Bacterial Meningitis

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KEYWORDS

• Bacterial meningitis • Pneumococcal meningitis • Meningococcal meningitis
• *Listeria monocytogenes* • Vaccine

KEY POINTS

- Community-acquired bacterial meningitis is a medical emergency with a high morbidity and mortality rate, even with effective antibiotics.
- Vaccines for *Streptococcus pneumoniae, Neisseria meningitidis*, and *Haemophilus influenzae*, may minimize the risk for invasive disease.
- Cerebral spinal fluid testing for cultures and/or polymerase chain reaction is critical to establish a diagnosis of bacterial meningitis.
- Antibiotics should be started as soon as possible, even if neuroimaging or a lumbar puncture is delayed.
- Adjunctive dexamethasone should be administered with the first dose of empiric antibiotics in patients with suspected bacterial meningitis.

INTRODUCTION

Meningitis results from the inflammation of the meninges and subarachnoid space.[1,2] Bacterial meningitis is an infectious diseases emergency, and in the absence of effective antibiotic treatment, it is often fatal.[2] Given the close proximity of the meninges to the brain cortex and parenchyma, bacterial meningitis may be complicated by significant long-term neurologic sequelae in up to 20% of cases.[1–3] Because of the significant public health impact of bacterial meningitis globally, the World Health Organization (WHO) has created a "global road map" to eliminate bacterial meningitis epidemics, optimize vaccine use to prevent new cases, and reduce disability caused by meningitis, by 2030.[2]

DISCUSSION

Epidemiology

Community-onset bacterial meningitis typically develops from either local extension or hematogenous spread of pathogens to the meningeal spaces.[1,4] *Streptococcus*

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Abbreviations	
CDC	Centers for Disease Control and Prevention
CT	computed tomography
PCN G	penicillin G
WHO	World Health Organization

pneumoniae, *Neisseria meningitidis*, and *Haemophilus influenzae* colonize the nasopharynx, and they primarily reach the meninges by crossing the blood–brain barrier, however, direct extension through bony defects caused by mastoiditis or otitis media, may also occur.[1,4] Bacterial meningitis may also develop from direct inoculation to the meninges following head trauma or invasive neurosurgical procedures.[4] Group B Streptococci (*Streptococcus agalactiae*) and *Listeria monocytogenes* are enteric organisms,[5] and *L.monocytogenes* is commonly associated with foodborne transmission.[6]

The most common causes of community-acquired bacterial meningitis in adults are *S. pneumoniae*, followed by *N. meningitidis*.[7] The differential diagnosis for bacterial meningitis in older adults also includes less common organisms such as Group B Streptococci (*Streptococcus agalactiae*), *H. influenzae*, and *L. monocytogenes*.[7] *L. monocytogenes* should specifically be considered in all adults with suspected bacterial meningitis who are greater than 50 years of age or immunocompromised; in one study, no cases of *Listeria* meningitis occurred in immunocompetent adults younger than 50 years of age.[8]

Vaccine history, underlying medical conditions, and exposure history can provide information about a patient's risk for bacterial meningitis (**Table 1**). Effective vaccines are available for *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*; however, serogroups not covered by vaccines are emerging.[9] There is currently no vaccine available against Group B Streptococci or *L. monocytogenes*. In addition, some pathogens follow a predictable seasonal pattern. *N meningitidis* peaks in late winter and early spring.[10] *H. influenzae* has a bimodal temporal pattern with peaks between September–December and March–May.[11]

The rate of asymptomatic carriage of *S. pneumoniae* varies greatly by age and environment, with an estimated 5% to 10% of adults having nasopharyngeal colonization, although this rate increases in adults with exposure to school-age children.[16] Development of immunity after nasopharyngeal colonization is unclear.[16] The incidence of invasive disease has been significantly reduced since the introduction of pneumococcal vaccines,[16] although new serotypes are emerging.[17] Currently, a single dose of pneumococcal 20-valent conjugate vaccine (PCV20) is recommended to all adults over age 65 years, if no prior pneumococcal vaccine has been administered.[18] Alternatively, pneumococcal 15-valent conjugate vaccine (PCV15) may be administered, followed by a dose of pneumococcal polysaccharide vaccine (PPSV23) a year later.[18] Additional recommendations by the Centers for Disease Control and Prevention (CDC) for repeat vaccination are available to recipients of prior pneumococcal vaccines.[18] Pneumococcal vaccination should be provided to individuals younger than 65 years old who are immunocompromised, living with human immunodeficiency virus (HIV), have acquired or functional asplenia, underlying cerebrospinal fluid (CSF) leaks or cochlear implant recipients, or a chronic medical condition diagnosis, such as diabetes, chronic cardiac/liver/kidney disease, tobacco or alcohol use disorder, or hemoglobinopathies.[18]

