ACUTE BACTERIAL MENINGITIS: FOCUSED UPDATE ON PATHOPHYSIOLOGY AND TREATMENT AMONG ADULTS IN "AFRICAN MENINGITIS BELT" OF NORTH-WESTERN NIGERIA

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ABSTRACT

Background: Cerebrospinal meningitis (CSM) is inflammation of the leptomeninges and underlying sub-arachnoid cerebrospinal fluid, (CSF) usually caused by bacterial infection. Several pathogenic microorganisms have been implicated in the etiology of cerebrospinal meningitis; among these, Neisseria Meningitides serogroup A (but now serogroup C) is the most common cause of outbreak of bacterial meningitis in the "African Meningitis belt". The disease is highly transmissible, with seasonal epidemics in many African countries located within the belt. "African meningitis belt" is a region of twenty five sub-Saharan countries stretching from Senegal in the west to Ethiopia in the east, with a total population of about five hundred million (500million) people. Since the introduction of the Men A conjugate vaccine (MenAfrivac), which protects against the most prevalent type of Neisseria Meningitides (serogroup A) by the government of Nigeria, with support from the Global Alliance for Vaccine Initiative (GAVI ), occurrence of the disease has reduced significantly in all states at risk, including North-Western states. However, Despite overall decrease in serotype A meningococcal infections, the risk of other types of Neisseria meningitides persists, as evidenced by the Laboratory tests that confirmed the predominance of Neisseria meningitidis serogroup C, in the ongoing outbreak of meningococcal meningitis in Nigeria. This update tends to shed light on the current literature, with specific focus on pathophysiology and treatment of cerebrospinal meningitis among adult, in the "meningitis belt" of North-Western Nigeria.

INTRODUCTION
Meningitis is a major global public health problem, with about 30 countries worldwide, including United State reporting serious out breaks in recent years.[1] A severe epidemic of Cerebrospinal Meningitis (CSM), occurred in Nigeria between January and June 1996. There were 109,580 recorded cases and 11,717 deaths, giving a case fatality rate of 10.7 per cent overall. This is the most serious epidemic of CSM ever recorded in Nigeria in this century.[1] Infection of the Central Nervous System (CNS) by pathogenic organisms is a common neurological disease condition in tropical Africa, with serious and significant repercussion. Bacterial cell wall compounds such as Lipopolysaccharides, peptidoglycans and lipoteichoic acid, possessed by both Gram positive and Gram negative bacteria, significantly enhances inflammatory response in the brain, which in turn plays a central role in morbidity, mortality and overall prognosis associated with bacterial infection of the CNS.[2,3]

Etiology
Neisseria meningitidis is an encapsulated gram-negative diplococcus, that grows well on solid media supplemented with blood and incubated in a moist atmosphere enriched with carbon dioxide. There are about thirteen serogroups of neisseria meningitidis, classified based on the group-specific capsular polysaccharide antigen: A, B, C, D, X, Y, Z, E, W-135, H, I, K and L. Out of these, ninety-eight percent (98%) of infections are caused by five encapsulated serogroups; A, B, C, Y, and W-135. N. meningitidis colonizes macrophage rich nasopharyngeal mucosa, this lead to activation of macrophages which in turn, produce Oxygen radicals such as peroxinitrite, superoxide (O2) and hydrogen peroxide (H2O2).[4] The oxidative stress generated by this host defense response, serve as stimulus for genetic transformation by N. meningitidis, a process the Organism use in maintenance of recombination and repair machinery of the cell. This is consistent with the general concept that, transformation benefits bacterial pathogens by facilitating repair of DNA damages, produced by the oxidative defenses of the host during infection.[5] This leads to persistence and dissemination of meningococci within the bloodstream Known as Meningococcemia. Clinically, meningococcemia present in one of the three recognizable patterns: (1) meningitis (2) meningitis with meningococcemia, or (3) meningococcemia without clinically apparent meningitis.
Pathophysiology

Neisseria meningitidis is a normal commensal carried by about 10% of adults in their Nasopharynx. From nasopharyngeal colonisation, the organism in a stepwise manner invade epithelial cells, followed by blood stream invasion with bacteremia, crossing of the blood brain barrier, by transcellular migration mechanism and later it infects the cell by sticking to it with long thin extension virulent factor called pili. This initiate an infectious cascade by the action of Pathogen-associated molecular pattern (PAMP), which provoke significant inflammatory responses. Pathogen-associated molecular patterns are recognized by Toll-like receptors (TLRs), located on the cell surfaces or internalized on the endoplasmic membranes, where they allow for bacterial nucleic acid recognition. Once in the cell a polysaccharide capsule enables the organism to resist phagocytosis.

