The Evaluation and Management of Bacterial Meningitis

Current Practice and Emerging Developments

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Background and Objective: Bacterial meningitis is a serious neurologic illness with significant morbidity and mortality if not recognized and treated promptly and appropriately. The presentation and management are influenced by host factors and the pathogenic organism; the purpose of this review is to highlight those differences and to survey the literature on current practices and emerging developments in evaluation and management.

Review Summary: Clinicians must have a high index of suspicion for bacterial meningitis. The classic symptoms of bacterial meningitis are fever, neck stiffness, altered mental status, and headache. Certain patient populations, such as the young and the immunocompromised, may have a blunted presentation, and for these patients, clinicians must have an especially low threshold for obtaining a lumbar puncture. When bacterial meningitis is suspected, antibiotic therapy should be initiated as soon as possible because early treatment is associated with a better outcome. In addition, the use of the corticosteroid dexamethasone has been shown to be helpful as an adjuvant therapy in specific clinical situations. New adjuvant therapies are being developed to lower the high rate of complications that currently occur in patients with bacterial meningitis.

Conclusions: Recent studies have altered the evaluation and management of bacterial meningitis. In addition, they have elucidated the mechanisms through which bacterial meningitis causes complications and have identified new targets for treatment.

Key Words: bacterial meningitis, diagnosis, management, prognosis, complications, dexamethasone, lumbar puncture

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Bacterial meningitis has been a topic of intensive research and is a well-understood and enigmatic disease. It is among the top 10 causes of infection-related deaths worldwide.[1] The incidence of bacterial meningitis is 4 to 6 cases per 100,000 persons in the developed world, and the condition is at least 10 times more common in the developing world, where it is nearly uniformly fatal because of the limited availability of antibiotics.[2,3] Where antibiotics are available, the morbidity and mortality of bacterial meningitis is significantly reduced, and yet it still causes mortality in 5% to 10% of patients and results in permanent neurologic deficits in 5% to 40% of survivors, depending on the patient population and the type of pathogen.[4]

Research studies over the prior 2 decades have resulted in earlier diagnosis and improved management of patients with bacterial meningitis. This article reviews that literature on clinical presentation, evaluation, treatment, and prognosis.

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PATHOGENESIS

Bacterial meningitis is the inflammation of the meninges (the pia, arachnoid, and subarachnoid space) that occurs when bacteria invade this normally sterile compartment. The exact site of entry into the central nervous system (CNS) is unclear. What is known is that the hematogenous route is the most common mode of entry and that a critical level of bacteremia is required to overcome the host defenses that prevent infection, namely the complement system and the blood-brain barrier. The blood-brain barrier is the system of nonfenestrated capillaries that sustains the brain parenchyma by supplying nutrients and maintaining homeostasis. The specialized endothelial cells that form the blood-brain barrier prevent passive diffusion and tightly regulate solute and particle entry and exit.[5,6] Only specially adapted pathogens with virulence factors like a polysaccharide capsule are capable of evading and bypassing the host defenses that protect the CNS against infection. The most common causes of bacterial meningitis are *Streptococcus pneumoniae*, *Neisseria meningitides*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Escherichia coli*, and *Streptococcus agalactiae.*

The most common causes of bacterial meningitis are S. pneumoniae, N. meningitides, L. monocytogenes, S. aureus, H. influenzae, E. coli, *and* S. agalactiae.

Other less common mechanisms of entry include (1) direct extension from a focus of infection, such as sinusitis or mastoiditis, and (2) direct CNS penetration and communication with a nonsterile area. Specifically, inoculation can occur through traumatic skull fracture, surgery, epidural puncture, and implantation of hardware, like a ventricular shunt or Ommaya reservoir.

When bacteria are in the subarachnoid space, the host defense mechanisms available to combat the infection are quite limited. Although there is a neutrophil response, concentrations of immunoglobulins are low in the cerebrospinal fluid (CSF), and there is minimal to no complement.[6] Bacterial invasion leads to neuronal apoptosis and micronecrosis, resulting in the numerous neurologic sequelae of bacterial meningitis. Neuronal cell death is thought to be due to the destructive effects of bacterial toxins and a misdirected immune response leading to a cascade of cytokine activation and uncontrolled inflammation.[7] The inhibition of this inflammatory response is a subject of intensive research because it has the potential to drastically reduce the morbidity and mortality of bacterial meningitis.

CLINICAL PRESENTATION

A triad of symptoms that is commonly associated with bacterial meningitis is fever, neck stiffness, and altered mental status. A

large prospective trial (n = 696), the Dutch Meningitis Cohort Study, found that the sensitivity of this triad is 44%,[8] a result that supports an earlier retrospective study, which found that the triad is present in two-thirds of patients with bacterial meningitis.[9] In evaluating patients for this condition, the Dutch study suggests that a history of headache should be elicited along with the triad as 2 of the 4 symptoms (fever, neck stiffness, altered mental status, and headache) are present in 95% of these meningitis patients.[8] Other common symptoms of bacterial meningitis are photophobia, nausea, vomiting, seizures, rash, and focal neurologic deficits. Their frequency is listed in Table 1.

