Chapter

Neonatal Bacterial Meningitis

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Abstract

Despite improvements in neonatal intensive care, neonatal bacterial meningitis continues to be a serious disease with mortality rates varying between 10 and 15%. Additionally, long-term complications are observed among 20–50% of survivors, depending on time of diagnosis and therapy and virulence of the infecting pathogen. It is more common during the neonatal period than at any other age with the estimated incidence of 0.25 per 1000 live births. The absence of specific clinical presentation makes diagnosis of meningitis more difficult in neonates than in older children. Culture of cerebrospinal fluid is the traditional gold standard for diagnosis of bacterial meningitis, so all newborn infants with proven or suspected sepsis should undergo lumbar puncture. However, deciding when to perform lumbar puncture and interpretation of the results are challenging. Although the pathophysiology of neonatal meningitis is complex and not fully understood, researches on diagnostic and prognostic tools are ongoing. Prevention of neonatal sepsis, early recognition of infants at risk, development of novel, rapid diagnostics and adjunctive therapies, and appropriate and aggressive antimicrobial treatment to sterilize cerebrospinal fluid as soon as possible may prevent the lifelong squeal of bacterial meningitis in newborn infants.

Keywords: neonate, meningitis, diagnosis, treatment, outcome

1. Introduction

Along with the Millennium Development Goals, under-5 mortality rate reduced by an impressive 53% globally, from 1990 until 2015 [1]. Forty-five percent of under-5 mortality now occurs in the first month of life. Besides intrapartum causes and preterm birth complications, infections are one of the leading causes of neonatal deaths [2]. Neonatal sepsis and meningitis are collectively responsible for 6.8% of the global under-5 deaths [3].

Neonatal meningitis is a devastating disease associated with significant mortality and morbidity in both developed and developing countries. The improvements in healthcare delivery systems over the last several decades, especially in developed countries, resulted in a decline in mortality, but the rate of neurological morbidities in infants who survive remains substantial and ranged from 20 to 50% [4–8]. However, the incidence and mortality of neonatal meningitis in developing countries remain unacceptably high, variably reported as 0.8–6.1 per 1000 live births and 40–58%, respectively [7].

Bacterial meningitis is more common in the neonatal period than at any other time, with higher incidence in preterm and chronically hospitalized infants [9–11]. Additionally, the epidemiology of bacterial meningitis, the corresponding pathogens, the immature immune system and its response to infection and outcomes are

distinctive to the neonatal period [12, 13]. A cerebral insult related to meningitis has a greater impact on the vulnerable, developing brain, so a younger age during disease is usually associated with a poorer outcome [14]. Therefore, overall improved recognition, evaluation, and aggressive antimicrobial treatment of bacterial meningitis in newborn infants are essential to lead to a reduction in the mortality and the lifelong squeals.

This chapter will focus on the epidemiology, etiology, pathogenesis, diagnosis, treatment, and outcome of neonatal bacterial meningitis.

2. Definition

Meningitis is defined as infection and inflammation of the meninges, subarachnoid space and brain vasculature [15]. Since epidemiology of neonatal meningitis is similar to that of neonatal sepsis, neonatal meningitis is also divided into early-onset and late-onset meningitis, based on timing of infection and presumed mode of transmission [16, 17]. The cutoff for these definitions is variable throughout the literature. Early-onset meningitis is typically defined as meningitis occurring within the first 3 or 7 days after birth, and especially those in the first 2 days after birth reflect vertical transmission of invasive organism from maternal genital tract flora. Late-onset meningitis is usually defined as infection occurring as early as 4 or 8 days after birth and as late as 28 days after birth, and it is attributed to organisms acquired from interaction with the hospital environment or the community [16–18]. In very low-birth weight preterm and high-risk term infants, many of whom have prolonged hospital stays, the description of late-onset meningitis may be applicable until hospital discharge regardless of the age at the time of the infection [16]. The distinction between two patterns is useful to guide therapy. However, this distinction does not necessarily be valid in the developing world, where unsanitary birth practices and newborn care at home or in hospitals confront newborns with the risk of acquiring environmental pathogens at or soon after birth [19, 20].

3. Epidemiology

Worldwide, the incidence of neonatal bacterial meningitis is between 0.22 and 2.66 per 1000 live births. However, the incidence varies by countries of different income levels [11, 20–22].

The incidence of culture-proven neonatal meningitis is estimated between 0.21 and 0.3 per 1000 live births in developed countries [4, 11, 23]. This number is probably underestimated since a lumbar puncture is not performed in up to 50% of infants who were evaluated for sepsis in the intensive care nursery [4], and when it is performed, it may be done after the initiation of antibiotics, likely biasing culture results [4, 24]. The incidence in very-low-birth weight (VLBW) infants may be as high as 1.4%, and about 5% of those with at least one lumbar puncture performed during the hospital stay suffer from late-onset meningitis [25]. Bacterial meningitis occurs in 25% of neonates with bacteremia [17], whereas in LVBW infants with meningitis, the rate of blood culture positivity is as much as 55% [25].

In developed countries, mortality from neonatal meningitis was nearly 50% in the 1970s, and then it has dropped to figures ranging from 10 to 15% [5, 7, 26–29]. However, long-term sequelae rates did not change, with up to 50% of survivors having long-term neurodevelopmental complications [4–8, 27]. In a prospective study including 444 cases of confirmed meningitis during 2001–2007, it was reported

that the case fatality for neonatal bacterial meningitis was 13%, but much higher in preterm babies (25%) [29].

It may be difficult to estimate the incidence in developing countries due to under-developed surveillance systems. A few community-based studies published from developing countries tend to reveal higher incidence of neonatal meningitis [20]. In these studies, the incidence of neonatal meningitis in the first week of life ranged from 0.8 to 6.1 per 1000 live births [4, 5, 20]. In developing countries, mortality from neonatal meningitis ranges from 40 to 58% [7]. It is very likely that most of the studies from developing countries have biases in selection of study population, which may have underestimated true incidence rates. Additionally, the lack of laboratory-based confirmation as well as varied clinical criteria and access to health care facilities and limited resources may lead to underreporting in these regions [20].

The most common organisms associated with neonatal meningitis are Group B Streptococcus (GBS), *Escherichia coli*, and *Listeria monocytogenes*, and GBS and *E coli* account for approximately two-thirds of all cases of neonatal meningitis [8, 30]. Thanks to the program consists of identifying pregnant women who are GBS carriers by screening and/or identifying the presence of risk factors that predispose the infants to infection, the incidence of early onset neonatal GBS sepsis in the United States has declined from 1.5 per 1000 live birth to 0.3 per 1000 live births. However, the incidence in late onset neonatal GBS infection appears to remain unchanged or even increasing [30–35]. Additionally, there is an increased incidence of Gram-negative bacteria, specifically antibiotic-resistant *E coli*, in early-onset infection in the preterm and VLBW infants [30].

4. Etiology

The types and distribution of organisms that commonly cause neonatal meningitis depend on age at presentation, location, and gestational age. The distribution of organisms observed in neonatal meningitis is similar to that of neonatal sepsis (**Table 1**) [4, 18, 23]. So, meningitis may be a component of early-onset, late-onset, and nosocomial infection.

