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REVIEW

Neuro-Intensive Care of Patients with Acute CNS Infections

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Summary Infections in the central nervous system (CNS) are caused by a wide range of microorganisms resulting in distinct clinical syndromes including meningitis, encephalitis, and pyogenic infections, such as empyema and brain abscess. Bacterial and viral infections in the CNS can be rapidly fatal and can result in severe disability in survivors. Appropriate identification and acute management of these infections often occurs in a critical care setting and is vital to improving outcomes in this group of patients. This review of diagnosis and management of acute bacterial and viral infections in the CNS provides a general approach to patients with a suspected CNS infection and also provides a more detailed review of the diagnosis and management of patients with suspected bacterial meningitis, viral encephalitis, brain abscess, and subdural empyema.

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Introduction

Infections in the central nervous system (CNS) are caused by a wide range of microorganisms resulting in distinct clinical syndromes including meningitis, encephalitis, and pyogenic infections, such as empyema and brain abscess. Appropriate identification and acute management of these infections often occurs in a critical care setting and is vital to improving outcomes in this group of patients. For the purposes of this review, we will focus on the clinical presentation, diagnosis, and management of acute bacterial meningitis, encephalitis, bacterial empyema, and brain abscess. Other important causes of acute CNS infections, such as postneurosurgical or post-traumatic meningitis are beyond the scope of this review and are covered elsewhere [1–3].

Infections of the CNS are uncommon, but a high index of suspicion is vital to appropriately diagnose and treat these infections. Patients with a CNS infection often have prolonged hospitalizations with critical care support, require a multitude of diagnostic tests and procedures, and can have poor outcomes. In cases of encephalitis, the direct medical costs in 1997 in the United States (U.S.) were approximately $28,151 per hospitalization, with encephalitis cases accounting for 19,000 hospitalizations, 230,000 hospital days, and 1400 deaths [4]. Unfortunately, more recent economic data is not available, although costs have undoubtedly increased dramatically. The incidence of encephalitis varies from 2 cases per 100,000 of the population to 13.7 per 100,000. The incidence of bacterial meningitis in the U.S. has decreased by 31% during the last

10 years from a rate of 2 per 100,000 in 1998 to 1.38 per 100,000 in 2007, largely due to a decreased incidence in the pediatric populations following introduction of vaccines for *Haemophilus influenzae* type B and *Streptococcus pneumoniae* [5]. The incidence of pyogenic infections in the CNS, such as cranial and spinal subdural empyema and brain abscess, is not well understood. Brain abscess accounts for approximately 1500 cases annually in the U.S. each year, and the incidence is estimated at 0.3 to 1.3 cases per 100,000 of the population annually [6]. Although these infections are rare, the high morbidity and mortality rates in the absence of appropriate care necessitate a thorough understanding of the acute management of these infections.

Initial Clinical Presentation

When evaluating a patient with a suspected CNS infection, the clinician must have a high index of suspicion in patients presenting with nonspecific signs and symptoms, such as fever, headache, and altered mental status or meningismus. In the case of suspected bacterial meningitis, the goal is to emergently initiate appropriate empiric antibiotic therapy, based on the age of the patient, the underlying disease status, and cerebrospinal fluid (CSF) Gram stain, if available. Retrospective cohort studies of patients with community-acquired bacterial meningitis have shown an increase in adverse outcomes when initiation of antimicrobial therapy is delayed following the initial visit to a physician or the emergency room (ER) [7]. This data is supported by 2 additional retrospective studies showing improved outcomes and decreased mortality in patients that receive antimicrobial therapy earlier in the course of the disease [8, 9]. The data is similar in patients with herpes simplex virus (HSV) encephalitis. Patients with HSV encephalitis who receive the first dose of acyclovir earlier in the course of disease have significantly lower mortality rates [10–12].