A history of headache should be elicited along with the triad since 2 of the 4 symptoms (fever, neck stiffness, altered mental status, and headache) are present in 95% of these meningitis patients.

In patients with symptoms of meningitis, signs of meningismus are sought on physical examination by attempting to elicit nuchal rigidity and the Kernig and Brudzinski signs. The Kernig sign is elicited by flexing the leg at the hip and extending the knee. The Brudzinski sign is elicited by flexing the patient's neck and observing for involuntary flexion of the legs. In the article introducing his sign, Josef Brudzinski reported that the sensitivity of the Kernig sign is 57% and that the sensitivity of his sign is 97%.[11] A more recent study found that the sensitivity of the Kernig sign is 9% and the specificity is 100%.[12,13] This result was substantiated by a prospective study (n = 297) that evaluated the Kernig and Brudzinski signs and found that their sensitivity is only 5% and that their positive predictive value is only 27%.[10] The diagnostic value of nuchal rigidity was only marginally better with a sensitivity of 30% and a positive predictive value of 26%. Nuchal rigidity was sensitive as a sign of bacterial meningitis in the subset of patients with severe meningeal inflammation (1000 WBCs/mL of CSF).

The clinical presentation of bacterial meningitis is highly dependent on the immune response, and therefore, on the status of the host's innate immune system. It is influenced by age, immunocompromising conditions, and disruption of anatomic barriers.

TABLE 1. Symptoms of Bacterial Meningitis, by Study

	Van de beek et al[8]	Durand et al[9]	Thomas et al[10]
Fever	522/678 (77%)	95%–99%	55/78 (71%)
Neck stiffness	569/685 (83%)	88%	38/79 (48%)
Altered mental status	477/696 (69%) GCS <14	78%	8/80 (10%) GCS <13
Headache	544/626 (87%)		69/75 (92%)
Photophobia			43/75 (57%)
Nausea/vomiting	449/610 (74%)		54/77 (70%)
Seizures	32/666 (5%)	23%	7/79 (9%)
Focal neurologic deficit	233/696 (33%)	28%	5/78 (6%)–motor 2/76 (3%)–sensory
Rash	176/683 (26%)	11%	

Unlike older children, who present similarly to adults, neonates and infants often present a diagnostic dilemma because they generally do not demonstrate the typical clinical findings. Rather their symptoms tend to be nonspecific and lower in intensity; the most common symptoms are fever, lethargy, irritability, respiratory distress, jaundice, reduced food intake, vomiting, and diarrhea. Seizures and a bulging fontanel occur in only a minority of neonates.[14]

Because their immune system is immature, signs of meningismus, seizures, and coma occur less often and appear later in infants with bacterial meningitis compared with their adult counterparts.[14,15] The signs of meningitis are more subtle in infants, and for this reason, the practice guideline published by the American Academy of Pediatrics states that lumbar puncture should be strongly considered for infants younger than 12 months of age with a first simple febrile seizure (FSFS) and considered for infants 12 to 18 months of age with a FSFS.[16] This recommendation has been questioned by some experts based on the available data. A recent retrospective cohort study identified no cases of meningitis among 271 infants aged 6 to 18 months, who received a lumbar puncture for a FSFS.[17] An earlier retrospective case series found no cases of bacterial meningitis that presented as fever and seizure in the absence of other symptoms.[18]

Elderly patients are another group that was thought to be difficult to diagnose because of small retrospective studies, which found that they had lower rates of headache, neck stiffness, and fever.[19–21] Those small studies were followed by a report based on data from the Dutch Meningitis Cohort Study, which found that the triad of fever, neck stiffness, and altered mental status was more common in patients aged >60 than patients aged <60: 58% versus 36%.[22] On further analysis, patients aged >60 had headache and neck stiffness less frequently than patients aged <60 (77% vs. 92% and 78% vs. 86%, respectively) but this difference was offset by an increase in altered mental status in the older patients compared with the younger patients (84% vs. 60%). In addition, the study reported that 2 of the 4 classic symptoms of bacterial meningitis (fever, neck stiffness, headache, and altered mental status) were present in 94% of the older patients compared with 95% in the cohort as a whole, which included adults of all ages. A subsequent study supports these findings; it identified higher rates of altered mental status in elderly patients (patients older than 65) in spite of lower rates of nuchal rigidity and headache.[23]

The Dutch Meningitis Cohort Study, which found that the triad of fever, neck stiffness, and altered mental status was more common in patients aged >60 than patients aged <60: 58% versus 36%.

Immunocompromised patients comprise a separate group that has a blunted presentation because of a deficient immune response. A study on a patient population with a high prevalence of immunocompromising conditions found that the sensitivity of the triad was far lower than the sensitivity reported in other studies—just 21%.[24] Immunocompromised patients have fewer symptoms not only because they mount a less vigorous immune response but also because they are susceptible to a larger array of pathogens.