Asymptomatic carriage of *N. meningitidis* occurs in approximately 5% to 10% of people, although development of invasive disease is uncommon.[10,19] Rates of nasopharyngeal carriage peaks in early adulthood, then subsequently declines.[20] Carriage

Table 1
Risk factors for bacterial meningitis[12–15]

Group	Most Common Bacterial Pathogens	Empiric Treatment (dosed for normal renal/ hepatic function)
Immunocompetent adult <50 y and no neurosurgical instrumentation	*S. pneumoniae* *N. meningitidis*	Cefotaxime 2 g IV q4-6h or Ceftriaxone 2 g IV q12 h plus Vancomycin 10 -20 mg/kg IV q8-12 h (goal serum trough 15-20 μg/mL)s
Adult >50 y and no neurosurgical instrumentation	*S.pneumoniae* *N. meningitidis* *L. monocytogenes* Group B Streptococci	Vancomycin 10 -20 mg/kg IV q8-12 h (goal serum trough 15-20 μg/mL) plus Ampicillin 2 g IV q4h plus Ceftriaxone 2 g IV q12 h or Cefotaxime 2 g IV q4-6h
Immunocompromised patients	*S. pneumoniae* *N. meningitidis* *L. monocytogenes* Group B Streptococci Gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin 10 -20 mg/kg IV q8-12 h (goal serum trough 15-20 μg/mL) plus Ampicillin 2 g IV every q4h plus Cefepime 2 g IV q8h or Vancomycin 10 -20 mg/kg IV q8-12 h (goal serum trough 15-20 μg/mL) plus Meropenem 2 g IV q8h
Patients with recurrent meningitis	*S. pneumoniae* *H. influenzae*	Cefotaxime 2 g IV q4–6h or Ceftriaxone 2 g IV q12 h plus Vancomycin 10 -20 mg/kg IV q8-12 h (goal serum trough 15-20 μg/mL)
Patients with potential disruption between skull or bloodstream and brain barrier (ex, basilar skull fracture, recurrent otitis media, sinusitis)	*S. pneumoniae* *H. influenzae* Group A β-hemolytic streptococci	Cefotaxime 2 g IV q4-6h or Ceftriaxone 2 g IV q12 h plus Vancomycin 10 -20 mg/kg IV q8-12 h (goal serum trough 15-20 μg/mL)
Patients with history of neurosurgery	*Staphylococcus species* Gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin 10 -20 mg/kg IV q8-12 h (goal serum trough 15-20 μg/mL) plus Cefepime 2 g IV q8h or Ceftazidime 2 g IV q8h
Patients with infective endocarditis	*S.aureus* Some Streptococcal species	Cefotaxime 2 g IV q4-6h or Ceftriaxone 2 g IV q12 h plus Vancomycin 10 -20 mg/kg IV q8-12 h (goal serum trough 15-20 μg/mL)

is felt to provide serotype-specific immunity.[10,19] Vaccination with the meningococcal ACWY (MenACWY) vaccine series is currently recommended to all adolescents, however, subsequent boosters should be provided to people at an increased risk for invasive disease: complement pathway deficiencies (either genetic or acquired through use of monoclonal antibodies that block C5, such as eculizumab and ravulizumab), asplenia (including functional asplenia seen in sickle cell disease), HIV disease, travelers to countries where disease is endemic (including the meningitis belt of sub-Saharan Africa or participation in the Hajj pilgrimage), college students residing in dormitories, military recruits, and microbiologists with potential risk for exposure.[18,21] Boosters of MenACWY vaccine should be provided every 5 years if the ongoing risk for invasive disease persists.[18]

Additional vaccination with serogroup B meninogococcal (MenB) vaccine should be provided to individuals with asplenia or complement deficiency.[18] It is available after a shared decision-making process to young adults up to age 23 years of age, particularly to college students living on campus.[18,21] Several outbreaks of invasive meningococcal disease related to Serogroup B have been reported in universities across the United States (US).[22] Deciding whether to administer MenB vaccine should consider the high rates of mortality and complications after contracting disease relative to the short duration of protection (1–2 years) and minimal impact on nasopharyngeal carriage.[18,21] Of note, the number of cases of invasive meningococcal disease has been increasing over the past couple years in the United States, primarily related to serogroup Y.[23] These cases have disproportionately impacted individuals who are 30 to 65 years of age, Black or African American people, and people living with HIV.[23]

