Bacterial Meningitis and Other Nonviral Infections of the Nervous System

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KEYWORDS

• Central nervous system • Meningitis • Spinal cord • Bacteria • Fungi

KEY POINTS

- Bacteria and fungi, owing to their intrinsic properties and the host responses they produce, result in relatively specific clinical syndromes when they infect the central nervous system.
- The infecting organism may produce symptoms and signs by interfering with the function of the nervous system tissue being invaded or compressed.
- The major impediments to the movement of both microorganisms and inflammatory substances from the systemic circulation into the central nervous system are the blood-brain and blood–cerebrospinal fluid barriers.
- The natural history of spinal cord compression caused by an epidural abscess highlights the need for alacrity in diagnosis and treatment.
- The definitive treatment of central nervous system infection depends on correct identification and antimicrobial treatment of the infecting organism, relief of excessive pressure or mass effect that it exerts, and modulation of the host's immune response to allow clearance of the organism while minimizing excessive inflammation.

HISTORY AND NOMENCLATURE

Infections of the central nervous system (CNS) were well known to the ancients; descriptions of meningitis date back to the 16th century. The major syndromes of neurologic infection were described by the great 19th century pathologists. Quincke's lumbar puncture needle, introduced in 1891, and more recently, computed tomography (CT) and magnetic resonance imaging (MRI), round out the current understanding of these disorders.

To understand CNS infections, one requires knowledge of anatomy, because the consequences of infection vary with both the anatomic spaces involved and the functions of the tissues located within them.[1] Although a few organisms can cross tissue planes, most infections initially manifest in a single space.

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Epidural infections are usually excluded from direct extension into, or immunologic effects compromising, CNS structures.[2] Their manifestations are primarily due to compression of adjacent tissues. Cranial epidural abscesses cause signs and symptoms corresponding to the increase in intracranial pressure (ICP) produced by the additional volume of alien tissue (eg, headache and altered consciousness), and to the compression of the brain beneath the abscess. Spinal epidural abscesses, in contrast, cause local pain, then nerve root compression, and finally spinal cord compression. Subdural empyema typically incites an inflammatory response in the underlying brain or spinal cord, causing findings out of proportion to the volume of inflammatory exudates produced.[3] Although either the dura mater or the pia mater may become infected, the term meningitis usually refers to infection in the subarachnoid space (SAS).[4] Rarely, infection is confined to the lining tissues themselves, producing pachymeningitis or arachnoiditis. When the infection is predominantly within the ventricular system, ventriculitis or ependymitis isdiagnosed.

The brain or spinal cord may develop focal bacterial or fungal infections, initially in the form of cerebritis or myelitis, which then typically evolve into a parenchymal abscess.[5] The blood vessels may also become infected, producing an arteritis (also termed vasculitis). When veins or venous sinuses are involved, the pathophysiologic consequences are typically due to thrombosis, called septic venous thrombosis or sinus thrombosis.[6] Although not truly parts of the nervous system, infections of the cranium or spinal column (osteomyelitis) or the bony sinuses (sinusitis) are important predecessors of CNS infection.[7]

ETIOLOGY

Bacteria and fungi, owing to their intrinsic properties and the host responses they produce, result in relatively specific clinical syndromes when they infect the CNS. Because the host's defenses play such an important part in shaping the signs and symptoms, abnormalities of host response may cause different syndromes in different patients infected with the same organism. The major infecting organisms are grouped by their syndromes and host characteristics in **Table 1**.

PATHOGENESIS

The infecting organism must first gain entry into the target tissue. The usual paths of infection include (1) hematogenous spread via the arterial blood, or (2) direct extension from another site of infection, such as infected bones or sinuses.[8] Direct extension occurs when trauma results in a direct communication between the external environment and the CNS. Once the organism has invaded, it must elude or subvert the local host defenses to survive and reproduce. These local host defense mechanisms may then invoke a more systemic response. These defensive responses are intended to clear the infection, but their effects are often deleterious to the nervous system tissue itself; many of the signs and symptoms of infection are consequences of the inflammatory response and its aftermath. The use of corticosteroids in the treatment of bacterial meningitis arose from the recognition that the host response was often the cause of further tissue damage.