Meningitis in an immunocompromised host can present in a subacute or indolent manner, and it may present in an atypical manner. In a retrospective case review of 49 immunocompromised patients, the major causes of infection were *Cryptococcus neoformans* (15/49), *L. monocytogenes* (10/49), *Aspergillus fumigatus* (7/49), and conventional bacterial species (11/49).[25] Acute disease occurred less frequently among these patients, especially when the causative organism was one of the nonconventional pathogens. Symptoms of meningeal inflammation were infrequent, and headache was comparatively reduced; however, fever remained a common symptom. This case series included a single case of tuberculous meningitis, a type of meningitis that can occur quite commonly in immunocompromised patients.

Tuberculous meningitis is particularly prevalent among indigent urban non-white populations with a high rate of HIV infection.[26] It typically presents with fever, malaise, headache, and personality changes. As the infection progresses in a subacute manner over 2 or 3 weeks, patients begin to exhibit the classic symptoms of meningitis, including headache, meningismus, vomiting, confusion, and focal neurologic findings. Atypically, tuberculous meningitis can present like acute bacterial meningitis or as a slow cognitive decline.[27]

Patients with cancer are commonly immunosuppressed because of chemotherapy; for this reason, meningitis in these patients often presents like it would in other immunocompromised patients. A recent retrospective survey looking at the clinical features of 79 cancer patients with confirmed bacterial meningitis found that only 5% of patients presented with the triad of fever, nuchal rigidity, and altered mental status.[28] In stark contrast to the data reported in Table 1, only 56% of patients had fever, 47% had headaches, 35% had altered mental status, and 14% had nuchal rigidity. A total of 28% of patients had just 1 symptom and 14% were completely asymptomatic. Bacterial meningitis is a particularly important consideration in cancer patients because they are subjected to a wide range of neurosurgical procedures and are therefore predisposed to developing the infection.

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DIAGNOSIS

Lumbar Puncture

The gold standard for diagnosing bacterial meningitis is lumbar puncture with Gram stain and culture. Computed tomography (CT) scans are routinely performed before lumbar puncture to identify space occupying lesions and other intracranial abnormalities like brain edema as these lesions raise intracranial pressure and place the patient at increased risk for uncal and cerebellar tonsillar herniation.[29]

There are published clinical indications for performing a CT scan before lumbar puncture, such as coma, hemiparesis, and papilledema. In the absence of these indications, it may be safe to proceed directly to lumbar puncture without first imaging the patient. A prospective trial of 301 patients with suspected meningitis identified a subgroup of patients who are at low risk of having an intracranial abnormality that can lead to herniation.[30] The patients in this subgroup were characterized by the absence of the clinical features listed in Table 2, and they had a normal CT scan 97% of the time. The 3% of patients in this low risk group with an abnormal CT scan received a lumbar puncture and showed no sign of herniation after 1 week.

TABLE 2. Clinical Features Predicting Increased Likelihood of Demonstrating a Lesion on Head CT That Would Possibly Preclude Lumbar Puncture in Patients With Bacterial Meningitis

>60 yr of age
Immunocompromised state
Central nervous system disease
Seizure in the past week
Altered level of consciousness
Inability to answer 2 consecutive questions correctly
Inability to follow 2 consecutive commands correctly
Gaze palsy
Abnormal visual fields
Facial palsy
Arm drift
Leg drift
Abnormal language

CSF Studies

Findings on lumbar puncture and standard CSF studies that may indicate bacterial meningitis include an elevated opening pressure, a white blood cell count of 100 to 10,000 cells/mm^3 with a predominance of polymorphonuclear leukocytes, an elevated protein concentration of >50 mg/dL, and a CSF to plasma glucose ratio below 0.6.[3]

Clues that can be used to supplement routine CSF analysis in diagnosing bacterial meningitis are an elevated CSF lactate (>4.2 mmol/L), serum c-reactive protein (CRP), and serum procalcitonin (PCT) concentration. An elevated CSF lactate concentration is an exquisitely sensitive test for acute bacterial meningitis; unfortunately, its clinical utility is limited since it can be elevated for other reasons, such as cerebral hypoxia/ischemia, anaerobic glycolysis, vascular compromise, and metabolism of CSF leukocytes.[31] The serum CRP level is less sensitive at detecting bacterial meningitis than CSF lactate, but more informative, given that a normal CRP has a high negative predictive value for bacterial meningitis.[32] Serum PCT is the newest and possibly most sensitive marker for distinguishing bacterial from nonbacterial meningitis.

Clues that can be used to supplement routine cerebrospinal fluid analysis in diagnosing bacterial meningitis are an elevated cerebrospinal fluid lactate (>4.2 mmol/L), serum c-reactive protein, and serum procalcitonin concentration.

