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Narrative Review

Effectiveness of Steroids in the Treatment of Bacterial Meningitis in Adults: Narrative Review

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Abstract

Bacterial meningitis is the 10th most common cause of death worldwide. Early detection and treatment can decrease the mortality and morbidity rates. In this review, the treatment regimen of bacterial meningitis will be discussed in adult patients based on the microorganism. The benefits of the usage of corticosteroid (Dexamethasone in particular) will be elaborated in lowering the rates of death and neurological complications. The results of different studies on patients in developed and developing countries will the presented. Also, meta- analysis studies will review the patients with different ages and those affected with different microorganism to emphasize the benefit of the corticosteroid regimen as a part of the bacterial meningitis treatment.

Keywords: Bacterial Meningitis, Adults, Treatment, Corticosteroid.

Definition and Epidemiology

Meningitis is defined as an inflammatory disease of the tissue layers covering the brain and the spinal cord, known as meninges, by a pathogen either bacterial or viral. The meninges is made of three layers: the Pia, Arachnoid, and Dura maters. Bacterial meningitis usually affects the arachnoid matter and Cerebral Spinal Fluid (CSF) which can be found in the subarachnoid space and the ventricles in the brain. Despite the usage of antibiotics in the treatment of bacterial meningitis in adults, the mortality and morbidity rates are still high worldwide. In a study done by Durand L and Calderwood on patients through a 27 year period stated that the 28% of the patients had focal neurological symptoms with fatality rates of 25%. [1]

The same study has discussed the prevalence of different organisms that affect adult patients. In community acquired meningitis, Streptococcus pneumonia was found to be the most common organism reaching to 37%. Neisseria meningitides was 13%, and Listeria monocytogenes was 10%. Only 4% of the patients were affected by H. influenza. [1]

A study by Thigpen and Whitney on adult patients with meningitis has demonstrated that fatality rates was up to 16.4% with an increase in the rate with the advanced age; 8.9% in patients aging from 18 to 34 while reaching up to 22.7% among those above 65 years of age. [2]

There is an inherent geographical variability in the pathogen in acute bacterial meningitis. In African countries, an association between the Human Immunodeficiency Virus (HIV) and the Listeriosis infection has been observed especially in patients with hematological diseases, organ transplant, advanced age, pregnancy, and chronic corticosteroid therapy. The risk of Listerisosis infection in HIV patients increases up to 280 folds compared to others. [3]

Pathogenesis

The clinical presentation of the disease is manifested due to the complex interaction between the pathogen and the host inflammatory response. Experiments on animal models have shown that the most important component in the induction of CSF inflammation and the blood brain barriers injury is the subscapular bacterial surface.[4] Cell wall constituents, such as teichoic acid and peptidoglycan, can cause a strong inflammatory response causing an impairment of the blood brain barrier due to the presence of the leukocyte, vascular deregulation, vasculitis, and increase in the intracranial pressure.[5] Other studies have suggested that the inflammatory response is created by the release of the proinflammatory cytokines. High concentration of cytokines such as IL1, IL6, and tumor necrosis factor, were seen in the analysis of the CSF of patients with pneumococcal meningitis infection. It is also believed that the high number of bacterial density and bacterial breakdown products can increase the inflammatory response and therefore increase the likelihood of neurological damages.[6-8]

Cerebral edema, increased intracranial pressure, and loss of cerebral autoregulation are the results of the injuries that occur to the cell of the blood brain barrier after the inflammatory response take place. All these consequences

will lead to brain ischemia, cytotoxic injury, and neural aptosis. As a result, patients usually face with neurological symptoms such as seizure, deafness, sensory or motor defect.[9-11]

Presentation and Diagnosis

The most common presentation of meningitis is fever, neck rigidity and change in the mental status. A study has shown that severe headache was presented in 84% of the patients, fever greater 38 c in 74% of patients, stiff neck in 74% of patients and Glasgow coma scale less than 14 in 71% of the patients. Less common symptoms such as seizure (23%), coma in (13%), cranial nerve palsy (9%) and rash (8%) was also found.[12,13]

On examination, active and passive neck flexion are crucial to preform to assess the meningeal irritation even if the patient does not complain about neck stiffness. The most common classical signs for meningeal irritation are Brudzinski sign, a hip flexion during passive neck flexion, and Kernig sign which is the inability to extend the knee fully when the patient is supine and the hip is flexed to a 90 degrees. These two signs have high sepecifity reaching to 95% and low sensitivity reaching to 5% only.[14]