When evaluating a patient with fever, headache, and mental status changes, the clinician must first determine whether the patient presents with encephalopathy or a possible CNS infection. Patients with encephalopathy are often afebrile and routine laboratory values may reveal a reason for an underlying metabolic or toxic encephalopathy. Once infection is suspected, the evaluation should continue emergently so that appropriate antibiotic therapy or surgical intervention can be initiated. Patients with suspected bacterial meningitis or encephalitis should have a lumbar puncture to obtain CSF for analysis of cell count and differential, protein, glucose, Gram stain, and bacterial culture. If viral encephalitis is suspected, specific studies of the CSF for viral pathogens, including appropriate viral-specific polymerase chain reactions (PCRs) and serologies, should be performed. Patients with a history of CNS lesions, immunosuppression, evidence of increased intracranial pressure, altered mental status, or focal neurologic signs should have neuroimaging studies performed prior to lumbar puncture. Given that many patients with infections in the CNS will present with similar findings of fever, headache, and neurologic changes, the differential diagnosis often remains broad prior to neuroimaging. The neuroimaging often delays initiation of antibiotic therapy in patients with suspected bacterial meningitis, so blood cultures should be obtained, and empiric antimicrobial therapy for bacterial meningitis should be initiated prior to neuroimaging. In pediatric patients with bacterial meningitis, CSF white blood cell (WBC) count and Gram stain sensitivity were not affected by parenteral antibiotic therapy administered prior to lumbar puncture [13]. The sensitivity of CSF culture was slightly decreased from 84% to 74% in patients that received parenteral antibiotic therapy within 4 hours prior to lumbar puncture, although sensitivity decreased further in those patients who had a longer duration of therapy (see as follows) [13]. However, the decrease in sensitivity of CSF culture is a reasonable consequence of administering antibiotic therapy earlier in the course of disease, and blood cultures obtained prior to antibiotics were positive in 66% of cases. When bacterial meningitis is first suspected, blood cultures should be obtained, quickly followed by initiation of empiric antibiotic therapy. The choice of empiric antimicrobial is discussed as follows.

Patients that require neuroimaging prior to lumbar puncture will require imaging sensitive enough to evaluate for a space-occupying lesion in the CNS. Magnetic resonance imaging (MRI) or computed tomographic (CT) scan with intravenous contrast are the most sensitive methods to exclude a space-occupying lesion in the CNS. MRI is the imaging procedure of choice in virtually all CNS infections, and typically it is more sensitive than CT for identifying infection-associated CNS tissue changes and better able to define areas of involvement. MRI is also a sensitive test for identifying brain abscess and subdural or epidural empyema that may present with nonspecific signs and symptoms consistent with other CNS infections. In patients with a space-occupying lesion in the CNS identified on MRI, lumbar puncture rarely adds useful additional information and is associated with an increase risk of brain herniation. These patients often require an emergent neurosurgical drainage procedure, which is both therapeutic and provides specimens for Gram stain and culture. Patients without evidence of space-occupying mass lesions can safely undergo lumbar puncture. In patients with imaging consistent with encephalitis, empiric treatment with parenteral acyclovir (30 mg/kg/day) should be considered in addition to empiric antimicrobial therapy, pending results of HSV PCR in the CSF sample.

By completing a thorough and expedient evaluation in patients with possible infections in the CNS, therapy can be started earlier and potentially decrease the risk of a poor outcome. Although a general approach will improve the evaluation of patients with CNS infections, specific diagnostic and management approaches will differ for each acute infection in the CNS. Some of these differences will be highlighted as follows.