A sensitive blood test that can be used to differentiate bacterial from nonbacterial meningitis is useful in refining treatment. At present, many patients with suspected bacterial meningitis and a negative CSF Gram stain receive antibiotics until bacterial meningitis can be excluded by microbiological testing or clinical course. Serum PCT measurements may be useful in deciding who should receive antibiotics in those situations based on studies in the pediatric[33–35] and adult literature.[36–39] A recent secondary analysis of pediatric trials with a cohort of meningitis patients who received serum PCT measurement on admission to the emergency department found that serum PCT at the 0.5 ng/mL threshold had the best sensitivity (99%; 95% CI, 97%–100%) and specificity (83%; 95% CI, 76%–90%) of all the biologic markers tested including CRP.[35] In adults, a multicenter trial reported a similar result; it found that the sensitivity of this assay is 87%, and the specificity is 100% at a threshold concentration of 2.13 ng/mL.[39] However, further study, including a large prospective trial, is still needed to validate its use.

The definitive study for diagnosis of bacterial meningitis is CSF culture on blood and chocolate agar plus brain heart infusion or thioglycolate broth. These cultures can take as long as 48 hours to yield a result. Fortunately, the causative organism can often be identified quickly and accurately by Gram stain. The factors that determine the detectability of the causative organism by Gram stain are CSF bacteria concentration, the use of concentrating techniques, the causative organism, and the prior administration of antibiotics.

Under ideal circumstances, Gram staining is highly sensitive. Dunbar et al found that Gram stain of CSF concentrated by cytocentrifugation was 92% sensitive and 99% specific at identifying the pathogen in patients who had not received antimicrobial therapy before lumbar puncture.[40] The sensitivity of CSF Gram stain is significantly reduced when the bacterial pathogen is a gram-negative bacilli or *L. monocytogenes*, and when a lumbar puncture is performed after the initiation of antibiotics.[31]

A retrospective study determined that third-generation cephalosporins sterilize the CSF fluid of meningococcus (ie, no growth on culture) in one-third of patients with meningococcal meningitis within 1 hour and in all patients by 2 hours.[41] It also demonstrated that antibiotics sterilize the CSF in the majority of patients with pneumococcal meningitis between 4 and 10 hours. Despite these results, the administration of antibiotics to a patient with suspected bacterial meningitis should not be delayed since early antibiotic treatment is associated with fewer adverse clinical outcomes.[42]

Besides Gram stain and culture, the pathogen responsible for bacterial meningitis can also be diagnosed with commercially available latex agglutination tests. They are simple to perform, organism specific, and yield results in less than 15 minutes. The sensitivity of these tests is fairly good: 78% to 100% for *H. influenzae* type B, 67% to 100% for *S. pneumoniae*, and 50% to 93% for *N. meningitides*.[31] These tests are particularly useful in the case of culture negative patients who received antibiotics before lumbar puncture. Among these patients, latex agglutination may be more sensitive at identifying the pathogen than CSF Gram stain and culture. Outside of this clinical situation, these tests rarely alter management or outcome.

An alternative to latex agglutination tests that is being developed are PCR-based diagnostic tests. There are 2 main types. The first type uses organism-specific primers to detect the presence of specific bacterial pathogens with high sensitivity and specificity. As a platform for performing these tests, real-time PCR is being investigated because it is quantitative and it allows the user to multiplex, that is amplify multiple targets in a single reaction tube using fluorescently labeled nucleic acid probes. A multiplex real-time PCR test that simultaneously detects *S. pneumoniae*, *H. influenzae*, *N. meningitides*, *E. coli*, *S. agalactiae*, *S. aureus*, *L. monocytogenes*, *and M. pneumoniae* was recently described.[43]

The other type of PCR-based diagnostic test is broad-range real-time PCR. Rather than testing for specific bacterial pathogens, broad-range real-time PCR tests for the presence of bacteria of any type through the use of primers against the conserved regions of the gene coding 16S rRNA. Reportedly, broad-range real-time PCR has a sensitivity of 100%, a specificity of 98.2%, a positive predictive value of 94.4%, and a negative predictive value of 100%.[44] In clinical practice, this test would be used to exclude bacterial meningitis and to make a decision about initiating empiric antimicrobial therapy. The role of PCR in detecting bacterial meningitis is still evolving. Like serum procalcitonin and latex agglutination tests, PCR-based detection methods may be useful in Gram stain negative patients, especially patients who have received antibiotics prior to lumbar puncture. As of today, PCR-based tests are not routinely available.

Polymerase chain reaction-based detection methods may be useful in Gram stain negative patients, especially patients who have received antibiotics prior to lumbar puncture.

The evaluation of tuberculous meningitis is fundamentally the same as the evaluation previously described for acute bacterial meningitis. As in the case of acute bacterial meningitis, lumbar puncture is essential for diagnosis. On CSF analysis, lymphocytic pleocytosis (100–500 cells/uL) is typically observed, CSF protein is generally elevated (100–500 mg/dL), and CSF glucose is generally decreased (typically <45 mg/dL).[27] CSF culture is routinely performed but of limited utility in diagnosing tuberculous meningitis because (1) its sensitivity is relatively low, reportedly between 45% and 90%, and (2) it takes 4 to 6 weeks for the results to return.

