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Pathophysiology and Management of Bacterial Meningitis in Pediatrics

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Review Article

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Abstract

Bacterial meningitis in children and infants is correlated with substantial morbidity and mortality. Bacterial meningitis is one of the most frequent central nervous system infections, which is prevalent in low-income countries. There are three types of neonatal meningitis such as early-onset meningitis (from 0–6 days); late-onset meningitis (from 7–29 days) and extremely late-onset meningitis (from 30–90 days). The intense inflammation within the subarachnoid space noted in lumbar cerebrospinal fluid, and the resulting neurological damage, are not the direct result of the pathogenic bacteria but rather of activation of the host's inflammatory pathways by the microorganisms or their products. All children who are suspected of having meningitis should have their cerebrospinal fluid examined unless lumbar puncture is contraindicated. The critical elements of managing pediatric meningitis involve prompt initiation of therapy, use of the appropriate antimicrobial with correct dosing and duration, attention to expected complications, and appropriate follow-up. In neonates, the primary empiric regimen used conventionally has been ampicillin and gentamycin. For infants whose cerebrospinal fluid is suspicious for bacterial meningitis, ampicillin (300 mg/kg per day divided every 6 hrs) and cefotaxime (200 to 300 mg/kg per day divided every 6 hrs) is appropriate.

Keywords: Bacterial meningitis; Management; Pathophysiology; Pediatrics

Abbreviations: ABM: Acute Bacterial Meningitis; BBB: Blood-Brain Barrier; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; CT: Computed Tomography; Hib: Hemophilus Influenza B Virus; HSV: Herpes Simplex Virus; MRSA: Methicillin Resistant Staphylococcus Aureus; SIADH: Syndrome Of Inappropriate Antidiuretic Hormone.

Introduction

Bacterial meningitis in children and infants is correlated with substantial morbidity and mortality. Bacterial meningitis is one of the most frequent central nervous system infections, which is prevalent in low-income countries [1]. There are three types of neonatal meningitis such as early-onset meningitis (from 0–6 days); late-onset meningitis (from 7–29 days) and extremely late-onset meningitis (from 30–90 days) [2]. Hemophilus influenzae type b, *S. Pneumoniae* and Neisseria meningitidis are the three organisms frequently correlated with acute bacterial meningitis in early childhood in western countries [3]. The recognized risk factors for pneumococcal meningitis involve group B Streptococcus-positive mothers, immunodeficiency, absence of opsonic bactericidal antibody, basilar skull fracture, prematurity, low birth weight, and young age, living in a dormitory, lack of immunization, throat infections, ventriculoperitoneal shunt, cochlear implants, and neurosurgery. Bacterial

meningitis classically presents with fever, headache, signs of meningeal irritation, and altered level of consciousness, but these symptoms and signs perhaps hard to detect or absent in some cases, particularly in neonates and infants. Neurological complications of bacterial meningitis involve cerebral infarction, cerebral abscess, subdural empyema, cerebritis, and intracerebral bleeding, and these can lead to long-term sequelae such as focal neurological deficits, hearing loss, cognitive impairment, and epilepsy. Bacterial meningitis is potentially fatal, and the mortality rate is 10 to 15% in neonates. Streptococcus pneumoniae is a major cause of invasive diseases such as pneumonia, sepsis, and meningitis [4,5].

Pathophysiology

The intense inflammations within the subarachnoid space noted in lumbar cerebrospinal fluid (CSF), and the resulting neurological damage, are not the direct result of the pathogenic bacteria but rather of activation of the host's inflammatory pathways by the microorganisms or their products. When the pathogens have entered the central nervous system, they replicate rapidly and liberate active cell wall or membrane correlated components such that, lipoteichoic acid and peptidoglycan fragments of gram-positive organisms, and lipopolysaccharide of gram-negative bacteria. Antibiotics that act on cell walls cause rapid lysis of bacteria, which can primarily cause accelerated release of these active bacterial products into the CSF. These potent inflammatory substances can stimulate macrophage-equivalent brain cells (eg, astrocytes and microglia), cerebral capillary endothelia, or both, to generate cytokines such as tumour necrosis factor, interleukin-1, and other inflammatory mediators such as interleukin-6, interleukin-8, platelet-activating factor, nitric oxide, arachidonic acid metabolites (eg, prostaglandin and prostacycline), and macrophage derived proteins. The cytokines activate adhesion promoting receptors on cerebral vascular endothelial cells and leucocytes, attracting neutrophils to these sites [6-8].