PATHOPHYSIOLOGY

The infecting organism may produce symptoms and signs by interfering with the function of the nervous system tissue being invaded or compressed, but many findings

Table 1
Common organisms and syndromes of central nervous system infection

Organism	Syndrome	Typical Patient Age	Initial Treatment Pending Sensitivities	Common Host Characteristics
Bacteria				
Streptococcus pneumoniae	Acute bacterial meningitis	Adult	Ceftriaxone and vancomycin	Normal; may be impaired
Neisseria meningitidis	Acute bacterial meningitis	Adolescent	Ceftriaxone	Normal
Hemophilus influenzae type B	Acute bacterial meningitis	Child	Ceftriaxone or ampicillin/ gentamicin	Normal
Listeria monocytogenes[25]	Acute bacterial meningitis	Infant	Ampicillin/gentamicin or trimethoprim/ sulfamethoxazone	Normal, associated with maternal infection
	Brain abscess (typically involving the pons, termed rhombencephalitis)	Any	Ampicillin/gentamicin or trimethoprim/ sulfamethoxazone	Normal
	Acute or subacute bacterial meningitis	Older adult	Ampicillin/gentamicin or trimethoprim/ sulfamethoxazone	Often immunocompromised
Staphylococcus aureus (coagulase-positive staphylococcus)	Acute bacterial meningitis	Any	Vancomycin	Anatomic or surgical defect in skull or meninges
	Brain abscess	Any	Vancomycin	Hematogenous dissemination (eg, endocarditis)
	Epidural abscess	Any	Vancomycin	Direct extension from osteomyelitis
Staphylococcus epidermidis (coagulase-negative staphylococcus)	Subacute bacterial meningitis	After neurosurgical procedures	Vancomycin	
Streptococcus agalactiae (group B streptococcus)	Acute or subacute bacterial meningitis	Newborns and older adults	Ampicillin	Colonization during delivery; gastrointestinal source of bacteremia

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Table 1
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Organism	Syndrome	Typical Patient Age	Initial Treatment Pending Sensitivities	Common Host Characteristics
Escherischia coli	Acute bacterial meningitis	Newborns or patients with anatomic or surgical defects	Ceftriaxone or cefotaxime	
Other gram-negative rods	Meningitis	Any	Cefepime	After neurosurgical procedures
	Brain abscess	Any	Ceftriaxone (or cefepime), vancomycin, and metronidazole	After neurosurgical procedures
Streptococcus milleri group	Brain abscess	Any	Ceftriaxone (or cefepime), vancomycin, and metronidazole	
Bacteroides species and other anaerobes	Brain abscess	Any	Ceftriaxone (or cefepime), vancomycin, and metronidazole	
Bacillus anthracis[26]	Meningitis	Any	Penicillin or ciprofloxacin	
Treponema pallidum[27]	Meningitis (secondary syphilis; later, meningovascular syphilis)	Any	Penicillin	Accelerated course in HIV patients
	Encephalitis (general paresis)	Older adults	Penicillin	
	Parenchymal neurosyphilis	Older adults	Penicillin	
	Tabes dorsalis	Older adults	Penicillin	
	Congenital neurosyphilis	Neonates	Penicillin	
Borrelia burgdorferi	Meningitis	Any	Ceftriaxone or doxycycline	
	Peripheral neuropathy	Any	Ceftriaxone or doxycycline	
Rickettsii (eg, *Rickettsia rickettsii*, Rocky Mountain spotted fever)	Encephalitis	Any	Doxycycline	

