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REVIEW

Management of Acute Bacterial Meningitis in Children

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Zain Alamarat[1]
Rodrigo Hasbun[2]

[1]Division of Infectious Diseases, Department of Pediatrics, UT Health, McGovern Medical School, Houston, TX, USA; [2]Division of Infectious Diseases, Department of Internal Medicine, UT Health, McGovern Medical School, Houston, TX, USA

Abstract: Acute community-acquired bacterial meningitis (ABM) in children continues to have high rates of neurological morbidity and mortality despite the overall declining rates of infection attributed to the use of vaccines and intrapartum Group B *Streptococcus* prophylaxis. Prompt diagnosis and early antibiotic therapy are crucial and should not be delayed to obtain cranial imaging. Differentiating bacterial from viral meningitis continues to be a clinical dilemma especially in patients with previous antibiotic exposure. Clinical models and inflammatory biomarkers can aid clinicians in their diagnostic approach. Multiplex polymerase chain reaction and metagenomic next-generation sequencing are promising tools that can help in early and accurate diagnosis. This review will present the epidemiology of ABM in children, indications of cranial imaging, role of different models and serum biomarkers in diagnosing ABM, and management including the use of adjunctive therapies and methods of prevention.

Keywords: management, CNS infection, meningitis, bacterial meningitis, children

Introduction

Acute bacterial meningitis (ABM) is a life-threatening bacterial infection of the meninges. The overall rates have been declining[1,2] since the introduction of vaccines against the three most common meningeal pathogens *(Haemophilus influenzae type b, Streptococcus pneumoniae, and Neisseria meningitides)* and by the introduction of intrapartum antibiotic prophylaxis for *Group B Streptococcus* (GBS). Worldwide, bacterial meningitis continues to be a neurological emergency associated with high mortality and morbidity requiring immediate evaluation and management.

Etiology by Age Group

Earlier studies in pediatric community-acquired bacterial meningitis have shown that five pathogens (*H. influenzae, S. pneumoniae, N. meningitidis, GBS and Listeria monocytogenes*) are the most common causes of bacterial meningitis.[3–5] More recent studies have shown that despite the changes in the incidence of each pathogen, these five pathogens remain the most common in the pediatric population.[1,6,7] The specific etiology depends on factors such as age, immune function, immunization status, genetics[8,9] and geographical location.

Despite the fact that these results represent data from the United States of America (USA), it holds true for developing countries; who carries the highest burden of the disease. In a recent systematic review and meta-analysis conducted to evaluate available data on the etiology of bacterial meningitis published globally in

Correspondence: Rodrigo Hasbun
Department of Internal Medicine, UT Health, McGovern Medical School, 6431 Fannin St. MSE 226, Houston, TX 77030, USA
Tel +1 (713) 500-7140
Fax +1 (713) 500-5495
Email Rodrigo.Hasbun@uth.tmc.edu

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the last five years, the frequency of seven bacterial types known to cause meningitis: *Escherichia coli, Haemophilus influenzae, Neisseria meningitidis, Streptococcus pneumoniae*, group B *Streptococcus, Staphylococcus aureus*, and *Listeria monocytogenes* was analyzed, with results being stratified by six geographical regions as determined by the World Health Organization, and by seven age groups.[10]

In this global review of the burden of meningitis, *S. pneumoniae* and *N. meningitidis* were the predominant pathogens in all age groups and regions, accounting for 25.1–41.2% and 9.1–36.2% of bacterial meningitis cases, respectively. *S. pneumoniae* infection was the most common cause of bacterial meningitis in the "all children" group, ranging from 22.5% (Europe) to 41.1% (Africa), and in all adults ranging from 9.6% (Western Pacific) to 75.2% (Africa). *E. coli* and *S. pneumoniae* were the most common pathogens that caused bacterial meningitis in neonates in Africa (17.7% and 20.4%, respectively). *N. meningitidis* was the most common in children aged ±1–5 years in Europe (47.0%) while *S. pneumoniae* was the most prevalent pathogen in children aged ±6–18 years.[10]

Neonates and Infants

Premature infants, neonates and infants less than 2 months of age represent the highest risk groups for bacterial meningitis in children. The predisposition to develop bacterial meningitis is similar to the risk of developing sepsis and can be due to the lack of maternal immunoglobulins that cross the placenta after 32-week gestation[11] and secondary to the immature immune system with impaired phagocytic ability of neutrophils and monocytes.[6]

The organisms that are commonly observed in neonatal meningitis are the same as those that cause neonatal sepsis with differences depending on postnatal age; early and late-onset neonatal meningitis occurs at ≤72 and >72 hours of life, respectively. Risk factors for developing neonatal meningitis include prematurity, maternal rectovaginal colonization with GBS, premature rupture of membranes, prolonged rupture of membranes >18 hours, invasive fetal monitoring, very low birth weight (<1500g), prolonged hospitalization, and presence of external devices (eg, reservoirs, shunts, catheters).[11]

