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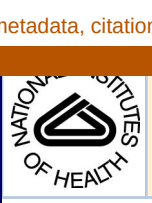

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Bacterial Meningitis in the Infant

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SYNOPSIS

Neonatal bacterial meningitis is an uncommon but devastating infection. Although the incidence and mortality have declined over the last several decades, morbidity among survivors remains high. The types and distribution of causative pathogens are related to birth gestational age, postnatal age, and geographic region. Confirming the diagnosis of meningitis can be difficult. Clinical signs are often subtle, and the lumbar puncture is frequently deferred in clinically unstable infants. When obtained, confirmatory testing with cerebrospinal fluid (CSF) culture is often compromised by antepartum or postnatal antibiotic exposure. While blood cultures and CSF parameters may be helpful in cases where the diagnosis is uncertain, bacterial meningitis occurs in infants without bacteremia and with normal CSF parameters. Newer tests such as the polymerase chain reaction are promising but require further study. Prompt treatment with appropriate antibiotics is essential to optimize outcomes. Successful efforts to prevent meningitis in infants have included the use of intrapartum antibiotic prophylaxis against Group B *Streptococcus* (GBS). Clinical trials investigating the use of a GBS vaccine for the prevention of neonatal GBS disease are ongoing.

Keywords

Neonatal bacterial meningitis; Very low birth weight; Lumbar puncture; Cerebrospinal fluid; Antibiotics; Vaccine

INTRODUCTION

Bacterial meningitis is a devastating infection associated with high mortality and morbidity in the neonatal population. Prompt diagnosis and treatment are essential to achieving good

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outcomes in affected infants. While overall incidence and mortality have declined over the last several decades, morbidity associated with neonatal meningitis remains virtually unchanged.[1, 2] Prevention strategies, adjunctive therapies, and improved diagnostic strategies have been the focus of recent research seeking to improve the outcomes.[3]

DESCRIPTION OF THE DISEASE

Meningitis is the acute inflammation of the meninges, subarachnoid space, and brain vasculature resulting from infection.[4] Neonatal meningitis is categorized as early and late onset, which is defined by the presence of signs of infection and organism isolation from cerebrospinal fluid (CSF) cultures at ≤72 hours and >72 hours of life, respectively.[3, 5–7]

EPIDEMIOLOGY

The incidence of neonatal meningitis varies by geographic location (Figure 1).[8–10] Compared with older age groups, the incidence of meningitis is highest during the neonatal period.[9, 16]

Developed Countries

The incidence of culture-proven neonatal meningitis is estimated at 0.3 per 1000 live births in developed countries. [2, 10, 16] This is likely an underestimation of the true incidence, however. For infants in the intensive care nursery who are evaluated for sepsis, 30–50% do not have a lumbar puncture (LP) performed.[6, 17] When an LP is performed, more than 75% of the time it occurs after the initiation of antibiotics, possibly biasing CSF culture results.[6, 17, 18].

In developed countries, mortality from neonatal meningitis ranges from 10–15%.[2, 8] In a prospective study including 444 cases of confirmed meningitis from 2001–2007, mortality in premature infants compared with term infants was >2-fold higher (26% vs. 10%, $p < 0.01$).[8] Up to 50% of infants with a history of meningitis will be neurologically impaired, with 25% having severe disability.[2, 8, 19] With advances in medical practices, the incidence and mortality associated with meningitis have declined over the past 40 years; however, morbidity remains unchanged.[19]

Developing Countries

In developing countries, the reported incidence of neonatal meningitis is much higher at 0.8–6.1 per 1000 live births, with a mortality of 40–58%.[9, 11] True values may actually be higher because of underreporting in regions with limited resources, diagnostic testing, and access to health care.[9]

ETIOLOGY

The types and distribution of organisms commonly observed in neonatal meningitis depend on postnatal age, location, and gestational age. The distribution of organisms seen in neonatal meningitis is similar to neonatal sepsis (Table 1.).[1, 6, 16]