The group B streptococcus (especially capsular serotype III) is the major causative pathogen, implicated in up to 50% of cases. Late-onset GBS sepsis is more likely to be complicated by meningitis when compared to early-onset GBS

Causative pathogen
Group B *Streptococcus*
Other streptococci and staphylococci (including especially group D streptococci, *Streptococcus pneumoniae*, *Staphylococcus epidermidis*†, and *Staphylococcus aureus*)
Escherichia coli
Other Gram-negative enteric bacteria (including *Pseudomonas aeruginosa*, *Klebsiella* and *Enterobacter* species, *Proteus* species, *Citrobacter* species, and *Serratia marcescens*)
Others (including *Haemophilus influenzae*, *Salmonella* species, and *Flavobacterium meningosepticum*)
Listeria monocytogenes

For more, see Ref. [18].
†Coagulase-negative staphylococci are particularly common etiologies in very-low-birth-weight infants with late-onset meningitis.

Table 1.
Bacteria causing neonatal meningitis in developed countries.

sepsis [36]. Colonization of the neonate with GBS may be acquired from maternal genital tract during delivery or from nosocomial sources [17]. The attack rate of the colonized newborn is approximately 1%. The risk factors that influence the attack rate include prematurity, dose and virulence of the organism, prolonged duration of ruptured membrane prior to the delivery, and maternal fever during labor [31]. Despite intrapartum antibiotic prophylaxis (IAP) to reduce vertical transmission of GBS infection, not all cases of early-onset GBS are prevented, and GBS continues to be the most common cause of early-onset disease in term neonates [4, 21, 37]. However, it is uncommon in developing countries, even if the prevalence of colonization in women has been reported as high as 22% and implementation of IAP is not possible [16, 38].

Escherichia coli is the second most common pathogen and represents 50% of gram-negative bacteria which account for 30–40% of cases of neonatal meningitis [4, 11, 30]. Most of *E coli* (80%) strains causing meningitis possessed the K1 polysaccharide capsular antigen which inhibits phagocytosis and resists antibody-independent serum bactericidal activity [39, 40]. With the implementation of IAP against GBS, *E Coli* has emerged as the most common cause of early-onset sepsis and meningitis among VLBW infants [41, 42], and it has become the leading cause of sepsis-related mortality in this weight group [43]. Additionally, there is a growing concern on emerging antimicrobial resistance in *E coli* infections [41]. *Klebsiella* spp. are the second most important Gram-negative bacteria causing neonatal meningitis, especially in developing countries [4, 7]. The other Gram-negative organisms less commonly isolated include *Enterobacter* spp.*, Pseudomonas aeruginosa, Citrobacter* spp., and *Serratia* spp. [17]. *Citrobacter* spp. are usually associated with brain abscesses, emphasizing the importance of brain imaging as part of the evaluation whenever *Citrobacter* is isolated from the CSF [23].

It has been estimated that *Listeria monocytogenes* accounts for approximately 5–7% of cases of neonatal meningitis [5, 28], since the incidence of neonatal *Listeria* infections has decreased substantially in recent years [44]. It continues to be important in contribution to significant morbidity and mortality because of its association with thrombo-encephalitis. Similar to GBS neonatal infections, early-onset Listeria disease is often sepsis whereas late-onset Listeria disease is often meningitis [45]. *Listeria* serotype IVb is responsible for almost all cases of meningitis caused by this organism [46]. *Listeria* may be acquired following placental invasion during pregnancy, passively during the birth process or following horizontal transmission from environmental sources [17, 45].

Coagulase-negative staphylococcus (CNS) and *Staphylococcus aureus* are commonly seen in very premature and high-risk neonates who require prolonged hospitalization, central venous catheters, external devices and ventilator support [5]. Other less common but important pathogens associated with neonatal meningitis include enterococcus, *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* [8, 18, 21]. Moreover, there is a wider range of more unusual and potentially antibiotic-resistant organisms causing late-onset meningitis in hospitalized patients [11, 18, 47–49].

5. Pathogenesis

Meningitis most commonly results as a consequence of hematogenous dissemination of bacteria via choroid plexus and cerebral microvasculature into the central nervous system during the course of sepsis [4, 15]. Rarely, meningitis may develop following the spread of an infection in the scalp or skull, and a contamination of open neural tube defect, congenital sinus tract, or ventricular device [4, 18, 50].

The early- and late-onset patterns of the disease have been associated with sepsis during the first month of life, as invasion of the meninges occurs in as many as 25% of infants with bacteremia [23, 50]. So, meningitis and sepsis typically share a common cause and pathogenesis.

Neonates are the most vulnerable of all age groups to infectious pathogens, because of immaturity of the immune system, as well as decreased placental passage of maternal antibodies, especially in preterm infants [16, 37]. All limitations of both initiate and adaptive immunity, decreased inflammatory and immune effector responses, and the deficient expression of complement and of antimicrobial proteins make fetus and neonate, particularly the premature neonate, susceptible to a wide variety of microorganisms [18, 51]. In addition to host susceptibility, obstetric and nursery practices, socioeconomic status, and the health and nutrition of mothers are important in determining neonates at risk for infection, and similarly, in the pathogenesis of neonatal sepsis and meningitis [18, 37].

Initial colonization of the neonate usually occurs in utero from ascending bacteria entering the uterus from vaginal environment after rupture of amniotic membranes [18, 37]. If delivery is delayed, microbial invasion of amniotic fluid may cause an acute inflammation of the fetal membranes, which is defined as chorioamnionitis [18, 37]. Infected amniotic fluid may lead to fetal systemic inflammatory response syndrome, stillbirth, preterm delivery, or neonatal sepsis following invasion of bacteria into the fetus through respiratory tract (fetal breathing), gastrointestinal tract (swallowing), skin, and ear [52]. Additionally, the neonate may be colonized with potentially pathogenic bacteria through the birth canal during delivery. Microorganism acquired by the neonate just before or during birth colonizes the skin and mucosa of multiple sites including the nasopharynx, conjunctivae, oropharynx, umbilical cord, and in the female infant, the external genitalia. Microorganisms can invade through any site where skin or mucosal barrier is disrupted [15, 17]. Bacteria may proliferate at the initial site of attachment without causing serious illness, or then, pass into the subepithelial blood vessel from where they can be transported to other parts of the body including the CNS [15, 18]. Transplacental hematogenous infection is also possible. *Listeria monocytogenes* is usually acquired transplacentally [4, 45]. In rare cases, hematogenous transmission of GBS, *S pneumoniae*, and *N meningitidi*s from maternal bacteremia has been reported as causes of early-onset neonatal meningitis [18, 37, 53].

As infants grow up, they are exposed to environmental microorganisms that might be pathogenic to them. Poor hand hygiene among caregivers and hospital personnel, nutritional sources, and contaminated equipment all can transfer microorganism from infected infants to uninfected infants [13, 37, 53]. Most VLBW and high-risk infants have one or more procedures that expose them to risk of infection during their hospital stay. Invasive devices such as venous or arterial catheters, endotracheal tubes, ventricular shunts, urinary catheters, and feeding tubes can insert pathogen into the body of the infant. Parenteral nutrition, exposure to prolonged courses of empiric antibiotics, H_2-receptor blocker or proton pump inhibitor use can also result in increased risk for late-onset infections [13, 18, 37, 54, 55].

