Corticosteroids in the treatment of bacterial meningitis in children

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Acute bacterial meningitis (ABM) is a life-threatening infection and has a mortality rate nearing 100% if left untreated. It has an estimated incidence of 2-5/100,000 in the Western world, yet it is one of the top ten causes of death in infectious diseases worldwide.

**Pathogenesis**

Bacterial meningitis involves infections of the tissues enveloping the brain, the meninges. These act as a protective layer between the brain and the rest of the body, but when infected with bacteria, this barrier is disrupted, thus allowing bacteria to enter the central nervous system. Bacterial invasion results in swelling and inflammation due to cytokines released by bacteria, thus giving rise to symptoms such as headache and fever. Further growth of bacteria leads to further chemical release from bacteria, giving rise to further symptoms e.g., meningism and confusion. If not treated at this stage, consciousness starts to be affected and intracranial pressure may possibly rise due to meningeal and even cerebral inflammation. This can lead to seizure, coma, as neuronal and cerebral injury ensues, eventually leading to death if untreated.

**Long term effects**

Due to the devastating effects ABM has on the brain, even though the infection is cured, damage to neurons can happen and have long-term effects on the affected individual. Intellectual and behavioral deficits are the most common effects seen after survival of ABM, accounting for 78% of sequelae in a recent study, neurological deficits for 14%, i.e., seizures, motor deficits, and cerebral palsy, while hearing loss was 7% and vision deficits 3%. It must be noted, that in this study that half of the 1433 survivors included had documented sequelae 5 years after the ABM and half of these had other bacterial aetiologies than N. meningitidis and S. Pneumoniae, which only accounted for 4% and 3% of ABM, respectively. Prevalence of these sequelae also vary greatly between countries and span from less than a tenth up to half of survivors of ABM; Iceland having a low prevalence.

**Different types of ABM**

Different types of bacteria in ABM call for different antibiotics. Therefore, one must consider the epidemiology and bacterial resistance in the country where the infecting agent is contracted. This paper focuses on Iceland, where neonates are at risk of contamination in utero or at birth with GBS, less frequently E. coli, and very seldomly Listeria and Klebsiella. Children from the age of 1 month until their teenage years are at more risk of contracting Neisseria meningitidis (other than serotype C), followed by streptococcus pneumoniae, and very rarely nowadays (because of vaccination), Haemophilus influenzae.

Between 1995 and 2010 there were 140 confirmed cases of ABM in children giving approximately 9 cases per year. The main bacterial imposters were Neisseria meningitidis in 2/3 of cases, streptococcus pneumoniae coming in second followed my streptococcus agalactiae. The introduction of national vaccination programmes for
Haemophilus influenza type b in 1989 and meningococcus C in 2002 have rendered infections with these organisms to almost nil, best depicted by a a highly significant age specific incidence reduction from 26 cases/100.000/year in 1975 to 1 case/100.000/year in 2010. Despite this dramatic reduction of ABM in children the therapy for ABM has changed little despite pharmacologic and medical advances.

**Adults**

In adults the benefit of corticosteroids along with antibiotics is well established and recommended in guidelines for the treatment of ABM. The corticosteroid of choice has hitherto been dexamethasone, which has yet to show true benefit in children with ABM. Therefore, one must seriously consider whether this should be the mainstay of therapy, whether other substances or medicines should be considered, or whether antibiotics and standard non-pharmacological supportive therapy are enough.

**Antibiotics**

The mainstay of therapy for ABM, both in children and adults, is a 3rd generation cephalosporin, along with penicillin, ampicillin or amoxicillin for children under the age of 3 months. If TB is suspected, then a regimen covering that should be initiated. Bacterial susceptibility also varies between countries, as e.g. in the US, where vancomycin is the standard in the empirical therapy of ABM.

**Corticosteroids**

Corticosteroids, steroidal hormones produced in the adrenal cortices, are the protagonist hormones regulating our day-to-day physiological stress. Cortisol, our main stress regulatory hormone, keeps the body up and running by regulating glucose and glycogen metabolism (hence its subclassification as a glucocorticoid), a key factors in human homeostasis, as well as having an anti-inflammatory effect.