Prior to routine administration of the *Haemophilus influenzae* type B (Hib) vaccine series to children, over 95% of cases of invasive disease were related to serotype B.[11] Currently, *H. influenzae* nasopharyngeal colonization is uncommon in adults, and diseases from other serotypes are emerging.[11] Individuals at an increased risk for invasive disease include adults older than 65 years, American Indian and Alaska Native people, people with acquired or functional asplenia, people with a diagnosis of sickle cell disease, people living with HIV, and people with immunodeficiencies.[11] One dose of Hib vaccine should be provided to people with asplenia who did not receive prior Hib vaccine, while a 3-dose series should be provided to recipients of a successful hematopoietic stem cell transplant, regardless of vaccination history.[18]

Recurrent meningitis may be seen in patients with a CSF leak, remote head trauma, or a neurosurgical procedure in the month prior to episode.[24] In a prospective cohort study from the Netherlands, approximately 3% of community-acquired bacterial meningitis cases had an associated CSF leak, most commonly in the setting of prior otolaryngological intervention, neurosurgery, or head trauma.[25] *S. pneumoniae* was the most frequently isolated organism in meningitis due to CSF leaks, however, most notably, 15% of *H influenzae* meningitis cases were due to a CSF leak.[25] Compared with meningitis unrelated to CSF leak, these cases presented earlier with less than 24 hours after symptom onset, had milder disease with more favorable outcomes, and had more recurrences.[25] Work-up for a potential need for surgical intervention should be considered in recurrent meningitis.[25]

Clinical Presentation

Prior studies from the Netherlands revealed that the classic triad of fever, neck stiffness, and altered mental status was present in only 44% of cases, however, 95% had at least 2 of 4 symptoms of headache, fever, neck stiffness, and altered mental status.[26] Similar findings have been supported by subsequent research.[27] Additional features may be more common depending on the pathogen. As an example, a

petechial rash starting in the extremities may occur in over 50% of patients with meningococcal meningitis; however, rashes are less common in other causes.[26–28] This rash may progress to purpura, gangrene, and limb loss.[28] Meningitis secondary to *S. pneumoniae* tend to have higher frequency of seizures, focal neurologic deficits, extrameningeal disease, and lower level of consciousness.[26,27] Patients with *S. pneumoniae* meningitis may have long-term complications such as intracranial bleeding, hydrocephalus, and hearing loss.[29]

Diagnosis

A lumbar puncture for CSF studies is crucial for diagnosis of meningitis, although patients with increased intracranial pressure can increase the risk for brain herniation.[30] As a result, the Infectious Diseases Society of America (IDSA) recommends a head computed tomography (CT) without contrast prior to obtaining a lumbar puncture in individuals who have an immunocompromising condition, history of CNS disease, focal neurologic disease, new-onset seizures within 1 week of presentation, papilledema, or an abnormal level of consciousness.[12] Adherence to these guidelines have been relatively low with many patients receiving neuroimaging as part of a routine bacterial meningitis work-up in the absence of these characteristics, which may result in a delayed diagnosis and poor outcomes.[30] In a retrospective review of individuals with community-acquired meningitis, a CT scan was obtained in 89% of patients, but only 1.5% had findings that would impact management.[30]

Blood cultures are recommended in all patients with suspected bacterial meningitis, and they should be obtained as soon as possible, ideally prior to starting antibiotics.[12] The yield of blood cultures varies depending on pathogen and preceding antibiotics,[31] however, they may be positive in up to 75% of cases.[27,32] From the studies of patients presenting with undifferentiated sepsis, preceding antibiotics may decrease the yield of blood cultures by 20%.[33]

Lumbar punctures should be obtained with an opening pressure, which is often elevated in patients with bacterial meningitis.[1] Cerebral spinal fluid should be sent for cell count, glucose, protein, and cultures. Most individuals with bacterial meningitis have classic findings for bacterial meningitis including a polymorphic pleocytosis, elevated protein, and low glucose.[1,13] A CSF: blood glucose of less than 0.23 is also suggestive of bacterial meningitis.[12] The pleocytosis and other CSF parameters start to normalize within the first 48 to 72 hours after antibiotics.[31,34] A CSF lactate level may be helpful in differentiating bacterial meningitis from aseptic meningitis, however, the discriminating power of this laboratory test is diminished by prior antibiotics.[13,31] The yield of CSF cultures also decreases with prior antibiotics. In a review of patients admitted with bacterial meningitis, the majority of CSF cultures remained positive for the first 4 hours after antibiotics, however, none were positive more than 8 hours after antibiotic administration.[31,35] Patients with *Listeria* meningitis may have atypical CSF findings, and in a prospective review from the Netherlands, 23% had no CSF parameters consistent with bacterial meningitis, while only 28% had a positive Gram stain.[8]

