Acute Community-Acquired Bacterial Meningitis

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Abstract

Community-acquired bacterial meningitis is a significant cause of morbidity and mortality. *Streptococcus pneumoniae* and *Neisseria meningitidis* are the most common causative organisms. The incidence of *Listeria monocytogenes* infection increases over age 50 years and in those with compromised cell-mediated immunity. Symptoms and signs are not sensitive or specific enough to diagnose community-acquired bacterial meningitis. A lumbar puncture for cerebrospinal fluid is needed to reach the diagnosis, to identify the organism, and to determine antimicrobial susceptibilities. Computed tomography of the head is not necessary in all patients prior to a lumbar puncture, only in immunocompromised patients and in those who have features suggestive of or who are at risk of increased intracranial pressure. Appropriate empiric antimicrobials should be started as soon as possible.

Keywords

Meningitis • Acute meningitis • Community-acquired bacterial meningitis Central nervous system infection • *Streptococcus pneumoniae* • *Neisseria meningitidis* • *Listeria monocytogenes* • Kernig's sign • Brudzinski's sign • Jolt accentuation • Neck stiffness • CSF pleocytosis

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Introduction and Epidemiology

Rapid diagnosis and management of acute community-acquired bacterial meningitis (ACBM) is important as delayed treatment has a poor prognosis. Meningitis is inflammation of the pia and arachnoid (the inner two layers of the meninges). Acute community-acquired meningitis can develop within hours to days and is usually viral or bacterial. Viral meningitis usually has a good prognosis, whereas bacterial meningitis is associated with significant rates of morbidity and death, so it is critical to recognize and differentiate them promptly. Meningitis from fungi and mycobacteria, especially tuberculosis, can rarely present acutely, but generally tend to be subacute to chronic (weeks to months), and occurs in patients with specific risk factors for those diseases. Fungal and mycobacterial meningitis should be considered under those circumstances, but their discussion is beyond the scope of this chapter.

The incidence, mortality, and morbidity, from ACBM, have decreased significantly, especially in high-income countries, probably as a result of vaccination and better antimicrobial and adjuvant therapy, but the disease still has a high toll. Still, in the United States, mortality remains at 10–20% [1, 2]. In the developing world, the mortality rates are as high as 50% [2]. In the United States, meningitis from all causes accounts for about 72,000 hospitalizations and up to $1.2 billion in hospital costs annually [3]. However, the incidence of bacterial meningitis has declined from 3 to 5 per 100,000 per year a few decades ago to 1.3–2 per 100,000 per year [1]. In the early 1900s in the United States, the death rate from bacterial meningitis was 80–100%. The use of intrathecal equine meningococcal antiserum during the first decades of the 1900s dramatically reduced the rate of death from meningococcal meningitis. With the advent of antimicrobial drugs in the 1930s and 1940s, the death rate from bacterial meningitis further declined [1].

The organisms that cause community-acquired bacterial meningitis differ somewhat by geographic region and by age. Surveillance data in the United States, from 1998 to 2007, show that the most common cause among adults is *Streptococcus pneumoniae*. Among young adults, *Neisseria meningitidis* is nearly as common as *S. pneumoniae*. The incidence of *Listeria* infections increases with age in adults [1]. The relative incidence of these organisms is similar in Europe and in most high-income countries [4].

The epidemiology of the disease also has changed in the last few decades due to the introduction of the conjugated vaccines against *H. influenzae* type b, *N. meningitidis* serogroup C, and 7-, 10- and 13-valent pneumococcal conjugate vaccines [5]. The most dramatic effect was after the introduction of the vaccines against *H. influenzae.* In 1986, about half the cases of acute bacterial meningitis were caused by *H. influenzae*, but a decade later, the incidence was reduced by 94% [3].

Pathogenesis

Most cases of CABM begin with colonization of the mucosal surface of the upper respiratory tract. In certain individuals, this leads to mucosal invasion and bacteremia. Not all organisms that cause bacteremia are capable of breaching the

blood-cerebrospinal fluid barrier to enter the subarachnoid space to cause meningitis. Very few organisms have this capacity, but *Haemophilus influenzae*, *N. meningitidis*, and *S. pneumoniae*, especially those strains that have a capsule, do [6]. Some patients are at higher risk of meningitis because of an abnormal communication between the nasopharynx and the subarachnoid space due to either trauma or a congenital anatomic abnormality. The organisms in these instances can directly spread from the nasopharynx to the meninges. Patients without a spleen or with an immunoglobulin deficiency are also more prone to infections from encapsulated organisms such as pneumococci and meningococci. The opsonizing immunoglobulins coat the capsule, helping phagocytes in the spleen to remove them from the bloodstream. A patient presenting with multiple episodes of bacterial meningitis merits evaluation for these conditions. In contrast, *Listeria* spp. and, rarely, Gram-negative bacteria enter the bloodstream through the gastrointestinal tract and then spread to the meninges.