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Early-Onset Meningitis

Despite the institution of maternal intrapartum prophylaxis, Group B *Streptococcus* (GBS) has remained the most common cause of neonatal sepsis and meningitis since the early 1980s, responsible for >40% of all early-onset infections.[2, 6, 20] *Escherichia coli* (*E. coli*) is the second most common pathogen and is isolated in 30% of all early-onset infections.[6] Since the 1990s, *E. coli* has emerged as the most common cause of early-onset sepsis and meningitis among very low birth weight (VLBW, <1500 g birth weight) infants.[21–24]

Late-Onset Meningitis

Late-onset meningitis is predominantly seen in premature infants, and the incidence is directly related to decreasing birth gestational age and weight.[25] Surveillance of 6956 VLBW infants from 1998–2000 found coagulase-negative staphylococci (48%) and *Staphylococcus aureus* (8%) to be the first and second most common pathogens, respectively.[7] *E. coli* (5%) and *Klebsiella* (4%) spp. were the most common gram-negative causes of late-onset infections.[5, 7] Although GBS (2%) was less common in this cohort, other studies found that infants were more likely to have confirmed meningitis with late-onset GBS sepsis compared with early-onset GBS sepsis (Table 2).[7, 26, 27]

PATHOGENESIS

While several mechanisms in the development of neonatal meningitis have been described, primary bloodstream infection with secondary hematogenous distribution to the central nervous system (CNS) is the most common (Box 1).[16] For this reason, the epidemiology and microbiology of neonatal meningitis is similar to neonatal sepsis.[1]

Early-Onset Infection

Organisms present in the maternal genitourinary tract ascend from the vagina and can infect the amniotic fluid through disruptions in the amniotic membranes, which the infant then aspirates.[28] Organisms can also colonize exposed neonatal skin and mucosa during passage through the birth canal and invade through barrier disruptions.[1] Organisms such as *Listeria monocytogenes* can also be transmitted transplacentally.[16] In rare cases, hematogenous transmission of GBS from maternal bacteremia has been reported as a cause of early-onset GBS infections in infants.[29]

Late-Onset Infection

Organisms can be acquired from the colonized mother, as seen with GBS.[30, 31] Poor hand hygiene among caregivers and hospital staff can result in the transfer of organisms between infected and uninfected infants.[32] Foreign, invasive devices such as ventricular reservoirs, ventricular shunts, endotracheal tubes, venous or arterial catheters, urinary catheters, and feeding tubes can also introduce pathogens to the infant.[16]. Exposure to prolonged courses of empirical antibiotics for suspected infections can also result in increased risk for late-onset infections.[33] Among 365 VLBW infants ≤32 weeks gestational age, infants exposed to empirical antibiotics ≥5 days had increased odds of developing late-onset sepsis (OR, 2.45 [95% CI, 1.28–4.67]).[34]

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Infection of the CNS

After attaching to the endothelium of the cerebral microvasculature and choroid plexus, bacteria can enter the CSF by several mechanisms (Box 2).[1, 4, 35] Inflammatory mediators are then released into the CSF in response to the presence of bacterial products, resulting in meningitis and increased permeability of the blood-brain barrier.[1, 31]

RISK FACTORS

Risk factors for the development of neonatal meningitis are similar to neonatal sepsis (Box 3).[5, 10, 36] Immaturity of the neonatal immune system, impaired phagocytic ability of neutrophils and monocytes, and diminishing maternal antibodies all contribute to increased risk of infections in both term and preterm infants.[4, 24] Because most maternal immunoglobulins do not cross the placenta before 32 weeks gestation, infants born extremely preterm are at significantly higher risk for infections.[10] Early initiation of breastfeeding may be protective against infections, however, due to transfer of immunoglobulin A.[37]

