1. Introduction
Bacterial meningitis is generally a devastating infection of the leptomeninges and underlying subarachnoid cerebrospinal fluid with a high mortality rate, particularly in the perinatal and neonatal infant. This is more worrisome because despite the more available potent antimicrobials and variably effective vaccines, the disease remains a significant cause of morbidity and mortality. Mortality rates could be as high as between 25 - 50% depending on which series as well as the area of practice, whilst morbidity, often neurologic, could be as elevated as 25 – 45%.

Many clinical and etiologic studies performed over the recent decades have demonstrated that different species of bacteria can precipitate Neonatal-Perinatal bacterial meningitis. Streptococcus agalactiae, Staphylococcus aureus, Group B β-Haemolytic streptococci [GBS], Gram-negative bacilli, Haemophilus influenzae type b, Neisseria meningitides, Listeria monocytogenes and Streptococcus pneumoniae have all been implicated as etiologic pathogens. The ranking profile of the major causative organisms, however, depends majorly on the region of practice.

The major burden of Neonatal-Perinatal bacterial meningitis occurs in the developing world, however, most evidence derives from wealthy countries even though the spectrum of disease, etiology and prognosis may differ.

In this Chapter, we would dilate on the available evidence of Neonatal-Perinatal bacterial meningitis in developing countries; provide its detailed pathophysiologic process/pattern; describe the relevant clinical features at presentation; discuss its diagnosis and management strategy with particular highlights of adjuncts of steroids; indicate relevant differences from well-resourced settings; provide relevant lacunae in knowledge and comment on feasible preventive methods.

2. Incidence of disease
Bacterial meningitis is undoubtedly more common in the neonatal-perinatal period than at any other time in life. This newborn’s gloomy feature of increased susceptibility to infection is due to its innate immature immune system that is deficient in humoral and cellular immune responses in phagocytic and in complement functions. In the developed/affluent
world, mortality has dropped from nearly 50% in the 1970s to <10% currently, but morbidity, however, remains substantial, with 20-58% of survivors developing serious neurological sequelae, such as deafness.

Most worrisome is the fact that its incidence, mortality and morbidity in the developing world have remained unacceptably high; variably reported as between 40-58%. With a documented incidence of \( \frac{6.5}{1000} \) live births, the disease has shown a rising trend in Nigeria as against other more affluent regions maintaining relatively stable rates of less than \( \frac{1}{1000} \).

### 3. Etiopathogenesis

The chance of occurrence of bacterial meningitis becomes highly likely in the newly born baby with presence of adverse risk factors. These risk factors can generally be grouped into Prenatal, Intrapartum, Natal or Postnatal categories; or into Maternal, Obstetrics, or Postpartum divisions. These include low birth weight [LBW], very low birth weight [VLBW] and preterm gestation; maternal risk factors of premature ruptures of membranes, prolonged rupture of membranes (> 24 hours), maternal colonisation with Group B Streptococcus (GBS), maternal chorioamnionitis, maternal peripartum pyrexia and low socioeconomic status. These factors are universally important and well recognized. Table 1 illustrates some of these factors.

<table>
<thead>
<tr>
<th>Obstetric Factors</th>
<th>Intrapartum Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum haemorrhage [1st and 2nd Trimester]</td>
<td>Preterm birth [no evidence of a non-infectious]</td>
</tr>
<tr>
<td>Chronic hypertension in pregnancy</td>
<td>Prolonged rupture of membranes (&gt;24hours)</td>
</tr>
<tr>
<td>Preecampsia and Eclampsia</td>
<td>Peripartum maternal pyrexia</td>
</tr>
<tr>
<td>HELLP syndrome [Haemolysis, Elevated Liver enzymes, Low Platelets, Renal dysfunction]</td>
<td>Fetal distress or hypoxia</td>
</tr>
<tr>
<td>Maternal infections [Urinary tract infection, Chorioamnionitis, Vaginal infection]</td>
<td>Delivery requiring instrumentation</td>
</tr>
<tr>
<td>Maternal age extremes [&lt;18 and &gt;40yrs]</td>
<td>Unexplained fetal tachycardia</td>
</tr>
<tr>
<td>Isoimmunization</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Some well known predisposal risk factors to the occurrence of Neonatal-Perinatal meningitis.
4. The main pathogens of disease