Bacterial Meningitis

Bacterial meningitis is a very important cause of infection in the CNS throughout the world. For the past 10 years in the United States (U.S.), the median age of patients with bacterial meningitis has increased from 30.3 years of age in 1998 to 1999 to 41.9 years of age in 2006 to 2007, largely due to lower rates of *H. influenza* type B (Hib) and *S. pneumoniae* meningitis in children following the widespread utilization of *S. pneumoniae* and Hib conjugate vaccines [5]. Despite a 31% decrease in incidence of disease, overall mortality rates in patients with community acquired bacterial meningitis remain unchanged at 15%, and the epidemiology of causative organisms also remains unchanged [5]. Overall, *S. pneumoniae* continues to be the predominant cause of bacterial meningitis in the U.S., accounting for 58% of cases, followed by group B streptococcus (18%), *Neisseria meningitides* (13.9%), *H. influenzae* (6.7%), and *Listeria monocytogenes* (3.4%). However, rates of specific etiologic organisms change according to specific age groups (Fig. 1). In pediatric cases 2 months old, group B streptococcus accounts for 86% of cases, and in cases >2 months of age, *S. pneumoniae* and *N. meningitidis* are increasingly important causes of bacterial meningitis, with the peak incidence of *N. meningitidis* in the 11- to 17-year-old age group. Given the rapidly fatal and aggressive course of *N. meningitidis* infection, ongoing studies to develop a serogroup B vaccine and improve vaccination rates with the current vaccine for serogroups A, C, Y, and W135 continue to be important priorities [14]. In adults >18 years of age, *S. pneumoniae* infection causes approximately 70% of the cases, followed by *N. meningitidis*, *H. influenzae*, group B streptococcus, and *L. monocytogenes* [5]. Adults >65 years of age and alcoholics have increased rates of infection with *L. monocytogenes* and have an increased chance of a poor outcome due to bacterial meningitis [5, 15].

Diagnosis

CSF analysis is the primary diagnostic procedure required to make a diagnosis of bacterial meningitis [16, 17].

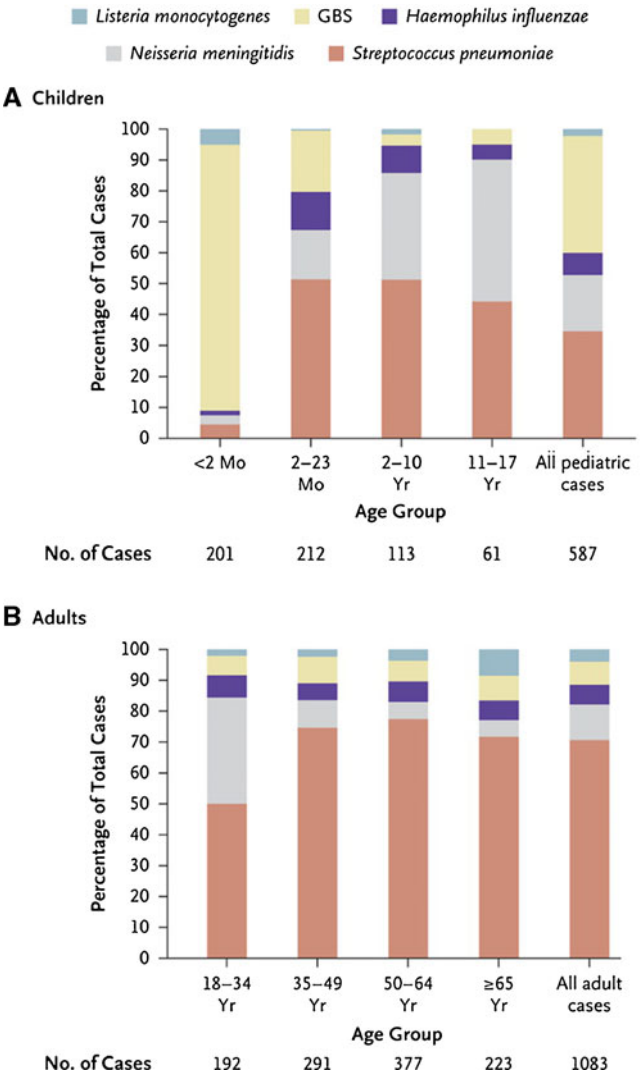

Fig. 1 Proportions of bacterial meningitis reported from 2003–2007 per age group. Panel A represents data from children and panel B represents data from adults. (Adapted from Thigpen et al. Bacterial meningitis in the United States, 1998–2007. NEJM 2011;64:2016–2025). GBS = Group B Streptococci; Mo = month; Yr = year