Diagnostic tests are mainly started with basic blood work up. Two aerobic blood cultures, complete blood count with differential are usually drawn from any patient with suspected infection.[15] Elevated white blood count is usually seen with a shift towards the immature form of the cells. Some patients have leukopenia and thrombocytopenia which is associated with poor outcomes.[16] In case of inability to obtain CSF culture, blood culture can be obtained in order to help the course of the diagnosis. Up to 50% to 90% of patients who have bacterial meningitis will have a positive blood culture. [13] It is mandatory for every patient suspected to have bacterial meningitis to have a Lumber Puncture (LP) to examine the CSF.[17] Patients with suspected spinal epidural abscess, thrombocytopenia, or suspected to have increased in the intracranial pressure must have LP done under extreme precautions. In case of a suspected mass lesion or increased intracranial pressure, patients must first have a head CT before the LP. Along with these situations, patients who are known to have HIV, have a focal neurological defect or papilledema, have a new onset of seizer or abnormal level of consciousness must have a brain CT first. However, inability to perform a CT scan or LP should not delay the empiric treatment for the patient.[18] Cerebral spinal fluid analysis should include: cell count and differential, glucose level, protein levels, and gram stain and culture. In case of bacterial meningitis, glucose levels are usually less than 40 mg/dL, protein concentration above 200 mg/dL, and WBC count above 1000/microL.[14]

Treatment

According to studies, the delay in the administration of antimicrobial medication has shown an increase in the rates of mortality and permanent neurological defects. According to a cohort study done on 173 patients with community acquired pneumonia, an increase in the mortality rate and unfavorable hospital outcome was seen in cases with a delay of treatment for more than six hours. [19]

After obtaining the CSF sample, empiric treatment should be immediately started based on the most common pathogen for the patient's age and comorbidities. The choice of the antimicrobial can be then modified to cover the pathogen which the results of the CSF culture and sensitivity shows. The route of the administration of the antimicrobial should always be intravenously able to penetrate to the CSF. Oral antimicrobial agents should be avoided, except for rifampin, as it is useful in the treatment of beta-lactam- resistance, Streptococcus pneumoniae and coagulase negative Staphylococcus.

The Antimicrobial Regimen

Streptococcus Pneumonia

It is the most common cause of meningitis in adults. The first line treatment is Vancomycin (15-20 mg/Kg IV every 8 to 12 hours) with Ceftriaxone (2 g IV every 12 hours) or Cefotaxime (2 g IV every 4 to 6 hours). The duration of the therapy is usually 10 to 14 days.[14]

Neisseria Meningitidis

The best treatment for gram-negative diplococcic is the third generation of cephalosporin such as Ceftoaxime or Ceftriaxone. The duration of the therapy is 7 days and the droplet precaution for the patient should remain 24 hours after the initiation of the treatment regimen.[14]

Haemophilus Influenza

The third generation of cephalosporin such as Ceftoaxime (2g IV every 6 to 8 hours) or Ceftriaxone (2 g IV every 12 hours) is the drug of choice in suspected H. influenza organism for 7 days course.

Listeria Monocytogenes

This is the most common organism to cause abscess formation in midbrain and brainstem leading to recurrent infections.[22] The drug of choice is Ampicilin (2 g every four hours) or Pencilin G (4 milion units every four hours). [21] Ampicilin should be continued for at least 21 days. In the case of penicillin allergy, patients can be started on trimethoprim sulfamethoxazole (TMP-SMX). [20]

Dexamethasone Regimen

Animal studies have shown that early treatment of IV Dexamethasone has decreased the numbers of subjects with hearing loss as a complication of bacterial meningitis.[23] In addition, other studies on patients who were diagnosed with bacterial meningitis and had Dexamethasone given to them as part of their treatment, had a lower CSF concentration of cytokines (IL-6, IL-8, and IL-10), lower CSF opening pressure, and higher ratio of CSF: plasma glucose.[24]