Once in the subarachnoid space, bacteria elicit a profuse inflammatory response, which can be damaging [6]. The inflammation in the subarachnoid space can extend along the Virchow-Robin spaces surrounding the blood vessels deep into the brain parenchyma. This perivascular inflammation can cause thrombosis in both the arterial and venous circulations. This inflammation can lead to intracranial complications such as hydrocephalous from blocking the arachnoid villi, cerebral edema, and strokes from thrombosis or vasculopathy involving the arterial or venous circulations [6, 7].

Organisms and Organism-Specific Risk Factors

Streptococcus pneumoniae is the most common cause of ACBM [1, 8, 9]. It can also cause a concomitant upper respiratory tract infection, pneumonia, and rarely endocarditis. Though it can affect any immunocompetent adult, those who are at a higher risk of infection are people without a spleen or/and with a primary or secondary immunoglobulin deficiency, including patients with multiple myeloma or human immunodeficiency virus infection.

Neisseria meningitidis is more common in children and young adults [6, 10]. It is easily transmitted and is associated with crowding, as in school dormitories and military barracks. People with congenital deficiencies of components of complement are at greater risk for both meningococcal and gonococcal infections. Patients with recurrent episodes of *Neisseria* infection should be evaluated for complement deficiency. Meningococcal infection is more commonly associated with a rash. The most common rash of meningococcal meningitis is a very transient, maculopapular rash that appears early in the course of the disease. More pathognomonic is a petechial rash due to thrombocytopenia, which can very rapidly progress to purpura, ecchymosis, and disseminated intravascular coagulation. The petechial rash is evident in 60% of adults and up to 90% of children [11], and it is most likely to appear in dependent areas (such as the back of a patient lying down) and in areas of pressure, such as under the elastic band of underwear or stockings.

Listeria monocytogenes infection is usually acquired through contaminated food such as raw vegetables, unpasteurized milk, cheese, and deli meats. It spreads from the gastrointestinal tract to the bloodstream and then to the meninges. It is an intracellular pathogen; thus, people at greater risk are those with poor cell-mediated immunity due to immunosuppressant medications such as steroids or tumor necrosis factor inhibitors. The rate of *Listeria* meningitis starts to increase with age, especially after age 50, probably due to immune senescence or decreased immunity with age.

Aerobic Gram-negative enteric bacilli like *Escherichia coli* usually cause meningitis after head trauma or neurosurgery and are uncommon causes of community-acquired meningitis. Disseminated strongyloidiasis should be suspected in any patient with community-acquired meningitis caused by enteric Gram-negative bacilli. *Strongyloides stercoralis* is a parasitic intestinal roundworm that is found in the tropics, in the subtropics, and in certain parts of the United States and Europe. The adult worm lives in the intestines where it lays eggs; the larvae are excreted in the stool. A small percentage of larvae penetrate the perianal skin and gut mucosa to cause an autoinfection. People may asymptomatically harbor the parasite for decades and then develop hyperinfection syndrome with dissemination to various organs when treated with immunosuppressive drugs such as steroids. In this syndrome, a significant proportion of the larvae penetrate the gut mucosa to enter the bloodstream and travel throughout the body, including the brain, carrying Gram-negative bacteria with them. The mortality rate of untreated hyperinfection syndrome can be greater than 70% [12]; thus, it is important to identify and treat it in the context of Gram-negative bacillary meningitis.

Clinical Signs and Symptoms

The classic triad of acute meningitis is fever, neck stiffness, and altered mental status. Other symptoms that have been described are photophobia, headache, presence of a rash, nausea, and vomiting [13, 14]. Signs that have been described are Kernig's sign (inability to allow full knee extension when the hip is flexed to a 90° angle), Brudzinski's sign (spontaneous flexion of the hips during attempted passive flexion of the neck), and jolt accentuation test (performed by asking a patient with a headache to quickly move his or her head twice horizontally; the result is positive if the headache worsens). The pathophysiologic rationale for the symptoms and signs is pia-arachnoid inflammation, raised intracranial tension, and irritation of cranial and spinal nerves from the inflammation.