Once the bacterium has entered into the systemic circulation, the polysaccharide capsule of the pathogen plays a key role in the survival of the pathogen in the hostile environment of the blood [15, 17, 56]. The polysaccharide capsule mediates resistance to complement-mediated lysis and phagocytosis by polymorphonuclear leukocytes and macrophages [15, 57]. The potential sites for bacteria entering the CNS are the cerebral microvascular endothelium of the arachnoid membrane and the choroid plexus epithelium where capillary endothelial cells are fused along the terminal edge by tight junctions [17]. The attachment of bacteria to microvascular endothelial cells and passage through the blood brain barrier (BBB) are promoted

by the interaction of specific bacterial factors with host receptors [57]. To facilitate crossing the BBB, *Streptococcus pneumoniae* interacts with cell wall phosphorylcholine and platelet activating factor receptor [8]. *Streptococcus agalactiae* uses the lipoprotein laminin-binding protein and K1 *E Coli* express type 1 fimbriae and the OmpA protein to contribute to the bacterium binding to cerebral endothelial cells [57–59]. The bacteria can cross the BBB transcellularly, paracellularly, and in infected phagocytes. Transcellular traversal occurs when the microorganism penetrates the cells without any evidence in the cells or intracellular tight-junction disruption [58]. *Streptococcus pneumoniae*, *Streptococcus agalactiae*, and *E. coli* can all cross the BBB via this mechanism [58]. Paracellular traversal occurs when microorganism penetrates between barrier cells [17]. *L monocytogenes* crosses the BBB by microbial penetration using transmigration within *L monocytogenes*-infected monocytes or myeloid cells across the BBB by a so-called Trojan horse mechanism [15, 58].

Once bacteria enter the cerebrospinal fluid, they are free to replicate and spread unchecked at least initially, as phagocytes, immunoglobulins, and complement components are excluded by the BBB. This bacterial multiplication goes on until bacteria die following the stationary growth phase or the exposure to the treatment with β-lactams that causes antibiotic-induced bacteriolysis. The subsequent release of subcapsular bacterial products such as peptidoglycan, lipoteichoic acids, lipoproteins, lipopolysaccharides, and bacterial DNA leads to an increased inflammatory response in the host [15, 59]. Many brain cells including astrocytes, glial cells, endothelial cells, ependymal cells, and resident macrophages can produce pro-inflammatory and anti-inflammatory cytokines in response to bacterial replication and its components [60, 61]. Although this inflammation is needed to eliminate the bacteria and allow the host to recover, it is also a major cause of brain injury in meningitis [11, 61].

Neuronal injury in bacterial meningitis is caused by several mechanisms, which have been identified by experimental studies during the last years [15, 60–62]. Neuronal injury likely results from a combination of the following events: dysfunctioning cerebral blood flow (increased BBB permeability, cerebral edema, vasospasm, vasculitis, cerebral venous thrombosis, and systemic hypotension), detrimental effects of inflammatory mediators (e.g., tumor necrosis factor-alpha, interleukin-1, and nitric oxide) and infiltrating cells (leukocytes, macrophages, and microglia), neurotoxicity (free radicals, proteases, and some microbial compounds), increased CSF outflow resistance, and excitatory amino acids, which finally lead to energy failure and cell death executed by caspases [15, 17, 60–63]. The mode of neuronal cell death in different regions of the brain depends on the strength and type of the noxious stimulus and may be a form of apoptotic, necrotic, or hybrid [62, 63]. For example, neuronal cell death occurs mostly as apoptosis in the dentate gyrus of the hippocampal formation, whereas it occurs mostly as necrosis due to focal ischemia in the cortex [15, 62, 63].

6. Risk factors

Since meningitis is most commonly a complication of bacteremia, the risk factors are similar to those that contribute to neonatal sepsis [4–6]. Risk factors for neonatal sepsis include maternal factors, neonatal host factors, and virulence of infecting organism. The most important neonatal factor is prematurity or low birth weight. Small preterm infants have a 3–10 times higher incidence of infection than full-term normal birth weight infants [4–6]. Immaturity of the immune system and diminishing transplacentally acquired maternal immunoglobulins in premature infants contribute

to increased risk of infections. Additionally, preterm infants often require prolonged hospital stay and so have one or more procedures such as parenteral nutrition, intubation, and central catheters that place them at risk for infection [18, 37]. Other host factors include hypoxia, acidosis, hyperbilirubinemia, hypothermia, galactosemia, indomethacin, lipid administration, and parenteral iron supplementation [37]. Maternal risk factors include GBS colonization or GBS bacteriuria, prolonged rupture of membranes of 18–24 hours or greater, chorioamnionitis, urinary tract infections, multiple pregnancies, and septic or traumatic delivery [13, 18, 37].

7. Clinical presentation

The earliest signs and symptoms of neonates with meningitis may be subtle and nonspecific, especially more problematic in premature infants [5]. The clinical presentation of neonatal meningitis is similar to those of neonatal sepsis without meningitis. Most commonly reported clinical features include temperature instability (62%), irritability or lethargy (52%), and poor feeding or vomiting (48%) [18]. However, in preterm infants, respiratory decompensation consisting of an increased number of apnea and bradycardia episodes and increased oxygen requirement are prominent clinical signs [50]. Term infants are more likely to have fever (>37.2°C), whereas preterm infants more frequently have hypothermia (<36°C) [64]. Other findings associated with neonatal meningitis include respiratory distress, jaundice, diarrhea and hepatosplenomegaly. However, all these features could not help to establish an early diagnosis of meningitis [18].

Neurologic signs of neonatal meningitis include irritability, alteration in consciousness, poor tone, tremors, seizures, high-pitched cry, twitching of facial or an extremity, focal signs including hemiparesis, gaze deviation, and cranial nerve deficits [4, 18]. Seizures are generally focal and seen in 40% of cases, and considering subtle ones is also possible [5, 18]. Since cranial sutures in the neonate are open and allow for expansion of the intracranial contents and for increasing head size, meningeal signs are not commonly seen. Bulging fontanelle occurs in about 25% of cases and nuchal rigidity in only 15% [28].

Early-onset neonatal infections are generally presented as sepsis or pneumonia, so meningitis is relatively less common. The signs of early-onset infection get to appear within the first 24–48 hours of life in 90% of affected cases [65]. However, late-onset sepsis, in addition to bacteremia, is frequently manifested as focal infections such as meningitis and osteomyelitis resulting from hematogenous seeding [11, 18]. Neonatal meningitis can complicate 14% of episodes of early-onset GBS sepsis and 54% of episodes of late-onset GBS sepsis [36], so the later condition is more likely to have specific signs of meningitis [28].

Lack of data on the timing of onset of features listed above makes it difficult for the early recognition of a baby with meningitis. Additionally, these features are likely to be affected by other factors such as gestational age, partial antibiotic treatment, and postnatal age [6]. Classical meningitic signs such as convulsions, bulging fontanel, altered mental status, and nuchal rigidity are often late findings that are associated with a worse outcome [5, 6]. So, the timing of the onset of clinical features may be crucial for early recognition, prompt management and potentially, better outcome [6]. Although several useful clinical features were defined to predict meningitis in children, the most accurate combination of clinical features to raise or lower suspicion of meningitis is still unclear. Furthermore, small infants presenting nonspecific but concerning features such as fever, lethargy, poor feeding, or irritability, should be approached with a high index of suspicion regardless of how well they appear [66].

Brain abscess, which can be presented by the findings of increased intracranial pressure, focal neurologic deficit, poor clinical response to antibiotic therapy, and new-onset focal seizures, occurs in about 13% of neonates with neonatal meningitis. However, the risk of brain abscess is increased in cases of meningitis caused by *Citrobacter koseri* (up to 75%), *Serratia marcescens*, *Proteus mirabilis*, and *Enterobacter sakazakii*. Therefore, when these pathogens are detected as the cause of the disease, neuroimaging should be performed even with no clinical indication [18, 28].

8. Diagnosis

Since the clinical signs and symptoms are nonspecific and similar to those seen in sepsis, CSF examination via lumbar puncture (LP) is essential to establish the diagnosis of bacterial meningitis and to identify the causative organism with antibiotic susceptibility testing [4]. LP should be performed in all neonates whose blood culture is positive and be considered in all neonates when sepsis is possible. As many as 40% of infants with meningitis who have a gestational age of ≥34 weeks do not have a positive blood culture at the time of their diagnosis [67]. Similarly, among VLBW infants who survived >3 days, one third of cases of meningitis have negative blood cultures [25]. Therefore, if LP is performed based on the presence of blood culture positivity, a significant number of cases of meningitis will be overlooked [11]. This means that if sepsis or meningitis is suspected, performing LP is mandatory.

Debate continues as to whether an LP should be performed on all babies suspected of sepsis or only on symptomatic babies. In the past, the LP had been a routine part of the evaluation of infants suspected of having sepsis, in conjunction with a complete blood cell count and blood cultures [17]. Meningitis in preterm infants with respiratory distress syndrome is unlikely, so an LP is not mandatory unless sepsis is suspected [68, 69]. Similarly, the yield of an LP from babies who are asymptomatic with or without maternal risk factors is likely to be very low [70]. However, during the first week of life, if the blood cultures yield a pathogenic organism or clinical features of sepsis exist, evaluation of CSF should be done [18]. It should be kept in mind that the use of intrapartum antibiotics makes blood culture results unreliable. In every infant older than 1 week, an LP is indicated as a routine part of the work-up for sepsis [17]. Performance of the LP is sometimes delayed due to cardiorespiratory instability, extreme prematurity with the risk of intraventricular hemorrhage, or thrombocytopenia, resulting in delay in diagnosis and prolonged and possibly inappropriate antibiotic use [25]. If it is not possible to perform an LP in the infant with presumed sepsis and meningitis, antimicrobials in doses sufficient for the treatment of meningitis should be initiated immediately following obtaining blood for culture. When the infant is stabilized, even if antibiotic therapy is being taken for several days, LP should be performed. A delayed LP is still likely to show the presence of CSF pleocytosis and abnormal CSF chemistry and thus confirms the diagnosis of meningitis, although CSF culture may be negative [4, 11, 23]. In such cases, real-time polymerase chain reaction (PCR) may have an important role as a better diagnostic tool, although its routine use in the context of neonatal infection is currently limited [11, 71].

Infants with suspected bacterial meningitis or late-onset sepsis should undergo a full laboratory evaluation consisting of a complete blood count with differential, blood culture, a urine analysis and culture (useful only after the third day of life), and lumbar puncture to examine the CSF [50]. Ancillary tests such as complete blood cell count, C-reactive protein, interleukin-6, and procalcitonin

have suboptimal sensitivity and specificity for the diagnosis of neonatal sepsis, but these diagnostic tests may be useful in supporting the diagnosis of infection as well as determining the length of therapy when they are serial abnormal and accompanied by clinical features of infection [23, 37, 50].

CSF culture is the gold standard method for diagnosing bacterial meningitis. So, it is important to perform an LP early in the course of illness, ideally before the administration of antibiotic therapy [72]. However, infants may be exposed to intrapartum or empiric antibiotics before performing an LP, making CSF parameters helpful in determining the likelihood of meningitis, because of the possibility of false CSF culture negativity in those with meningitis [4].

9. Examination of cerebrospinal fluid

Although examination of the CSF is highly important in supporting the diagnosis of meningitis, interpretation of CSF findings can be challenging in newborn infants [72]. Values for both the cellular and chemical parameters of CSF are different for neonates than for older infants and children, and also vary according to gestational age, birth weight, and chronologic age (**Table 2**) [73–77]. The cell content and protein concentration in the CSF of a healthy neonate are higher than those of older infants, whereas CSF glucose levels may be as low as 30 mg/dl in

Age [Ref.]	WBC/mm^3	Protein (mg/dL)	Glucose (mg/dL)
Term neonates evaluated in the nursery setting† [73]			
≤7 days (n: 130)	Median (IQR): 3 (1–6); 95th percentile: 23	Median (IQR): 78 (60–100); 95th percentile: 137	Median (IQR): 50 (44–56); 5th percentile: 35
8 days to 6 months (n: 140)*	Median (IQR): 2 (1–4); 95th percentile: 32	Median (IQR): 57 (42–77); 95th percentile: 158	Median (IQR): 52 (45–64); 5th percentile: 38
Term neonates evaluated in the emergency department setting‡			
≤28 days (n: 3467) [74]	Mean: 5.5; 95th percentile: 16	Mean (±SD): 69.9 (±25.7); upper bound: 127	Mean (±SD): 45.7 (±8.0); lower bound: 25
<28 days (n: 278) [75]	Mean (range): 6.1 (0–18.0)	Mean (range): 75.4 (15.8–131.0)	Mean (range): 45.3 (30.0–61.0)
28–56 days (n: 318) [75]	Mean (range): 3.1 (0–8.5)	Mean (range): 58.9 (5.5–105.5)	Mean (range): 48.0 (30.5–65.5)
Preterm very low birth weight (<1500 g) neonates			
≤7 days (n: 88) [76]	Mean (range): 7.1 (0–30)	Mean (range): 144 (51–270)	Mean (range): 50.4 (11–138)
≤28 days (n: 45) [77]	Mean (range): 5 (0–44)	Mean (range): 148 (54–370)	Mean(range): 67 (33–217)

WBC: white blood cell count; SD: standard deviation; IQR: interquartile range; CSF: cerebrospinal fluid; neonatal intensive care unit; and n: number of cases.
†CSF was obtained from infants evaluated for sepsis in the NICU setting.
**In this study, only a small proportion of infants were aged >28 days.*
‡CSF was obtained in the emergency department during evaluation for possible infection; infection was excluded by sterile cultures (CSF, blood, and urine). Infants with positive polymerase chain reaction for enterovirus were also excluded.

Table 2.
Characteristics of cerebrospinal fluid in term and preterm neonates without bacterial meningitis.

term infants and as low as 20 mg/dl in preterm infants [77]. CSF protein is higher in preterm versus term infants. Moreover, the values of CSF parameters in neonates with and without confirmed meningitis may overlap [72].

Characteristic CSF findings of neonatal bacterial meningitis include polymorphonuclear pleocytosis, hypoglycorrhachia, and increased protein concentrations [8]. Cerebrospinal fluid white blood cell (WBC) counts of >21 cells/mm^3 in infants with gestational age ≥ 34 weeks have a sensitivity and specificity of approximately 80% to suggest confirmed meningitis. However, this cut off may be resulted in a missed diagnosis in 13% of infants with confirmed meningitis, since neonatal meningitis can also occur with normal CSF parameters without bacteremia [4, 67]. If CSF is examined so early, before meninges are not inflamed enough, CSF findings may not be definitive for bacterial meningitis, requiring the repeat LP 24–48 hours later. In a neonate, a CSF WBC count of >20 cells/mm^3 is consistent with meningeal inflammation, and suggests bacterial meningitis [4]. The number of WBCs in the CSF is higher in neonates with meningitis caused by Gram-negative bacteria than those caused by Gram-positive bacteria [78], and can be up to thousands, with predominantly polymorphonuclear leukocytes in the early course of the disease [18, 28]. The level of CSF protein is considered a poor predictor of neonatal meningitis because of considerable overlap of values between infants with and without confirmed meningitis [4, 67]. In general practice, a CSF protein of 170 mg/dl in preterm and > 100 mg/dl in term infants is interpreted in favor of neonatal bacterial meningitis. However, caution should be employed when interpreting CSF parameters in preterm infants [79, 80].

Antibiotic treatment before the LP is a common practice because LPs are not being performed in all cases [5]. When patients with true meningitis are exposed to antibiotics for up to 24–36 hours, CSF WBC values remain elevated without significance. However, CSF protein values decrease but still remain higher than normative values, whereas CSF glucose values show rapid normalization [72, 81]. So, because of limited impact of pretreatment antibiotics on CSF WBC, it does not prevent the diagnosis of meningitis up to 24 hours. Additionally, once CSF is obtained, the sample should be analyzed as soon as possible, otherwise a delay in laboratory analysis may result in the decline in measured WBC [82].

Gram stain of CSF is useful in providing an early presumptive etiologic diagnosis, especially Gram-negative bacteria, since the culture of CSF can take up to 48 hours [6]. Its positivity rates depend on the CSF concentration of bacteria, so the absence of the organism on Gram stain does not exclude meningitis [8]. In cases of meningitis caused by *L. monocytogenes*, Gram stain is frequently negative due to the low number of bacteria in the CSF [17].

Traumatic LP is defined as the presence of blood in the CSF obtained, and occurs very frequently in neonates, with reported incidences ranging from 35 to 46% [72]. This condition makes the interpretation of CSF results more complicated. Adjustment of CSF WBC in traumatic LPs does not improve the diagnosis of neonatal bacterial meningitis, and adjustment can result in loss of sensitivity with marginal gain in specificity [72]. CSF protein may be elevated in the presence of blood contamination from a traumatic LP [83]. It may be useful to repeat the LP 24–48 hours later, so that normal WBC can exclude bacterial meningitis, but frequently it is inconclusive. Neonates in whom the LP is traumatic should be treated with antibiotic presumed meningitis, until results of CSF culture are available.

Among nonculture tests of CSF, the PCR has been useful in the identification of infecting bacteria including *Streptococcus pneumoniae*, *E coli*, GBS, *S aureus*, and *L monocytogenes*, with higher detection rate of any CSF pathogen compared with traditional cultures (72% vs. 48%) in patients with antibiotic administration

[71]. However, the use of PCR is limited to selected cases for now, and before used routinely, requires further researches and institutional facilities [84, 85]. Since PCR neither detects all causes of CNS infection nor provides any information on antimicrobial susceptibility, it should be used in conjunction with standard microbiologic tests. A number of CSF biomarkers such as tumor necrosis factor a, interleukin (IL) 1b, IL-6, IL-8, IL-10, IL-12, IL-17, C-reactive protein, procalcitonin, and lipocalin 2 have been examined for differentiating bacterial meningitis from viral meningitis and noninfectious origins, and the results have been encouraging [8, 86]. However, the validity and use of these biomarkers in clinical practice have been limited, and the interpretation of the results of these assays should be done with caution.

10. Differential diagnosis

Besides sepsis and other specific infections, symptoms and signs may be due to noninfectious conditions such as cardiac, pulmonary, gastrointestinal, and metabolic disorders [11, 18]. Disorders mimicking the neurological features of meningitis include intracranial hemorrhage, ischemic stroke, hypoxic–ischemic encephalopathy, injuries, and inborn errors of metabolism [11, 18]. Conditions where CSF culture is negative despite CSF changes include infectious and noninfectious causes of aseptic meningitis, partially treated bacterial meningitis, parameningeal infected focus such as abscess, and intraventricular hemorrhage. Since some of the pathogens that cause aseptic meningitis have specific therapy, a comprehensive evaluation including viral, anaerobic, mycoplasma, and fungal cultures, antigen detection, PCR, and serology should be performed [18]. Elevated CSF protein values and leukocyte counts and hypoglycorrhachia may develop in preterm infants after intraventricular hemorrhage. Many nonpyogenic congenital infections (toxoplasmosis, cytomegalovirus, herpes simplex virus, and syphilis producing aseptic meningitis) can also produce alterations in CSF protein values and leukocyte counts. [18, 50].

11. Antimicrobial treatment

Eradication of the infecting pathogen from the CSF is entirely dependent on antimicrobial therapy which should be initiated as soon as possible after the evaluation which is suggestive of bacterial meningitis [8]. Since clinical presentation may be subtle and nonspecific and the outcome may be devastating, a low threshold for initiating antimicrobial therapy is necessary without knowledge of the specific pathogen [6]. Decisions on which antibiotics to use empirically are designed to cover the likely pathogens based on the age of the patient (e.g., early-onset meningitis), specific risk factors, data regarding pathogens and their susceptibility within nursery, and the ability to penetrate the CSF [8, 87, 88]. The initial choice of intravenous antibiotics for neonates suspected of having meningitis must cover both Gram-positive and Gram-negative organisms [89]. Efficient elimination of bacteria depends also on the relationship between the concentration of antibiotic in the CSF and the minimal bactericidal concentration (MBC) for the infecting pathogen [17]. Then, antibiotics are modified according to culture and antibiotic susceptibility tests, as indicated.

Initial empirical therapy for early-onset bacterial meningitis must include a combination regimen containing ampicillin and an aminoglycoside (e.g., gentamicin) to cover GBS, *E coli*, and *L monocytogenes*, whereas a regimen including a third-generation cephalosporin (e.g., cefotaxime) is preferred when meningitis resulting

from a Gram-negative organism is strongly suspected [8, 18]. This empirical antimicrobial therapy should be continued until the pathogen and its antibiotic susceptibility are identified. Since eradication of Gram-negative bacteria from CSF is often delayed and high rates of ampicillin resistance among E. coli isolates have been reported, cefotaxime is the agent of choice, thanks to its higher CSF bactericidal activity [89, 90]. However, when the use of cefotaxime is routine, rapid emergence of cephalosporin-resistant strains, especially *Enterobacter cloaca*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *E coli*, and *Serratia* species, can occur (via inducible beta-lactamases), even during therapy [91–94]. It is recommended that such infections should be treated with a carbapenem (usually meropenem), in combination with an aminoglycoside, since carbapenem resistance has recently emerged among Gram-negative bacilli [50, 95, 96]. Therefore, meningitis caused by Gram-negative bacteria need to be closely monitored, which includes repeating LP for documentation of CSF sterility and brain imaging studies with clinical indications [8, 97].

There is a synergy for ampicillin and gentamycin in the treatment of meningitis caused by GBS, and this combination should be continued until sterility of the CSF has been documented [17]. Afterwards, single therapy with penicillin or ampicillin should be used for 14 days [97]. Although GBS is also susceptible to cephalosporins, the use of the narrower agent, like penicillin, will minimize any potential impact on antibiotic resistance among other pathogens [87]. Infection caused by *L monocytogenes* and *Enterococcus* should be treated with ampicillin and gentamycin, since both are resistant to cephalosporins [17, 87]. When the CSF has been sterilized and the patient has improved clinically, ampicillin alone can be used to complete therapy. Because of high rate of ampicillin resistance among *E. coli* and other Gram-negative organisms, a combination of cefotaxime (or ceftazidime in the case of *P. aeruginosa*) and an aminoglycoside, usually gentamicin, is preferable. Once sterility of the CSF is documented, the aminoglycoside can be discontinued and the appropriate beta-lactam should be continued for a minimum of 21 or 14 days after the CSF is sterile, whichever is the longest [17–19, 87, 97].

Initial empirical therapy for late-onset bacterial meningitis usually depends on whether the infection is community or hospital acquired. For babies admitted from home, an empiric antibiotic combination of amoxicillin or ampicillin and cefotaxime is likely to provide excellent cover for possible pathogens, with good CSF penetration [5, 11, 88]. In areas where there are high rates of cephalosporins resistance among *Streptococcus pneumonia,* initial treatment of meningitis may include high doses of third-generation cephalosporins in association with vancomycin before the results of antibiotic susceptibility [98]. Although the implementation of pneumococcal vaccination led to a near disappearance of vaccine serotypes resistant to β-lactams, it also contributed to the emergence of the 19A serotype, which was particularly resistant to antibiotics [98]. Some community-based studies from developing countries have reported increasing resistance, particularly of Gram-negative organism to first-line and even second-line antibiotics [88]. Therefore, in the choice of empirical antibiotics, the resistance pattern of possible pathogens in the community should also be considered.

For babies already in hospital or discharged recently from hospital, initial antimicrobial therapy should be chosen according to the pathogen commonly seen in that particular nursery and their susceptibility pattern [11]. There are various factors that may influence the likely spectrum of causative pathogens, especially their risk of unusual or multidrug resistant bacteria [5, 18]. These include prior exposure to broad-spectrum antibiotics, the presence of central venous lines, ventriculoperitoneal shunt, or ventricular reservoir, parenteral nutrition, and their risk of acquiring infections through nosocomial transmission [5, 55, 99, 100]. Therefore,

empirical therapy may include ampicillin (if GBS, *L monocytogenes* or enterococci are suspected), nafcillin, or vancomycin and an aminoglycoside, and cefotaxime, or meropenem, depending on the predominant pathogen seen in the neonatal unit [50, 97]. Meningitis with organisms such as CNS, which is more common in neonates requiring prolonged hospitalization, need for central venous catheters, and surgical manipulations or placement of a ventriculoperitoneal shunt due to intraventricular hemorrhage and hydrocephalus [55, 100], can be treated with nafcillin or vancomycin, assuming that the isolate is susceptible [18, 50, 101]. The duration of therapy is generally 14–21 days after CSF sterilization, with removal of any foreign body if possible [18, 50, 101]. Meropenem is recommended for treatment of neonatal meningitis that is caused by MDR Gram-negative organisms, although it is approved for use only in infants aged older than 3 months for bacterial meningitis or complicated intra-abdominal infections due to limited data on meropenem use in neonates [97, 102]. Metronidazole is the treatment of choice for infection caused by *Bacteroides fragilis* and other anaerobic organisms [18, 50].

The recommended antimicrobial treatment based on causative organism and dosage of common antibiotics used for neonatal meningitis are provided in **Tables 3** and **4** [4, 50, 87, 97, 103, 104].

Although the intraventricular or intrathecal route of administration of antibiotics is able to achieve higher antibiotic concentrations in the CSF and eliminate the bacteria more quickly, intraventricular antibiotics in combination with intravenous antibiotics resulted in a three-fold increased relative risk for mortality compared to standard treatment with intravenous antibiotics alone and should be avoided [105]. However, it remains an option in patients who already have a ventricular drain in place and persistently positive CSF cultures [101].

In the cases of neonates with bacteremia and CSF findings indicative of meningitis with negative CSF culture (obtained before or after antibiotic therapy), the antimicrobial therapy should be continued with meningeal doses as if they have proven bacterial meningitis [97, 106].

The role of routinely repeating CSF evaluation during treatment in a neonate with confirmed meningitis is controversial. Some experts recommended that an LP should be repeated routinely at 48–72 hours after initiation of appropriate antimicrobial therapy to document CSF sterilization, as persistence of positive cultures despite treatment may result in a greater risk of complications and poor outcomes [87, 107]. Gram-positive bacteria usually clear rapidly (within 24–48 hours) from the CSF, whereas Gram-negative bacteria may persist for several days in severe cases [18, 97]. A delayed clearance of a Gram-negative organism may be an indication for antimicrobial resistance and prompts a change in therapy or diagnostic neuroimaging showing a purulent focus of the disease such as an emphysema, obstructive ventriculitis, or brain abscess requiring additional intervention or increased duration of antimicrobial therapy [18, 97, 108]. Additionally, performing repeating LP is also reasonable for discontinuing combination therapy. Delayed sterilization of the CSF is associated with an increased risk of poor outcome [17, 87, 109]. So, a repeat LP may have therapeutic and prognostic significance. Conversely, some experts recommend a repeat LP only if the patient does not exhibit a satisfactory clinical response by 24–72 hours after initiation of antimicrobial therapy or show a complicated clinical course, including seizures, abnormal neuroimaging, or prolonged positive CSF cultures [4, 110]. The decision of whether to perform an LP before completion of therapy in the neonates with meningitis caused by GBS, *L. monocytogenes*, and Gram-negative bacteria can be based on clinical course including seizures, significant hypotension, prolonged positive CSF cultures, and abnormal neuroimaging [50].

Causative organism	Recommended therapy	Comment
Initial therapy, CSF abnormal but organism unknown	Ampicillin IV *and* gentamicin IV, IM *and* cefotaxime IV	Cefotaxime is added if meningitis is suspected or cannot be excluded. Alternatives to ampicillin in nursery-acquired infections: vancomycin or nafcillin. Alternatives to cefotaxime: ceftazidime, cefepime, or meropenem (limit use to multidrug-resistant organisms in nursery (e.g., extended-spectrum b-lactamase-producing organisms).
Bacteroides fragilis spp.	Metronidazole IV	Alternative: meropenem.
Coliform bacteria (*E coli*, *Klebsiella* sp., *Enterobacter* sp., *Citrobacter* sp., and *Serratia* sp.)	Cefotaxime IV, IM, *and* gentamicin	Discontinue gentamicin when clinical and microbiologic response is documented. Alternative: ampicillin if organism is susceptible; meropenem or cefepime for multiresistant organisms. Lumbar intrathecal or intraventricular gentamicin usually not beneficial.
Chryseobacterium meningosepticum	Vancomycin IV *and* rifampin IV, PO	Alternatives: clindamycin and ciprofloxacin
Group A *streptococcus*	Penicillin G *or* ampicillin IV	
Group B *streptococcus*	Ampicillin *or* penicillin G IV *and* gentamicin IV, IM	Discontinue gentamicin when clinical and microbiologic response is documented
Enterococcus spp.	Ampicillin IV, IM, *and* gentamicin IV, IM; for ampicillin-resistant organisms: vancomycin *and* gentamicin	Gentamicin only if synergy documented
Other streptococcal species	Penicillin *or* ampicillin IV, IM	
Gonococcal	Ceftriaxone IV, IM *or* cefotaxime IV, IM	Duration of therapy uncertain (5–10 days?)
Haemophilus influenzae	Cefotaxime IV, IM	Ampicillin if β-lactamase negative
Listeria monocytogenes	Ampicillin IV, IM, *and* gentamicin IV, IM	Gentamicin is synergistic in vitro with ampicillin but can be discontinued when sterilization is achieved
Staphylococcus epidermidis (or any coagulase-negative staphylococci)	Vancomycin IV	Add rifampin if cultures are persistently positive Alternative: linezolid
Staphylococcus aureus	MSSA: nafcillin IV; MRSA: vancomycin IV	Gentamicin may provide synergy; rifampin if cultures are persistently positive. Nafcillin is superior to vancomycin for treatment of methicillin-sensitive S aureus
Pseudomonas aeruginosa	Ceftazidime IV, IM *and* aminoglycoside IV, IM	Meropenem *or* cefepime are suitable alternatives
Ureaplasma spp.	Doxycycline IV *or* azithromycin IV	Alternatives: ciprofloxacin
Mycoplasma hominis	Clindamycin *or* doxycycline IV	Alternatives: ciprofloxacin

IM, intramuscularly; IV, intravenously; MSSA: methicillin-susceptible S. aureus; MRSA: methicillin-resistant S. aureus; PO, periorally.
†Adapted from Ref. [50].

Table 3.
Recommended antimicrobial treatment for neonatal bacterial meningitis.†

Antibiotic	Susceptible bacteria	Dose per kilogram		Comments
		Body weight ≤ 2000 g	Body weight > 2000 g	
Penicillin G	GBS	100,000 U ≤7d old, every 12 h 8–28 d old, every 8 h	100,000 U ≤7 d old, every 8 h 8–28 d old, every 6 h	Monotherapy acceptable if GBS is confirmed by culture and clinical improvement is observed
Ampicillin	GBS *L. monocytogenes* *Enterococcus* sp.	50 mg ≤7d old, every 12 h 8–28 d old, every 8 h	50 mg ≤7d old, every 12 h 8–28 d old, every 8 h	17–78% of *E. coli* isolates are resistant Poor CNS penetration
Gentamicin/ Amikacin	*E. coli* *Klebsiella* sp. *Enterobacter* sp. *Pseudomonas* sp. *Citrobacter* sp. *Serratia* sp.	5 mg/15 mg ≤7d old, every 48 h 8–28 d old, every 36 h	4 mg/15 mg ≤7d old, every 24 h 8–28 d old, every 24 h	Poor CNS penetration Synergistic effect with ampicillin in treatment of *L. monocytogenes* *Pseudomonas* sp. may require combination therapy with a second agent Require therapeutic drug monitoring
Cefotaxime	*E. coli* *Klebsiella* sp. *Enterobacter* sp. *Citrobacter* sp. *Serratia* sp.	50 mg ≤7d old, every 12 h 8–28 d old, every 8–12 h	50 mg ≤7d old, every 12 h 8–28 d old, every 8 h	Good CNS penetration Used instead of gentamicin in cases of suspected or confirmed meningitis Not active against *L. monocytogenes* or *Enterococcus* sp.
Meropenem	*E. coli* *Klebsiella* sp. *Enterobacter* sp. *Citrobacter* sp. *Serratia* sp. *Pseudomonas* sp.	40 mg ≤14 d old, every 12 h 14–28 d old, every 8 h	40 mg ≤14 d old, every 8 h 14–28 d old, every 8 h	Good CNS penetration Limit use to multidrug resistant organisms (e.g., extended-spectrum beta-lactamase-producing organisms)
Vancomycin	Coagulase-negative staphylococci *S. aureus* *Enterococcus* sp.	15 mg ≤7d old, every 24 h 8–28 d old, every 12 h	15 mg ≤7d old, every 12 h 8–28 d old, every 8 h	Variable CNS penetration Effective against methicillin-resistant *S. aureus* Requires therapeutic drug monitoring
Nafcillin	Methicillin-sensitive *S. aureus*	50 mg ≤7d old, every 12 h 8–28 d old, every 8 h	50 mg ≤7d old, every 8 h 8–28 d old, every 6 h	Good CNS penetration Superior to vancomycin for treatment of methicillin-sensitive *S. aureus*

GBS, group B streptococcus; CNS, central nervous system; g, gram; d, day.
†Adapted from Refs. [4, 87, 97, 102, 103].

Table 4.
Dosage of antibacterial drugs commonly used to treat neonatal meningitis.†

12. Neuroimaging

Neuroimaging is recommended to assist in defining the potential complications of neonatal meningitis [50, 87]. Ultrasonography, which is a safe, convenient, and noninvasive method, can be done at bedside early in the course of the disease. It provides rapid and reliable information regarding ventricular size, the presence of hemorrhage, and development of hydrocephalus [111, 112]. It is also useful to detect periventricular white matter injury which may initially be manifested by increased periventricular echogenicity and later by cystic periventricular leukomalacia, ventriculitis, echogenic sulci, and extracerebral fluid collections [113, 114]. Computed tomography is rapid and easy imaging modality, but carries the risk of neonatal brain to radiation. It is useful to provide information on whether the course of meningitis has been complicated by hydrocephalus, brain abscess, or subdural collection. These findings may have a role in decision-making for potential neurosurgical interventions or duration of antimicrobial therapy [28, 87]. Magnetic resonance imaging (MRI) is the best currently available modality for evaluation of the neonatal brain [115]. It provides information on the status of white matter, cortex, subdural and epidural spaces, and even the posterior fossa, when performed either early or late in the course of the disease. It is useful to document the distribution pattern, severity, and complications of the disease [115, 116]. It has also been used in providing the best prognostic information [28]. For these reasons, it is recommended that at least one brain MRI should be performed on every case of neonatal meningitis, especially those caused by organisms that have a propensity for formation of intracranial abscesses [17, 28, 87]. Ideally in all cases, MRI scans must include pre-contrast and post-contrast-enhanced T1-weighted and T2-weighted images in at least two perpendicular planes. Fluid attenuated inversion recovery (FLAIR) sequence and diffusion weighted imaging (DWI) are preferred whenever purulent collections are suspected because of their high sensitivity in showing pus accumulation [115].