Molecular testing of cerebral spinal fluid is increasingly being used to aid with the diagnosis of bacterial meningitis. CSF polymerase chain reaction (PCR) testing is more rapid, can detect fewer organisms, and has more sensitivity than cultures in detecting bacterial meningitis.[36] Real-time PCR assays have a high level of accuracy for diagnosis of *S. pneumoniae*, *N. meningitidis*, and *H. influenzae*, even when cultures are negative, and they may be useful in patients who have received antibiotics previously.[37] PCR testing may stay positive for up to a week after antibiotic administration.[38]

Treatment

Antibiotics should be given as soon as possible to adults with suspected community-acquired bacterial meningitis, and administration should not be postponed, even if necessary diagnostic work-up is delayed (**Fig. 1**). High rates of mortality have been reported in patients who receive antibiotics more than 2 hours after initial presentation.[39] Delaying lumbar punctures while waiting for a head CT can result in later antibiotic administration and an increased mortality, and neuroimaging prior to a lumbar puncture to minimize risk for brain herniation is warranted in only certain cases.[40] Guidelines recommend providing the first dose of antibiotics within an hour of initial presentation to the hospital.[13]

Empiric antibiotics should be targeted against common bacterial pathogens encountered in community-acquired meningitis. Ceftriaxone 2 grams administered intravenously every 12 hours provides coverage for *S. pneumoniae*, *N. meningitidis*, and *H. influenzae*. Intravenous vancomycin is added for *S. pneumoniae* isolates that may be resistant to ceftriaxone, defined in CSF infections as a minimum inhibitory concentration (MIC) greater than 2 μg/mL.[13,41] Invasive *S. pneumoniae* with extended-spectrum cephalosporin resistance in US adults has been decreasing due to pneumococcal vaccines targeting resistant serotypes, and it was recently estimated to be about 2.7%.[42] Additional coverage for *L. monocytogenes* with ampicillin should be provided in adults who are immunocompromised or over 50 years of age.[13] Although beyond the scope of this article, additional coverage for herpes simplex virus may also be warranted until CSF studies are available, as it is treatable and may have long-term sequelae if untreated.[43]

Starting adjunctive dexamethasone at the same time as antibiotics is recommended in all adults with suspected bacterial community-acquired meningitis.[27,44] In a

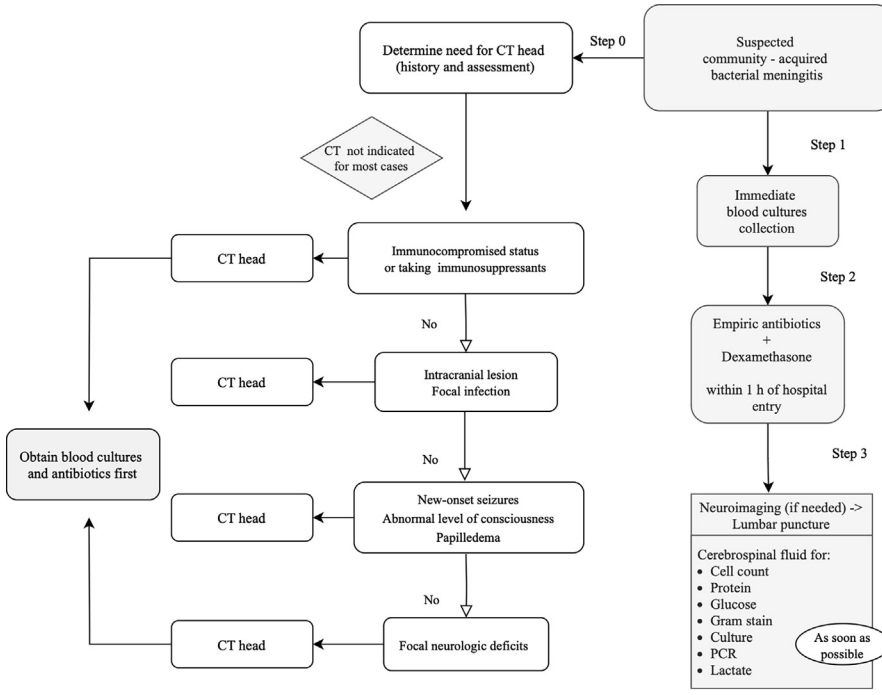

Fig. 1. Diagnostic work-up for bacterial meningitis.[12]