Lumbar puncture in patients with bacterial meningitis carries a risk of brain herniation [18, 19]. Patients with space-occupying lesions in the CNS (e.g., brain abscess, subdural empyema, subdural hemorrhage, brain tumor, or necrotic temporal lobe in herpes simplex encephalitis) may present with symptoms that appear identical to bacterial meningitis, and lumbar puncture may be complicated by herniation [18, 20]. Emergent neuroimaging to evaluate for a CNS space-occupying lesion should be completed prior to lumbar puncture in patients who have new onset seizures, focal neurologic signs on examination, a history of a space-occupying CNS lesion, an immunocompromised state, signs of increased intracranial pressure, or moderate-to-severe impairment of consciousness [18, 19, 21]. However, empiric treatment for bacterial meningitis should not be

delayed while awaiting neuroimaging prior to lumbar puncture. A delay in the initiation of antimicrobial therapy can result in poor outcomes. Retrospective studies have shown that the median delay between time of arrival at the emergency department and antibiotic administration was 4 h, and poor outcomes were associated with delayed antimicrobial therapy [7]. Among patients with a worsening condition while waiting in the ER, delay in antimicrobial therapy longer than 6 h after arrival to the ER was associated with increased risk of death [22]. If neuroimaging is required prior to lumbar puncture, blood cultures should be obtained and empiric antimicrobial therapy should be emergently initiated.

In patients with bacterial meningitis, CSF opening pressure is often elevated due to increased edema and inflammation in the CNS [23]. The CSF findings are important to define the differential diagnosis in patients with suspected bacterial meningitis. A cellular pleocytosis is present in most patients with bacterial meningitis (cell counts from 100–10,000 WBC per cubic mm) and 80 to 95% of patients will exhibit a neutrophil predominance on the cell count differential [20, 23–25]. Some cases of lymphocytic predominance are reported, as well as cases with no pleocytosis (5-10% of cases) in the CSF, which are both associated with poor outcomes [26]. Protein levels in the CSF are often elevated at >50 mg per dL, and CSF glucose levels are typically decreased to <40% of coincident serum glucose [20, 23–25]. Gram stain and culture of the CSF are the current gold standards for diagnosis of bacterial meningitis. Gram stain sensitivity is between 60 and 90% and can provide rapid identification of an etiologic organism [21, 23]. Culture of the CSF provides a specific diagnosis in 88% of cases not receiving antibiotic therapy prior to lumbar puncture [13]. A retrospective cohort study in children revealed that 72% of CSF cultures were positive following <4 h of antibiotic therapy prior to lumbar puncture [13]. Sensitivity of CSF cultures decreased to 55% following initiation of antibiotic therapy >4 h prior to lumbar puncture. However, prior antibiotic therapy had no significant impact on Gram stain sensitivity.

Bacterial antigen tests in the CSF have limited sensitivity and are not recommended for routine use, but may be helpful in patients with negative CSF Gram stain and culture in the presence of other clinical findings consistent with bacterial meningitis [21]. PCR assays for common bacterial ribosomal sequences exhibit promise as a rapid diagnostic tool, but are subject to false-positive results [27, 28]. PCR assays may be useful in cases of bacterial meningitis with negative Gram stain and culture or in cases with prior antibiotic therapy. Further studies will establish the usefulness of this rapid assay in the acute care setting. Determination of CSF lactate concentrations may be useful in differentiating bacterial from nonbacterial meningitis in patients that have received prior antimicrobial therapy [29]. CSF lactate concentrations of >4.0 mmol/L were considered a positive finding in favor of bacterial meningitis and may be especially helpful in the diagnosis of bacterial meningitis following neurosurgery [29].