The commonly involved pathogens of Neonatal-Perinatal bacterial meningitis often differ from community to community, region to region and continent to continent. The pathogens also frequently correlate with the degree of development, advancement and environmental hygiene, and thus what we encounter in the developing world differs from that of the developed, affluent world. In developed countries, the predominant pathogens identified from cerebrospinal fluid [CSF] are GBS, *Escherichia coli*, *Listeria monocytogenes*, other...
**Table 2. Etiology of neonatal bacterial meningitis in developing countries**

Gram-negative enteric bacteria and *Streptococcus pneumoniae*. Infections in the neonatal period are frequently divided into ‘early onset’, (first 5–7 days, implying vertical transmission) when frequently isolated bacteria include GBS, *E. coli* and *Listeria*...
monocytogenes, and ‘late onset’, (after the first week of life, implying nosocomial or community acquired infection), when common organisms include Gram negative organisms, *staphylococci* and GBS.

However, in the developing world, the pathogen profile appears different with most studies isolating *Staphylococcus aureus* and other gram negative organisms as leading culprits. Although the rate of isolates of *Escherichia coli* and *Klebsiella aeruginosa* are similar between the developed and developing regions of the world, however, there remains a very significant less encounter with GBS in the latter.

The speculated reasons for this difference are multi-factorial, and could include cultural difference in modes of genital care, population differences in colonisation, genetic differences in immune response and possibly geographic differences in laboratory techniques for pathogen isolation and reporting. Table 2 highlights the pathogen profile and pattern of Neonatal-Perinatal meningitis in developing countries.

A good evaluation was a WHO-supported multi-centre study [covering Ethiopia, The Gambia, Papua New Guinea and the Philippines], but it only attempted to determine etiological agents responsible for serious infections in young infants [≤90 days]. However, this study was limited by identifying only 40 cases of neonatal meningitis, and the findings varied immensely between centres, which narrowed the conclusions that could be drawn. It is pertinent that unusual pathogens were identified in some other studies, e.g. *Neiseria Meningitidis*, *Haemophilus Influenzae* type b, and *Salmonella typhimurium*. Table 2 is particularly worthwhile as it demonstrates the geographic differences of causal pathogens of Neonatal-Perinatal meningitis, which could serve as good guide to empirical antibiotic therapy.

5. Pathophysiology

**Method of acquisition:** Meningitis is basically an infection of the meninges (membranes that surround the brain and spinal cord) that enters through the bloodstream from other parts of the body. Meningococcal disease was first described as early as 1805, when an outbreak spread through Geneva, Switzerland. However, it was not until 1887 that a causative agent of meningococcal meningitis was identified. The pathogens that cause bacterial meningitis are very common and live naturally in the back of the nose and throat. At any given time, 10% of the populations are carriers of the disease but never actually become sick. In fact, most cases of meningitis are acquired through exposure to asymptomatic carriers.

Meningitis can be spread via nose and throat secretions [e.g. coughing, sneezing]. However, meningitis is not considered to be a highly contagious disease. Casual contact or breathing in the air where a person with meningitis has been normally would not expose someone to meningitis because the causative organisms cannot live outside the body for much long to allow their survival.

Acute bacterial meningitis usually develops from an invasion of bacterial pathogens from mucosal surfaces in nasopharynx, sinus cavities, and middle ear space into the bloodstream. It can also result from head injuries, penetrating wounds, or neurologic surgeries.

In neonatal-perinatal infants, mother-to-infant transmission and aspiration of intestinal and genital tract secretions during labour and delivery are common modes of transmission.
However, the most implicated mode of acquisition of infection is via the haematogenous route in preponderant cases worldwide.