Cochrane meta-analysis, adding corticosteroids resulted in a significant reduction of hearing loss and short-term neurologic sequelae (defined as within 6 weeks of discharge) in higher income countries.[45] In addition, patients with bacterial meningitis secondary to *S. pneumoniae* had significantly reduced mortality.[45] There are no randomized control trials addressing when starting dexamethasone is no longer helpful, but if not receiving immediately, available guidelines support adding dexamethasone up to 4 hours after initiation of antibiotics.[13]

Continuation of adjunctive dexamethasone use had not been routinely recommended in adults if pathogens other than *S. pneumoniae*[12,13] or *H. influenzae*[13] are isolated. Additional studies have suggested no adverse effects and potential benefit when adjunctive dexamethasone is used in patients with meningococcal meningitis.[44,46] Some authorities now advocate continued use of dexamethasone for 4 days in most cases of bacterial meningitis unless *L. monocytogenes* is isolated.[44] Results from the MONALISA national prospective cohort study suggested an increase in adverse outcomes in adults with *Listeria* meningitis who receive steroids.[47] More recent data using a larger patient sample of patients receiving early dexamethasone in *Listeria* meningitis suggest that there may be some benefit.[48]

The recommended choice and duration of antibiotics to target specific causes of meningitis are included in **Table 2**. In general, if intravenous vancomycin and ceftriaxone are started empirically, and *H. influenzae*, *N. meningitidis*, or ceftriaxone-susceptible *S. pneumoniae* are isolated, then vancomycin can be discontinued.[12] If *S. pneumoniae* is resistant to ceftriaxone, both ceftriaxone and vancomycin should be continued for the duration of therapy,[12] due to the risk for poor penetration of intravenous vancomycin across the blood–brain barrier.[49] Meningitis secondary to *N. meningitidis* or *H. influenzae*, should be treated for a minimum of 7 days.[12,13] *S. pneumoniae* meningitis should be treated for 10 to 14 days.[12,13] The preferred regimens for *L. monocytogenes* meningitis are penicillin G (PCN G) or ampicillin, which should be administered for at least 21 days.[12,13] Group B Streptococci (*Streptococcus agalactiae)*[12] and *Staphylococcus aureus*[13] meningitis should be treated with a targeted CNS-dosed regimen for a minimum of 14 days, while patients with meningitis related to gram-negative rods other than *N. meningitidis* or *H. influenzae* should be treated for at least 21 days.[12] In patients with suspected bacterial meningitis but no identified pathogen, antibitocs should be continued for a minimum of 14 days.[13]

S. pneumoniae, *N. meningitidis*, and *H. influenzae* are normal nasopharyngeal flora, and they are spread through respiratory droplets.[5] Patients with suspected bacterial meningitis should be placed on droplet precautions for at least the first 24 hours of effective antimicrobial therapy.[51] Additionally, chemoprophylaxis should also be administered to all close contacts, regardless of vaccination status, as soon as possible, but no later than 14 days after exposure.[10] Close contacts are defined as any household members, any exposure at a childcare center, and anyone having direct exposure to oral secretions within 7 days prior to an infected person's symptom onset.[10] Health care workers exposed to respiratory secretions or managing the airway of an infected person should also receive chemoprophylaxis.[10]

Recommended chemoprophylaxis regimens for invasive meningococcal disease have $\geq$90% effectiveness in eradicating nasopharyngeal carriage.[10] These regimens include: ciprofloxacin 20 mg/kg (maximum 500 mg) orally once, ceftriaxone 250 mg administered once intramuscularly, rifampin 10 mg/kg (maximum 600 mg) orally every 12 hours for 2 days, or azithromycin 10 mg/kg (maximum 500 mg) orally once.[10] The number of cases of ciprofloxacin-resistant invasive meningococcal diseases in the United States have increased dramatically since 2019, despite a 75% decrease in invasive meningococcal disease, primarily related to resistant *Neisseria meningitidis*

Table 2
Antibiotic regimens for bacterial meningitis[12,13,50]

Microorganism	Suggested Regimen	Potential Alternatives	Duration
Streptococcus pneumoniae			
Penicillin susceptible (MIC<0.1 μg/mL)	Penicillin G or ampicillin	Ceftriaxone, cefotaxime, or chloramphenicol	Minimum 10 d
Penicillin resistant (MIC 0.1 - 1.0 μg/mL), third-generation cephalosporin susceptible (MIC <2 μg/mL)	Ceftriaxone or cefotaxime	Cefepime, meropenem, or moxifloxacin	Minimum 10 d
Cephalosporin resistant (MIC ≥2 μg/mL)	Vancomycin plus ceftriaxone or cefotaxime, +/- rifampin	Vancomycin plus moxifloxacin	Minimum 10 d
Neisseria meningitidis			
Penicillin susceptible (MIC <0.1 μg/mL)	Penicillin G, or ampicillin	Ceftriaxone, cefotaxime, or chloramphenicol	Minimum 7 d
Penicillin resistant (MIC ≥0.1 μg/mL)	Ceftriaxone or cefotaxime	meropenem, ciprofloxacin, or chloramphenicol	Minimum 7 d
Listeria monocytogenes	penicillin G or ampicillin	Trimethoprim-sulfamethoxazole or meropenem	Minimum 21 d
Haemophilus influenzae			
β-Lactamase negative	Ampicillin	Ceftriaxone, cefotaxime, chloramphenicol, or ciprofloxacin	minimum 7 d
β-Lactamase positive	Ceftriaxone or cefotaxime	Cefepime, ciprofloxacin, or chloramphenicol	Minimum 7 d
Group B Strepotococci	Penicillin G or ampicillin	Ceftriaxone, cefotaxime, or vancomycin	Minimum 14 d
Gram-Negative Bacilli			
no *Pseudomonasaeruginosa* present	Ceftriaxone or cefotaxime (if susceptible)	Cefepime, ceftazidime, meropenem, or ciprofloxacin (if susceptible)	Minimum 21 d

including *Pseudomonas aeruginosa*	Cefepime or ceftazidime (if susceptible)	Meropenem or ciprofloxacin (if susceptible)	Minimum 21 d
Staphylococcus species			
Methicillin-sensitive	Nafcillin,	Vancomycin, linezolid, trimethoprim-sulfamethoxazole, daptomycin, or ceftaroline	Minimum 14 d
Methicillin-resistant	Vancomycin	Trimethoprim/sulfamethoxazole, daptomycin, ceftaroline linezolid	Minimum14 d

serogroup Y (NmY) strains.[52] The CDC now recommends an alternative regimen in areas having 2 or more cases of ciprofloxacin-resistant invasive meningococcal disease and ≥20% of invasive meningococcal disease being caused by ciprofloxacin-resistant strains over a 12-month period.[52]

SUMMARY

Bacterial meningitis is a medical emergency due to the high mortality rate as well as complications in long-term survivors. *S. pneumoniae* is the most common cause of bacterial meningitis, however, individuals may be at risk for other organisms based on immune status, medical comorbidities, and exposure history. Vaccinations against *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* should be provided to individuals at higher risk for invasive disease. Adults who are immunocompromised or older than 50 years of age are at risk for *Listeria* meningitis, and as there is no available vaccine, special attention must be made toward food intake and preparation. Empiric antibiotics and dexamethasone should be administered within an hour of presentation in all patients with suspected bacterial meningitis, even if neuroimaging and a lumbar puncture are delayed. Cerebral spinal fluid studies are necessary to establish a diagnosis of bacterial meningitis, and CSF PCR testing may be helpful if antibiotics were previously received. Droplet precautions should be provided for the first 24 hours of effective antibiotic therapy. If a diagnosis of meningococcal meningitis is established, chemoprophylaxis should be provided to all close contacts.

CLINICS CARE POINTS

- Vaccines should be provided to all adults at an increased risk for bacterial meningitis secondary to *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*.
- Empiric antibiotics and adjunctive dexamethasone should be administered as soon as possible in all patients with suspected meningitis, even if neuroimaging and CSF studies have not yet been obtained.
- To improve diagnostic yield of bacterial meningitis, all patients should have blood cultures, CSF cultures, and when available, CSF PCR testing.
- Patients should be placed on droplet precautions for the first 24 hours of effective antibiotic therapy.
- All adults who have had close contact with the individuals diagnosed with meningococcal meningitis should receive chemoprophylaxis.

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