Only a few studies of the diagnostic accuracy of signs and symptoms of acute meningitis have been done. Fourteen retrospective studies examined this issue, but they were heterogeneous with respect to patient age, immunosuppression status, and clinical presentation, as well as to how meningitis was diagnosed (via culture or cerebrospinal fluid analysis), making the results difficult to interpret and reach a consensus [15]. Retrospective studies are more prone to bias, as they lack a control group, and examiner bias is more likely. Based on retrospective data, the combination of fever, neck stiffness, and altered mental status has a sensitivity of only 0.46 [15].

Four prospective studies examined symptoms and signs. Thomas et al. [16] evaluated 297 patients with clinically suspected meningitis. In a study by Uchihara and Tsukagoshi [17], a single examiner was used to evaluate patients presenting with fever and headache, with only 54 patients in this series. Waghdhare et al.'s study included 190 patients with suspected meningitis, where the examiners were blinded to the CSF analysis results [18]. Nakao et al.'s study was a prospective study in 230 patients presenting to two inner city ERs with suspected meningitis [19].

A symptom, sign, or a test's diagnostic accuracy can be assessed with sensitivity, specificity, and positive and negative likelihood ratios. A test with a low value for negative likelihood ration (preferably less than 0.1) is good for ruling out a disease and that with a high positive likelihood ratio (greater than 10) is good for inclusion of a disease. For the prospective studies that evaluated symptoms, the 95% confidence intervals (CIs) of the positive and negative likelihood ratios include the value 1 (a simple interpretation of that would be that the likelihood of finding these features is the same in patients with meningitis when compared with those without meningitis). Based on these prospective studies, the presence of nausea and vomiting, headache, or neck pain does not reliably rule in meningitis. Similarly, the absence of these does not rule it out.

The CIs of the positive and negative likelihood ratios for signs like those of the symptoms included the value 1 (see Table 2.1 for the exact values). Jolt accentuation looked promising in Uchihara and Tsukagoshi's study as a sensitive sign, but it did not perform that well in subsequent studies (see Table 2.1). In the physical

Table 2.1 Diagnostic accuracy of signs in acute meningitis

	Sensitivity (%)	Specificity (%)	Positive likelihood ratio (+LR)	Negative likelihood ratio (−LR)
Neck stiffness				
Thomas et al. [16]	30	68	0.94	1.02
Uchihara and Tsukagoshi [17]	14.7	100	6.6	0.83
Waghdhare et al. [18]	39.5	70.3	1.33	0.86
Nakao et al. [19]	13	80	0.6	1.1
Kernig's sign				
Thomas et al. [16]	5	95	0.97	1
Uchihara and Tsukagoshi [17]	8.8	100	4.2	0.92
Waghdhare et al. [18]	14.1	92.3	1.84	0.93
Nakao et al. [19]	2	97	0.8	1
Brudzinski's sign				
Thomas et al. [16]	5	95	0.97	1
Waghdhare et al. [18]	11.1	93.4	1.69	0.95
Nakao et al. [19]	2	98	1	1
Jolt accentuation				
Uchihara and Tsukagoshi [17]	97.1	60	2.4	0.05
Waghdhare et al. [18]	6.06	98.9	5.52	0.95
Nakao et al. [19]	21	82	1.2	1

examination, the presence or absence of fever, neck stiffness, Kernig's sign, Brudzinski's sign, or jolt accentuation could not reliably rule in or rule out acute meningitis. In summary, the history and physical examination are not sufficient to determine whether a patient has meningitis. If a patient is suspected of having meningitis, a lumbar puncture is needed.

Diagnostic Tests

Blood and CSF Cultures

Blood for cultures should be drawn before antimicrobial treatment is started [20–22]. Although they are positive only 19–70% of the time, they can help identify the pathogen and antimicrobial susceptibilities, especially when CSF cultures are negative [23–25]. Lumbar puncture for CSF studies is essential to make the diagnosis, to identify the organism and its susceptibility to various antibiotics. If lumbar puncture can be performed immediately, it should be done before starting antibiotics, to maximize the yield of cultures. Pediatric studies show that after starting antibiotics, complete sterilization of the cerebrospinal fluid can occur within 2 h for *N. meningitides* and within 4 h for *S. pneumoniae* [22]. However, starting antimicrobials should not be delayed if a lumbar puncture cannot be done expeditiously as such a delay can adversely affect the prognosis [26, 27].