CLINICAL PRESENTATION

The clinical signs of neonatal meningitis can be subtle and nonspecific (Box 4).[16, 19, 38] Meningitic signs such as convulsions, irritability, bulging fontanel, and nuchal rigidity are often late findings that are associated with poor outcomes.[2, 10, 38]

Exposure to intrapartum antibiotic prophylaxis (IAP) against GBS has led to concerns that the signs of neonatal infections could be delayed or masked. Several studies have determined no significant difference in the clinical presentation of early-onset GBS disease between infected infants with and without prior exposure to IAP.[20] Signs of early-onset sepsis manifested in 90% of infected infants within the first 24 hours of life.[20]

DIAGNOSIS

To confirm the diagnosis of neonatal meningitis, an LP is needed to collect CSF. Positive growth on the CSF culture provides identification of the offending organism and enables refinement of therapy.[2, 39] The LP is frequently deferred during the septic workup due to concerns of exacerbating clinical deterioration in the sick infant.[39–41]

Performing or Deferring the LP

Because the LP is an invasive procedure with risks, it is difficult to determine which infant should receive one as part of the septic workup.[40, 41] Among infants with positive blood cultures, up to 30% will have a concurrent positive CSF culture.[42] However, in infants with confirmed meningitis, 15–38% will have a negative blood culture.[27, 43–45] In rare cases, the blood and CSF cultures can be discordant.[44] Approaches in which only infants with confirmed bacteremia are evaluated for meningitis will result in missed diagnoses of meningitis.

The incidence of meningitis among asymptomatic infants with risk factors is very low (<1%).[46, 47] When clinical signs can be attributed to noninfectious causes, such as

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respiratory distress syndrome or transient tachypnea of the newborn, clinical judgment is required in deciding when to perform an LP.[43] Among 238 infants admitted for respiratory distress without other symptoms, 17/238 (7%) infants had a positive blood culture, and none were found to have meningitis.[48]

The current recommendation is to perform an LP on all clinically stable infants suspected to have early- or late-onset sepsis and who are exhibiting signs of infection.[20, 39, 43] Whenever possible, the LP should be performed prior to the administration of antibiotics.

Interpreting CSF Parameters

Infants are often exposed to intrapartum or empiric antibiotics prior to receiving an LP, which can result in falsely negative CSF cultures in those with meningitis.[18] In these cases, CSF parameters are used to help determine the likelihood of meningitis.

CSF indexes vary according to age, with normal values in infants poorly defined.[16, 44, 45] Common practice states that a CSF leukocyte count ≥20/mm^3 is suggestive of bacterial meningitis in the infant.[16] A study involving 1064 infants demonstrated that infants <28 days old without bacterial meningitis had a median CSF leukocyte count of 3/mm^3 and 95th percentile value of 19/mm^3.[49] However, in a study evaluating 9111 infants ≥34 weeks gestational age, the use of 20/mm^3 as a cutoff resulted in a missed diagnosis in 13% of infants with confirmed meningitis.[44] Several infants with confirmed meningitis had normal CSF parameters without bacteremia. CSF protein and glucose were considered poor predictors of meningitis due to considerable overlap of values between infants with and without confirmed meningitis. A study of 4632 infants <34 weeks gestational age reached similar conclusions in the preterm population.[45] There is great difficulty in predicting the diagnosis of meningitis solely based on CSF parameters, suggesting that CSF culture continues to be the gold standard for diagnosis.

Ancillary Tests

The polymerase chain reaction (PCR) has been explored as a diagnostic tool for meningitis. In addition to improved sensitivity and specificity, PCR also allows quicker detection of pathogens compared with traditional cultures.[50] A real-time PCR assay designed to detect multiple pathogens including *Streptococcus pneumonia*, *E. coli*, GBS, *S. aureus*, and *L. monocytogenes* had an overall higher detection rate of any CSF pathogen compared with traditional cultures (72% vs. 48%).[51] Among patients exposed to antibiotics before collection of CSF, PCR had a higher detection rate compared with culturing (58% vs. 29%).[51] Further testing is needed before PCR can be used routinely in the diagnosis of bacterial meningitis.[52]

Other tests used to aid in clinical decision-making include the complete blood count with differential and C-reactive protein. Studies examining the usefulness of these tests in the diagnosis of neonatal bacterial meningitis are limited (Table 3).