In the developed region around the world, a randomized trial was carried out on 301 patients in Europe to assess the efficacy of the addition of Dexamethasone in the treatment of bacterial meningitis in regards to mortality and neurological complications. After taking the CSF sample, the patients were randomly assigned to have IV Dexamethasone (10 mg every 6 hours for four days) or a placebo. Most patients were given Amoxicilin as an antimicrobial agent. The patients were reviewed after 8 weeks of treatment. Patients who had Dexamethasone had reduced mortality rates of 7% compared to placebo patients who had 15% death rates. Also, the unfavorable neurological outcomes were 15% in Dexamethasone patients compared to placebo patients who had 25% death rates.[25] However, a study compared the results of two cohort studies in adult patients with meningococcal meningitis in Netherlands. The first study followed patients from the year of 1998 to 2002 and included 258 subjects. The second study had 100 patients followed up from 2006 until 2011. The first study included 17% of the patients who had dexamethasone as a regimen in their treatment, while in the second study, 90% of the patients had Dexamethasone. The results of the studies showed no significant difference in the reduction of the hearing loss complication (only 3% in the first study and 8% in the second) or death (4% in the first and 11% in the second). These two studies have suggested that the usage of Dexamethasone in the treatment of meningococcal meningitis does not cause harm and might have small unproven benefits.[26]

In contrast, a study was done in sub – Saharan Africa (in Malawi) involving 465 patients, 90% of which were HIV positive, whom received Dexamethasone or placebo for four days with intravenous or intramuscular Ceftriaxone. The results showed that after 40 days of treatment, there was no significant differences in mortality rates and disability outcomes (56% in Dexamethasone patients and 53% in placebo).[28]

Another randomized, double blinded trail involving 435 patients from Vietnamese (with less than 1% who had positive HIV) found no reduction in the death rates when comparing to patients who had received Dexamethasone to those who had placebo. However, when the number of subjects was reduced to 300 patients, the risk of death in one month was reduced significantly (RR 0.43; 95% CI 0.20-0.94). Also, the risk of disabilities and death was reduced in six months as well (OR 0.56; 95% CI 0.32-0.98). The pathogen causing the disease were identified and included *Streptococcus suis* (39%), *S. pneumoniae* (18%), *N. meningitis* (6%), and other gram-negative organisms (10%). It was also noted that the outcomes were better for patients who had *Streptococcus suis* compared to the other organisms.[29]

Several Meta- analyses studies were held out to compare the efficacy of adding Dexamethasone. A recent study carried out in 2015 included 4121 subjects from 25 randomized trails. The included subjects were both children and adults and from the developing and developed world. No difference was detected in the rates of mortality in patients who had received Dexamethasone and the ones who had not in both high and low income counties. A subgroup analysis, however, was done to assess the benefit of Dexamethasone in the treatment of meningitis based on the pathogen and it has shown that patients who were affected with S. pneumonia had lower mortality rates compared to patients who had Haemophilus influenza or N. meningitides. In addition, lower rates of hearing loss (RR 0.67, 95% CI 0.51-0.88) and short term neurological sequels (RR 0.83, 95% CI 0.69-1.00) was seen in patients who had received Dexamethasone. However, no significant reduction in the long term neurological sequel was seen in patients (RR 0.90, 95% CI 0.74-1.10).[27]

On the other hand, patients who had lived in high income countries had reduced rates of hearing loss (RR 0.51, 95% CI 0.35-0.73) and short term neurological sequel (RR 0.64, 95% CI 0.48-0.85) compared to low income countries where no significant reduction was appreciated. Interestingly, it has also shown that the usage of Dexamethasone increases the chances of recurrent fever (RR 1.27, 95% CI 1.09-1.47) but no other complication.[27]

Conclusion

Bacterial meningitis is one of the most common infections affecting the adult population. If left untreated, it can lead to serious and irreversible neurological complications. The usage of early administration of Dexamethasone, alongside the proper antimicrobial for the affording organism, has been suggested to help improve the mortality and decrease the rates of permanent neurological complications. In developed countries, some studies show that Dexamethasone can help in reducing the mortality and morbidity rates, while others revealed minimal improvement with the administration of Dexamethasone. On the other hand, developing countries where rates of HIV infection are high and poor nutrition is observed, no significant difference was seen with the usage of the Dexamethasone. However, improvement was seen in patients who were identified to have *Streptococcus suis* pathogen in the CSF analysis. Adding

more, meta-analysis studies demonstrated that patients diagnosed with Streptococcus pneumonia had lower mortality rates and neurological complications. All these studies have shown that administrating Dexamethasone to patients with suspected meningitis as a part of the treatment does not have a significant role in outcomes and might be only improving in patient with Streptococcus infection.

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Authors' Contribution

All authors pass the four criteria for authorship contribution based on the International Committee of Medical Journal Editors (ICMJE) recommendations.

Conflict of Interests

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