Pneumococcal meningitis usually arises in the setting of sustained bacteraemia that permits bacterial penetration across the blood-brain barrier and into the subarachnoid space. Once present in the central nervous system, bacterial multiplication incites host cell toxicity and release of a broad range of cytokines [e.g., Interleukin-1, Interleukin-6, and Tumour Necrosis Factor-α] that increase inflammation and vascular permeability. This is the same pattern with the other meningitis-causing pathogens. The resulting injury to the cerebral microvasculature causes brain edema that in turn leads to intracranial hypertension. Unless treated, this process usually leads to mortality and/or increased morbidity, such as neural deafness.

The importance of *S. pneumoniae* as a cause of childhood meningitis has been well described. *S pneumoniae* is also by far the most common pathogen recovered from community-acquired recurrent meningitis, accounting for a majority of cases of recurrent meningitis, even in the newborn infant. The overall case-fatality rate is close to 30%.

*H. influenzae* type *b* meningitis, once the most prevalent form of meningitis in children, is now rarer in the developed world because of successful immunization practices [*H. influenzae* type *b* conjugates vaccine] in the past 2 decades. In fact, incorporation of this vaccine into the routine immunization schedule resulted in a 94% decline in the number of cases of meningitis caused by *H. influenzae* type *b* in developed countries.

### 5.1 Detection of cases

The meninges have no host defenses to fight off invading organisms. One of the most important things to determine when meningitis is suspected is whether it is bacterial or viral. If a bacterial pathogen is the culprit, it is essential to identify the specific causative agent so that the appropriate antibiotics can be prescribed immediately. If left untreated, bacterial meningitis can lead to severe complications such as brain damage, hearing loss, epilepsy and death. Viral meningitis on the other hand, is generally less severe and typically resolves on its own.

The specific diagnosis of Neonatal-Perinatal bacterial meningitis remains protean and problematic. Its identification generally depends on a high index of suspicion. Clinically, the disease is often subtle and indistinguishable from that a metabolic problem or any illness solely due to sepsis, and without meningitis. The symptoms commonly include, lethargy, fever – which is better described as temperature instability, excessive crying with difficulty at being consoled, irritability, poor feeding, apprehension, and subtle and/or frank neonatal seizures. Neck stiffness or nuchal rigidity is often not detectable because of relative immaturity of the cranio-spinal nerve bundles with deficient myelination, but may rarely be present. Other problems are bulging anterior fontanelle, opisthotonic posturing and any other non-specific neurological features.

Positive culture of CSF remains the gold standard for diagnosis and should be performed on all neonates where sepsis is suspected unless a contraindication exists. However, in view of the anatomic immaturity of the blood-brain-barrier area, caution should be employed when interpreting CSF parameters in the premature neonate.
Gram stains of CSF may also provide useful information, even if CSF culture is not available. Simultaneous blood cultures are often positive in 40–80% of cases. Furthermore, it is notable that Neonatal-Perinatal meningitis can be present even in the absence of CSF pleocytosis, and CSF protein and glucose levels are age related. The simultaneously assessed CSF:Blood glucose relationship should not be less than 50% in any neonate, and solely detected hypoglycorracia [CSF sugar of 0-<1.3mmol\L] is always diagnostic.

5.2 Diagnostic methods

Early diagnosis of Neonatal-Perinatal bacterial meningitis is very crucial. Because the symptoms of meningitis can closely mimic other viral illnesses, many clinicians miss the diagnosis and prescribe inappropriate treatments. In many cases, a missed diagnosis can have fatal consequences. All healthcare givers should be aware that early recognition of the symptoms can be a matter of life and death, and they should become familiar with all possible signs and symptoms. A careful and thorough diagnostic work-up must be undertaken.

A detailed work-up line is shown in Table 3. The specific microbiological culture procedure of all major fluid areas of the body, i.e. blood, CSF and urine should be performed. This is often referred to as a ‘Panculture Procedure’, and has the value of identifying those neonates or perinates that could have a concomitant septicemia and nephritis [UTI]. This is vital and highly needed since it has been well documented in several reports, that as highly as 30% of newborn infants with septicemia also have concomitant meningitis.