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Repeating the LP

The need for a repeat LP during treatment in an infant with confirmed meningitis has been debated. Some experts recommend routinely repeating an LP in all patients at 48 hours, whereas others suggest repeating an LP only if clinical conditions are not improved by 24–72 hours after beginning therapy.[56–59]

In a retrospective study of 14,018 infants, 221 infants were identified as having culture-positive meningitis, with 118 infants (53%) receiving ≥2 LPs during the treatment course.[56] Among infants with available mortality data receiving ≥2 LPs, 6/23 (26%) infants with repeat positive cultures died compared with 6/81 (7%) infants with repeat negative cultures (p=0.02). No significant difference in mortality was seen among the 81 (7%) infants with a repeat negative culture compared with the 90 (12%) infants with meningitis with no repeat LP (p=0.32). A survey of 109 pediatricians and neonatologists across northwest England found that 89 (82%) practitioners did not routinely repeat the LP in infants with bacterial meningitis unless clinically indicated.[57]

TREATMENT

Antimicrobial Therapy

Prompt initiation of antibiotics is critical. Delays in treatment are associated with increased mortality and morbidity.[60] Empiric antimicrobials used in suspected meningitis require adequate CSF penetration and sensitivity against the most probable pathogens.[10, 60] Upon identification of the pathogen and its susceptibilities, antimicrobial coverage should be adjusted accordingly (Table 4).

Duration of Antimicrobial Therapy

For uncomplicated meningitis, the minimum recommended treatment durations are the following:[10, 61, 64]

- 14 days for GBS, *L. monocytogenes*, and *S. pneumonia*
- 21 days for *Pseudomonas* and gram-negative enteric bacteria such as *E. coli*

Longer treatment courses are recommended for infants with meningitis with delayed clinical improvement after beginning therapy or with complications such as brain abscesses, ventriculitis, or brain infarctions.[62]

Adjunctive Therapy

In an effort to improve outcomes in infants with meningitis, several adjunctive therapies have been explored, including the use of intraventricular antibiotics, dexamethasone, intravenous immunoglobulins, granulocyte or granulocyte macrophage colony stimulating factor, and oral glycerol.[2] At present, none of the proposed adjunctive therapies are used in routine practice.

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LONG-TERM OUTCOMES

Survivors of neonatal meningitis are at considerable risk for long-term neurologic impairment.[68, 69] A prospective study that followed 1717 survivors of neonatal meningitis through 5 years of age found that those who had neonatal meningitis were 10 times more likely to have moderate or severe disability than children who never had meningitis.[68] Certain characteristics can help identify infected infants at the highest risk for a poor outcome (Box 5).[70, 71]

PREVENTING NEONATAL MENINGITIS

Intrapartum Antibiotic Prophylaxis

Since the adoption of IAP use in 1996 and universal antenatal screening for GBS colonization in 2002, the incidence of early-onset GBS infections has decreased significantly from 1.8 cases per 1000 live births in 1990 to 0.26 cases per 1000 live births in 2010.[72] The incidence of late-onset GBS disease remains unaffected by IAP use.[30, 72]

IAP use has also been implicated in the increased proportion of non-GBS early-onset infections seen in VLBW infants. Since the late 1990s, *E. coli* has surpassed GBS as the predominant pathogen observed in early-onset infections among VLBW infants.[6, 21–23] This likely reflects the success of IAP in reducing the incidence of early-onset GBS infections rather than an increase in the incidence of non-GBS infections.[73] This change in proportion of non-GBS early-onset infections has not been observed in term infants.[6]

Reports from single-center studies have associated frequent use of ampicillin for IAP with an increase in ampicillin-resistant *E. coli* infections, particularly in premature infants.[22, 74] However, rates of ampicillin-resistant *E. coli* have also increased in the general community.[20] Furthermore, a multicenter trial involving 389 infants with confirmed early-onset sepsis found that, when comparing infants exposed and not exposed to IAP, frequencies of ampicillin-resistant *E. coli* infections were not significantly different.[6] Although GBS has become increasingly resistant to clindamycin and erythromycin, sensitivity to ampicillin remains unchanged.[75].