Tests that are used to make the diagnosis in the interim are acid-fast bacillus smears, CSF PCR, and adenosine deaminase activity (ADA). The sensitivity of acid-fast bacillus smears at detecting *M. tuberculosis* is highly variable and is both protocol and operator dependent; in contrast, commercial PCR test are standardized and were shown in a recent meta-analysis to have a sensitivity of 56% and a specificity of 98%.[27,45] The sensitivity and specificity of ADA as a test for tuberculous meningitis varies from study to study depending on the cut-off above which the test is considered positive; the reported sensitivity of the assay ranges from 44% to 100% and the specificity ranges from 71% to 100%.[46] ADA is elevated whenever there is a cell-mediated immune response because it plays a role in lymphocytic proliferation and differentiation.[47] For this reason, it can be elevated in other neurologic diseases, and as an upshot, a low cut-off improves sensitivity but decreases specificity. The principal advantages of the ADA assay are that it is inexpensive, rapid, and simple to perform, and so it is particularly valuable as a diagnostic option where PCR-based tests are impractical.

Neuroradiology

Neuroradiology is an increasingly important modality in the diagnosis of bacterial meningitis. It is especially useful for diagnosing tuberculous meningitis because tuberculous meningitis leads to the formation of a thick leptomeningeal exudate involving the basal portion of the brain.[48] The common triad of tuberculous meningitis found on neuroimaging is basal meningeal enhancement, hydro-

TABLE 3. Components of the Risk Score for Prognosis in Bacterial Meningitis

Points	0	1	2	4	5	6	8	9	10	12	13	14	16
Age	20		30	40		50	60		70	80			
Tachycardia*	No								Yes				
Glasgow Coma scale	15	14	13	12	11	10	9	8	7	6	5	4	3
Cranial nerve palsy	No							Yes					
CSF leukocyte count†	High										Low		
CSF Gram stain	Gram−	No	Other							Gram+			

*The authors defined tachycardia as >120 beats/min.
†A low CSF leukocyte count was defined as <1000 cells/mm^3.
CSF indicates cerebrospinal fluid.

TABLE 4. Risk of Unfavorable Outcome Based on Calculated Risk Score

Score	0	5	10	15	20	25	30	35	40	45	50	55	60	65
Percentage of unfavorable outcome	3.2	5.1	8.2	13	20	29	40	52	64	75	83	89	93	96

cephalus, and supratentorial and brain stem infarctions. Gadolinium-enhanced T1-weighted MR imaging is considered the most sensitive modality for detecting basal meningeal enhancement; however, it may also be visualized on CT scan. The hydrocephalus seen on imaging is typically of the communicating form because of impaired CSF resorption; however, tuberculous meningitis can also cause obstructive hydrocephalus because of a narrowing of the aqueduct or one of the ventricles. The cerebral infarctions that are seen are often hemorrhagic lesions that result in cavitation, and they often involve the basal ganglia and internal capsule. Less commonly, they involve the large vascular territories of the anterior and middle cerebral arteries.

In the future, imaging may also have a role in diagnosing acute bacterial meningitis. A recent study showed that gadolinium-enhanced FLAIR may be useful in detecting early meningitis.[49] In this study, 27 patients with signs and symptoms of meningitis received a magnetic resonance imaging within 3 hours of clinical evaluation in the emergency department. Of those 27 patients, 7 patients had viral meningitis and 5 patients had bacterial meningitis by CSF analysis; gadolinium-enhanced FLAIR demonstrated abnormal meningeal enhancement in all 12 patients.

PROGNOSIS

After the diagnosis of bacterial meningitis is made, it is important to assess the risk of complication so that the patient may be monitored accordingly. Weisfelt et al devised and validated a scoring system, which can be used to predict the risk of an unfavorable outcome at 1 hour after admission.[50] This scoring system uses 6 variables: age, heart rate, Glasgow Coma Scale score, cranial nerve palsies, CSF leukocyte count, and Gram stain findings. Points are assigned for each variable (Table 3), summed up, and the total score is used to determine the risk of an unfavorable outcome (Table 4), which is defined as a Glasgow Outcome Scale score of less than 5—an outcome of moderate disability or worse.

THERAPY

Antibiotics

Bacterial meningitis is a medical emergency that warrants early intervention with antimicrobials. Retrospective data shows an intuitive association between early initiation of antimicrobials, a better clinical course, and improved outcome.[31] This association is supported by observational studies, like the PNEUMOREA study, which demonstrated an increase in 3-month mortality among patients with pneumococcal meningitis when antibiotics were delayed for more than 3 hours.[51] For this reason, antibiotics should be initiated soon after bacterial meningitis is suspected or proven and should not be delayed if lumbar puncture cannot be performed in a timely manner.

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Early empiric treatment of bacterial meningitis should be tailored to the patient's age, immune status, and setting of acquisition (factors to consider include antibiotic sensitivities and community acquisition vs. nosocomial acquisition). A common combination used for community-acquired bacterial meningitis in children and adults in response to the development of penicillin-resistant pneumococcus is vancomycin plus a third-generation cephalosporin, that is, cefotaxime or ceftriaxone. In patients at risk for *L. monocytogenes*, specifically those more than 50 years of age and the immunocompromised, empiric therapy should also include ampicillin.