CSF Molecular Diagnostics

Molecular diagnostic tests have the potential for rapid results, and there is now an FDA-approved commercially available test. The FilmArray Meningitis/Encephalitis (ME) Panel is a multiplexed in vitro diagnostic test for the simultaneous, rapid (~1-h) detection of 14 pathogens directly from CSF specimen including bacteria (*Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Streptococcus agalactiae)* [28]. However, there is limited published data on the diagnostic performance (sensitivity and specificity) for pathogens in adult bacterial meningitis.

Imaging

A computerized tomography of the brain is considered in the workup of acute meningitis as there are other mimicking conditions or complications of meningitis that can cause increased intracranial pressure and the possibility of brain herniation complicating a lumbar puncture. For ethical and practical reasons, it would be difficult to evaluate the need for a CT brain prior to LP in a randomized clinical trial. Hasbun et al. [29] performed a study to evaluate if any features on clinical

presentation can predict abnormal findings on CT of the head suggestive of elevated intracranial pressure and thus the risk of herniation. The study included 301 adults with suspected meningitis. It found that abnormal findings on CT were unlikely if all of the following features were absent at baseline:

- Immunocompromised state
- History of central nervous system disease (mass lesion, stroke, or a focal infection)
- New onset of seizure (≤1 week from presentation)
- Specific abnormal neurologic findings (e.g., an abnormal level of consciousness, inability to answer two consecutive questions correctly or to follow two consecutive commands, gaze palsy, abnormal visual fields, facial palsy, arm drift, leg drift, abnormal language)

The absence of these baseline features made it unlikely that CT brain would be abnormal (negative likelihood ratio 0.1, 95% CI 0.03–0.31) [29].

According to the guidelines from the Infectious Diseases Society of America (IDSA) [30], if none of those features is present, blood cultures and a lumbar puncture can be done immediately without performing a CT brain, followed by empiric antimicrobial therapy. If any of the features is present, blood cultures should be obtained first, and then empiric antimicrobial therapy started, followed by CT of the brain to look for contraindications to a lumbar puncture (Fig. 2.1 – modified from IDSA guidelines 1).

Lumber Puncture, CSF Cell Counts, Chemistry, and Gram Stain

These studies should be done stat, as they help determine whether bacterial meningitis is present and, if so, whether the cause is likely bacterial or viral. *The opening pressure* is elevated (usually > 180 mm H_2O) in acute bacterial meningitis. The diagnostic accuracies (likelihood ratios) of the CSF tests were analyzed in a systematic review by Straus et al. using a positive CSF culture as a reference standard [31].

CSF white blood cell count is raised and is predominantly neutrophilic, in acute bacterial meningitis. A CSF WBC count of 500/μL or higher increased the likelihood of meningitis (+ LR of 15; 95% CI, 10–22), and a count of less than 500/μL lowered the likelihood (−LR 0.3, 95% CI, 0.2–0.4) [31, 32].

CSF glucose level is lower in bacterial meningitis than in viral meningitis. Because the glucose levels in the CSF and the blood equilibrate, *the ratio of CSF glucose to serum glucose* has better diagnostic accuracy than the CSF glucose level alone. The equilibration takes place within a few hours, so the serum glucose level should be ordered at the same time lumbar puncture is done. The CSF/blood glucose ratio would be the preferred form which is a better predictor of bacterial meningitis than the CSF white blood cell count. Bacterial meningitis is likely if the ratio is