The CSF must be examined for general appearance, consistency, and tendency to clot. CSF analysis should include cell counts (including a WBC differential), glucose and protein analysis, and Gram staining of the centrifuged sediment. The use of C-reactive protein [CRP] levels has been shown to play an important role in differentiating among the various types of meningitis. More recently, some workers recommended the use of serum procalcitonin level for better diagnostic and prognostic value than CRP or leukocyte count to distinguish between bacterial and viral meningitis. Their cases were, however, older children of 4months and above. It requires validation in the neonate and perinate.

Polymerase chain reaction has remained sensitivity and quick in detecting and differentiating between viral and bacterial meningitis.

The hands, ears, nose, throat and sinuses should be checked for the possible source of infection, and a latex agglutination test to detect bacterial antigens of *Staphylococcus aureus, Streptococcus pneumoniae, Neisseria meningitides, Haemophilus influenzae* type b, *Group B* Streptococcus, *Klebsiella* sps and *Escherichia coli* strains, can aid in the diagnosis of Neonatal-Perinatal bacterial meningitis. However, this test may lack sensitivity unless ultrasonic enhancement is used.

Newborn infants with suspected bacterial meningitis should also undergo testing for glucose, serum electrolytes and blood urea nitrogen, which could indicate the degree of dehydration and identify hyponatraemia and hypoglycaemia; common symptoms of meningitis.

Clinical clues signaling the presence of bacterial meningitis may include sinusitis, otitis, mastoiditis, infective endocarditis and characteristic skin infections [such as those seen in infections caused by herpes, simplex virus, varicella-zoster virus]. Cardiovascular instability
or focal neurologic signs such as papillary changes, hemi-paresis, and ocular palsies are indicative of bacterial meningitis. Patechial and purpuric rashes usually indicate meningococcaemia or *H. influenzae* meningitis. Presence of arthritis may suggest the presence of *H. influenza* and *N. meningitides*, and head trauma or a chronically draining ear usually signals pneumococcal meningitis.

<table>
<thead>
<tr>
<th>Name of Test</th>
<th>Outcome</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pan-Cultures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Urine [Suprapubic]</td>
<td>Presence of pathogens</td>
<td>Definitive isolation of aetiology</td>
</tr>
<tr>
<td>- Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Sputum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Lumbar Puncture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grain stain</td>
<td>Presence of Bacteria</td>
<td>Useful in directing Empiric antimicrobial Therapy</td>
</tr>
<tr>
<td>Chest radiograph Pulmonary infiltrates, oedema</td>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td>Arterial Blood Gas</td>
<td>Low PCO2, low arterial pH</td>
<td>Complications of Concomitant sepsis initially yielding respiratory Alkalosis and later Metabolic acidosis.</td>
</tr>
<tr>
<td></td>
<td>Low bicarbonate</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Levels as low as 20% with Rebound to 80%</td>
<td>Infection and sepsis progression</td>
</tr>
<tr>
<td>WBC</td>
<td>Elevated or elevated</td>
<td>Infection</td>
</tr>
<tr>
<td></td>
<td>Immature forms (left shift). Total WBC &lt;4000/mm3</td>
<td></td>
</tr>
<tr>
<td>Immature-to-Total Ratio</td>
<td>&gt;/0.2</td>
<td>Sepsis\Meningitis</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>In term or near-term infants 2 serial measurements (12-24 hrs after onset of Symptoms) &gt;10ml/L</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt;100,000/microliter</td>
<td>Complications of Sepsis\Meningitis (Coagulation Abnormality)</td>
</tr>
<tr>
<td>Glucose</td>
<td>Hypoglycaemia</td>
<td>Sepsis\Meningitis</td>
</tr>
</tbody>
</table>

Table 3. Tests commonly utilized in the diagnosis of Neonatal-Perinatal bacterial meningitis

Bacterial meningitis in the newborn can be difficult to distinguish from other infectious diseases. To aid in the differential diagnosis, physicians should take a complete epidemiologic history, including contact with sick persons; maternal dietary habits, and/or
illicit drug use; medication history; exposure to insects, rodents, or arthropods; and recent travel history.