GBS Vaccine

Vaccines against GBS can reduce the number of missed opportunities for screening and IAP administration due to false-negative screens, precipitous deliveries, or extremely preterm births.[6, 72] Maternal immunity to the most common serotypes of GBS can be transferred passively to the infant and protect against early- and late-onset infections.[76] A trivalent GBS vaccine has shown promise in phase I and II trials, with another phase II trial currently recruiting participants (Table 5).[76]

SUMMARY

Neonatal meningitis is a devastating disease that requires a high index of suspicion, prompt diagnosis, and rapid treatment. While the incidence and mortality have declined with improved neonatal intensive care practices and universal adoption of preventative screening

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and prophylaxis programs, the associated morbidity remains unchanged. Performing an LP to collect CSF is critical to confirming the diagnosis, determining the causative pathogen, and refining antimicrobial therapy. Through better diagnostic practices and development of vaccines, there is great hope that we may further reduce the burden of this devastating disease.

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Mechanisms for Development of Neonatal Meningitis

1	Primary bloodstream infection with secondary hematogenous spread to CNS
2	Presence of an infectious foci with secondary bloodstream infection and hematogenous spread (e.g., osteomyelitis)
3	Presence of an infectious foci with direct extension into the CNS (e.g., sinus infection)
4	Primary CNS infection resulting from disruptions due to head trauma, neurosurgery, or congenital defects (e.g., myelomeningocele)

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Bacterial Mechanisms for Entry into the Cerebrospinal Fluid

1	Transcellular movement across the endothelial cell (e.g., GBS, *Escherichia coli*)
2	Paracellular movement by disruption of intercellular tight junctions
3	Transport across the blood-brain barrier and blood-CSF barriers within phagocytes (e.g., *Listeria monocytogenes*)

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Risk Factors for Neonatal Meningitis

1	Prematurity
2	Maternal rectovaginal GBS colonization
3	Chorioamnionitis or maternal fever
4	Premature rupture of membranes
5	Prolonged rupture of membranes >18 hours
6	Invasive fetal monitoring
7	Very low birth weight (<1500 g)
8	Prolonged hospitalization
9	Presence of external devices (e.g., reservoirs, shunts, catheters)

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Clinical Signs of Neonatal Meningitis

1	Fever or hypothermia
2	Irritability or lethargy
3	Hypotonia
4	Feeding intolerance or vomiting
5	Respiratory distress
6	Apnea
7	Bradycardia
8	Hypotension
9	Poor perfusion
10	Seizures
11	Bulging anterior fontanel
12	Nuchal rigidity
13	Jaundice
14	Hypo- or hyperglycemia
15	Diarrhea

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Predictors of Poor Neurologic Outcomes in Survivors of Bacterial Meningitis

1	Seizures lasting >72 hours
2	Presence of coma
3	Hypotension requiring inotropic support
4	White blood cell count ≤5000 x 10^9/L
5	Abnormal electroencephalogram findings

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KEY POINTS

- Neonatal bacterial meningitis is uncommon but associated with high mortality and morbidity.
- Group B *Streptococcus* (GBS) is the most common cause of neonatal meningitis.
- *Escherichia coli* has recently become the most common pathogen isolated from very-low-birth-weight infants with meningitis.
- Infants with culture-proven meningitis can have negative blood cultures and normal cerebrospinal fluid parameters.
- All infants exhibiting signs of infection and with suspected early- or late-onset sepsis should undergo a lumbar puncture.
- A GBS vaccine for the prevention of neonatal GBS disease including meningitis is currently under development.

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Best Practices Box

What is the current practice?

Neonatal Bacterial Meningitis

Best Practice/Guideline/Care Path Objective(s)

- Promptly diagnose with performance of lumbar puncture
- Begin antibiotics without delay
- Reduce mortality and prevent long-term neurodevelopmental impairment

What changes in current practice are likely to improve outcomes?

- Collection of CSF in all stable, symptomatic infants suspected of early- or late-onset infections with additional signs beyond respiratory distress
- Increased vigilance in identifying and treating mothers with GBS colonization
- Introduction of an effective GBS vaccine in the prevention of neonatal GBS disease

Is there a clinical algorithm?

Major Recommendations

- Perform a lumbar puncture on all clinically stable infants with suspected sepsis and meningitis (Grade 1B)
- Begin empiric antibiotics in all cases of suspected sepsis and meningitis (Grade 1A)
    - For suspected early-onset meningitis, consider ampicillin and gentamicin or cefotaxime in infants
    - For suspected late-onset meningitis, consider vancomycin in addition to ampicillin and gentamicin or cefotaxime
- Repeat the lumbar puncture in infants who fail to demonstrate clinical improvement 24–48 hours after initiation of antibiotics (Grade 1B)
- Repeat lumbar punctures are unnecessary in infants who demonstrate rapid clinical improvement after initiation of antibiotics and at end of successful therapy (Grade 1B)
- All infants with a history of bacterial meningitis should be followed long-term for development of neurological sequelae (Grade 1A)

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Summary statement

A high-index of suspicion, prompt diagnosis, and rapid initiation of antibiotics are essential to reducing mortality and morbidity associated with neonatal bacterial meningitis.

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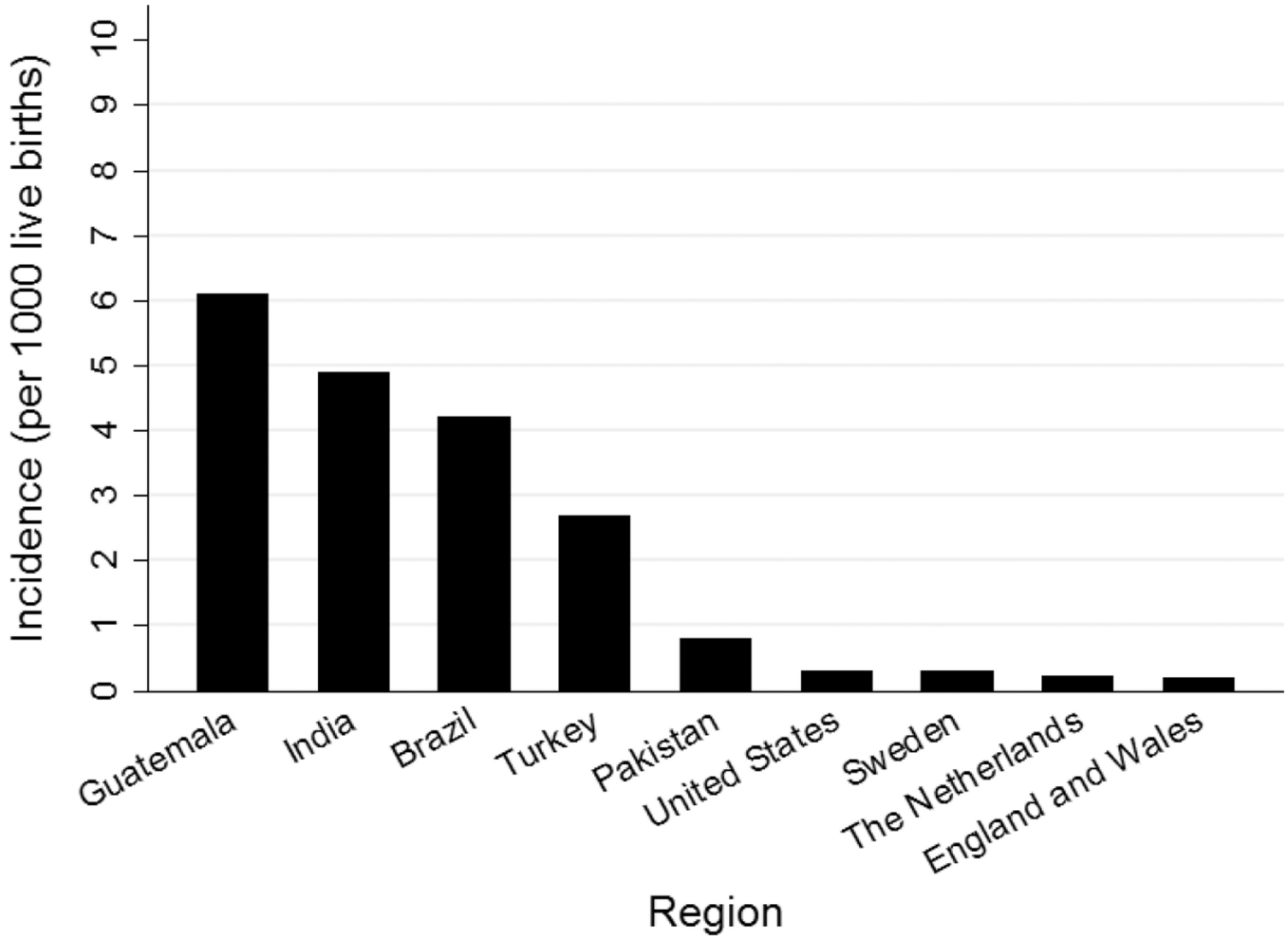

Figure 1.
Incidence of neonatal meningitis across the world. Data from references 2, 11–15.

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Table 1

Common pathogens of meningitis and commonly used empiric antibiotics

Type	Major Pathogens	Empiric Antibiotics
Early-onset	Group B *Streptococcus*	Ampicillin
	E. coli	Gentamicin
	L. monocytogenes	Cefotaxime
	S. pneumoniae	
Late-onset	Coagulase-negative *Staphylococcus*	Vancomycin
	S. aureus	Gentamicin
	E. coli	Cefotaxime
	Klebsiella sp.	Ampicillin
	Enterococcus sp.	
	Enterobacter sp.	
	Pseudomonas sp.	
	Group B *Streptococcus*	

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Table 2

Infants with late-onset vs. early-onset group B *Streptococcus* (GBS) sepsis complicated by meningitis

N (ref)	Years	Study Population	Proportion of Infants with Late-Onset GBS Sepsis Complicated by Meningitis, n (%)	Proportion of Infants with Early-Onset GBS Sepsis Complicated by Meningitis, n (%)	*P*
347 (26)	2001–2003	23–43 weeks GA ≤90 days PNA Confirmed GBS sepsis	84/136 (62)	33/206 (16)	<0.001
179 (27)	1997–2004	31–40 weeks GA Confirmed GBS sepsis	13/24 (54)	22/155 (14)	<0.01

GA, gestational age; PNA, postnatal age.

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Table 3

Available studies on biomarkers for neonatal meningitis

Biomarker	N (ref)	Study Population	Notable Findings
Complete blood count differential ratio $\left(\frac{\%lymphocytes+\%monocytes}{\%polymorphonuclear\ leukocytes+\%band\ forms}\right)$	72 (53)	Term <4 weeks PNA	Complete blood count differential ratio <1.5 as cutoff for predicting bacterial meningitis, test achieved the following: sensitivity=100% specificity=67% positive predictive value=47% negative predictive value=100%
	40 (54)	Term <28 days PNA	Used same cutoff values as above study on different cohort achieved the following: sensitivity=70% specificity=54% positive predictive value=39% negative predictive value=81%
Peripheral white blood cell count	8312 (44)	≥34 weeks GA 0–150 days PNA	Use as predictor for bacterial meningitis had positive likelihood ratio <1.0 Neither sensitive nor specific
C-reactive protein, cerebrospinal fluid	23 (55)	28–41 weeks GA 0–6 weeks PNA	1/7 infants without infection, 0/5 infants with sepsis without meningitis, and 2/11 infants with meningitis had C-reactive protein >1 mg/dl Levels do not distinguish between infants with meningitis from those with no confirmed infection

GA, gestational age; PNA, postnatal age.

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Table 4

Common antibiotics used to treat neonatal meningitis

Antibiotic (ref)	Susceptible Bacteria	Notes
Penicillin G (61)	GBS	Monotherapy acceptable if GBS confirmed by culture and clinical improvement is observed
Ampicillin (2, 6, 62, 63)	GBS *L. monocytogenes Enterococcus* sp.	17–78% of *E. coli* isolates resistant Poor CNS penetration Requires higher doses for meningitis
Gentamicin (2, 62, 64)	*E. coli Klebsiella* sp. *Enterobacter* sp. *Pseudomonas* sp. *Citrobacter* sp. *Serratia* sp.	Poor CNS penetration Synergistic effect with ampicillin in treatment of *L. monocytogenes* *Pseudomonas* sp. may require combination therapy with a second agent Requires therapeutic drug monitoring
Cefotaxime (24, 62, 64)	*E. coli Klebsiella* sp. *Enterobacter* sp. *Citrobacter* sp. *Serratia* sp.	Good CNS penetration Used instead of gentamicin in cases of suspected or confirmed meningitis Not active against *L. monocytogenes* or *Enterococcus* sp.
Meropenem (64, 65)	*E. coli Klebsiella* sp. *Enterobacter* sp. *Citrobacter* sp. *Serratia* sp. *Pseudomonas* sp.	Good CNS penetration Limit use to multidrug resistant organisms (e.g., extended-spectrum beta-lactamase-producing organisms)
Vancomycin (62, 66)	Coagulase-negative staphylococci *S. aureus Enterococcus* sp.	Variable CNS penetration Effective against methicillin-resistant *S. aureus* Requires therapeutic drug monitoring
Nafcillin (66, 67)	Methicillin-sensitive *S. aureus*	Good CNS penetration Superior to vancomycin for treatment of methicillin-sensitive *S. aureus*

GA, gestational age (weeks); PNA, postnatal age (days); SCr, serum creatinine (mg/dL).

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Table 5

Group B *Streptococcus* (GBS) vaccine clinical trials

ClinicalTrials.gov Identifier (ref)	Phase	Objectives	Vaccine	Subjects	N	Design	Study Period
NCT00645346 (77)	I	Safety, tolerability, and immunogenicity	GBS glycoconjugate	Healthy non-pregnant women ages 18–40 years	130	Randomized, single-center, single-blind, placebo-controlled	2008–2009
NCT01193920 (78)	Ib/II	Safety and immunogenicity	Trivalent GBS	Healthy non-pregnant and pregnant women ages 18–40 years	380	Randomized, single-center, single-blind, placebo-controlled	2010–2012
NCT01446289 (79)	II	Immune response; amount of vaccine-induced antibody transferred to infant	Trivalent GBS	Healthy pregnant women ages 18–40 years	86	Randomized, multicenter, single-blind, placebo-controlled	2011–2013
NCT02046148 (80)	II	Safety and immunogenicity; placental transfer of GBS antibodies; levels of GBS antibodies in infants; levels of GBS antibodies in breast milk	Trivalent GBS	Healthy pregnant women ages 18–40 years	75	Randomized, multicenter, double-blind, placebo-controlled	2014–2015