Higher bacteria			
Nocardia	Brain abscess	Any	Cell-mediated immunity defects
Actinomyces	Brain abscess	Any	
Mycobacteria			
Mycobacterium tuberculosis[28]	Meningitis	More severe in children	
	Brain abscess (tuberculoma)	Any	
	Epidural abscess (Potts disease)	Any	
Mycobacterium avium complex	Meningitis	Any	HIV patients most commonly affected
	Encephalitis	Any	HIV patients most commonly affected
Mycobacterium leprae	Peripheral neuropathy	Any	
Fungi[29]			
Aspergillus spp[30]	Brain abscess	Any	Granulocytopenic patients
	Meningitis	Any	
Cryptococcus neoformans[31]	Meningitis	Any	Patients with HIV infection and others with cell-mediated immune defects (especially steroids)
	Brain abscess	Any	Patients with HIV infection and others with cell-mediated immune defects (especially steroids)
Coccidioides immitis	Meningitis Brain abscess	Any	Geographically limited
Candida albicans (and other species)	Meningitis	Any	
	Brain abscess	Any	
Rhizopus, *Mucor*, and related fungi	Meningitis with vasculitits	Any (usually adults)	Acidotic patients

reflect the inflammatory response produced by the host in response to the infection. In bacterial meningitis, the structural barriers imposed by the dura and the arachnoid provide substantial protection from bacterial invasion. However, infection by direct extension, usually from the skull (including the sinuses), does occur, presumably because the inoculum of the infecting organism is too large for containment by the extradural defenses. Whether the organisms reach the SAS by traversing these membranes, or via hematogenous spread, the SAS itself provides a relatively favorable location for bacterial or fungal replication. The SAS and the brain are often considered immunologically "privileged" sites, because they are extensively protected by anatomic barriers, but at the same time they partially exclude many of the cells and substances (eg, complement); when infection does occur, they are in part immunologically deprived.[9]

The major impediments to the movement of both microorganisms and inflammatory substances from the systemic circulation into the CNS are the blood-brain and blood-cerebrospinal fluid (CSF) barriers. Anatomically, these barriers reside in the investment of cerebral capillaries (which themselves have tight junctions) by astrocytic foot processes, which completely envelop the cerebral microvasculature. These barriers normally regulate the transit of molecules from the bloodstream into the brain. However, inflammation and trauma can damage the barrier, making it much less selective; matrix metalloproteinase-9 is probably a major mediator of this effect, which is not completely deleterious, because it allows many antimicrobial agents to enter the CNS in higher concentrations when an infection is present. Endogenous substances, such as complement, also cross in higher concentrations, but generally less than those of the blood. Antibodies needed to combat infection also cross, but as the inflammatory response continues, local plasma cells will produce considerably more immunoglobulin locally.[10]

The cellular components of the immune response are less dependent on changes in blood-brain and blood-CSF barrier function than the humoral components. About half of the resident macrophages of the CNS, microglia, are derived from bone marrow precursors and easily pass in and out of these otherwise protected spaces. When inflamed, the CNS releases activated complement components, cytokines (eg, tumor necrosis factor, interleukin (IL)-1β, IL-6, IL-8, and IL-10), and chemokines, which attract neutrophils and other inflammatory cells. The initial response to infection causes neutrophils in small vessels to begin rolling along the endothelial surface due to the effect of selectins; these cells are then attached to the vessel wall by integrins and soon migrate through the vessel wall under the influence of IL-8. The initial neutrophilic response to most infections is followed by other components of the macrophage/monocyte system, and the eventual arrival of lymphocytes, some of which will become plasma cells and produce antibody locally.