Despite the institution of intrapartum prophylaxis, GBS remains the leading cause accounting for approximately 40% of early-onset neonatal meningitis cases.[11,12] *Escherichia coli* (*E. coli*) is the second most common cause accounting for 30% of cases in the USA and 17.7% in Africa[10,11,13] and is the leading cause of early-onset meningitis and sepsis in neonates with very low birth weight (<1500 g birth weight).[14] Studies in the USA showed significant increase in the rate of *E. coli* early-onset neonatal infections between 1991–1993 and 1998–2000; 3.2 to 6.8 per 1000 live births, while there was no significant increase in 2002–2003; 7.0 per 1000 live births.[15,16] In late-onset neonatal meningitis, GBS and *E. coli* are the two most common pathogens.[11] Of note, there has been a significant reduction in the incidence of *L. monocytogenes* meningitis in this age group due to the efforts in decreasing the incidence of listeriosis during pregnancy by reducing food-borne contamination.[7]

Children After the Neonatal Period

Despite the significant reduction in the incidence of meningitis in this age group after the introduction of vaccines to the three most common meningeal pathogens, *S. pneumoniae* and *N. meningitides* remain the most common organisms causing community-acquired bacterial meningitis[7,17–19] followed by GBS and gram-negative bacilli organisms.

Development of Resistant Strains

Due to the global use of antibiotics, multi-drug resistant bacterial strains have emerged posing serious challenges to treating physicians. In a report published from Europe and the Mediterranean region, *N. meningitidis* isolates with reduced susceptibility to penicillin have been detected but not yet to the extended-spectrum cephalosporins (eg, cefotaxime or ceftriaxone).[20] Chloramphenicol, Rifampin and low level (MIC 0.12–0.25 mg/L) resistance to fluoroquinolones have also been reported. Penicillin-resistant *S. pneumoniae* isolates have been recently increasing with varying rates ranging from 30% in France and Spain to less than 3% in the more northern countries. The resistance to penicillin is often associated with a decreased susceptibility to other beta-lactams but ceftriaxone, cefotaxime and the carbapenems are less affected. Resistance to macrolides is also widespread, being particularly high in the Mediterranean region: >30% in Italy; 40% in France; 30% in Greece and around 45–50% in Spain but low levels of fluoroquinolone resistance have been detected *H. influenzae* isolates had shown increasing rates of ampicillin resistance with special attention to non-lactamase-producing ampicillin-resistant strains while rates of fluoroquinolones resistance have remained very low.

Cranial Imaging in Suspected Meningitis

The clinical features of bacterial meningitis can be subtle, variable, and non-specific or absent in the pediatric population especially in neonates and infants.[11] Neuroimaging is not essential for the diagnosis or management in the majority of patients with acute bacterial meningitis. The Infectious Diseases Society of America (IDSA) guidelines recommend that infants and children with the following should have a cranial computed tomography (CT) scan done:[21] history of central nervous system disease (CSF shunts, hydrocephalus, head trauma, post neurosurgery, space-occupying lesions), immunocompromised, papilledema, or focal neurological deficits (except palsy of abducens or facial nerve).[18,22,23] In the absence of these clinical features an abnormal CT is rare and furthermore a normal CT does not mean a lumbar puncture (LP) is safe as patients can still herniate. In a nationwide prospective cohort study, 1533 adults with community-acquired bacterial meningitis were evaluated. In this cohort 47 patients (3.1%) had possible deterioration after an LP, a cranial CT was performed for 43/47 patients (91%) of which 17/43 (40%) was reported normal and the most common finding was generalized cerebral edema in 13/43 (30%),[24] similar data in children do not exist. In neonates and infants (as long as the anterior fontanelle is open), cranial ultrasound can be a useful diagnostic method when bacterial meningitis is suspected. Ultrasound abnormalities are observed in approximately 65% of patients with uncomplicated bacterial meningitis and up to 100% in patients with severe neurological symptoms.[25] The spectrum of characteristic signs visualized in patients with bacterial meningitis using ultrasound and doppler imaging may aid in a quick preliminary diagnosis and initiation of treatment, which can have a significant impact on the patient's prognosis.[26]

CT or MRI of brain can be useful in showing meningeal enhancement, areas of ischemia due to secondary vasculitis, define pathology of the base of skull that may be causative and require rapid therapeutic intervention and surgical consultation and to identify potential sources of infection such as fractures of the paranasal sinus or petrous bone as well as inner ear infection and mastoiditis. Despite this, LP remains the only tool in diagnosing or excluding bacterial meningitis. It is a relatively safe procedure, but minor and major complications can still happen.[27]

Diagnosis

When ABM is suspected, early diagnosis and prompt empirical antibiotics are paramount. An LP for cerebrospinal fluid (CSF) analysis and culture remains key for diagnosis.[21,28] Characteristic CSF findings for bacterial meningitis consist of polymorphonuclear pleocytosis (WBC >1000 Cells/μL, 80–90% polymorphonuclear cells), hypoglycorrachia (CSF glucose <40 mg/dL, a ratio of CSF to serum glucose of ≤0.4 in children and ≤0.6 in term neonates) and elevated CSF protein levels >150 mg/dL.[21,29,30] In the pediatric population, CSF indexes vary with age, with poorly defined normal values especially in infants.[11] Gram stain and culture remains the most important tool for diagnosis of ABM. They are cheap and well-validated tools but the sensitivity varies by different age groups, types of meningeal pathogens and by the use of previous antibiotic therapy.[26–31] The sensitivity of the Gram stain in neonates is ~60%[31] while in children it ranges from 50% to 63%.[32,33] The sensitivity also ranges by pathogen: 90% in *S. pneumoniae* meningitis,[34,35] 80% in *N. meningitides*, 50% in Gram-negative bacillary meningitis, and 30% in *L. monocytogenes*.[35] The effects of antibiotic pretreatment on the microbiological yield of ABM were studied in 231 children.[31] Antibiotic pretreatment was significantly associated with a lower sensitivity of the CSF and blood cultures but had no impact on the sensitivity of the CSF Gram stain.[31]

Differentiation of Bacterial from Viral or Aseptic Meningitis

Use of Antibiotic Therapy in Aseptic (Viral) Meningitis

Aseptic meningitis is an acute community-acquired syndrome presenting with CSF pleocytosis, negative CSF gram stain and culture, with no parameningeal focus or a systemic illness. In children, this syndrome is common, mostly caused by viruses (eg, enteroviruses) and has a good clinical outcome. Despite this, the majority of patients with aseptic meningitis continue to be admitted to the hospital and receive unnecessary empirical antibiotics, which increases the length and cost of hospital stay.[36–41] In a recent large epidemiological study for children presenting with meningitis or encephalitis in the U.S, 6665 patients' ≤ 17 years of age were identified. Despite that approximately two-thirds had a viral etiology, the majority were admitted to the hospital and up to 92.2% received empirical antibiotics.[36]

In a retrospective observational cohort study, 509 patients with aseptic meningitis were identified of which 105 (21%) were children. Children were more likely to have at least one viral study (CSF PCR or arbovirus

serology) sent compared to adults (75.2% vs 61.3%, P=0.008) and also were less likely to have an unknown infectious etiology (60.9% vs 85.6%, P<0.001). Empiric antibiotic therapy was given to the majority of patients (77.4%) with children receiving them more frequently than adults (92.3% vs 73.5%, p <0.001).[37]

CSF Profile and Clinical Models

Definitive differentiation between viral and bacterial meningitis depends on the results of the CSF culture, which may take up to 3 days, and other CSF parameters can greatly overlap between both entities (see Table 1). Several clinical models were developed to aid physicians in differentiating viral from bacterial meningitis. One study evaluated 422 patients ≥1 month of age with acute bacterial or aseptic meningitis. This study suggested a model where it was found that a CSF glucose level less than 34.2 mg/dl, a CSF-blood glucose ratio less than 0.23, a CSF protein level greater than 220 mg/dL, CSF pleocytosis greater than 2000 leukocytes/mm3, or more than 1180 neutrophils/mm3 in the CSF were individual predictors of bacterial infection with 99% certainty or better.[42]

Another model that was derived and validated only in children is the Bacterial Meningitis Score. This risk score can identify patients at low risk (BMS =0) or high risk (BMS≥2) of having ABM depending on the following predictors: positive CSF Gram stain for bacteria, CSF protein > or =80 mg/dL, peripheral absolute neutrophil count > or =10,000 cells/mm3, seizure before or at time of presentation, and CSF absolute neutrophil count > or =1000 cells/mm3, attributing 2 points for a positive Gram stain and 1 point for each of the other variables.[43] A meta-analysis performed to evaluate the performance of the Bacterial Meningitis Score in children with CSF pleocytosis showed a combined sensitivity of 99.3%, specificity 62.1% and negative predictive value 99.7%.[44] As the majority of patients with meningitis present with a negative Gram stain and a positive CSF Gram stain is diagnostic of a bacterial etiology, a more clinically useful risk score that excludes a positive Gram stain should be done in children as it has been done in adults.[45]

Inflammatory Markers and Biomarker

In children, serum inflammatory markers can also be of help in differentiating viral and bacterial meningitis. Multiple studies have been conducted to identify biomarkers that can help clinicians in their assessment of patients. Normal C-reactive protein (CRP) and procalcitonin values have good diagnostic accuracy in excluding all bacterial infections including those causing meningitis but they are not widely used in clinical practice.[46–48] Serum concentration of CRP greater than 80 mg/dl[41] and elevated serum procalcitonin level (0.5-ng/mL) can be helpful in identifying patients with ABM. One study showed that a procalcitonin level >0.5 ng/mL was 99% sensitive and 83% specific for ABM,[47] while another study showing a value of >2 ng/mL was 100% sensitive and 63% specific.[48] This latter study also showed that the procalcitonin level could also be used to follow the response to antibiotic therapy.

CSF lactate was found to be a useful tool to differentiate bacterial from viral meningitis when elevated.[49–51] In one study a cut-off of 54mg/dL had a sensitivity of 90%, specificity of 100%, positive predictive value of 100%,

Table 1 Cerebrospinal Fluid Characteristics in Children with and without Meningitis (Viral, Bacterial) According to Age[18,89,90]

	CSF WBC Count Cells/mm3	Neutrophils	CSF Protein Concentration mg/dL	CSF Glucose Concentration mg/dL
Term neonate 0–28 days[a]	5.5(6.0)	20–60%	69.9 (25.7)	45.7 (8)
0–7 days	15.3(30.3)		80.3(30.8)	45.9(7.5)
8–14 days	5.4(4.4)		69.0(22.6)	54.3(17)
15–21 days	7.7(12.1)		59.8(23.4)	46.8(8.8)
22–28 days	4.8(3.4)		54.1(16.2)	54.1(16.2)
Young infant <60 days[b]	3.6(4.3)	20–60%	53.2(21.2)	48.1 (8)
Healthy Children	<6	None	20–40	40–80
Bacterial	>1.000	85–90%	100–150	<1/2 serum to N
Viral	<1.000	20–50%	40- <100 g/dl	>1/2 serum

Note: [a,b]CSF WBC, Protein concentration and glucose values are provided as mean (standard deviation).

and negative predictive value of 96.3%, with an accuracy of 97.2%.[49] Two meta-analyses conducted to evaluate the role of CSF lactate in differentiating viral from bacterial meningitis, one including 25 studies with 1692 patients (adults and children)[52] and the other including 31 studies with 1885 patients,[53] concluded that the diagnostic accuracy of CSF lactate is better than that of the CSF white blood cell count, glucose concentration, and protein level in patients who did not receive prior antimicrobial therapy.[52,53]

CSF Diagnostic Studies

The gold standard to make a diagnosis of bacterial meningitis still relies on identifying the pathogen by CSF culture but this is hampered by the administration of previous antibiotic therapy.[12,15,17] Sterilization of the CSF occurs rapidly after the initiation of parenteral antibiotics; with complete sterilization of *N. meningitidis* within 2 hours and the beginning of sterilization of *S. pneumoniae* by 4 hours and GBS by 8 hours into therapy.[54] Non-culture-based diagnostic methods include testing the CSF for the *Streptococcus pneumoniae* antigen, multiplex PCRs and metagenomic sequencing.

The *Streptococcus pneumoniae* BinaxNOW® antigen is an inexpensive and rapid (~15 minutes) immunochromatographic test that has 99–100% sensitivity and specificity in ruling in or out pneumococcal meningitis.[55] In patients with prior antibiotic therapy, the antigen testing detected 25% of culture-negative cases.[56] These studies have been done in children in countries from Asia and Africa but have not been validated in adults or in high-income countries. Another rapid, non-culture based method is multiplex PCR. The Film Array meningitis/encephalitis (ME) panel (BioFire Diagnostics, Salt Lake City, UT) received FDA clearance in 2015 and utilizes a sample of 200 µL of cerebrospinal fluid (CSF) to identify in 1 hour the presence of 14 pathogens (*Escherichia coli K1, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, S. pneumoniae, cytomegalovirus (CMV), enterovirus (EV), herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human herpesvirus 6 (HHSV-6), human parechovirus (HPeV), varicella zoster (VZV), Cryptococcus neoformans/C. gattii*). Diagnostic correlation studies with CSF sample banks positive for the targets identified by the test have an agreement of greater than 90%.[57] A retrospective analysis of 291 residual CSF samples (tested positive by routine methods) using the Film Array ME panel demonstrated an overall percent positive agreement (PPA) of 97.5% (78/80) for bacterial pathogens, 90.1% (145/161) for viruses, and 52% (26/50) for *Cryptococcus neoformans/C. gattii*.[58] In patients with suspected fungal meningitis, a CSF cryptococcal antigen should also be done.

Another promising approach for the diagnosis of meningitis or encephalitis is metagenomic next-generation sequencing (mNGS). A recent, 1-year, prospective, multicenter study involving hospitalized patients presenting with idiopathic meningitis, encephalitis, or myelitis (the Precision Diagnosis of Acute Infectious Diseases [PDAID] study) was conducted to evaluate the utility of the mNGS assay for identification of pathogens in patients with neurologic infection confirmed by routine diagnostic testing, including culture and polymerase chain reaction (PCR) assay in CSF.[59] In this study, 204 pediatric and adult patients were enrolled, a total of 58 infections were diagnosed in 57 patients. Among these 58 infections, mNGS identified 13 that were not identified by clinical testing and 19 concurrent diagnoses with the available clinical testing. Although the highest diagnostic yield resulted from a combination of mNGS of CSF and conventional testing which can provide reassurance that the diagnosis is correct and help rule out active infections in patients with suspected autoimmune encephalitis, mNGS proved to have potential usefulness in diagnosing pathogens that were either not considered by treating clinicians or had tested negative by conventional testing.

Miller et al developed and analytically validated a clinical CSF mNGS assay. In their study, the test accuracy was evaluated by blinded mNGS testing of 95 patient samples, revealing 73% sensitivity and 99% specificity compared to original clinical test results, and 81% positive percent agreement and 99% negative percent agreement after discrepancy analysis. Subsequent mNGS challenge testing of 20 positive CSF samples prospectively collected from a cohort of pediatric patients hospitalized with meningitis, encephalitis, and/or myelitis showed 92% sensitivity and 96% specificity relative to conventional microbiological testing of CSF in identifying the causative pathogen.[60] Despite the potential benefit of mNGS assay for pan-pathogen detection, results need to be interpreted with caution especially in patients with very high CSF WBC counts.

Management

Empirical Antibiotics Therapy

It is important to assure that empirical antibiotics are administered in timely manner, cover the most common

etiological agents, can achieve good concentrations in the CSF and are bactericidal against the targeted bacterial pathogens. Several retrospective and prospective studies especially in adults showed that delay in antibiotic treatment >6 hours is associated with adverse outcomes.[41,61–64] In a retrospective chart review of 171 cases of bacterial meningitis in children and adults, mortality rate increased from 7.9% for patients who received antibiotics in the emergency center (meantime of administration 1.8 hours) to 29% for patients who received inpatient antibiotics (meantime 6–9 hours).[62] While another prospective, multicenter, observational study of 156 adults hospitalized for pneumococcal meningitis study showed that delay in antibiotic treatment >3 hours and isolation of penicillin-nonsusceptible *S. pneumoniae* strains were independent predictors of mortality.[64]

In neonates, although the American Academy of Pediatrics (AAP) Committee on Infectious Diseases, the Infectious Disease Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommends use of ampicillin plus cefotaxime or gentamicin,[18,21,65] use of cefotaxime is reasonable given the increasing resistance of *E. coli* and other Gram-negative enteric organisms to ampicillin and due to the suboptimal CSF penetration by gentamicin (see Table 2).[66] The prevalence of *S. pneumoniae* strains that are relatively resistant to penicillin (MIC 0·1–1·0 μg/mL) or highly resistant to penicillin (MIC greater than 1·0 μg/mL) is increasing, and many of the penicillin-resistant pneumococci have reduced susceptibility to third-generation cephalosporins which lead to increasing rates of treatment failure.[21,67,68] As a result to that, vancomycin plus either cefotaxime or ceftriaxone should be used as empirical antibiotics in children presenting with signs and symptoms of ABM in the United States or Europe where the incidence of ceftriaxone-resistant pneumococcus is >1%.[18,21,30,65] When the causative organism and its antibiotic susceptibilities are determined, specific targeted therapy can be provided.

Length of Therapy

In neonates, 14 days of antibiotics is sufficient in uncomplicated meningitis caused by GBS, *L. monocytogenes*, or *S. pneumoniae*; while 21 days is recommended Gram-negative bacilli meningitis. In children; uncomplicated meningitis caused by *N. meningitidis* 5 to 7 days, *H. influenzae* 7 to 10 days, *S. pneumoniae* 10 to 14 days, *L. monocytogenes* 14 to 21 days and a minimum of 21 days for Gram-negative bacilli. Longer antimicrobial treatment courses are necessary for complicated meningitis, such as subdural empyema, ventriculitis, brain abscess, and suppurative venous sinus thrombosis.[18]

Repeat LP

While some experts recommend that all cases of neonatal meningitis should get a repeat LP after 24 to 48 hours of therapy to confirm CSF sterilization,[66] the AAP and IDSA recommend that only neonate with meningitis due to gram-negative bacilli should undergo repeat LP.[18,21,69] End of therapy LP may be warranted in cases where CSF culture remained positive after 48–72 hours of therapy, or in neonates with persistent abnormal neurological findings, especially focal deficits. CSF values of neutrophils >30%, glucose <20 mg/dL, or CSF-to-blood glucose ratio <20% are non-reassuring and in these circumstances, CSF examination as well as neuroimaging can assist in determining an optimal duration of antibiotic therapy to prevent relapse.[18,66]

In children; a repeat LP is not routinely recommended in patients who respond appropriately to antimicrobial therapy. Except in the case of meningitis due to *S. pneumoniae*; If the organism is cephalosporin-nonsusceptible, the AAP recommends considering a repeat LP at 48 to 72 hours to verify CSF clearance of the bacteria,[18] while the IDSA and the AAP guidelines based on expert opinion suggest considering a repeat LP after 48–72 hours of therapy if: 1) the organism is penicillin or cephalosporin –non-susceptible, 2) the patient's condition has not improved or is worsening, or 3) the patient has received dexamethasone which can obscure clinical features such as fever, headache, and nuchal rigidity.[11,18,21,70]

Adjunctive Therapy

In neonatal meningitis, the role of adjunctive therapies such as dexamethasone, glycerol, immunoglobulins, granulocyte-macrophage colony-stimulating factor (GM-CSF) has not been well studied and is not recommended or used in clinical practice.[11,71–73]

In children, randomized trials showed that adjunctive dexamethasone 0.6 mg/kg of body weight daily, with the first dose being given before or with the first dose of antibiotics, for 4 days decreases overall hearing loss and severe neurological sequelae in children with bacterial meningitis in high-income countries while in low-income countries, no benefit was established.[71] The most likely cause of this

Table 2 The Most Common Organism Causing Acute Bacterial Meningitis per Age Group with the Recommended Standard Therapy Based on in vitro Susceptibility Testing[18,21,30,69,70,91–95]

Age Group	Organisms	Treatment (Intravenously) Dose/kg/day	Length of Therapy (Uncomplicated Meningitis)
Term Neonates-early onset	***GBS***	**Penicillin G** (infant ≤7days) 250 000.0-450 000.0 U divided in 3 doses **OR** **ampicillin** (infant ≤7days) 200.0-300.0 mg divided in 3 doses	14 days
	L. monocytogenes	**Penicillin G** (infant ≤7days) 250 000.0-400 000.0 U divided in 4-6 doses **OR** **ampicillin** (infant ≤7days) 200.0-300.0 mg divided in 3 doses **+** **gentamicin** (infant ≤7days) neonate (weight ≤ 2kg) 5.0mg/kg every 48 hours neonate (weight >2kg) 4.0 mg/kg every 24 hours	14-21 days
	E. coli (gentamicin should be added until CSF is sterile)		21 days
	- **ampicillin-susceptible**	**ampicillin** (infant ≤7days) 200.0-300.0 mg divided in 3 doses	
	- **ampicillin resistant, cefotaxime susceptible**	**Cefotaxime**[a,b] (infant ≤7days) neonate (weight > 2kg) 100.0-150.0 mg divided every 2-3 doses **gentamicin** (infant ≤7days) neonate (weight ≤ 2kg) 5.0 mg/kg every 48 hours neonate (weight >2kg) 4.0 mg/kg every 24 hours	
Term Neonates-Late onset	***GBS***	**Penicillin G** (infant >7days) 450 000.0-500 000.0 U divided in 4 doses **OR** **ampicillin** (infant >7days) 300.0 mg divided in 4 doses	14 days
	L. monocytogenes	**Penicillin G** (infant >7days) 250 000.0-400 000.0 U divided in 4-6 doses **OR** **ampicillin** (infant >7days) 300.0 mg divided in 4 doses **+** **gentamicin** (infant >7days) neonate (weight ≤ 2kg) 5.0 mg/kg every 36 hours neonate (weight >2kg) 4.0-5.0 mg/kg every 24 hours	14-21 days
	E. coli (gentamicin should be added until CSF is sterile)		21 days
	- **ampicillin-susceptible**	**ampicillin** (infant >7days) 300.0 mg divided in 4 doses	
	- **ampicillin resistant, cefotaxime susceptible**	**cefotaxime**[a,b] (infant >7days) neonate (weight > 2kg) 150.0-200.0 mg divided in 3 to 4 doses **gentamicin** (infant >7days) neonate (weight ≤ 2kg) 5.0 mg/kg every 36 hours neonate (weight >2kg) 4.0-5.0 mg/kg every 24 hours	

(*Continued*)

Table 2 (Continued).

Age Group	Organisms	Treatment (Intravenously) Dose/kg/day	Length of Therapy (Uncomplicated Meningitis)
Infants and Toddlers	***GBS***	**Penicillin G** 450 000.0-500 000.0 U divided in 4 doses **OR** **ampicillin** 300.0 mg divided in 4 doses	14 days
	E.coli (gentamicin should be added until CSF is sterile)		21 days
	- ampicillin-susceptible	**ampicillin** 300.0-400.0mg divided in 4 to 6 doses can substitute the cephalosporin	
	- ampicillin resistant	**Ceftriaxone** 100.0 mg divided in 2 doses **OR** **cefotaxime** 200.0-300.0 mg divided in 4 doses **PLUS** **gentamicin** 7.5 mg divided in 3 doses	
	L. monocytogenes	**Penicillin G** 250 000.0-400 000.0 U divided in 4-6 doses **OR** **ampicillin** 300.0 mg divided in 4 doses **+** **gentamicin** 7.5 mg divided in 3 doses	21 days
	S. pneumonia		10 to 14 days
	Penicillin MIC[c] ≤0.06 µg/ml	**Penicillin G** 250 000.0-400 000.0 U divided in 4-6 doses(max 24 million U/day) **OR** **ampicillin** 300.0-400.0 mg divided in 4 to 6 doses (max 12g/day) **OR Ceftriaxone** 100.0 mg divided in 2 doses (max 2.0g/dose, 4.0g/day) **OR cefotaxime** 225.0-300.0mg divided in 3 to 4 doses (max 2.0g/dose)	
	Penicillin MIC > 0.12µ g/ml AND cefotaxime/Ceftriaxone MIC ≤0.5 µg/ml	**Ceftriaxone OR cefotaxime** (dose as mentioned above)	
	Penicillin MIC > 0.12µg/ml AND cefotaxime/Ceftriaxone MIC >1.0 µg/ml	**Vancomycin** 60.0 mg divided in 4 doses **PLUS Ceftriaxone[d] OR cefotaxime**	
	N. meningitides		5-7 days
	Penicillin MIC≤0.1 µg/ml	**Penicillin G** 300 000 U divided in 4-6 doses (max 12 million /day) **OR** **ampicillin OR cefotaxime OR Ceftriaxone** (dose as in *S. pneumonia)*	
	Penicillin MIC 0.1-1.0µg/ml	**cefotaxime OR Ceftriaxone** (dose as in S. pneumonia)	
	H. influenzae		7 to 10 days
	β- Lactamase negative [e]	**ampicillin** (dose as in S. pneumonia)	
	β- Lactamase positive	**Ceftriaxone OR cefotaxime** (dose as in S. pneumonia)	

(*Continued*)

Table 2 (Continued).

Age Group	Organisms	Treatment (Intravenously) Dose/kg/day	Length of Therapy (Uncomplicated Meningitis)
Children and Teenagers	***N. meningitidis*** ***S. pneumoniae,*** ***H. influenzae***	Doses as mentioned above	Duration as mentioned above

Notes: [a]If cefotaxime is not available or resistant, a carbapenem should be substituted for neonates and infants younger than 91 days and ceftriaxone or ceftazidime for older infants and children. [b]If neonate <2 kg smaller doses and longer intervals should be used. [c]MIC = Minimum inhibitory concentrations. [d]Consider adding Rifampin if ceftriaxone MIC ≥2 μg/mL and organism is rifampin susceptible. [e]β- Lactamase negative, ampicillin-resistant strains have been described, use ampicillin with caution if MIC is 1–2 μg/mL.

disparity is that patients in low-income countries present late to care with advanced disease, making early steroid administration extremely difficult if not impossible, highlighting the importance of the early administration of the steroids. The efficacy of adjunctive steroids in children with bacterial meningitis vary by pathogen: in *H. influenzae*, dexamethasone causes reduction in severe hearing loss and reduces inflammatory markers in the CSF,[71,74] in *S. pneumoniae*, there is no effect of dexamethasone on mortality but some effect on severe hearing loss if given early[34,75] and in *N. meningitidis* it might decrease mortality but there is no effect on hearing or other neurological sequelae.[71] Despite the variability on the data published, the AAP and IDSA recommend dexamethasone 0.15 mg/kg per dose intravenously every 6 hours for 2 days for patients with *H. influenzae* meningitis and indicates that empiric use might be considered for suspected *S. pneumoniae* meningitis in infants and children 6 weeks of age and older.[11,18,21]

The use of other adjunctive therapy such as osmotic therapy (glycerol) has been reviewed in a Cochrane review,[76] which included 5 trials with 1451 participants, 4/5 studies are in children; glycerol had no effect on death but may reduce neurological deficiency and deafness although the evidence is incomplete and unequivocal results could not be derived.

Supportive Care

Serious life-threatening complications of ABM (septic shock, inadequate ventilation, cerebral herniation, cerebral infarction and seizures) often occurs in the first 2–3 days therefore patient should be cared for in the intensive care setting to assure close monitoring of their cardiopulmonary status.[15,26] Recently, delayed cerebral infarctions (DCI) have been reported in up to 4% of adults with bacterial meningitis that have been associated with the use of adjunctive dexamethasone.[77] The cause of DCI in bacterial meningitis is currently unknown. Fluid and electrolyte resuscitation must be administered to attain appropriate blood pressure and cerebral perfusion.[78] In the most recent Cochrane meta-analysis, there was no significant difference detected between the maintenance-fluid and restricted-fluid groups in number of deaths or acute severe neurological sequelae, except for those patients with spasticity and seizure in favor of maintenance fluid.[79] Early tracheal intubation and mechanical ventilation should be considered in patients with signs of ongoing shock, respiratory failure, impaired mental status (reduced or fluctuating level of consciousness), raised intracranial pressure or intractable seizures.[78]

Approximately one-third of infants and children with bacterial meningitis will have markedly reduced cerebral blood flow primarily due to cerebral edema and increased intracranial pressure.[80] Early signs of increased ICP can be managed by elevating the head of the bed. However, late signs of increased ICP (apnea, bradycardia, hypertension and sluggish or dilated pupils) require more aggressive therapy with mannitol, intubation and hyperventilation.

Seizures usually occur early in the illness, are generalized, can be controlled easily with standard anticonvulsant and have limited prognostic significance. However focal seizures, difficult-to-control seizures, or seizures occurring more than 48 hours after admission should raise concerns for underlying complications; such as vascular disturbance, brain abscesses or subdural empyema.

Outcome

Despite the decline in the incidence of bacterial meningitis in children, it continues to be associated high morbidity and mortality rates that depend on the age group, pathogen, country and the time period of the study.

In neonates, mortality rates ranges from 10% in developed countries to 58% in developing countries.[46,48] In a recent prospective study for infants <90 days from the United Kingdom and Ireland, mortality rate was 9%, with 23% rate of serious central nervous system complications in the form (seizures, motor disorder, hydrocephalus with or without a ventriculoperitoneal shunt, hearing loss or extradural collection requiring neurosurgical intervention) in the survivors.[41] In

this study, mortality was associated with prematurity, coma on admission and *S. pneumoniae* as a causative agent, while the risk of serious CNS complications was associated with temperature instability, seizures, elevated CSF protein and *S. pneumoniae* as the causative agent.

In children, mortality rates range from less than 5% to 15%. Seizures, hearing loss and developmental delay are the most common CNS complication associated with bacterial meningitis.[18,33,34,81] *S. pneumoniae* is associated with the worst outcome when compared to other pathogens with 10% mortality and 20–30% morbidity.[19,34] Other predictors of death and long-term neurological sequelae are decreased level of consciousness (Glasgow coma scale score (GCS) < 8), cranial nerve palsy, seizures, low CSF white blood cell count, positive gram stain/culture and abnormal findings of ultrasonography and CT imaging.[17,18,34,81]

Prevention

In neonates, the introduction of intrapartum antibiotic prophylaxis (IAP) in 1996 had significantly decreased the incidence of early-onset GBS disease but had no effect on late-onset disease. The current screening method implemented since 2002 likely misses a significant portion of colonization during pregnancy due to false-negative screens, precipitous deliveries and extreme preterm delivery.[11,72] Efforts are ongoing for the development of GBS vaccine to cover the most common GBS serotypes causing neonatal disease which will induce maternal immunity that can be transferred passively to the infant to protect against early and late-onset disease.[82–84]

In children, the best way to prevent the most common etiological agents for bacterial meningitis (*H. influenzae, S. pneumoniae, N. meningitidis)* continues to be compliance with timely childhood vaccination against these organisms, which will also aid in providing herd immunity in neonates and infants who are either not or under vaccinated.

A special population at increased risk for *S. pneumoniae* meningitis are patients with cochlear implants who were found to have 30 times more the incidence of pneumococcal meningitis than that of an age-matched cohort in the general population in the U.S.[85] Studies have shown that pneumococcal vaccination was effective in preventing meningitis induced via the hematogenous route but not through direct extension from the middle ear.[86–88] So the current recommendation is that all current and future recipients of cochlear implants should be immunized against *S. pneumoniae*. In addition to vaccination, providing chemoprophylaxis to close contacts of patients with *H. influenzae* and *N. meningitidis* should be provided to prevent and eradicate carrier state and secondary cases.

Future Perspectives

Globally, bacterial meningitis remains a significant cause of neurological morbidity and mortality in children. Future efforts should focus on prevention by improving access and adherence to vaccination in children to the most common meningeal pathogens (*S. pneumoniae, N. meningitidis, H. influenzae* type b) and to group B streptococcus screening and therapy in pregnancy. Furthermore, future pentavalent vaccines for *N. meningitidis* could further decrease meningococcal meningitis due serogroup B or even eliminate sub Saharan Africa outbreaks due to non-Meningococcal group A serotypes. Improving health infrastructure in developing countries could improve access to care that could help reduce the morbidity and mortality in infants and children presenting with bacterial meningitis. Lastly, availability of rapid multiplex PCR panels could help in differentiating viral vs bacterial meningitis to aid in improving the time to diagnosis and therapy for bacterial meningitis.

Conclusion

Despite the decreased incidence in children due to vaccination and other preventive measures, community-acquired bacterial meningitis continues to be associated with high neurological morbidity and mortality. Prompt antibiotic therapy and adjunctive steroids in some etiologies is paramount in improving clinical outcomes. CT scan is indicated but should not delay antibiotic therapy in case of history of central nervous system disease, immunocompromised state, papilledema, or focal neurological deficits. Clinical models such as the Bacterial Meningitis Score and biomarkers such as serum CRP, procalcitonin and CSF lactate can be useful tools to differentiate bacterial from viral meningitis. Repeat LP is not routinely recommended in patients who respond appropriately to antimicrobial therapy. Future studies should continue to explore the utility of multiplex PCR and metagenomic next-generation sequencing (mNGS) in the evaluation patients with suspected ABM.

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