Management

The choice of antimicrobial therapy is based on the age of the patient, underlying risk factors for disease (e.g., immunocompromise, trauma, neurosurgery), and patterns of antimicrobial resistance in the community (Table 1). According to Infectious Diseases Society of America (IDSA) practice guidelines for the management of bacterial meningitis, poor outcomes are associated with advanced clinical severity of disease, and empiric antimicrobial therapy for suspected or proven bacterial meningitis should be initiated as soon as possible after the diagnosis of bacterial meningitis is suspected [29]. Results from CSF Gram stain, culture, and susceptibility testing will allow modifications and refinements in empiric antimicrobial therapy. Due to the emergence of penicillin-resistant *S. pneumoniae* infections, current empiric standard therapy for suspected adult bacterial meningitis includes vancomycin and a third-generation cephalosporin, such as ceftriaxone or cefotaxime) [21]. In cases of suspected Listeria infection (e.g., age >65, alcoholism, pregnancy, atypical CSF profile), empiric therapy should include ampicillin or penicillin G, as cephalosporins have limited activity against this organism [29, 30].

Adjunctive corticosteroid therapy for bacterial meningitis is started in patients to treat the underlying cerebral edema, inflammation, and increased intracranial pressure (ICP). Adjunctive corticosteroids improve outcomes in infants and children with *H. influenzae* type B and in adults with *S. pneumoniae* meningitis [31, 32]. A randomized, double-blind, placebo-controlled trial evaluating the efficacy of corticosteroid therapy found that the addition of corticosteroids reduced the risk of unfavorable outcome from 25 to 15% and reduced mortality from 15 to 7% [32]. The benefit was greatest in patients with intermediate severity of disease and *S. pneumoniae* infection. Practice guidelines published in 2004 from the IDSA state that consideration should be given to administer adjunctive dexamethasone in patients with suspected or proven bacterial meningitis, and adjunctive dexamethasone should be initiated in all adult patients with suspected or proven pneumococcal meningitis [29]. Recent studies in the developing world suggest no clear benefit with adjunctive corticosteroid therapy in children and adults [33, 34], and these data were analyzed in a large meta-analysis, which questioned the mortality benefit for corticosteroid therapy

Table 1 Empiric Antibiotic Therapy for Bacterial Meningitis*

Predisposing Factor	Common Pathogen	Empiric Antimicrobial Therapy
Age		
<2 months	Group B streptococcus, *E. coli*, *L. monocytogenes*, *H. influenzae*, *S. pneumoniae*	Ampicillin plus cefotaxime or ampicillin plus aminoglycoside
2-23 months	*S. pneumoniae*, N. meningitidis, group B streptococcus, *H. influenzae*	Vancomycin plus a third- generation cephalosporin
2-50 years	*S. pneumoniae*, *N. meningitidis*	Vancomycin plus a third-generation cephalosporin
>50 years	*S. pneumoniae*, *N. meningitidis, L. monocytogenes, H. influenzae*	Vancomycin, ampicillin, and a third-generation cephalosporin
Head Trauma		
Basilar skull fracture	*S. pneumoniae*, *H. influenzae*, group A streptococci (*S. pyogenes*).	Vancomycin plus a third-generation cephalosporin
Penetrating trauma	S. aureus, coagulase-negative staph., gram-negative bacilli	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
Postneurosurgical	Gram-negative bacilli (P. aerginosa), S. aureus, coagulase-negative staph.	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem

*Adapted from Tunkel et al. IDSA Practice Guidelines for Bacterial Meningitis, 2004

in patients in the developing world [35, 36]. The underlying etiology of different responses to corticosteroid therapy in the developed world and the developing world are not clear. A recent observational study from the Netherlands found that mortality from bacterial meningitis had decreased from 30 to 20% after steroid therapy became widely used as a general standard of care [37]. Administration of corticosteroid therapy in cases of *S. pneumoniae* meningitis was also found to preferentially benefit patients >55 years of age in another study from a developed country [35, 37]. Based on the IDSA guidelines and recent data, patients with suspected or proven *S. pneumoniae* meningitis in the developed world should receive adjunctive dexamethasone therapy. Data to support initiation of adjunctive dexamethasone therapy in patients in the developing world with bacterial meningitis is less clear and must be left to the discretion of the treating physician.