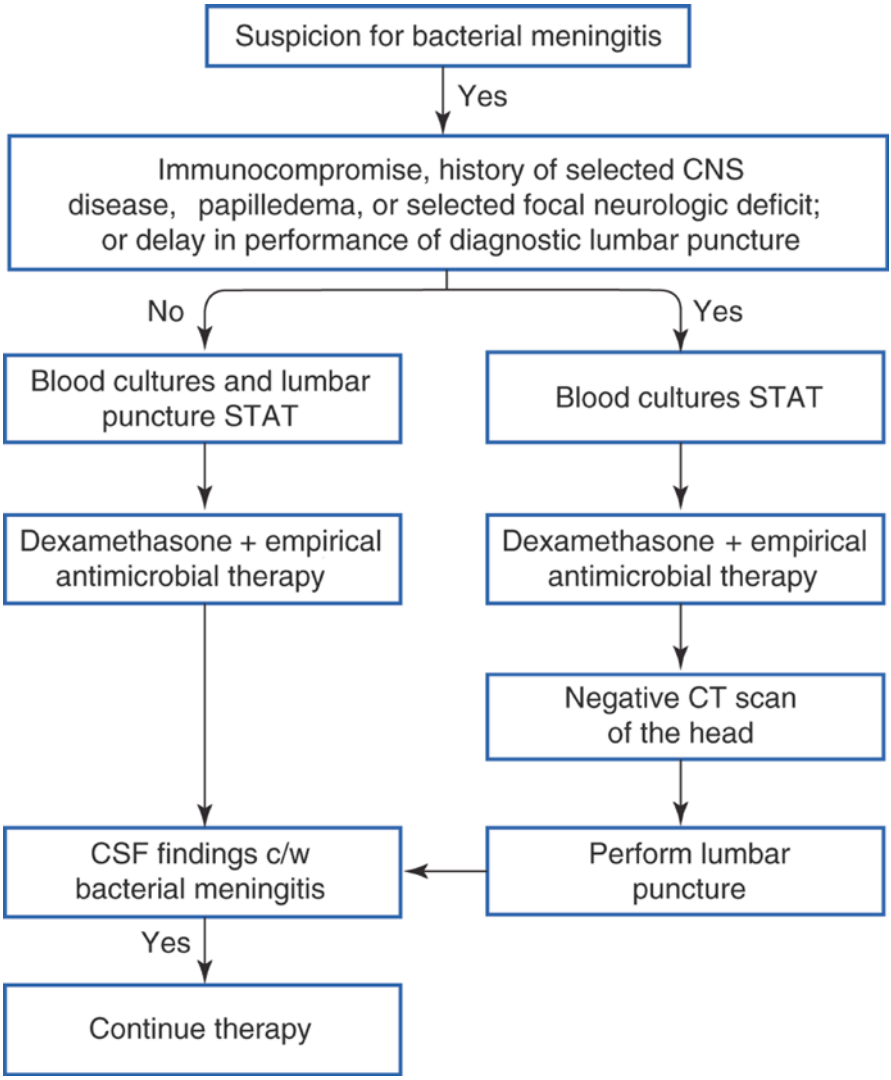

Fig. 2.1 Management algorithm for suspected bacterial meningitis (Adapted from Tunkel et al. [30])

lower than 0.4. A CSF/blood glucose ratio of 0.4 or less increased the likelihood of bacterial meningitis (+LR 18; CI, 12–27), but a normal value lowered the likelihood (−LR 0.31; 95% CI, 0.21–0.45) [31].

CSF lactate level is a good diagnostic test for evaluation of CABM. A CSF lactate level greater than 31.5 mg/dL (3.5 mmol/L) is predictive of meningitis (+LR 21; 95% CI, 14–32), and a value lower than that makes the diagnosis unlikely (−LR, 0.12; 95% CI, 0.07–0.23) [31].

CSF protein shows a mild to marked elevation in bacterial meningitis but is normal to elevated in viral meningitis and in a lot of other CNS diseases, so is of limited diagnostic value.

Gram stain of the cerebrospinal fluid can be done quickly. *S. pneumoniae* is a Gram-positive diplococcus, and *N. meningitidis* is a Gram-negative diplococcic. *Listeria* is a Gram-positive rod and *E. coli* is a Gram-negative rod. If no bacteria are seen, the information is not helpful in ruling out bacterial meningitis (−LR 0.14; 95% CI, 0.08–0.27). If it is positive, it is almost 100% specific for bacterial meningitis due to the organism seen (+LR 735; 95% CI, 230–2295) and so can identify the pathogen days before the culture results [31].