Diagnostic Criteria

All children who are suspected of having meningitis should have their CSF examined unless lumbar puncture is contraindicated. Lumbar puncture contraindications involve focal neurologic deficits, signs of enhanced intracranial pressure, uncorrected coagulopathy, and cardiopulmonary compromise. For patients who have signs of elevated intracranial pressure, lumbar puncture should be deferred until computed tomography (CT) scan is performed. If a mass lesion, hemorrhage, midline shift, effacement of the basilar cisterns, or effacement of the sulci is noted, lumbar puncture should be deferred and antimicrobial therapy started promptly and also is significant to note that normal findings on CT scan do not exclude elevated intracranial pressure, and the patient should be reassessed after lumbar puncture is performed [9,10]. Bacterial meningitis is described by CSF pleocytosis (WBC often greater than 1.0103 /mcL (1.0109 / L)), with a predominance of polymorphonuclear leukocytes. The glucose concentration frequently is less than one half of the measured serum value, and the protein value usually is greater than 1.0 g/dL (10 g/L). The Gram stain is extremely helpful if positive and perhaps indicates the need to expand antimicrobial coverage, but the clinician should be aware that Gram stain findings never should be used to narrow the spectrum of empiric coverage [11].

Treatment

The critical elements of managing pediatric meningitis involve prompt induction of therapy, use of the appropriate antimicrobial with correct dosing and duration, attention to anticipated complications, and appropriate follow-up [12]. Choice of antibiotic treatment entails the selection of agents that are effective against the probable pathogens and are able to attain adequate bactericidal activity in CSF. The estimated bactericidal power of various antimicrobial drugs in CSF cultures has been extrapolated to man from calculation of different pharmacokinetic and pharmacodynamic variables. The primary empiric regimen chosen for treatment should be broad enough to cover the potential organisms for the age group affected [13-15]. In neonates, the primary empiric regimen used conventionally has been ampicillin and gentamycin [16]. For infants whose CSF is suspicious for bacterial meningitis, ampicillin (300 mg/kg per day divided every 6hrs) and cefotaxime (200 to 300 mg/kg per day divided every 6hrs) is appropriate. In the young infant, if the Gram stain suggests pneumococcus, vancomycin (60 mg/kg per day given every 6hrs) should be added. For children older than 2 months of age, vancomycin (60 mg/kg per day divided every 6hrs) plus ceftriaxone (100 mg/kg per day given in one dose or divided into two doses) or cefotaxime (200 to 300 mg/kg per day divided every 6hrs) should be used for empiric coverage [17-21]. Considering that quick intervention is necessary, empirical treatment with broad-spectrum antibiotics such as vancomycin is very frequent [22,23]. The antibiotics have to pass the blood-brain barrier (BBB) to reach the CSF. First, the penetration of an antibiotic into the CSF is dependent on the type and structure of the antibiotic itself. Furthermore, some disease-specific factors influence antibiotics' pharmacokinetics in CNS infections. Essential factors to consider in antibiotic dosage are meningeal inflammation, elevated renal clearance, and drainage volume [24].

Vancomycin, a glycopeptide antibiotic, has a broad application area and is effective against most Gram-positive cocci and bacilli. Vancomycin is predominantly

used in methicillin resistant Staphylococcus aureus (MRSA) infections and also against other Gram-positive β-lactam-resistant bacteria. In combination with β-lactams such as ceftazidime and meropenem, vancomycin is used as an empiric treatment against ventriculitis and meningitis. Due to its high molecular weight of ~1450 Da and hydrophilicity, its penetration into the CSF when meninges are not inflamed is relatively poor [25,26]. Recommended total daily doses of vancomycin in healthcare-associated meningitis and ventriculitis are 60 mg/kg every 6hrs in children with normal renal and hepatic function [27].