Viral Encephalitis

When evaluating a patient with possible encephalitis, it is important to first distinguish between: 1) infectious processes, 2) encephalopathy, and 3) postinfectious immune-mediated processes, as exemplified by acute disseminated encephalomyelitis (ADEM) [38]. Encephalopathy refers to diffuse cerebral dysfunction without associated inflammation. The most common causes of encephalopathy relate to exposure to toxins (e.g. alcohol, licit or illicit drugs) or metabolic dysfunction (e.g. hypoxia, hypoglycemia or hyperglycemia, electrolyte disorders, renal and hepatic failure). The presence of fever, headache, peripheral leukocytosis, and CSF pleocytosis all favor encephalitis instead of encephalopathy. Although some encephalopathies may produce focal neurological signs, these are more typical in encephalitis, as are focal seizures. Patients with encephalitis frequently have neuroimaging abnormalities, and may show focal electroencephalographic (EEG) abnormalities or specific patterns of dysfunction that are rarely seen in encephalopathy.

In the differential diagnosis of cases of suspected viral encephalitis, it is important to also consider autoimmune causes of encephalitis including postinfectious encephalomyelitis or ADEM, as well as the increasing number of syndromes caused by antibodies against neural antigens, including the N-methyl D-aspartate (NMDA) receptor and voltage-gated potassium channels (reviewed in Vincent et al. [39]). ADEM is an inflammatory demyelinating disease of the CNS that follows an infection or vaccination, typically after a delay of 1 to 4 weeks with an incidence of 0.4 to 0.8 per 100,00 of the population [40–42]. Most cases are monophasic and associated with MRI findings of diffuse or multi-focal subcortical and central white matter lesions with increased signal on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences [41, 43]. A clear preceding infection or vaccination is found in approximately two-thirds of pediatric cases and half of adult cases [41–43]. Historically, the most common antecedents were measles, varicella, rubella, and mumps, although the frequency of these illnesses has declined in much of the world due to effective vaccination campaigns. More recent studies have stressed the importance of antecedent infections caused by influenza A and B, hepatitis viruses, nonspecific flu-like upper respiratory tract infections, and nonviral infectious agents, including mycoplasma [42]. Post-vaccination cases of ADEM are rare with

the newer vaccines now in general use, but have been reported with vaccines against measles, Japanese encephalitis virus, poliovirus, tetanus toxoid, influenza, and hepatitis B (reviewed in Huynh et al. [41]).

ADEM is a postinfectious or post-vaccination immune-mediated process rather than a consequence of direct viral or microbial injury to the CNS; therefore, CSF cultures and PCR studies show no evidence of an infecting pathogen, and brain tissue specimens do not show direct evidence of infection (e.g., no inclusions, microbial antigens, or nucleic acid and negative cultures). The basic CSF profile in ADEM is similar to that frequently seen in infectious encephalitis, including a pleocytosis with a predominance of lymphocytes, a normal glucose, and a normal or elevated protein. The presence of oligoclonal bands in the CSF or evidence of pathogen-specific intrathecal antibody synthesis (immunoglobulin M [IgM], increased CSF/serum immunoglobulin G [IgG] ratio) are more typical of encephalitis than ADEM. Conversely, significant elevations of CSF myelin basic protein are more common in ADEM, but can occur in encephalitis when significant white matter injury occurs. Pathological examination of brain tissue, if performed, allows definitive differentiation of ADEM from encephalitis. ADEM typically exhibits perivenular inflammation and demyelination, whereas encephalitis exhibits pathological evidence of perivascular and parenchymal inflammation, neuron, and glial cell death, and evidence of viral infection (viral inclusions, antigen staining, or viral nucleic acid).

Once an infection of the CNS is considered in the differential diagnosis, the evaluation and initiation of therapy should progress quickly. In cases of bacterial meningitis and herpes encephalitis, studies have shown that delay in therapy increases morbidity and mortality. When evaluating a patient with a possible infection of the CNS, the initial diagnostic goals are to obtain CSF for appropriate studies and to perform neuroimaging, preferably MRI unless contraindicated. Patients with suspected encephalitis will have altered consciousness or focal neurological findings and will usually require neuroimaging, preferably MRI, prior to lumbar puncture. In patients with suspected bacterial meningitis, as well as encephalitis, empiric antibiotic therapy should be initiated after blood cultures are completed if lumbar puncture is delayed for neuroimaging (see previously). Empiric acyclovir therapy should also be initiated in patients with suspected Herpes simplex encephalitis, pending results of diagnostic studies [38, 44].

If encephalitis is suspected, MRI, which is more sensitive, provides more detailed diagnostic information than CT, and is the neuroimaging procedure of choice. Neuroimaging studies can provide valuable clues that can assist in specific diagnosis of encephalitis. The most common abnormalities include areas of increased signal on T2 and FLAIR sequences. Diffusion-weighted imaging sequences may demonstrate abnormalities from before, or more extensive images than those seen in T2 and FLAIR sequences [45–49].

CSF examination is part of the basic testing in all patients with suspected encephalitis or meningitis [29, 38]. CSF from patients with viral encephalitis is typically characterized by a lymphocytic pleocytosis with a normal glucose concentration and a normal-to-elevated protein concentration. This pattern is similar to that seen in ADEM. The presence of neutrophils rather than lymphocytes, as the predominant cell type, occurs frequently in patients with West Nile virus (WNV) neuroinvasive disease [50], and tick borne encephalitis virus [51], and can also occur with Eastern equine encephalitis [52].

The suggested CSF diagnostic studies for immunocompetent adults in the U.S. with suspected encephalitis include a CSF opening pressure, cell count and differential, protein and glucose concentrations, Gram stain, and bacterial cultures. Initial viral studies of the CSF should include PCR studies for HSV, Varicella zoster virus (VZV), enteroviruses, and West Nile virus (WNV) IgM serology (in the summer and early fall seasons). Although viral CSF cultures have a high specificity when positive, they are insensitive and not routinely recommended for diagnostic purposes. Additional diagnostic tests are guided and prioritized by the clinical and epidemiologic clues obtained during evaluation of the patient. With immunocompromised patients, a series of diagnostic tests may be indicated based on the clinical and epidemiologic context of the patient (Table 2). EEG testing can be helpful in evaluating the type and frequency of seizures, and the presence of non-convulsive status epilepticus. The degree and severity of slowing is a sensitive indicator of the presence and severity of metabolic encephalopathies. Specific EEG patterns may suggest an increased likelihood of specific diagnoses (see EEG as follows).

Clinical Features

The presence of specific sets of neurological signs and symptoms by themselves does not allow unequivocal diagnosis of a specific cause of encephalitis. However, findings on neurological examination can increase the likelihood of some etiologic agents and reduce the likelihood of other pathogens, thereby facilitating and guiding confirmatory diagnostic testing. The most common focal neurologic signs associated with encephalitis include hemiparesis, aphasia, ataxia, cranial nerve palsies, myoclonus, and seizures [53]. Other important neurological findings include loss of temperature and vasomotor control as a result of autonomic dysfunction, and either diabetes