Bacterial meningitis that occurs in proximity to neurosurgery or head trauma requires empiric antibiotics targeting a different set of pathogens, the most common being coagulase-negative *Staphylococcus*, *S. aureus*, and Gram-negative bacilli.[5] Ventricular shunts are a common cause in that they have an infection rate between 10% and 15%.[52] These infections are typically treated with antibiotics, removal of the infected device, and installation of an uninfected drainage device. Intravenous antibiotics may be insufficient in certain shunt infections, necessitating intraventricular or intrathecal antibiotics.[52,53]

TABLE 5. Recommended Specific Antibiotic Therapy for Bacterial Meningitis Based on Cultured Organism

Organism	Recommended Antibiotic Therapy
S. pneumoniae	Vancomycin plus ceftriaxone or cefotaxime
N. meningitides	Penicillin G or third-generation cephalosporin (ceftriaxone or cefotaxime)
L. monocytogenes	Ampicillin or penicillin G
S. agalactiae	Ampicillin or penicillin G
H. Influenzae	Ceftriaxone or cefotaxime
E. coli	Ceftriaxone or cefotaxime
M. tuberculosis (non-drug resistant)[54]	Isoniazid, rifampin, pyrazinamide, and ethambutol for 2 mo, followed by isoniazid and rifampin for 7 to 10 mo

Regardless, antibiotic selection should be refined after the pathogen has been identified. Antibiotic selection is summarized in Table 5.

Dexamethasone

A contradiction in the treatment of bacterial meningitis is that antibiotics are fundamentally important and a cause of complications. Antibiotics cause bacteriolysis and inflammation of the subarachnoid space and are therefore responsible for many of the neurologic complications of the disease.[55,56] Averting this inflammation may preclude subsequent damage, and for this reason, the anti-inflammatory corticosteroid dexamethasone is routinely administered shortly before or concurrently with antibiotics.

The efficacy of adjuvant dexamethasone in improving outcomes varies considerably depending on the study population. Compelling evidence in favor of using dexamethasone as an adjuvant therapy in adults was unavailable until 2002 since earlier trials were either small or included children and adults, and were therefore inconclusive.[57–60]

The large prospective, randomized, double-blind trial (n = 301) that established the use of adjuvant dexamethasone in adults found that patients who received dexamethasone had a significantly lower risk of an unfavorable outcome than patients who received placebo (15 vs. 25%, relative risk [RR], 0.59; 95% confidence interval [CI], 0.37–0.94; $P = 0.03$); moreover, patients in the dexamethasone treatment group had a lower mortality rate than the placebo group (7 vs. 15%, RR, 0.48; 95% CI, 0.24–0.96; $P = 0.04$).[61] This study further demonstrated that adjuvant dexamethasone was helpful in patients with pneumococcal meningitis but that it provided no additional benefit in patients with meningococcal meningitis. Given this finding, some have argued that dexamethasone should only be continued in patients with diplococci on CSF Gram stain or in cases of culture confirmed *S. pneumoniae* in blood or CSF.

The large prospective, randomized, double-blind trial that established the use of adjuvant dexamethasone in adults found that patients who received dexamethasone had a significantly lower risk of an unfavorable outcome than patients who received placebo.

This initial study was followed by a randomized controlled trial that enrolled 435 Vietnamese patients more than 14 years of age with suspected bacterial meningitis. This study identified a statistically significant improvement in outcome in the dexamethasone treatment group in the subgroup of patients with confirmed bacterial meningitis. Within this subgroup, treatment with dexamethasone reduced mortality at 1 month (RR, 0.43; 95% CI, 0.20–0.94), and it reduced the risk of death or disability at 6 months (odds ratio [OR], 0.56; 95% CI, 0.32–0.98).[62] A concerning result apparent on further analysis was that adjuvant dexamethasone significantly increased mortality at 1 month in patients with clinical features of bacterial meningitis but were culture negative. Because this study occurred in a part of the developing world where tuberculosis is endemic, the authors hypothesized that this increase in mortality was due to tuberculous meningitis.

In other developing countries, dexamethasone has not been shown to be effective as an adjuvant therapy for bacterial meningitis. A prospective, randomized, double-blinded, placebo-controlled trial investigated the use of dexamethasone in adult Malawian patients.[63] The study found that dexamethasone was ineffective in reducing morbidity or mortality at 40 days and had no effect on outcome even within the subgroup that had benefited the most in prior studies—the subgroup with pneumococcal meningitis. The resource-poor Malawian population differed from the patient population studied in the Vietnamese trial, in that 90% of the patient population in the Malawian trial was HIV-positive versus just 1% in the Vietnamese trial. Likewise, dexamethasone failed to improve outcomes in a trial on Malawian children; there was no difference in death rate or the rate of sequelae in the dexamethasone treatment group compared with the placebo group.[64] The rate of HIV infection was lower in this trial than in the adult trial but still high. Of the 459 patients tested, 34% were HIV-positive.