Meropenem

Meropenem is a broad-spectrum carbapenem antibiotic that is used in a broad range of serious infections, involving CNS infections. It has activity against Gram-positive and Gram-negative pathogens and is particularly significant as empirical treatment of serious bacterial infections in hospitalized patients [28]. Recommended total daily dose of meropenem in healthcare-associated ventriculitis and meningitis is 120 mg/kg in infants and children and 6 g in adults, both in a dosing interval of 8 hrs. All children with bacterial meningitis had taken dexamethasone currently for the first 4 days of therapy [29]. The duration of treatment for neonatal meningitis based on the clinical response and duration of positive CSF cultures after treatment is started. Ten to 14 days is frequently satisfactory for disease caused by group B Streptococcus and L monocytogenes, and a minimum of 3 weeks of treatment is needed for gram-negative enteric meningitis. Enterococcus meningitis is frequently treated for 2–3 weeks [30].

Adjunctive Corticosteroids in Bacterial Meningitis

Adjunctive treatment has decreased rates of mortality, severe hearing loss, and neurologic sequelae importantly in adults who have community-acquired bacterial meningitis. For children beyond the neonatal age groups, available data suggest that the use of adjunctive corticosteroids perhaps beneficial for Hib meningitis and could be considered in cases of pneumococcal meningitis. The dose of dexamethasone for bacterial meningitis is 0.6 mg/kg per day divided into four doses and administered IV for 4 days. The first dose should be given before or concomitantly with antibiotics [31]. Eg: Dexamethasone for amelioration of meningeal inflammation.

Supportive and Adjunctive Treatment

Adequate oxygenation, prevention of hypoglycaemia and hyponatraemia, anticonvulsant treatment, and measures designed to reduce intracranial hypertension and to inhibit fluctuation in cerebral blood flow are crucial in the management of patients with bacterial meningitis. Optimum cerebral perfusion can be maintained by controlling fever to decrease the brain's metabolic demands, by maintaining arterial blood pressures within normal limits, and by hyperventilation to decrease arterial carbon dioxide tension to a range of 25–30 mm Hg [32]. 30º bed head elevation, antipyretic agents, avoidance of vigorous and common intratracheal suctioning and intubation, correction of hyponatraemia and SIADH, hyperventilation, use of mannitol, and high-dose barbiturate therapy for reduction of raised intracranial pressure.

Seizures and Focal Complications

Neurologic complications of meningitis should be anticipated. Altered level of consciousness, seizures, elevated intracranial pressure, subdural effusions, and focal neurologic deficits are most frequent. Neurologic effects perhaps manifest as cranial nerve palsy, monoparesis, hemiparesis, gaze preference, visual field defects, aphasia, and ataxia. Focal neurologic deficits frequently are the consequence of vascular damages. Eg) anticonvulsant drugs (lorazepam, diazepam, phenytoin, and phenobarbital) to control and prevent seizures [33].

Normal saline or lactated Ringer solution is appropriate, and pressor support perhaps necessary in cases of hemodynamic instability to control shock occurred as bacterial meningitis complication. Cerebral edema in patients who have bacterial meningitis is caused by a variety of mechanisms that lead to elevate in the intracellular fluid volume of the brain. The increases in intracellular fluid volume leads to a subsequent accelerate in intracranial pressure. Cerebral edema and the resultant enhance in intracranial pressure can cause a variety of signs and symptoms, ranging from headache, nausea, and vomiting to altered mental status, cranial nerve palsies, cushing triad (bradycardia, hypertension, and abnormal respiratory pattern), and tonsillar herniation. Treatment for patients who are suspected of having cerebral edema depends on the severity and commences with fluid restriction. In the face of cerebral edema that has signs of accelerated intracranial pressure, diuretics, mannitol, and corticosteroids also can be considered [34,35].

Conclusion

Hemophilus influenzae type b, *S. Pneumoniae* and Neisseria meningitidis are the three organisms frequently correlated with ABM in early childhood in western countries. For patients who have signs of elevated intracranial pressure, lumbar puncture should be deferred until computed tomography (CT) scan is performed. If a mass lesion, hemorrhage, midline shift, effacement of the basilar cisterns,

or effacement of the sulci is noted, lumbar puncture should be deferred and antimicrobial therapy started promptly. The duration of treatment for neonatal meningitis depends on the clinical response and duration of positive CSF cultures after treatment is started. Ten to 14 days is frequently satisfactory for disease caused by group B Streptococcus and L monocytogenes, and a minimum of 3 weeks of treatment is needed for gram-negative enteric meningitis. Enterococcus meningitis is often treated for 2–3 weeks. Recommended total daily doses of vancomycin in healthcare-associated meningitis and ventriculitis are 60 mg/kg every 6 hrs in children with normal renal and hepatic function.

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