Management

Antimicrobial Therapy

Empiric antimicrobial therapy must be started as soon as feasible. Most studies of the timing of antimicrobial drugs are retrospective and even when prospective included a very heterogeneous population [26, 27, 33]. Proulx et al. [27] in a retrospective study found that if antibiotics were given within 6 h of the time the patient presented to the emergency department, the case fatality rate was only 5–6%. If treatment started 6–8 h after presentation, the death rate was 45%, and if it started from 8 to 10 h after presentation, the death rate was 75%. In a prospective, multicenter, observational study of 156 consecutive adults hospitalized for pneumococcal meningitis, an interval of greater than 3 h between hospital admission and administration of antibiotics was associated with an increase in 3-month mortality (odds ratio 14.12; 95% CI, 3.93–50.9) [26]. Most experts would agree that starting antimicrobials early would be beneficial in an emergency like acute bacterial meningitis.

CSF concentrations of most antimicrobial drugs are considerably less than in the serum due to poor penetration of the blood-CSF barrier. Thus, the dose for treating meningitis is usually higher than the regular dose. For example, for the treatment of pneumococcal pneumonia, ceftriaxone is used at a dose of 1 g every 24 h, but for pneumococcal meningitis, the dose is 2 g every 12 h.

Empiric treatment of community-acquired bacterial meningitis in immunocompetent adults up to 50 years of age consists of a third-generation cephalosporin such as cefotaxime 2 g intravenously every 4 h or ceftriaxone 2 g intravenously every 12 h, which covers most *S. pneumoniae* and *N. meningitides* strains [30]. The IDSA guidelines recommend adding vancomycin empirically in suspected *S. pneumoniae* meningitis when there are concerns about drug-resistant pneumococcal strains [30]. For vancomycin, 45–60 mg/kg intravenously per day divided into every-6-h or every-8-h doses would achieve better CSF concentrations [34]. In patients over age 50 or those with a cell-mediated immunodeficiency, empiric therapy should also include ampicillin 2 g intravenously every 4 h to cover *Listeria*. It is important to tailor therapy to the results of Gram stain, culture, and susceptibility as they become available.

Role of Corticosteroids

Glucocorticoids, especially dexamethasone, have been well studied as adjunctive therapies in bacterial meningitis. The rationale behind their use is that the profuse inflammatory response to the bacterial components in the CSF by itself has deleterious effects and steroids can reduce that.

In 2004, a Cochrane meta-analysis [35] of five randomized clinical trials, including 623 adults with bacterial meningitis, found a significant reduction in the death rate for patients who received steroids: the death rate was 12% in patients who received steroids versus 22% in those who did not (odds ratio 0.6; 95% CI 0.40–0.81). This led to an IDSA practice guideline recommendation that in adults with suspected or proven pneumococcal meningitis, dexamethasone would be beneficial [30]. But since then, many more studies have emerged from Europe, South America, Malawi, and Vietnam. Cochrane meta analyses [36, 37] including these studies with 4121 participants was published recently. In this analysis, corticosteroids were associated with a nonsignificant reduction in mortality (17.8% versus 19.9%; risk ratio (RR) 0.90, 95% CI 0.80–1.01). They also had lower rates of severe hearing loss (RR 0.67, 95% CI 0.51–0.88), any hearing loss (RR 0.74, 95% CI 0.63–0.87), and neurologic sequelae (RR 0.83, 95% CI 0.69–1.00). In subgroup analyses, steroids reduced mortality in *S. pneumonia* meningitis, but not in *N. meningitides* and *H. influenza* meningitis. The beneficial effects on morbidity were seen in high-income countries, but not in low-income countries. Based on these findings, the authors recommended the use of steroids in high-income countries, though the strength of the evidence was not optimal.

The recommended steroid is dexamethasone 0.15 mg/kg intravenously and should be preferably started with or before the first dose of antimicrobials and administered every 6 h for 4 days [30]. Steroids should be given closer to antimicrobial administration to prevent inflammation secondary to antimicrobial-induced bacteriolysis. Though there is no strong data, the ESCMID guideline consensus recommendation is to start steroids up to 4 hours after starting antimicrobials [4].

Other Treatments

Therapeutic hypothermia has been shown to be neuroprotective in postanoxic encephalopathy and neurotrauma, but has been shown not to be helpful and might even be harmful in bacterial meningitis. A randomized controlled trial done was stopped early due to increased mortality in the intervention arm. More patients died in the hypothermia group (25 of 49 patients [51%]) compared to the control group (15 of 49 patients [31%]; relative risk [RR], 1.99; 95% CI, 1.05–3.77; P = 0.04) [38]. Osmotic agents like glycerol, which are used to reduce intracranial pressure, were not shown to be beneficial. Other therapies like antiepileptics and hypertonic saline have not been well studied [4].

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