Another virulent factor possessed by meningococcal organisms is Lipo-oligosaccharide endotoxin (LOS). Meningococcal LOS interacts with human cells, following which it produces proinflammatory cytokines and chemokines, including interleukin 1 (IL-1), IL-6, and tumor necrosis factor (TNF). Which are the cytokines implicated in causing elevation of temperature that may progress to septic shock. LOS in combination with cytokines and free radicals damage the vascular endothelium, producing platelet deposition and vasculitis, which leads to widespread vascular injury characterized by endothelial necrosis, intraluminal thrombosis, and perivascular hemorrhage. Furthermore, deleterious effects of cytokines play a major role in the pathogenesis of meningococcemia by causing severe hypotension, reduced cardiac output, and increased endothelial permeability. Multiple organ failure, shock, and death may ensue as a result of anoxia in vital organs and massive Disseminated Intravascular Coagulation (DIC). Patients with severe meningococcemia may develop thrombosis and hemorrhage in the skin, the mucous membranes, the serosal surfaces, the adrenal sinusoids, and the renal glomeruli. Thrombosis of the glomerular capillaries may cause renal cortical necrosis. Thrombi containing numerous leukocytes are occasionally found in the lungs, and extensive intra-alveolar hemorrhage can occur. The fibrinolytic system in meningococcal disease is down-regulated as well, reducing plasmin generation and removing an aspect of endogenous negative feedback to clot formation. In addition, plasminogen activator inhibitor levels are dramatically increased, further reducing the efficacy of the endogenous tissue plasminogen activator.
Inflammation of cardiac muscles may result in fatal Myocarditis in adults with meningococcal infections. Myocardial dysfunction in meningococcal infection occur as a result of release of various proinflammatory mediators (e.g., nitric oxide, TNF-alpha, IL-1B) that have a direct negative inotropic effect on the heart, thereby depressing myocardial function.\textsuperscript{[13,14]} Meningococcal infection also leads to human coronary microvascular thrombosis, vasculitis, and vascular leakage.\textsuperscript{[15]} Other factors that negatively affect myocardial function are acidosis, hypoxia, hypoglycemia and electrolyte disturbances, such as hypokalemia, hypocalcemia, hypomagnesemia and hypophosphatemia.

Central nervous system manifestations of meningococcal meningitis occur as a consequence of multifactorial pathological processes, that includes but is not limited to: (1) Indirect inflammatory processes, such as cytokine release, ischemia, vasculitis, and edema (2) Direct bacterial toxicity and (3) Systemic effects, including shock, seizures, and cerebral hypoperfusion. Additionally, cerebral edema may be caused by increased secretion of CSF, decreased reabsorption of CSF and derangement in the function of blood-brain barrier. Increased intracranial pressure (ICP) secondary to cerebral edema, loss of cerebrovascular autoregulation, and reduced arterial perfusion pressure secondary to shock reduce cerebral blood flow in bacterial meningitis. Reduced cerebral blood flow with vasculitis and thrombosis of cerebral vessels may cause ischemia and neuronal injury. Cerebrovascular complications occur frequently during bacterial meningitis and can consist of cerebral infarctions, subarachnoid haemorrhage, intracranial haemorrhage and venous sinus thrombosis.\textsuperscript{[16,17,18,19,20]}

**Treatment**

Although many meningococcal infections rapidly improve when treated with antibiotics, meningococcal disease may quickly progress in some cases; the time lag from the appearance of the first symptoms to death may be only a few hours. Because the mortality rate in meningococcal disease is high (10%), all patients with fever and petechiae during epidemics warrant urgent initial assessment and treatment, and subsequent careful and repeated assessment for Cerebrospinal meningitis. The initial assessment should be conducted to identify major clinical problems. The following findings may help in the identification of severely ill patients whose condition may deteriorate: (a) Shock (b) Rapidly extending rash (c) Low WBC count (d) Coagulopathy (e) Deteriorating level of consciousness.\textsuperscript{[21,22,23,24]}
Empiric antibiotic treatment

The choice of empiric antibiotic treatment is based on the age of the patient, and the previous experience about the regional rate of reduced susceptibility of Neisseria meningitidis to penicillin and/or third-generation cephalosporins. There has been reported cases of a proportional increase in meningococcal strains with decreased susceptibility to penicillin in meningococcal meningitis patients. Therefore, patients with suspected meningococcal meningitis caused by bacterial strains, that on the basis of the local epidemiology are likely to be resistant to penicillin, a third generation cephalosporin should be provided until in vitro susceptibility testing is performed. The recommended duration of treatment is seven days. However, Antibiotic treatment can be adjusted and optimized after identification of the pathogen through culture and antibiotic susceptibility testing. In patients with CSF suggestive of bacterial meningitis in whom the CSF culture and other tests (e.g. PCR) remains negative, and the pathogen is not identified from other sites (e.g. blood culture, petechial rash culture), the recommendation is to continue empiric treatment for a duration of at least two weeks. However, depending on the clinical condition of the patient, this may need to be extended.