13. Adjunctive therapy

Bacterial meningitis in the newborn infant is characterized by high risk of mortality and serious neurological sequelae among most survivors. It is believed that most sequelae occur as a result of neural injury during the acute inflammatory process that characterizes bacterial meningitis. Given that corticosteroids may help attenuate the acute inflammatory process, adjuvant corticosteroid treatment in children with bacterial meningitis may reduce mortality in *S pneumoniae* meningitis but not in *H. influenzae* nor *N. meningitidis* meningitis, and severe hearing loss among children with *H. influenza* meningitis but not among those with meningitis due to non-Haemophilus species [117]. Additionally, these beneficial effects of corticosteroids have been reported in the reports from high-income countries, but not in those from low-income countries, probably due to the types of pathogens prevalent in the developing world, delay in the initiation of appropriate antibiotic treatment, partial treatment involving indiscriminate antibiotic use outside of hospitals, or lack of facilities [7]. A few studies suggest that some reduction in death and hearing loss is evident when adjunctive steroids are used in the treatment of neonatal meningitis, but experimental animal studies reported that adjunctive treatment with corticosteroid is associated with an increase in hippocampal neuronal apoptosis [118]. In conclusion, it should not be used routinely in the treatment of neonatal meningitis due to limited data [119].

Similarly, the limited studies showed that glycerol, when used as osmotic therapy, may reduce neurological deficiency and deafness in adults and children with acute bacterial meningitis [120], but it is not currently recommended in neonates with bacterial meningitis [4].

14. Complications

Short-term neurological complication of neonatal bacterial meningitis includes cerebral edema, increased intracranial pressure, ventriculitis, cerebritis, hydrocephalus, brain abscess, cerebrovascular disease including ischemic arterial stroke and cerebral venous thrombosis, and subdural effusion or empyema [18, 121]. Cerebral edema results from vasogenic changes, cytotoxic cell injury, and occasionally inappropriate antidiuretic hormone secretion [28]. Ventriculitis, which occurs in about 20% of neonates with meningitis caused by Gram-negative organisms, is a result of bacterial entry into the CNS through the choroid plexus [28, 121, 122]. Inflammatory exudate covers the epidermal lining and the choroid plexus, disrupts ependymal lining, and causes subependymal venous thrombosis and eventually necrosis [28]. It is usually associated with obstruction of CSF outflow [121]. Cerebritis results from extension of exudate along perivascular space [18, 28]. Hydrocephalus, which occurs in approximately one-quarter of neonates with meningitis, develops as a result of fibrous inflammatory exudate obstructing CSF flow through the ventricular system or dysfunction of arachnoid villi [18, 28, 122, 123]. Cerebral infarction occurs in approximately 30% of neonates with meningitis and is frequently hemorrhagic [28, 124]. The mechanisms leading to cerebrovascular complications in bacterial meningitis are not completely understood and likely are multifactorial [15, 62]. Brain abscesses, which occur in approximately 10 percent of patients with neonatal meningitis, may result from a hematogenous spread of microorganism into infarcted brain, or by local spread [28, 121]. Subdural effusions occur in approximately 11% of neonates with meningitis and rarely cause clinically significant finding and lead to empyema. [28, 121].

Neonates with bacterial meningitis should be monitored for signs of these complications throughout their treatment. It must be suspected when there is a failure to respond clinically and microbiologically to appropriate antimicrobial therapy, or a focal neurologic deficit, or new-onset seizures, especially focal seizures, or when there are signs of increased intracranial pressure such as bulging fontanelle, accelerated head growth, bradycardia, hypertension, and separation of the cranial sutures [18, 121]. Acute deterioration in an otherwise stable neonate with meningitis can occur if the abscess ruptures into ventricular system or subarachnoid space [28, 121]. In case of suspicion regarding these complications, additional evaluation including neuroimaging studies, neurosurgical consultation, and prolonged duration of antimicrobial treatment may be required.

15. Outcome

In developed countries, the rate of mortality from bacterial meningitis among neonates has declined substantially from nearly 50% in the 1970s to figures currently ranging from 10 to 15% [4, 5, 26–29]. In developing countries, the mortality rate is much higher at 40–58% [7]. Mortality is higher among preterm infants, in cases with meningitis caused by microorganism that causes vasculitis and brain abscess and in late-onset cases [26–29]. Risk factors involved in higher mortality rate and severe disability are low birth weight or prematurity, history of symptoms

for >24 hours before admission, leukopenia (<5000/mm^3) and neutropenia (<1000/mm^3), seizures lasting longer than 72 hours, coma, focal neurologic deficits, ventilator support, the need for inotropes, higher CSF protein level, and delayed sterilization of the CSF [4, 5, 24, 26–29, 109, 121–125].

Long-term complications in survivors are mental and motor disabilities including mental retardation, learning disabilities, cerebral palsy, and behavioral problems, seizures, hydrocephalus, language disorders, hearing loss, and impaired visual acuity [4, 5, 14, 27]. Approximately 20% of survivors have severe disability and another 35% have mild to moderate disability [4, 5, 122]. Neonatal meningitis caused by *S. pneumoniae* and Gram-negative bacteria carries a worse prognosis [24, 50, 122, 126]. All infants experienced with bacterial meningitis should be followed long-term for development of neurological sequelae.

16. Prevention

Intrapartum antibiotic prophylaxis for GBS colonized women or based on the presence of clinical risk factors is efficacious against early onset GBS disease but has no impact on late-onset disease, when most GBS meningitis occurs [5, 127]. The incidence of late-onset GBS disease remains unaffected by IAP use [33, 35]. Vaccines against GBS can reduce the number of missed opportunities due to various reasons. So, maternal immunity to the most common serotypes of GBS (serotypes Ia, Ib, and III) can be transferred passively to the fetus and protect against invasive infection in infancy due to covered serotypes [128]. Clinical trials of a trivalent GBS vaccine are encouraging in this regard. In the case of pneumococcal meningitis, the 10- and 13-valent conjugate vaccines may be protective for infants aged <3 months [5].

The prevention of the spread of the pathogens responsible for neonatal sepsis and meningitis also has an impact on disease burden [6]. Several interventions, which can be introduced at the community level, with prevention strategies applied during the antenatal, intrapartum, and early neonatal period, will reduce the number of early-onset diseases [16, 129]. Prevention of nosocomial infections is based on strategies that aim to limit susceptibility to infections by enhancing host defenses, interrupting transmission of organisms by healthcare workers, and by promoting the judicious use of antimicrobials [130].

17. Summary

Bacterial meningitis is associated with significant morbidity and mortality in the neonatal population. Although overall incidence and mortality have declined over the last several decades, morbidity associated with neonatal meningitis remains unchanged. Prompt diagnosis and treatment are mandatory to improve both short- and long-term outcomes. CSF culture obtained via LP is the gold-standard method for the diagnosis of meningitis, which is the key to rapid institution of effective antimicrobial therapy. Prevention strategies, adjunctive therapies, improved diagnostic strategies, and development of vaccines may further reduce the burden of this devastating disease.

Conflict of interest

The author declares no conflicts of interest.

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