Major epidemic of meningitis frequently occur during the hot dry seasons. Sub-Saharan Africa is plagued by the highest meningitis \([N. \text{ meningitides}]\) disease burden, is usually referred to as the “meningitis belt”.

5.3 Treatment intervention

It cannot be overemphasized that treatment must be started early in the course of the disease, especially as it is of bacterial aetiology. Prompt intervention can reduce the risk of death to below 15%. If not treated as a medical emergency, bacterial meningitis can lead to seizures, coma, increased intracranial pressure, nerve damage, stroke and even death.

By identifying the causative agent, the appropriate antibiotic can be administered. The baby’s age, co-morbidities and the status of his or her immune system can aid in this identification. For example, immunocompromised patients are at particular risk for infection with \(S. \text{ pneumoniae}, N. \text{ meningitidis}, \text{Listeria monocytogenes}\), and aerobic Gram-negative bacilli. In the developing countries, \(S. \text{ aureus}\) remains a highly predominant organism in the neonatal age, whereas GBS is rarely encountered. Antibiotic intervention only improves the baby’s prognosis if the antimicrobial therapy is administered before the patient’s clinical condition has deteriorated. If antibiotics are started when the baby is already in an advanced stage of the disease, the chances of survival is poor.

Administration of antibiotics can also protect the development of the disease among children, or parents who have been exposed to another case of meningitis. According to some investigators, giving the appropriate antibiotics to household contacts of the patient with meningococcal disease can reduce their risk of infection by 89%. Antibiotic therapy must be effective against common causative pathogens and must achieve adequate bactericidal activity without toxicity in the CSF. Most often used antibiotics include; ampicillin or penicillin and an aminoglycoside \([\text{e.g. Gentamicin}]\) or a third-generation cephalosporin, such as ceftriaxone or cefotaxime. The recommendation of ceftriaxone includes the awareness that it may cause biliary sludge leading to jaundice in the neonate. Such caution appears to be theoretical, as in practice, the problem rarely occurs. Penicillin and gentamicin are widely available, cheap and the first line antimicrobial therapy in many resource-poor settings. In developed countries, initial therapy often includes some combination of three agents: Penicillin, an aminoglycoside and a third-generation cephalosporin - considered by some school-of-thought to be over use and miss use of antibiotics.

First-line therapy is usually either ampicillin and gentamicin or ampicillin and cefotaxime, or ceftriaxone and gentamicin. The value of the cephalosporins is their widely spaced dosage regimen with satisfactory better compliance. The use of cephalosporins has coincided with a reduction in mortality from neonatal meningitis in developed countries but with no associated fall in morbidity.

Gentamicin remains an effective antimicrobial, despite its small therapeutic window. Despite the fears of its causing renal toxicity and deafness, there is no documented occurrence of these complications during clinical use.
Third-generation cephalosporins (cefotaxime and ceftriaxone) are active against the major pathogens of neonates worldwide, including aminoglycoside-resistant strains. They have good CSF penetration and achieve adequate therapeutic concentrations in the CSF. Third-generation cephalosporins were recommended in the multi-centre WHO study group of serious infections in young infants.

If available, vis-à-vis a resource-poor setting, cefotaxime and ceftriaxone are currently recommended for use in Neonatal-Perinatal bacterial meningitis in view of the added advantage of a longer half-life, allowing less frequent administration.

However, it is pertinent that empiric antibiotic choice should be tailored to local epidemiology, early versus late infections and whether the infection was nosocomially acquired.

### 5.4 Adjunctive therapy

The use of corticosteroids as an adjunct to antibiotic therapy has been shown to render treatment of bacterial meningitis more effective, especially in children by reducing CSF inflammation and hearing loss. This has been shown conclusively for disease caused by *H. influenzae* type b and *S. pneumoniae* and it is, therefore, now routinely used worldwide. Its efficacy is said to improve if administered before, or along with the antibiotics. Though few studies have documented the valuable effects of steroids [dexamethasone] as an adjunct in neonatal meningitis, more evaluation requires to be done without timidity or over anxiety by clinicians. **Table 4** elucidates the improved outcome with its use in Nigeria.

