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REVIEW

Update on acute bacterial meningitis in children

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Abstract

Acute bacterial meningitis is a life-threatening infection of the membranes lining the brain. The causative organisms vary according to age and immune status and include group B streptococcus, Escherichia coli, Listeria monocytogenes, Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis and Staphylococcus aureus. Neisseria meningitidis is the primary cause of meningitis epidemics and historically has been the main cause of bacterial meningitis in the African Meningitis Belt (AMB). Antibiotic treatment including duration of therapy depends on the causative organism. The recent introduction of a meningococcal conjugate vaccine directed against serogroup A Neisseria meningitidis in childhood immunisation programmes in the AMB has been remarkably successful dramatically reducing the incidence of serogroup A meningitis.

Introduction

Acute bacterial meningitis is a severe life-threatening infectious disease of the membranes lining the brain with an associated high morbidity and mortality.[1,2] It affects all age groups, causing up to 15 million infections worldwide. Young children and the elderly are the most commonly affected.[1]

Globally, the epidemiology of bacterial meningitis has changed considerably over the past few decades following the introduction of conjugated vaccines against the most common etiologic agents. However, cases are still reported with the highest incidence occurring in children in sub-Saharan Africa.[3]

Traditionally, laboratory diagnosis of bacterial meningitis relies on the identification of the offending agents through examination of the cerebrospinal fluid (CSF) obtained from lumbar puncture. Recent advances in the diagnostic workup have resulted in more rapid identification of the causative bacteria.[4,5] In 2016, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) published a comprehensive guideline on the diagnosis and treatment of community-acquired bacterial meningitis in hospitals, providing up-to-date scientific evidence for best medical practice.[6] No such comprehensive evidence-based guidelines exist for resource-limited settings. This review highlights the key points of the ESCMID guideline and discusses the challenges for diagnosis and treatment faced in resource-limited settings including sub-Saharan Africa.

Epidemiology

The causative organisms of community-acquired acute bacterial meningitis vary according to age and immune status. Most cases are caused by group B streptococcus (*Streptococcus agalactiae*), *Escherichia coli, Listeria monocytogenes, Haemophilus influenzae* type B, *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Staphylococcus aureus*.[1,3–6]

In neonates, it is typically caused by *Streptococcus agalactiae* (group B Streptococcus) and *E. coli*.[1,6] Group B Streptococcus (GBS) colonizes the birth canal and infects the newborn during delivery. Recent studies have examined, with mixed outcomes, the effect of prophylactic intrapartum antibiotics and maternal vaccination on vaginal colonization by GBS and whether these interventions impact the incidence of GBS meningitis in neonates.[2]

E. coli is the next most important cause of neonatal meningitis. In various studies performed in four European countries, it accounted for 21% of cases seen.[6]

After the neonatal period, the common meningeal pathogens are *Streptococcus pneumonia, Neisseria meningitidis* and *Haemophilus influenzae*, accounting for more than 77% of cases.[1,3] *S. pneumoniae* remains the most common cause of community-acquired bacterial meningitis in children in developing countries despite the introduction of various polyvalent pneumococcal vaccines. Various studies have reported a decrease in the incidence of pneumococcal meningitis in children in well-resourced countries following vaccination, although not all serotypes are included in the vaccines.[1] In some resource-limited countries, pneumococcal vaccines are not fully rolled out leading to high morbidity and mortality from pneumococcal meningitis. The case fatality rate of pneumococcal meningitis is 10-20% in high-income countries and 30-40% in resource-limited countries, with a global estimate of 0.7 to 1.0 million deaths annually among children less than 5 years of age.[1,4]

Haemophilus influenzae affects children under 6 years with peak incidence between 6 to 12 months of age. Although there are several serotypes, type B accounts for >90% of *H. influenzae* meningitis.[4] Following the introduction of *H. influenzae* type B conjugate vaccines, *H. influenzae* now accounts for only 7% of cases of bacterial meningitis.[1] In the United States, H. influenzae meningitis is now seen primarily in children who are not immunized.[5]

Neisseria meningitidis often causes meningitis in epidemics. In several resource-limited countries including many parts of sub-Saharan Africa, major epidemics are caused primarily by serogroup A, although epidemics from other serogroups have been reported. The attack rates during these epidemics can approach 1% of the population.[1,4] To prevent transmission from a patient to close contacts, chemoprophylaxis with ciprofloxacin, ceftriaxone or rifampicin is recommended.[4,6] Meningococcal polysaccharide vaccines to specific populations are recommended for prevention of outbreaks. The introduction of a serogroup A meningococcal conjugate vaccine in the African meningitis belt has been a remarkable success. The rollout started in Burkina Faso which saw a drastic reduction in the incidence of serogroup A meningitis cases and a fall in carriage of serogroup A from 0.39% to 0%. In Chad, a similar reduction in carriage was seen from 0.75% to 0.02%, conferring an important additional benefit

of herd immunity.[7] Currently, many African countries working together with the WHO, have introduced the meningococcal A conjugate vaccine into childhood immunization programmes as part of the WHO global road map to defeat meningitis by 2030.[8]

Listeria monocytogenes causes about 9% of acute bacterial meningitis worldwide, with highest incidence in infants, the elderly and the immunosuppressed such as individuals with malignancies or post-transplantation. Outbreaks can develop from eating salami, raw vegetables, seafoods, unpasteurized milk or homemade goat cheese. The mortality rate is up to 30% but may be elevated in patients with pre-existing comorbidities.[4]

Staphylococcus aureus is a major cause of hospital- acquired meningitis, accounting for about 5% of cases in children with a mortality rate of about 30%. *S. aureus* meningitis occurs due to post-operative complication or via hematogenous spread in hospitalized children.[4] Methicillin- resistant strains are increasingly becoming important in hospital-acquired *S. aureus* meningitis.[9]

Risk factors

Maternal risk factors for acute bacterial meningitis in neonates include chorioamnionitis, endometritis, group B Streptococcal colonization, and prolonged duration of intrauterine monitoring exceeding 12 hours. Host risk factors in neonate and infants include prematurity, low birth weight, traumatic delivery, fetal hypoxia, urinary tract abnormalities, dermal sinus tract of the spine, galactosaemia, Down syndrome and congenital heart diseases.[4]

In older children, the risk factors for acute bacterial meningitis include poor socio-economic background, malnutrition, day care attendance, asplenia, primary immunodeficiency, HIV infection, sickle cell anaemia, recent or current respiratory tract infection, recent exposure to a case of meningococcal or *Haemophilus influenzae* meningitis, CSF leakage, intracranial shunts, penetrating head trauma, dermal sinus of the spine, cochlear implants and lack of immunization.[4]

The risk for invasive infections, including meningitis is increased in immuno-compromised states such as HIV infection, diabetes mellitus, asplenia, cancer and immunosuppressive therapy. HIV-infected children have a higher risk of invasive pneumococcal infections. Highly active anti-retroviral therapy (HAART) reduces this risk but leaves it still higher than for children without HIV infection. The most common pathogen in immunocompromised children is *S. pneumoniae*, but other pathogens such *as L. monocytogenes, E. coli*, *Salmonella* species and *S. aureus* are also frequently encountered.[1]

The most common risk factor for recurrent bacterial meningitis in children is congenital anatomical defects. Other risk factors include head trauma, CSF leakage, and immunodeficiencies resulting from HIV infection, asplenism and complement component deficiencies.[1]

Clinical features

The symptoms and signs of bacterial meningitis in children depend on the age of the child, the duration of illness and the immune status of the host.[5] In neonates and infants, the classical features may be subtle and non-specific, and may include temperature instability (hypothermia or fever), lethargy, sleepiness, jitteriness, irritability, poor feeding, vomiting, diarrhoea, respiratory distress, bulging fontanelles, hypotonia, seizures and impaired consciousness. Older children may report headaches, neck pain, photophobia, nausea, back pain and confusion in addition to fever, vomiting, irritability, seizures and altered mental status.[4–6]

Classical signs of meningeal irritation seen in bacterial meningitis include neck stiffness, Kernig's sign and Brudzinski's sign. Focal neurological findings and signs of raised intracranial pressure may also be elicited. However, these signs may be absent in younger children and the immunocompromised. Cushing's triad, comprising systemic hypertension, bradycardia and respiratory depression, is often a late sign.[5] It is important to note that there is no clinical sign of bacterial meningitis that is present in all patients.[6]

Diagnostic workup

Examination and culture of the cerebrospinal fluid (CSF) obtained from lumbar puncture (LP) is the key to the diagnosis of bacterial meningitis. LP is quite invasive and should be performed only after carefully ruling out contraindications such as cardiopulmonary instability, bleeding tendencies, localized infection of the skin of the lower back, ongoing seizures, and signs of raised intracranial pressure. In well-resourced centres, a CT scan of the brain is done to evaluate the possibility of increased intracranial pressure before performing a LP.[4–6] In centres where CT scans are not available, clinical characteristics can be used to identify patients with increased intracranial pressure and thus increased risk of brain herniation.[6]

The following CSF parameters should be determined for patients with acute bacterial meningitis:

- CSF opening pressure: this is usually increased to 200-500 mmH20 in older children. In infants and younger children, the opening pressure may be lower.
- CSF appearance: this is usually cloudy but may be clear.
- CSF leukocyte (WBC) count: this is typically elevated to 1000-3000/mm^3. However, in the immunosuppressed child, the WBC count may be lower. Also, in neonatal meningitis, the CSF leukocyte count is frequently normal or slightly elevated.[6]
- WBC differential: predominantly neutrophils (polymorphonuclear leukocytes).
- CSF glucose concentration: this is usually reduced to <40mg/dL. It is best to compare the CSF glucose to the serum level at the time of the LP. The normal CSF glucose is about two-thirds the serum level.
- CSF protein concentration: usually elevated above the upper limit of 0.4 g/L.
- CSF lactate: this is usually raised in bacterial meningitis. Studies have shown that CSF lactate has a better diagnostic accuracy than leukocyte count. It is however less specific as it cannot differentiate bacterial meningitis from other CNS diseases such as encephalitis and seizures.[6]
- Gram stain: a positive Gram stain depends on the concentration of bacteria in the CSF. The average positivity rate is >75%. Cytospin centrifugation increases the chances of detecting organisms in Gram-stained CSF.[5]
- Culture and antibiotic sensitivity: this also depends on the concentration of bacteria in the CSF and whether the patient has previously received antibiotics. In such children, an increased WBC count and protein concentration are sufficient to establish the diagnosis.[4,5]

Other alternative diagnostic tests include latex agglutination which detects bacterial antigens in the CSF. Newer techniques such as multiplex polymerase chain reaction (PCR) on the CSF are now widely used in well-resourced countries to provide a faster and more accurate diagnosis of bacterial meningitis.[4–6]

Serum inflammatory markers may help differentiate between bacterial and viral meningitis. In children with meningitis, elevated C-reactive protein and pro-calcitonin are associated with bacterial infections.[6] However, in situations where there is coexisting pneumonia or sepsis, these inflammatory markers have little value for the diagnosis of bacterial meningitis.[1,6]

Blood cultures may detect the responsible organism, if CSF cultures are negative or not available. Blood culture positivity rate is different for each causative organism. It is reported to be about 75% for pneumococcal meningitis, 50- 90% for *H. influenzae* meningitis and 40-60% for meningococcal meningitis.[1] The yield of blood cultures decreases if the patient is pre-treated with antibiotics.[1,6] The ESCMID guideline recommends performing blood cultures in patients with suspected bacterial meningitis before the first dose of antibiotics are administered.[6]

Neuroimaging may be helpful in identifying complications such as cerebral infarcts, subdural empyema, intracranial abscess, and hydrocephalus. Where resource availability permits, it is also recommended to perform cranial imaging before an LP in patients with focal neurologic deficit, severely altered mental status (Glasgow coma score <10), new-onset seizures, or severely immunocompromised state. In patients lacking these characteristics, cranial imaging before an LP is not recommended.

Antibiotic treatment

Performing a lumber puncture to obtain CSF for diagnostic work-up should not delay the start of antibiotics. It is strongly recommended to start antibiotics as soon as possible in patients with acute bacterial meningitis.[10] The ESCMID guideline recommends that time from clinical suspicion to antibiotics administration should not exceed 1 hour. Whenever the LP is delayed, empirical treatment should be started on clinical suspicion, even if the diagnosis has not been established.[6]

Empirical treatment in neonates should include a penicillin plus cefotaxime or an aminoglycoside. In older children, the ESCMID recommends cefotaxime or ceftriaxone plus vancomycin or rifampicin.[6]

The specific antibiotic treatment in bacterial meningitis is based on antimicrobial susceptibility testing. After identification of the pathogen through culture and antibiotic sensitivity testing, the antibiotic treatment can be optimized. The duration of antibiotic treatment depends on the culture isolate. *For S. pneumoniae*, the treatment is typically for 10- 14 days. For meningococcal meningitis, the patient should be treated with antibiotics for 7 days. Where *L. monocytogenes* is isolated, the treatment should be for at least 21 days. Patients with *H. influenzae* meningitis should receive 7-10 days treatment with antibiotics.[1] In neonates with group B *Streptococcus* meningitis, it is recommended to treat for 14-21 days, while those with Gram negative isolates should be treated for a minimum of 21 days.[11]

Table 1. Specific antibiotic therapy for bacterial meningitis based on bacterial isolate from the CSF[9–11]

Cerebrospinal fluid isolate	Standard therapy	Minimum duration of treatment
Streptococcus pneumoniae	Penicillin G or ampicillin 3rd generation cephalosporin (cefotaxime/ ceftriaxone) Vancomycin (plus 3rd generation cephalosporin)	10-14 days
Haemophilus influenzae	Ampicillin 3rd generation cephalosporin Meropenem (plus 3rd generation cephalosporin)	7-10 days
Neisseria meningitidis	Penicillin G or ampicillin 3rd generation cephalosporin	7 days
Listeria monocytogenes	Ampicillin or penicillin G	21 days
Streptococcus agalactiae	Ampicillin or penicillin G (aminoglycoside or cefotaxime may be added)	
Gram negative organisms in neonates	Aminoglycoside (ampicillin, cefotaxime or ceftazidime may be added)	21 days
Staphylococcus aureus Methicillin sensitive Methicillin resistant	Nafcillin or cloxacillin Vancomycin (trimethoprim/ sulphamethoxazole or rifampicin may be added)	Varies (based on successful treatment of primary focus or removal of intracranial implant)
No pathogen isolated	Empirical treatment	2 weeks minimum

For *S. aureus* meningitis, the optimal duration of treatment varies and should be based on the simultaneous treatment of both the CNS and the primary infection such as endocarditis, skin and soft tissue infection, and epidural abscess, as well as removal of infected shunts and intracranial devices. Where an infected shunt is removed, placement of a new shunt should be followed by continuation of

antibiotic therapy for at least 14 days.[9]

The recommended treatment for patients in whom no pathogen can be detected should be according to the empiric regimen for a minimum duration of 2 weeks.[6] Table 1 below summarizes the common antibiotic treatment and duration for various CSF isolates.

Adjunctive treatment

The outcome of bacterial meningitis is related to the severity of inflammation in the subarachnoid space. Thus, immunomodulation of the inflammatory response with corticosteroids influences the neurologic outcome in survivors such as hearing loss, aphasia, ataxia, paresis and cognitive impairment, especially in those in whom the causative agent is either *S. pneumoniae* or *H. influenzae*.[4] Dexamethasone is the most widely used corticosteroid in children with bacterial meningitis beyond the neonatal age group. It is recommended that the treatment with dexamethasone should be started with the first dose of antibiotics or within 4 hours of starting antibiotics. Expert opinion suggests that dexamethasone should be stopped if the patient is discovered not to have bacterial meningitis or if the causative organism is found to be a species other than *S. pneumoniae* or *H. influenzae,* although some experts advise that adjunctive corticosteroid should be continued irrespective of the causative bacterium.[4,6]

Other adjunctive treatments with proven benefits in bacterial meningitis include acetaminophen and antiepileptic treatment. Acetaminophen has been considered to improve the inflammatory response and decrease fever. However, in a randomized control trial in Malawian children, no beneficial effect was observed.[12] Antiepileptic treatment should be used in children with prolonged or recurrent seizures.

The use of osmotic agents such as glycerol, mannitol and hypertonic saline in children with bacterial meningitis remains controversial with some authors suggesting no potential beneficial effect.[6]

Nursing management consists of effective delivery of antibiotic therapy, fluid management and supportive care.[13]

Prophylaxis

There is a very high risk of meningococcal disease in individual who are close contacts of persons with meningococcal meningitis. This risk may be averted by taking prophylactic antibiotics. The ESCMID guideline strongly recommends that close contacts of patients with meningococcal meningitis receive prophylactic antibiotics consisting of either ceftriaxone, ciprofloxacin or rifampicin.[6] Close contacts are defined as household contacts, childcare centre contacts and anyone directly exposed to oral secretions of the patient.

Vaccination

Many cases and deaths from bacterial meningitis can be prevented through vaccination. In the past 20 years, there has been significant progress in reducing the incidence of meningitis globally. Although the burden of bacterial meningitis is greatest in the meningitis belt of sub-Saharan Africa, it remains a threat in all countries worldwide. The WHO recommended vaccination programmes against some of the bacterial agents are yet to be introduced in many countries. In 2017, stakeholders from governments, health organizations, academia and civil society called for a global vision action to "defeat meningitis by 2030". The WHO is coordinating this action and has developed a roadmap to that effect. This initiative seeks, among other goals, to make vaccines more widely available.[8]

To achieve these goals, there are enhanced efforts to encourage all recommended immunizations and promote high levels of vaccine coverage for bacterial meningitis at national levels. Conjugate vaccines have been introduced into childhood immunization programmes of many low- and middle-income countries and have dramatically reduced the burden of meningitis caused by *N. meningitidis*, *S. pneumoniae* and *H. influenzae* type b, but their global uptake needs to be enhanced.[7,8]

The goals of the WHO roadmap for defeating meningitis by 2030 are:

- To eliminate bacterial meningitis epidemics
- To reduce cases of vaccine-preventable bacterial meningitis by 50% and deaths by 70% and
- To reduce disability and improve quality of life after meningitis due to any cause.[8]

Complications

Common complications of acute bacterial meningitis in neonates include sepsis, seizures, and hydrocephalus. Patients with sepsis should be evaluated to determine whether other foci of infection are present, such as pneumonia and endocarditis and treated according to guidelines for the management of sepsis.

Seizures may be clinical or subclinical. If not clinically evident, EEG should be done to detect subclinical seizures and antiepileptic treatment provided accordingly. Neonates with meningitis should have transcranial ultrasound or cranial MRI to rule out hydrocephalus. If detected, external ventricular drain or shunt can be placed.[6]

Older children and adults with bacterial meningitis may also suffer seizures and hydrocephalus. In addition, other common complications are stroke (both ischaemic and haemorrhagic), subdural empyema, abscess, sinus thrombosis and hearing loss. Neuroimaging can help to identify ischaemic infarcts, bleeds, empyema, abscess, or sinus thrombosis. Patients with haemorrhagic stroke, empyema or abscess are managed surgically. All children with bacterial meningitis should have hearing assessment to evaluate for hearing loss. Hearing loss needs to be detected early during the disease course in order to ensure appropriate referral and early treatment.[6]

After recovery, children may suffer neuropsychologic sequelae. such as poor cognitive abilities and school failures. Such children will benefit from neuropsychology evaluation and appropriate rehabilitation.[6]

Conclusion

Acute bacterial meningitis is a serious neurologic illness with significant morbidity and mortality if not treated promptly and adequately. The etiologic agents vary with different age groups and are influenced by host risk factors and immune status. The classical presentations in patients with bacterial meningitis are fever, neck stiffness, headache, and altered mental status. However, in neonates and young children, the presentation may be subtle requiring a high index of suspicion. CSF microscopy, chemistry, Gram stain and culture remain the best approach to confirming the diagnosis, though new technologies are being deployed in well-resourced centres. When bacterial meningitis is suspected, antibiotic treatment should be started as soon as possible for better outcomes. The use of adjuvant corticosteroids has been shown to be helpful in specific clinical situations.

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