Dexamethasone is a synthetic corticosteroid, about 25 times as potent as natural cortisol has a half-life of 3 hours in healthy adults and 4.3 hours in children older than 3 months, and pharmacodynamic (metabolic) effects lasting for up to 72 hours. As other corticosteroids, dexamethasone has an anti-inflammatory effect, thus lessening the intrathecal, as well as systemic, inflammation in ABM. This seems to be the case in adults, yet the question remains whether there is true benefit of dexamethasone administration in children with ABM?

The use of adjunctive corticosteroids is indicated in ABM in adults and children over the age of 3 months. British and German guidelines agree on the combined therapy of antibiotics and dexamethasone, for children older than 3 months of age. American guidelines suggest considering corticosteroids in infants as young as 6 weeks of age, with pneumococcal meningitis, after considering both the risks and benefits. Another important factor is to administer dexamethasone prior to, or concurrently with, the first dose of antibiotics in children with ABM, but not later than one hour after the first dose as this has not shown to improve outcome.
Adults

Adults with ABM caused by Streptococcus pneumoniae, have been shown to benefit from dexamethasone, where hearing loss, neurological sequelae and death are lower than in placebo groups or those not receiving dexamethasone. This rings true only for patients in the developed world, as these results have not proved the same in developing countries.

Death

To date, none of the studies focusing on paediatric populations in high-income countries have shown a reduction in mortality with the use of corticosteroids in the therapy of ABM. An excellent study from US showed no difference in mortality, with or without corticosteroids, which was not affected when subanalysed for causative pathogen.

Hearing loss

As hearing loss is one of the most prominent sequelae following survival of ABM, this was especially analysed in a Cochrane review from 2010, as well as the severity of the hearing loss. In children where H. Influenzae was the infecting agent, significant reduction in hearing loss was found when corticosteroids were administered. Infection with other organisms did not show significant benefit for hearing outcome.

Severe hearing loss however was affected by corticosteroids in high-income countries where there was a significant reduction of severe hearing loss. This difference was not observed in an Icelandic study published in 2002, where there was no significant reduction in hearing loss between those treated with corticosteroids and those that weren’t.

Further, the Cochrane review showed a relative risk of 0.74 for any hearing loss in ABM caused by any organism. This raises the question, whether corticosteroids are protective at all for hearing, when the organism in not H. influenzae? The conclusion of the Cochrane review is benefit of corticosteroids and recommends them as adjuvant therapy for ABM in children, yet states that evidence for the conclusion is not optimal.

Other sequelae

A study from 2006 showed better academic achievements in children receiving corticosteroids and surviving pneumococcal meningitis than those who did not receive dexamethasone. However, the Cochrane review (analysis of failed to show patients) failed to show a significant reduction of other neurological sequelae than hearing loss, between patients receiving dexamethasone, and those who didn’t.

Discussion

It is difficult to reach a definitive conclusion on whether or not to administer corticosteroids in the case of ABM, especially with no studies to date showing definitive positive effects on disease outcome. Considering the results of reviews and meta-analyses of research on ABM in children, as well as various national
guidelines, one would be reluctant not to administer dexamethasone when faced with clinical meningitis in a child. However, considering the few cases of definite ABM in Iceland per year, and essentially the eradication of Haemophilus influenzae associated meningitis, the only meningitis in which the benefits of concomitant corticosteroid administration with antibiotics has been proven, it is difficult to recommend dexamethasone as a rule in the therapy of ABM in Iceland. This is further supported by aetiology, as the main microbes causing ABM nowadays in Iceland are Neisseria meningitidis, in which corticosteroids are not recommended, and Streptococcus pneumoniae, for which further research is need. Further, if the corticosteroids are not administered before, or within an hour of, the first antibiotic dose, then possible benefits of them are even further diminished.

**Conclusion**

Therefore, the conclusion of this essay is that corticosteroids in Iceland should not be routinely administered to those suspected of ABM. Careful evaluation of clinical signs and symptoms, consultation with a senior paediatrician (preferably one specialized in paediatric infections and/or neurology), prior therapy, and neurological affection must all be taken into account, before taking the decision of administering corticosteroids or not in children suspected of ABM.
References


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