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Recovery with disability, %</th>
<th>Full recovery, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone Use, n=21</td>
<td>48</td>
<td>19</td>
<td>76.2</td>
</tr>
<tr>
<td>No Dexamethasone Use, n=18</td>
<td>55.6</td>
<td>11.1</td>
<td>33.3</td>
</tr>
</tbody>
</table>

* The disabilities and handicaps were: hearing-defects, subdural effusion, hydrocephalus, hemiparesis and recurrent afebrile seizures.

**Table 4.** Value of steroids (dexamethasone) and quality of recovery from Neonatal-Perinatal bacterial meningitis.

There was significant less mortality and improved full recovery with adjunctive use of steroids, *p*=0.006.

### 5.5 The interplay of bacterial resistance

Penicillin resistance is mediated by alterations in penicillin binding proteins (PBPs). PBPs are membrane-bound enzymes that catalyze the terminal steps in the assembly of the bacterial cell wall. The key PBPs involved in penicillin susceptibility includes PBP 1a, 1b, 2a, 2b, and 3. Strains with reduced susceptibility to penicillin also exhibit reduced susceptibility
to beta-lactam drugs such as cephalosporins. \textit{S. pneumoniae} resistance to other antibiotic classes is also now widespread, and includes resistance to macrolides, trimethoprim-sulfamethoxazole, chloramphenicol, and quinolones. Multiple mechanisms mediate resistance and are briefly described in Table 5. Drug resistance to a single class of antibiotics may also be mediated by multiple mechanisms. Acquired resistance to a particular class of antibiotics increases the likelihood that the strain will be resistant to other classes of antibiotics. For example, 94\% penicillin-susceptible strains of \textit{S. pneumoniae} were recently found to be susceptible to azithromycin, but 17\% of penicillin-resistant strains were azithromycin-susceptible.

Resistance to macrolides, and trimethoprim-sulfamethoxazole is also widespread. Macrolides resistance is mediated by either an efflux pump [low-level resistance] or a ribosomal methylase [high-level resistance].

Penicillin-resistant strains are often resistant to cephalosporins such as ceftriaxone and cefotaxime. Vancomycin is active against all strains of \textit{S. pneumoniae} but vancomycin-tolerant strains have now been described. The individual members of the fluoroquinolone class demonstrate differential activity against \textit{S. pneumoniae}.

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>Mechanism of Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>Target-site alteration: Altered penicillin-binding Proteins</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Efflux-pump [low-level resistance]</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Target-site alteration: Alteration of DNA gyrase or Topoisomerase IV</td>
</tr>
<tr>
<td>Trimethoprim-Sulfamethoxazole</td>
<td>Metabolic by-pass pathway</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Enzymatic destruction: Acetyltransferase</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Target-site alteration: Alteration of the beta-subunit of RNA polymerase</td>
</tr>
</tbody>
</table>

Table 5. Mechanisms of antibiotic resistance of \textit{S. pneumoniae}

6. Conclusion

It is intriguing that Neonatal-Perinatal bacterial meningitis continues to be a major cause of morbidity and mortality in the developing world. It is vital that more efforts are required for its control rather than the offer of appropriate diagnosis and treatment. It is majorly necessary that efforts must be directed to community health education, provision of regular
information, and a versatile up-keep of hygiene and routine cleanliness. The importance of immune boosting through vaccinations and their acceptance is further worthy, as prevention is always better than cure. Important differences in aetiology have been noted but early and focused treatment of established disease, with the use of steroid adjunct, remains essential.

7. References


Meningitis is a medical emergency requiring a rapid diagnosis and an immediate transfer to an institution supplied with appropriate antibiotic and supportive measures. This book aims to provide general practitioners, paediatricians, and specialist physicians with an essential text written in an accessible language, and also to highlight the differences in pathogenesis and causative agents of meningitis in the developed and the developing world.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following: