Chapter 6

Neonatal Meningitis

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Abstract

Neonatal meningitis continues to be a problematic issue of neonatology and pediatric infectious diseases with its incidence of 0.8–6.1 in 1000 live births, high case fatality rate, and neurological sequelae. Major risk factors for contracting meningitis in the newborn period include maternal peripartum infection, premature rupture of membranes, premature birth, fetal hypoxia, septic or traumatic birth, low birth weight, and galactosemia. The leading causative agent is group B streptococci (in almost half of the cases), and a quarter of cases are due to *Escherichia coli*. Vertical transmission from the mother is often the route of infection. Neonatal meningitis may not be distinguishable clinically from neonatal sepsis without meningitis. Meticulous care should be taken to perform lumbar puncture whenever the patient's status permits since it is an indispensable tool for diagnosis. Initial empirical therapy may consist of ampicillin and cefotaxime, ampicillin and gentamicin, or ampicillin + gentamicin + cefotaxime during the first week of life. Ampicillin + gentamicin + cefotaxime for nonhospitalized infants and the same combination with the replacement of ampicillin with vancomycin for infants still in hospital are suitable options after the first week.

Keywords: infants, neonate, newborns, lumbar puncture, spinal tap, meningitis

Core tips: The incidence of meningitis in newborn period is so high that is incomparable to any other period in human life. The case fatality rate varies between 13 and 59% with respect to country of origin. Neurological sequelae, primarily hearing loss, continue to be an important issue with rates of 20–58% in neonates who manage to survive this relentless disease. Enteroviruses and *Enterobacter sakazakii*, which has been detected to contaminate infant formula, are emerging pathogens of neonatal meningitis. cerebrospinal fluid (CSF) glucose to serum glucose ratio is not a reliable indicator of meningitis in the first 28 days of life, because newborns often receive intravenous glucose infusions and serum glucose concentrations can rise abruptly with stress. Lumbar puncture should always be performed as soon as the infant becomes clinically stable

and suitable for the procedure. If *Listeria monocytogenes* grows in CSF or is suspected as the causative organism from the Gram smear, it is advisable to add ampicillin to vancomycin + gentamicin combination, because CSF concentrations of vancomycin are not bactericidal for Listeria.

1. Introduction

Neonatal meningitis continues to retain its importance all over the world as an infectious disease because of its morbidity. Medical facilities that enable physicians to keep more and more premature infants alive in economically developed countries and, on the contrary side, limitations in access to healthcare systems in economically developing countries keep neonatal meningitis on the medical agenda in an era of highly developed antimicrobial management and immunization.

2. Epidemiology

The incidence of meningitis in newborn period is so high that is incomparable to any other period in human life. Accurate determinations of incidence may not be possible due to lack of reporting by healthcare personnel and difficulties encountered by patients in access to healthcare institutions in economically underdeveloped countries. Nevertheless, it is estimated that 40,000–900,000 new cases of neonatal meningitis occur annually in these countries [1]. The incidence of neonatal meningitis, which is thought to be roughly one in 1000 live births, was reported to be 0.8–6.1 in 1000 live births in an article in which the results of 32 studies, carried out after 1990, have been reviewed [2].

A great progress has been made in this field of infectious diseases, at least in economically developed countries, with the decline of mortality rate from 50% of the past 40 years to that of 10–15% of today; however, almost no change has occurred in neonatal meningitis in terms of mortality in economically developing countries and morbidity worldwide [3]. The case fatality rate varies between 13 and 59% with respect to country of origin. Neurological sequelae, primarily hearing loss, continue to be an important problem with rates of 20–58% in the neonates who manage to survive this relentless disease [1, 4].

Turkey, once an economically developing country, where meningitis constitutes less than 1% of the reported causes of infant mortality, sets a good example of how natural health indices are affected favorably by slight increases in national income. According to the World Bank data, as of 2015, neonatal mortality rate in Turkey is seven per 1000 live births [an 80% decline from the rate (33) in 1990] [5, 6]. Yapıcıoğlu and colleagues reported the meningitis incidence as 1.4% among healthcare-associated infections in their university hospital's neonatal unit in Turkey [7].

3. Risk factors

Major risk factors of neonatal meningitis are low birth weight (<2500 g), premature birth (before 37th week of gestation), premature rupture of membranes (before the onset of labor

or regular contractions), septical or traumatic birth, fetal hypoxia, maternal peripartum infection, galactosemia, and urinary tract infection [3].

4. Etiology

In economically developed countries, owing to implementation of intrapartum antibiotic prophylaxis beginning in the second half of 1990s, the incidence of early-onset group B streptococcus infections declined, whereas that of late-onset group B streptococcus infections remained the same [8]. Group B streptococci (GBS) and *Escherichia coli* are responsible for about half and a quarter of neonatal bacterial meningitis cases, respectively. These agents are succeeded in order of frequency by *Listeria monocytogenes* or Gram-negative bacteria other than *E. coli* in some texts, *Streptococcus pneumoniae*, group a streptococci, and nontypable *Haemophilus influenzae*. Gram-positive organisms other than GBS are encountered as pathogens more often in very-low-birth-weight (<1500 g) infants. Although rarely, *Neisseria meningitidis* may cause meningitis in newborns [3, 9].

Despite the data from economically developed countries, GBS predominance in neonatal meningitis has been observed to be replaced by Gram-negative bacteria in economically underdeveloped countries. *Klebsiella pneumoniae* is the most common Gram-negative bacillus and is followed in frequency by *E. coli*.

The most likely causative pathogens in the first three days of life are GBS, *E. coli*, other enteric bacilli, and *L. monocytogenes*. In addition to these, other Gram-negative organisms, such as *Serratia marcescens, Pseudomonas aeruginosa*, and *Citrobacter koseri*, should also be listed as likely pathogens in neonates of four days of age and older. In neonates who have left their first seven days in life behind, *Acinetobacter, Stenotrophomonas*, multidrug-resistant *Klebsiella*, and Gram-positive organisms that have not been mentioned above should be considered as causative agents [10].

Neonatal infections caused by herpes simplex virus (HSV) occur one in 3200–10,000 live births. These infections, which may manifest as neonatal meningitis, constitute 0.2% of neonatal hospitalizations and 0.6% of neonatal deaths in hospital in the United States of America [11].

Fungal meningitis occurs on the grounds of risk factors, such as prematurity, central venous catheter, congenital immunodeficiency, and long-term antibiotic therapy. The most common fungal cause of neonatal meningitis is *Candida albicans* [12].

Enteroviruses and *Enterobacter sakazakii*, which has been detected to contaminate infant formula, are emerging pathogens of neonatal meningitis [13, 14].

5. Pathophysiology

Neonates are apt to develop sepsis and meningitis more than all other individuals of all ages due to relative deficiencies in humoral and cellular immune responses. Preterm and term infants are deficient in complement in terms of quantity and quality, which leads to susceptibility to infections by encapsulated bacteria. In infants younger than 32 weeks of gestational

age, transfer of maternal circulating antibodies through placenta occurs only in minute quantities. Neutrophil reserves of a neonate can easily become exhausted, since they are 20–30% of that of an average adult [15].

The causative agent of neonatal meningitis is usually transmitted to fetus vertically during labor. When the etiology is bacterial, histopathologic findings of meningitis in newborns are similar, irrespective of the specific agent. Another similarity is observed in the inflammatory responses of newborns, older children, and adults, the only exception being the paucity of plasma cells and lymphocytes in the subacute phase of meningeal reactions in newborns. The most common finding is purulent exudate in meninges and ependymal surfaces of ventricles. Perivascular inflammation is also observed in some patients. This may further proceed to arteritis of various degrees with phlebothrombosis and thrombophlebitis in the subependymal region. Hydrocephalus and encephalopathy were detected in half of the infants died from meningitis. Unlike older infants (3–12 months of age), subdural effusion is rare in neonates. Interleukin-1β is present in high concentrations in the meninges and brain tissue of the infants who have succumbed to the infection [16].

6. Physical examination

Clinical findings of neonatal meningitis are similar to those of neonatal sepsis with or without meningitis. It is not possible to predict with physical examination alone whether the infant has sepsis, meningitis or both. The most common (60%) finding is the alteration in body temperature. This alteration may become manifest as either fever (>38°C) or hypothermia (<36°C). Fever is usually observed in term infants, whereas preterms have a stronger tendency to develop hypothermia [3]. Skin vesicles should suggest HSV in the etiology of meningitis,

Finding	Frequency (%)
Alteration in body temperature (either hypothermia or hyperthermia)	60
Irritability or lethargy	60
Seizures	20–50
Bulging of fontanel	25
Nuchal rigidity	15
Poor feeding	50
Dyspnea	33–50
Apnea	10–30
Jaundice	28
Diarrhea	20

Table 1. Physical examination findings found in neonatal meningitis and their frequencies [1, 3].

but vesicles may not appear in the early stages or may not occur at all through the course of the disease as is the case in 20% of the newborns with systemic HSV infection. In the absence of vesicles, it is impossible to differentiate HSV meningitis from bacterial meningitis or meningitis due to other agents [11]. Seizures are seen more often in Gram-negative bacterial meningitis rather than in meningitis caused by Gram-positive bacteria. It is inadvisable to rely on the presence of bulging anterior fontanel or nuchal rigidity, because only a few infants (25 and 15%, respectively) with meningitis demonstrate these signs [3]. Neurologic signs usually appear after the second day, whereas mainly systemic signs predominate in the first 48 h. Physical examination findings in neonatal meningitis and their frequencies are summarized in **Table 1**.

7. Laboratory tests

First tests to be performed include complete blood count with differentials and cultures (urine and blood). Detection of growth in urine culture could be a reflection of metastatic dissemination of the organism to the bladder, thus cannot be relied upon as a locator of infection in young infants [1].

Lumbar puncture (LP) is an irreplaceable diagnostic tool in neonatal meningitis. Cerebrospinal fluid (CSF) obtained through LP should be examined directly and as Gram- and Giemsa-stained smears under microscope, cultured, and, if needed, sent for polymerase chain reaction. Direct microscopy should be performed as soon as possible, because the later it is performed, the more likely the erythrocytes and leukocytes undergo cellular lysis and escape detection. LP should ideally precede the initiation of antimicrobial therapy, but if, delayed for any reason, such as deteriorating clinical status of the patient, empirical antibiotic therapy should be started immediately.

Interpretation of CSF findings is more difficult in neonates than in older children, since the glucose, protein concentrations, and cell count of CSF are higher due to the high permeability of the blood-brain barrier (**Table 2**).

Age	Erythrocytes (μL/L)	Leukocytes (μL/L)	Protein (mg/dL)	Glucose (mg/dL)
Preterm: <7 d	30 (0–333)	9 (0–30)	100 (50–290) (mostly <200)	54 (27–99)
Preterm: >7 d	30	12 (2–70)	90 (50–260) (mostly <150)	54 (27–99)
Term: <7 d	9 (0–50)	5 (0–21)	60 (30–250)	54 (27–99)
Term: >7 d	<10	3 (0–10)	50 (20–80)	54 (27–99)

d: day(s).

Table 2. Means and normal ranges of cerebrospinal parameters in neonates [12].

Many experts accept 20–30/μL as the cutoff value for pleocytosis. Decreased CSF glucose, increased CSF protein, and pleocytosis may indicate either bacterial or viral (especially HSV) meningitis. If only one of these parameters is in the normal range, this cannot be accepted as an evidence against the presence of meningitis. If all three parameters are normal, then it can be presumed that meningitis is not present; nevertheless, keeping in mind that completely normal CSF findings may be observed during the very early course of neonatal meningitis, the most prudent approach would be to repeat LP after 24–72 h in such borderline cases. If the infant had meningitis, pleocytosis and other abnormalities consistent with meningitis would be detected in CSF obtained in this second LP [3]. Ample number of erythrocytes in CSF may be interpreted as a clue to HSV meningitis if the physician is sure that the LP was not traumatic. Pleocytosis is more marked in bacterial and Gram-negative meningitides than in viral and Gram-positive meningitides [1].

CSF protein concentrations higher than 100 mg/dL in term infants and 150 mg/dL in preterm neonates are consistent with bacterial meningitis. CSF protein may also be found to be high in parameningeal infections like brain abscess, congenital infections, and intracranial hemorrhage [3].

The glucose concentration is said to be consistent with bacterial meningitis if it is below 30 mg/dL in term newborns and 20 mg/dL in preterm infants. CSF glucose to serum glucose ratio is not a reliable indicator of meningitis in the first 28 days of life, because newborns often receive intravenous glucose infusions and serum glucose concentrations can rise abruptly with stress [3]. In case of a bloody tap, assessing the CSF leucocyte count by correcting it with respect to that of the peripheral blood is not recommended in that it decreases the sensitivity and provides only a slight increase in specificity. When LP is traumatic, the wisest thing to do is to assume the patient as if she/he had meningitis and start empirical therapy [17]. Since sitting position with the legs flexed provides the widest interspinous spaces and it is sufficiently safe, it should be favored for sick neonates whenever the infant's condition permits a spinal tap [18].

Although, as noted above, signs of sepsis and meningitis intertwine in the newborn period, some neonatologists consider that it is unnecessary to perform LP on neonates evaluated for sepsis, especially those with early neonatal sepsis [19, 20]. Blood cultures are negative in one-third of neonates with meningitis who are very low birth weight and born over 34 weeks of gestation [1]. Thus, in case LP is not performed, a significant portion of neonates with meningitis would not get a correct diagnosis and would not be observed for the likely complications of meningitis; for that reason, the author is in favor of the opinion that LP should always be performed as soon as the infant becomes clinically stable and can tolerate the procedure if it has not been possible to be performed at the first suspicion of meningitis. It should be kept in mind that findings of CSF inflammation last for a considerably long duration (days, sometimes weeks), which allows the clinician diagnose or exclude the diagnosis of meningitis.

Ultrasonography is valuable in the follow-up, especially for the cases, in which hydrocephalus has developed as a complication of meningitis. If the disadvantage of radiation exposure is left aside, computed tomography can accelerate the decision making of ventriculostomy in cases of hydrocephalus and surgical drainage in patients with cranial abscesses. Magnetic resonance (MR) is the imaging modality of choice in conditions, such as focal neurologic

abnormalities, resistant infection, and clinical deterioration. MR is the most precise tool for the diagnosis of complications, like sinus vein thrombosis, ventriculitis, and subdural deposits. Electroencephalography has no diagnostic value in neonatal meningitis [12].

8. Diagnosis

History of premature or prolonged labor, intrauterine scalp monitorization, traumatic birth, and maternal peripartum infection should be noted.

Physical signs may be subtle in neonatal meningitis, in which either fever or hypothermia may be the only clue to diagnosis. Pleocytosis under direct microscopy or the presence of bacteria in Gram smear suggests meningitis. Definitive diagnosis is made with the isolation of causative organism in CSF.

The differential diagnosis includes other causes of neonatal seizures, partially treated meningitis, intracranial abscess, intracranial hemorrhage, intracranial aneurysm, cerebral vein thrombosis, head trauma, and congenital metabolic diseases.

9. Management

In the meningitides with the onset in the first 3–6 days of life, the empirical therapy should be ampicillin + cefotaxime, ampicillin + gentamicin, or, if there is a very high probability that the causative organism is Gram negative, as in the case of detection of Gram-negative bacilli on smear, it should be ampicillin + gentamicin + cefotaxime [10].

After the first 3–6 days of life, ampicillin + gentamicin + cefotaxime for infants from outside of a healthcare facility, and vancomycin + gentamicin + cefotaxime for previously or currently hospitalized newborns would be appropriate choices [1, 10]. If *L. monocytogenes* grows in CSF or is suspected as the pathogen from the Gram smear, it is advisable to add ampicillin to vancomycin + gentamicin combination, because CSF concentrations of vancomycin are not bactericidal for Listeria [10].

Dosages of recommended drugs are depicted in **Table 3**.

Dexamethasone therapy, which is used for older children, is not recommended for neonatal meningitis [1, 10].

Acyclovir (20 mg/kg/dose, every 8 h, for 14–21 days) should be administered to all neonates with HSV disease, regardless of manifestations and clinical findings [21].

For newborns whose CSF shows growth of a pathogen, the duration of therapy should be 14 days for Gram-positive organisms and 21 days for Gram negatives if neither any complication nor resistance to therapy is present. If a growth is detected in blood culture but not in CSF, while CSF shows signs of inflammation, a therapy duration of 10 days for Gram-positive organisms and 14 days for Gram negatives would suffice. Empirical antimicrobial therapy

	Weight < 1200 g	Weight = 1200–2 000 g	Weight = 1200–2000 g	Weight > 2000 g	Weight > 2000 g
Antibiotic	Age: 0–4 wk	Age: 0–7 d	Age > 7 d	Age: 0–7 d	Age > 7 d
Ampicillin	50, every 12 h	50, every 12 h	50, every 8 h	50, every 8 h	50, every 6 h
Gentamicin	2.5, every 18 h	2.5, every 12 h	2.5, every 8 h	2.5, every 12 h	2.5, every 8 h
Cefotaxime	50, every 12 h	50, every 12 h	50, every 8 h	50, every 12 h	50, every 8 h
Vancomycin	15, every 24 h	10, every 12 h	10, every 12 h	10, every 8 h	10, every 8 h

wk: week(s); d: day(s); h: hour(s).

Table 3. Dosages (mg/kg) of some antibacterial drugs used for neonatal meningitis [15].

for well-appearing infants with negative blood and CSF cultures and negative inflammatory findings in CSF may safely be discontinued 48–72 h after receiving negative CSF culture results from the microbiology laboratory [10].

LP should be repeated after 24–48 h after the beginning of antimicrobials for CSF is expected to become sterile in 24–48 h with appropriate therapy. In some centers, successful therapy for HSV meningitis is confirmed with a negative polymerase chain reaction in CSF, obtained with a repeat LP at the end of a 21-day antiviral therapy.

10. Complications and follow-up

Early complications of neonatal meningitis are increased: intracranial pressure, ventriculitis, cerebritis, hydrocephalus, brain abscess, cerebral infarction, and subdural effusion or empyema [22]. Late complications include hearing loss, abnormal behaviors, developmental retardation, cerebral palsy, focal motor deficits, seizures, and hydrocephalus, some of which may develop due to neonatal sepsis or cerebritis in infants without meningitis. Neonates recovered from meningitis should be referred for brainstem evoked auditory response audiometry 6–8 weeks after completion of therapy and then followed regularly for visual, auditory, and cognitive functions.

11. Prognosis

Case fatality rate is highest in meningitides due to Gram-negative organisms (17%), which are succeeded by those caused by fungi (12%) and Gram-positive bacteria (6%) [10, 23].

12. Conclusion

Taking Turkey as an example, a PubMed search by the author using the Medical Subject Headings terms groups “infant meningitis Turkey,” “newborn meningitis Turkey,” “neonate meningitis Turkey,” “infant meningitis Turkish,” “newborn meningitis Turkish,” and

"neonate meningitis Turkish" revealed only two recent, relatively large-scale studies on the epidemiology of neonatal meningitis in Turkey, which points to the need for more local data in this field [24, 25].

Conflict-of-interest

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Author contribution

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