The CNS lacks lymphatics, so the debris of inflammation exits the parenchyma via the perivascular (Virchow-Robin) space. This space is actually a continuation of the SAS along penetrating blood vessels. Inflammatory infiltrate in this space is one of the pathologic criteria of many types of infection.[11] The accumulation of this debris in the SAS contributes to the development of cerebral arterial vasculitis and cerebral venous thrombosis, common complications of diseases such as bacterial meningitis. This observation has led to a resurgence of interest in continuous lumbar CSF drainage to decrease inflammation.[12]

Neuronal damage is partially mediated by the effects of nitric oxide (NO) and excitatory amino acids. NO is released by inflammatory cells and by neurons in the course of normal function, but when inflammatory cells undergo an oxidative burst to kill micro-organisms, the excessive NO triggers apoptosis in neurons, particularly in the

hippocampi.[13] The involvement of microglia via toll-like receptors in this process indicates that the innate immune system of the brain also participates in this potentially deleterious process.[14] Understanding of the role of excitatory amino acids continues to evolve; blocking their effects may stop seizures but not apoptosis.[15]

Foreign bodies in the CNS provide locales for bacteria to multiply, with some protection from immune surveillance and attack. The bacteria involved are often less pathogenic than the usual causes of meningitis (eg, infection of ventriculo-peritoneal shunt tubing often involves *Staphylococcus epidermidis*, which produces a disease that is initially much less severe than *Staphylococcus aureus*). However, the presence of the foreign body also makes both the host immune attack and the antibiotic treatment incompletely effective; foreign bodies must often be removed to cure such an infection.

Increased ICP causes 2 major problems: interference with cerebral blood flow, and shift of structures within the cranium.

Seizures are a common manifestation of supratentorial intracranial infections, except for epidural abscesses.

NATURAL HISTORY

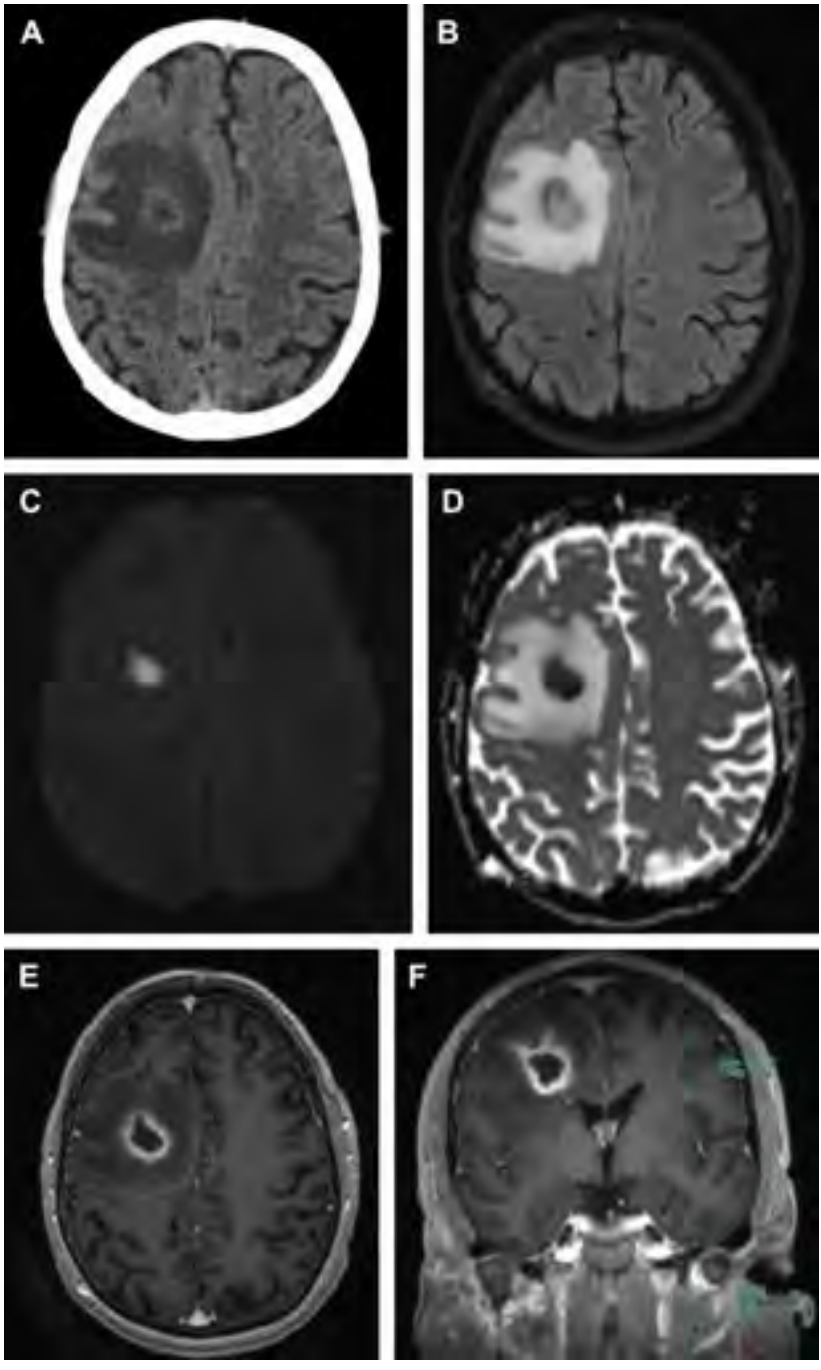
In the pre-antibiotic era, the natural history of most CNS infections was dismal. A few patients would recover spontaneously from bacterial meningitis, but the mortality often exceeded 90%. Epidural abscesses of the cranium or spine could be drained surgically and thus had some possibility of improvement, and brain abscesses could sometimes be treated by resection.

The prognosis of these conditions changed drastically with the availability of antimicrobial agents. The mortality of bacterial meningitis has fallen to about 30%. This percentage has remained relatively constant over the past 6 decades, which probably reflects the coincidence of more effective drugs with the development of antibiotic resistance among bacteria and the increasing number of immunocompromised patients. Data for the other, less numerous, infections are less clear but generally show a substantial benefit of antibiotic treatment.

The survivors of CNS infections are frequently left with serious neurologic compromise. Seizures and neurologic deficits are common following the otherwise successful treatment of brain abscesses and subdural empyemas. Patients who have recovered from bacterial meningitis, including tuberculous meningitis, frequently have chronic problems related to vascular complications; cranial nerve deficits are also common. Meninigitis in children may result in developmental delay; in these patients, one should exclude hearing loss as a contributor to a decline in school performance after meningitis, because auditory nerve problems are very frequent.

Tubercular and fungal meningitides generally develop signs and symptoms more chronically. Hydrocephalus, due to impairment of CSF flow at the base of the brain, and strokes, as a consequence of arterial inflammation in the circle of Willis, may be the initial manifestations. In patients with T-cell defects, cryptococcal meningitis is relatively common.

Brain abscesses may arise either by contiguous extension from a paranasal mastoid sinus or by hematogenous dissemination. The presentation depends on the organism, the location of the abscess, and the host response. About half of brain abscess patients are afebrile and have normal peripheral white blood cell counts. Seizures are a common presentation, with headache also common but often mild. Abscesses that appear to be mature, with a well-defined capsule and a core of nectrotic material on CT or MRI scans, may still be in a phase of cerebritis pathologically.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The natural history of spinal cord compression caused by an epidural abscess highlights the need for alacrity in diagnosis and treatment. When the condition is diagnosed and treated at the stage of local pain, complete recovery is typical, but if intervention is delayed until radicular symptoms are present, the spinal cord is spared but the nerve roots may not recover. When long tract findings appear, permanent disability may develop within hours; this constitutes a medical and surgical emergency, which must be managed immediately.

DIAGNOSIS

The diagnosis of acute bacterial meningitis with virulent organisms such as *Streptococcus pneumoniae* in a normal host is rarely unsuspected. The previously healthy patient who presents with headache, fever, and nuchal rigidity but without coma or focal neurologic signs should undergo a lumbar puncture as quickly as possible. If this test is delayed for other diagnostic studies, empiric antibiotic treatment for the most rapidly fatal organisms should be given, after blood cultures are obtained but before the patient undergoes radiologic studies.

CSF analysis is the cornerstone of diagnosis in the meningitides. The CSF of the typical patient with bacterial meningitis will have a neutrophilic pleocytosis, a low-glucose concentration (less than 30% of the contemporaneous plasma glucose), and an elevated protein concentration. However, antibiotic therapy, even oral antibiotics given for another reason, may shift the pleocytosis to lymphocytes within hours; this same shift may be seen early in the course of viral encephalitides and rarely with brain abscesses.

The Gram stain of the CSF often yields clues that are important both diagnostically and therapeutically, but in some bacterial meningitides the Gram stain may not demonstrate an organism; *Listeria monocytogenes* is the most important example of this phenomenon. If listeriosis is suspected, the therapeutic regimen should be expanded (see below in the Treatment section).

CSF analysis rarely yields useful microbiologic information in patients with epidural abscesses or subdural empyemas and should not be performed routinely in these patients.

Fig. 1. Different imaging studies of a brain abscess. (*A*) Unenhanced CT scan of a brain abscess. The hypodense central portion of the abscess revealed cerebritis on histologic examination, rather than necrotic material. The larger hypodense area is edema surrounding the isodense wall of the abscess itself. (*B*) Fluid attenuation inversion recovery image of the brain abscess. The edema surrounding the abscess has a high T2 signal. The fluid attenuation inversion recovery sequence suppresses the CSF signal, improving the recognition of vasogenic (extracellular) edema around the abscess. Note the midline shift. The patient presented with a single seizure without other complaints and had only subtle signs of right hemisphere dysfunction. (*C*) Diffusion-weighted image of a brain abscess. The white area indicates restricted diffusion, reflecting cytotoxic (intracellular) edema. (*D*) Apparent diffusion coefficient (ADC) map of a brain abscess. Although the ADC map has poorer spatial resolution than the diffusion-weighted image (*C*), the dark center of the lesion confirms that the bright area seen on the diffusion-weighted image reflects restricted diffusion rather than vasogenic edema. (*E*) Axial T1-weighted postinfusion image showing enhancement in the wall of the abscess corresponding to the area of new blood vessel growth; these vessels lack a mature blood-brain barrier and allow the diffusion of gadolinium into the tissue. (*F*) Coronal T1-weighted image of a brain abscess. Note the contralateral shift of the falx; this can compress the anterior cerebral arteries, resulting in ipsilateral or bilateral infarction in these territories. Also note the effacement of the right lateral ventricle.

If cryptococcal meningitis is suspected, an India ink preparation of the CSF may reveal budding yeast. More commonly, though, the diagnosis is confirmed by the presence of cryptococcal antigen in serum and CSF.

Fungal and tubercular meningitides will usually present with a lymphocytic pleocytosis. Because obstruction to CSF flow is a major problem with some of these infections, the CSF protein concentration may be very high. The CSF glucose concentration may be exceptionally low in patients with advanced tubercular meningitis. The initial differential diagnosis of patients with these more chronic meningitides is quite broad, and noninfectious causes need to be considered.[16]

Localized infections may present with focal neurologic findings, in which case the signs and symptoms will dictate the appropriate imaging study. **Fig. 1** shows the appearance of a *Fusobacterium* brain abscess on CT and with varying MR sequences. Although it is tempting to infer that the MR appearance of a lesion can definitively exclude a neoplasm, this is not yet the case, and pathologic confirmation remains a necessity.

TREATMENT

The definitive treatment of CNS infection depends on the correct identification and antimicrobial treatment of the infecting organism, relief of excessive pressure or mass effect that it exerts, and modulation of the host's immune response to allow clearance of the organism while minimizing the deleterious consequences of excessive inflammation. Empiric therapy is based on knowing the local epidemiology and antibiotic sensitivities of the organisms likely causing meningitis, and understanding the particular risk factors of the patient.[17] For example, patients with T-cell defects are at increased risk for *Listeria* meningitis, so their initial therapy should include ampicillin (perhaps with an aminoglycoside) or trimethoprim/sulfamethoxazole. If the differential diagnosis includes viral encephalitis, empiric treatment with acyclovir should be added until either another diagnosis is proven or a polymerase chain reaction study for herpes simplex virus is negative.

The emergence of penicillin and, to a lesser extent, cephalosporin resistance in pneumococci led to several changes in the empiric treatment of meningitis. Thus, empiric therapy for acute bacterial meningitis now includes a third-generation cephalosporin (eg, ceftriaxone) as well as vancomycin. Unfortunately, corticosteroid administration decreases the penetration of vancomycin into the CSF; this has limited enthusiasm for the use of steroids before antibiotic administration.[18] Nosocomial meningitides are more likely to involve resistant gram-negative rods, and the empiric regimen should include a fourth-generation cephalosporin (eg, cefepime) or a carbapenem, perhaps in concert with intrathecal or intraventricular aminoglycoside.[19]

Patients with meningitis often have nonconvulsive seizures, and their altered consciousness may be the consequence of nonconvulsive status epilepticus. Such patients should undergo continuous electroencephalogram monitoring for at least 3 days to exclude this phenomenon and guide its therapy.[20]

The use of antibiotics alone is usually inadequate in the treatment of abscesses. Thus, cranial and spinal epidural abscesses and subdural empyemas almost always require surgical or CT-guided drainage in addition to antibiotics for resolution. The situation with brain abscesses is more problematic. At the point in time when the abscess appears to have developed a capsule when viewed by CT or MR imaging, the tissue is usually still in the histologic state of cerebritis, rather than having a necrotic center that could be drained. Obtaining a sample of the infected tissue for microbiologic studies as soon as possible is important regardless of the age of the abscess, but

it may be necessary to drain or resect the abscess later when it has become more mature. Second, one must choose antimicrobial agents that will achieve a useful concentration in the infected tissue. Epidural abscesses, for example, are outside of the CNS and can be treated with antibiotics that do not penetrate with brain. Clindamycin does not achieve useful concentrations in the CSF and should not be used to treat meningitis. Third, potent drugs, such as the third-generation cephalosporins, are very effective in sterilizing the CSF of many organisms causing meningitis, but the rapid release of bacterial cell wall components into the CSF prompts a profound inflammatory response, and this response is a cause of some of the complications of meningitis, such as seizures and sensorineural hearing loss. Treatment with corticosteroids before or just after the first dose of the antibiotic decreases this inflammatory response and seems to lower the incidence of some of these complications, and may provide a survival benefit.[21]

Because many brain abscesses are caused by anaerobic or mixed aerobic-anaerobic infection, empiric treatment should include metronidazole or meropenem. If metronidazole is used, the patient should also receive ceftriaxone (or cefepime if indicated based on exposure to resistant gram-negative rods), and vancomycin until Gram stain and culture results are available.

Osmotic therapy with either mannitol or hypertonic saline remains the mainstay of treatment of increased ICP.[22] Steroids may be useful in the treatment of brain abscesses, once appropriate antibiotic therapy is initiated. Hyperventilation works by reducing cerebral blood flow and should be reserved for extreme situations, such as the reversal of herniation, while waiting for osmotic agents to work, or to keep the patient alive until surgical treatment can be performed emergently.

Cranial and spinal epidural abscesses compress the CNS tissue below them and may produce permanent neurologic damage or death if the pressure is not relieved surgically in a timely manner. Subdural empyemas generally produce less mass effect, but the inflammatory response they incite damages the underlying cortex; they too should be removed expeditiously.

Fungal meningitides and abscesses should generally be treated with amphotericin pending identification of the organism and determination of its sensitivities. Tubercular infections may need empiric treatment with up to 5 agents until sensitivities are known.[23] When these infections occur in the setting of the acquired immunodeficiency syndrome, antiretroviral therapy should usually be delayed until the patient shows improvement in the signs and symptoms of infection to decrease the likelihood and severity of the immune reconstitution syndrome.[24]

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