Adjunct therapy

While use of steroid such as dexamethasone may be indicated in the treatment of known or suspected pneumococcal meningitis in adults and in children with H influenzae type B meningitis, steroid is of no benefit in meningococcal meningitis. A Cochrane Database Systematic review subgroup analysis showed that, corticosteroids reduced mortality in pneumococcal meningitis but not in meningitis due to other pathogens. In a related development, subgroup analyses showed that use of corticosteroids was beneficial in studies performed in high-income countries with a high standard of medical care, but no effect was observed in studies performed in low-income countries. Therefore, if started empirically, steroid should probably be discontinued as soon as N meningitides is retrieved especially in low-income countries.

Treatment of complications

Shock and increased Intracranial pressure (ICP), which are underlying processes in meningococcal disease that lead to death, may coexist. Any patient with cool extremities, prolonged capillary refill time, and tachycardia should be considered to have shock.
Therefore, basic life support should include the administration of oxygen at a rate of 10-15L/min by means of a facial mask.

After basic life support and antibiotics are administered, the next priority is treating shock. The initial therapy for shock is volume replacement at a rate of 20mL/kg. A satisfactory response to volume replacement is a reduction in heart rate and improved peripheral perfusion. The first bolus of fluid may be repeated to achieve this response. The patient's condition may stabilize with only volume replacement, but the patient requires close monitoring and reassessment to detect further signs of shock or pulmonary edema.\[25\] Patients who do not respond to initial volume replacement require further volume replacement and may need inotropic support, such as the use of dopamine or dobutamine (10-20mcg/kg/min), which may be administered via a peripheral vein pending when the central venous access is established. Patients with persistent hypotension may require an infusion of adrenaline (0.1-5 mcg/kg/min), which must be administered via central venous access.\[26,27,28\]

**Surgical intervention**

Half of the adults with bacterial meningitis develop focal neurologic deficits during their clinical course, and one third of patients develop haemodynamic or respiratory insufficiency.\[31\] The diagnostic evaluation in these patients should consist of cranial CT or MRI, repeated lumbar puncture and EEG.\[32\] When hydrocephalus or space-occupying lesions, such as subdural empyema, brain abscess or intracerebral haemorrhages, are detected on neuroimaging, neurosurgical intervention may be warranted to prevent cerebral herniation. In most patients with obstructive hydrocephalus, placement of an external ventricular drain is indicated. In patients with communicating hydrocephalus who are awake and can be monitored clinically, invasive measures such as repetitive lumbar punctures or placement of an external lumbar drain can be considered but might not be necessary.\[33,34\]

**Prognosis**

Poor prognostic factors in acute bacterial meningitis include: extremes of age, altered consciousness level on admission, onset of seizures within 24 hours of admission, respiratory distress and raised intracranial pressure. Other indices of poor prognosis include comorbid conditions, delay in initiation of therapy, hypotension, CSF glucose level of <0.6 mmol/l, and WBC count of < 5000/μl.\[1\] Additionally, specific genetic polymorphisms are likely to predispose individuals to mortality in severe sepsis. An association has been described between increased risk of mortality in children with meningococcal disease and
polymorphisms in the IL-1 cluster. An innate anti-inflammatory cytokine profile (low level of TNF and high level of IL-10) is also associated with fatal meningococcal disease. A study of adults with fulminant meningococcemia found that four biochemical variables serve as poor prognostic factors: (1) Plasma fibrinogen level of 1.5 g/L or less (sole adverse prognostic variable) (2) Factor V concentration of 0.2 or less (3) Platelet count lower than 80 $X 10^9$/L (4) Cerebrospinal fluid (CSF) leukocyte count of 20 $X 10^6$/L or greater.\[^{34,35,36}\]

CONCLUSION

Meningitis is a serious public health problem associated with high mortality and morbidity. Particularly in the dry "African meningitis belt" with scarce resources. Since the introduction of the Men A conjugate vaccine (MenAfrivac), which protects against the most prevalent type of *Neisseria Meningitides* (serogroup A) by the government of Nigeria, occurrence of the disease has reduced significantly in all states at risk including North-Western states. However, the risk of other types of Neisseria meningitides persists, as evidenced by the laboratory tests that confirmed the predominance of Neisseria meningitidis serogroup C in the ongoing outbreak of meningococcal meningitis in Nigeria. Therefore, prompt treatment and intensifications of preventive strategies including mass immunization and housing programmes are advocated.

REFERENCES


