)

Adapted from McIntyre et al. 1997

depend on the physician's personal experience of treating pneumococcal meningitis; there is no data for use of steroids in treating meningococcal meningitis or other less common central nervous system pathogens. For pneumococcal meningitis the administration of dexamethasone has to be *before* or *with* the antibiotics.

It may be reasonable to administer dexamethasone to adults with poor prognostic factors:

- Marked alterations in conscious level.
- Focal or lateralised neurological signs.
- Raised intracranial pressure at lumbar puncture or radiological (oedema on computerised axial tomography [CAT] or magnetic resonance imaging [MRI] of the brain).

This creates a major practical problem as most patients with complicated meningitis tend to present symptoms and signs that usually require CAT or MRI imaging of the brain before lumbar puncture is carried out. Under these circumstances, empiric therapy with broad cover antimicrobial agents plus or minus high dose intravenous acyclovir is usually administered in view of the potential delays involved with brain imaging and subsequent CSF sampling when it is deemed safe.

Steroids and Tuberculous meningitis

Tuberculous meningitis is associated with a mortality of around 20%-30%. Poor prognostic markers include extreme of age, advanced disease, hydrocephalus, coexistence of miliary disease and a marked decrease in CSF glucose. Complications of tuberculous meningitis include cerebral infarction, cranial nerve palsies, hydrocephalus, and the ectopic anti-diuretic hormone syndrome. The role of steroids in adult tuberculous meningitis is unclear but corticosteroids probably improve neurological outcomes of, and decrease mortality caused by, tuberculous meningitis of moderate severity.[48] Steroids appear to be able to improve signs and symptoms of the disease even before the resolution of the infection. This can occur quite rapidly after only a few doses. CSF indices, e.g. opening pressure, protein concentration, and white cell count are significantly improved by steroids, and may worsen when the steroids are withdrawn.[49, 50] They do not appear to significantly decrease the penetration of antituberculous drugs.[51] At least three studies have demonstrated that steroids reduced mortality in late tuberculous meningitis.[52-54] In a recent study in children, Schoeman *et al*. found that dexamethasone therapy lowered mortality in stage III tuberculous meningitis and improved the response of tuberculomas as well as reducing the incidence of tuberculomas. In this study, steroids did not have any significant effect on intracranial pressure and hydrocephalus and did not have any effect on the frequency of basal ganglia infarcts or on the size of the infarcts.[54] A large study from China showed that steroids significantly decreased the mortality in patients with stage II and III disease (Table 3).[55]

TABLE 3
Clinical staging of patients with tuberculous meningitis.

Stage	
I (early)	Non-specific symptoms and signs; no clouding of consciousness, no neurological deficits.
II (intermediate)	Lethargy or alteration in behaviour, meningeal irritation, minor neurological deficits (cranial nerve).
III (advanced)	Abnormal movement, convulsions, stupor or coma, severe neurological deficits (pareses).

Adapted from MRC report. Lancet 1948;1:582[56]

Prednisolone should be given to those in stage II and III and those with impending or established spinal block. The recommended dose is at least 60 mg daily for three to six weeks followed by a tapering of the dose over two to four weeks. Furthermore, prednisolone should be given if patients with tuberculous meningitis show any deterioration after the initiation of antituberculous therapy.

Is there a role for steroids in patients with pneumococcal meningitis complicated by cerebral infarction?

There has been no controlled study examining this aspect but success has been reported in an isolated case report.[56]

Mannitol and Meningitis

Hypertonic mannitol treatment has been shown to significantly reduce CSF pressure in rabbit experimental *H. influenzae* type b meningitis,[57] experimental pneumococcal meningitis in rats[58] and in children.[59] It should be considered in patients with impaired conscious levels, lateralised neurological signs, markedly raised opening pressure at lumbar puncture or evidence of cerebral oedema on brain scanning.[60]

Fluids

Hyponatraemia in children with bacterial meningitis is mostly induced by fluid volume depletion.[61] In a randomised controlled clinical trial of fluid restriction in children with acute meningitis, fluid restriction increased the likelihood of adverse outcome.[62] Conversely, the effect of liberal fluid supplementation in experimental *E. coli* meningitis did not aggravate brain oedema.[63]

Fluid should therefore not be restricted in patients with bacterial meningitis and patients should be kept euvolaemic.

SUMMARY

There are no clinical trials of corticosteroids as adjunctive therapy in the treatment of community-acquired bacterial meningitis in adults. Data extrapolated from animal models and clinical studies in children suggest that it may have a role in adult bacterial meningitis. However, given the different microbial aetiology in adults its use can only be supported in pneumococcal and tuberculous meningitis. However, in the case of pneumococcal meningitis, it should be given before or at the same time as the antibiotics to be effective. Logistically, this may be a problem; those with moderately severe meningitis quite often require brain imaging before lumbar puncture and diagnosis of pneumococcal meningitis. For tuberculous meningitis, use of steroids is recommended for those in stage II and III severity.

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