Adjuvant dexamethasone for childhood bacterial meningitis has been carefully studied and has only been shown to be helpful in preventing severe hearing loss. A meta-analysis of randomized controlled trials between 1988 and 1996 by McIntyre et al demonstrated that dexamethasone lowered the rate of severe hearing impairment among pediatric patients with *H. influenzae* type B (combined OR, 0.31; 95% CI, 0.14–0.69).[65] This meta-analysis also concluded that dexamethasone may be protective against severe hearing loss in pediatric patients with pneumococcal meningitis when given before or concurrently with antibiotics (combined OR, 0.09; 95% CI, 0.0–0.71). This result was upheld by subsequent meta-analysis, including a Cochrane Systematic Review from 2007, which found that dexamethasone reduced the rate of hearing loss in children (RR, 0.61; 95% CI, 0.44–0.86) based on the results of 15 randomized controlled trials.[66]

A Cochrane Systematic Review from 2007 found that dexamethasone reduced the rate of hearing loss in children (RR, 0.61; 95% CI, 0.44–0.86) based on the results of 15 randomized controlled trials.

Adjuvant dexamethasone has not been demonstrated to reduce mortality in children with bacterial meningitis. The Cochrane Systematic Review on corticosteroids for acute meningitis reported a mortality rate of 13.6% in the dexamethasone treatment group compared with a mortality rate of 13.5% in the placebo group.[66] This finding was bolstered by a recent retrospective cohort study on

2780 children who received treatment for bacterial meningitis at tertiary care centers in the United States; it found that treatment with corticosteroids failed to improve mortality and time to discharge.[67]

On the basis of these results, it is unclear whether pediatric meningitis patients should receive adjuvant dexamethasone in countries like the United States, where vaccination has virtually eliminated *H. influenzae* type B meningitis and has helped to reduce the rate of pneumococcal meningitis. The official position of the American Academy of Pediatrics is that adjuvant dexamethasone may be appropriate for infants and children 6 weeks of age and older, although they qualify that recommendation by stating that, "Experts vary in recommending the use of corticosteroids in pneumococcal meningitis; data are not sufficient to demonstrate clear benefit in children."[31,68]

Dexamethasone is the only adjuvant therapy that is in routine clinical use. An adjuvant therapy that has been suggested as an alternative to dexamethasone in children is oral glycerol. This agent may prevent the neurologic complications of bacterial meningitis by drawing water away because of its hyperosmolarity. Its use as an adjuvant therapy in children ages 2 months to 16 years is supported by one prospective, double-blind trial that identified a statistically significant reduction in neurologic sequelae (such as blindness, quadriplegia, hydrocephalus requiring a shunt, and severe psychomotor retardation) in the glycerol treatment group compared with the placebo group (OR, 0.31; 95% CI, 0.13–0.76, $P = 0.01$).[69] Further research is being conducted to determine the role of glycerol in the treatment of bacterial meningitis.

COMPLICATIONS

Bacterial meningitis is still a common cause of morbidity because of a wide range of CNS and systemic complications. A study evaluating the complications of bacterial meningitis concluded that complications occurred in 50% of patients: 81% had a CNS complication, 44% had a systemic complication, and 26% had both.[70] The most common CNS complications were brain swelling, cerebral herniation, hydrocephalus, brain abscess, intracerebral hemorrhage, and cerebrovascular arterial or venous complications (such as vessel wall irregularities, focal dilatations, occlusions, and thrombosis). The most common systemic complications were septic shock, adult respiratory distress syndrome, disseminated intravascular coagulation, and hyponatremia.

Bacterial meningitis results in cerebrovascular compromise by causing venous sinus thrombosis early on in its course and narrowing of the large basal arteries—most likely due to arteritis of the vasa vasorum.[71] These cerebrovascular complications of bacterial meningitis can reduce the flow of blood to the brain and result in infarction, cytotoxic edema, and increased intracranial pressure.[70] Tuberculous meningitis is particularly notorious for causing infarction.[72]

Disrupted autoregulation may aggravate the situation created by cerebrovascular compromise by further increasing intracranial pressure and causing herniation in these patients.[70,73] Herniation can also be caused by brain edema and hydrocephalus. Brain edema in the context of bacterial meningitis may be cytotoxic (due to ischemia) or vasogenic (due to increased blood-brain barrier permeability), and the hydrocephalus can be communicating or obstructive. Obstructive hydrocephalus occurs less frequently than communicating hydrocephalus and typically occurs in the setting of ventriculitis. Ventriculitis is the infection and inflammation of the ventricular system; this type of infection can block the CSF outflow track precipitating interstitial edema, and it can occur early on in the course or as a late complication of bacterial meningitis.

Cranial epidural abscess and subdural empyema are 2 uncommon pyogenic complications of bacterial meningitis. Cranial epidural abscesses develop between the dura mater and the skull and generally cause headache, fever, and nausea. They usually do not cause neurologic dysfunction because the brain parenchyma is protected from the infection by the dura mater and the infection is typically localized. Infratentorial subdural empyema is more worrisome than cranial epidural abscess because of a high mortality rate (34%).[5] This pyogenic complication should be suspected in a patient with concurrent otitis, sinusitis, or mastoiditis and neurologic findings consistent with an infratentorial lesion.

Neurologic dysfunction arises from infarction, herniation, abscess formation, and general inflammation. Hearing loss is a particularly common neurologic deficit among meningitis patients: 5% to 35% of patients with bacterial meningitis develop permanent sensorineural hearing loss, making it the most common cause of acquired hearing loss.[74] Although still incompletely understood, hearing loss in these patients is likely because of a combination of factors: labyrinthitis, damage to the cochlear neuroepithelial cells, and ischemic damage.

Five percent to 35% of patients with bacterial meningitis develop permanent sensorineural hearing loss, making it the most common cause of acquired hearing loss.

Seizure is another common neurologic complication of bacterial meningitis. A recent study based on data from the Dutch Meningitis Cohort Study found that seizures developed in 17% of study subjects and occurred most commonly among patients with pneumococcal meningitis.[75] Seizures in these patients are thought to be caused by cortical inflammation. The mortality rate of meningitis patients with seizures significantly exceeds the mortality rate of patients without them: 41% versus 16%. Likewise, focal neurologic abnormalities are more common among patients with seizures than those without them: 41% versus 14%. Risk factors for the development of seizures are a distant focus of infection (sinusitis, otitis, pneumonia), an immunocompromised state, tachycardia, and a low Glasgow Coma Scale score on admission.

Subtler forms of neurologic dysfunction have also been identified through formal neuropsychological testing. Bacterial meningitis adversely affects the academic performance of school age children because of impaired neuropsychological/cognitive function, problems with behavior and social functioning, and gross neurologic deficits.[76] On neuropsychological testing, pediatric survivors of bacterial meningitis had significantly lower IQ scores, and they performed worse in all areas of cognitive function, including reading ability, visuomotor coordination, learning memory, and executive skills. Among adults, cognitive dysfunction occurred at significantly higher rates among survivors in all domains tested, including attention, executive function, visuoconstructive functions, and verbal and nonverbal memory.[77]

FUTURE DIRECTIONS

Unchecked inflammation of the CNS in the setting of bacterial meningitis has been implicated as a cause of neuronal cell death and neurologic complications. Adjuvant dexamethasone has proven to be useful in preventing some, but not all, of the immune mediated com-

plications of bacterial meningitis, which is why alternative adjuvant therapies for bacterial meningitis is an active subject of study.

Avenues being explored include the neutralization of proinflammatory bacterial products such as lipopolysaccharide, peptidoglycan, and teichoic acid, and the attenuation of the inflammatory response. Investigators are attempting to modify the inflammatory response by limiting leukocyte migration and altering the cytokine milieu with neutralizing antibodies, inhibitors of activating enzymes, regulators of gene transcription, and recombinant proteins.[4]

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a promising regulatory cytokine that is released by activated neutrophils and is elevated in the CSF of patients with bacterial meningitis. It is believed to have anti-inflammatory properties within the CNS. Studies performed in a TRAIL-deficient meningitis mouse model report an exaggerated influx of granulocytes and monocytes into the CSF, and the leukocytes were found to have a prolonged life span, resulting in increased inflammation and neuronal damage.[78] Returning TRAIL to these TRAIL-deficient mice effectively reduced CNS inflammation and neuronal apoptosis, which is why it is expected to be beneficial as an adjuvant therapeutic.

Another small molecule that has shown promise as an adjuvant therapeutic in animal models is brain-derived neurotrophic factor. This agent was found to be protective against inflammatory damage in the cerebral cortex and hippocampus.[79]

In addition, cellular dysfunction at the level of the blood-brain barrier, vasculature, and brain parenchyma is being investigated in the hope that it will lead to adjuvant therapies that can prevent specific neurologic/neuropsychiatric complications of the infection.

CONCLUSION

Bacterial meningitis is a fulminant disease that needs to be treated aggressively with antibiotics early on in the course of the infection. Therefore, this diagnosis has to be considered in any patient who presents with symptoms of the clinical triad (fever, neck stiffness, and altered mental status) or any of the following: headache, photophobia, nausea, vomiting, seizure, rash, or focal neurologic deficits. Among children and the immunocompromised, bacterial meningitis may have a blunted clinical presentation. As an upshot, clinicians must have a high index of suspicion when treating these patients and even nonspecific complaints in certain clinical contexts should trigger investigation with lumbar puncture, Gram stain, and culture.

Advances have been made in diagnosing and treating bacterial meningitis that have only begun to improve outcomes. Continued research into biochemical markers, PCR tests, imaging techniques, and adjuvant therapies will further reduce complications, such as cerebral infarction, cerebral herniation, seizure, and neuropsychological deficits. Progress toward this end will mitigate the enormous toll bacterial meningitis can have on human life.

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