Table 2 Laboratory Studies for Other Causes of Encephalitis

Infectious Agent	CSF Studies	Serum Studies
HIV	PCR	PCR, IgG/Western blot
Epstein Barr virus	PCR	IgM to VCA, IgG to early and nuclear antigens
HHV6	PCR	
Mycoplasma pneumoniae	PCR	IgM and IgG
Mycobacterium tuberculosis	PCR, AFB stain, culture	
Varicella zoster	PCR and IgG	Paired Serum IgG with CSF sample
LaCrosse		IgM and IgG
St. Louis encephalitis	IgM	IgM and IgG
Eastern equine encephalitis	IgM	IgM and IgG
Venezuelan equine encephalitis	IgM	IgM and IgG
Cryptococcus	Antigen titer	
Coccidiomycosis	Complement fixation titer	
Syphilis	VDRL	RPR and treponemal-specific antibody test
Borrelia		IgM and IgG
Rickettsia		IgM and IgG

AFB = Acid fast bacilli; CSF = cerebrospinal fluid; HHV6 = human herpes virus 6; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; PCR = polymerase chain reaction; RPR = Rapid Plasmid reagin; VCA = viral capsid antigen; VDRL = venereal disease research laboratory

insipidus or syndrome of inappropriate antidiuretic hormone (SIADH) resulting from hypothalamic dysfunction. Signs of Parkinsonism (bradykinesia, rigidity, or rest tremor) may suggest infection with a *Flavivirus* (WNV, St. Louis Encephalitis virus (SLEV), Japanese Encephalitis virus (JEV)) and frontotemporal signs, such as aphasia, memory impairment, and personality changes, may suggest limbic encephalitis from HSV, human herpes virus 6 (HHV6) infection, a neoplastic etiology, or a non-neoplastic autoimmune encephalitis. Seizures occur in encephalitides that involve the cortex (e.g., HSV encephalitis) and less commonly with *Flavivirus* infections (WNV, St. Louis Encephalitis (SLE), JEV) that involve predominantly deep gray matter structures, such as the basal ganglia and thalamus. Brainstem involvement can occur with HSV, enterovirus 71 infections, and *Flaviviruses* (WNV); whereas cerebellitis is associated with Epstein Barr virus (EBV), VZV, mumps, and *Flavivirus* (WNV, SLEV) infections. *Flavivirus* infections (WNV, JEV), enterovirus 71, and poliovirus (poliomyelitis) infections can cause disease in the anterior horn of the spinal cord, resulting in acute flaccid paralysis. The frequency of cranial nerve palsies varies greatly in patients with encephalitis. Cranial nerve palsies are common in several nonviral infections that can mimic viral encephalitis (Lyme disease, syphilis, tuberculosis, fungal infections) and most commonly produce peripheral facial palsy (VII), vestibular or cochlear dysfunction (VIII), or paralysis of extraocular movements (III, IV, VI). Cranial nerve palsies are generally infrequent in viral encephalitis, unless there is concomitant brainstem involvement. However, WNV infection and VZV vasculopathy have been associated with palsies of a variety of cranial nerves (see specific sections).

The general physical examination also provides important clues that assist in the diagnosis of encephalitis. Skin rashes are common and characteristic for VZV, WNV, some enteroviruses, human immunodeficiency virus (HIV), measles, and rubella, and may occur with a variety of nonviral infections, including Lyme disease, syphilis, Mycoplasma, Rickettsia, Anaplasma, and Ehrlichia. Oral mucosal ulcerations may suggest herpangina and an enterovirus or HSV infection. Ocular findings including chorioretinitis occur with WNV, cytomegalovirus (CMV), and Bartonella (cat scratch). Parotitis, orchitis, and oophoritis can occur with mumps and lymphocytic choriomeningitis virus (LCMV) infections.

Diagnostic Tests

Neuroimaging

Unless specifically contraindicated, all patients with suspected infectious encephalitis should have an MRI scan performed. The sensitivity and specificity of different patterns of neuroimaging abnormalities for the diagnosis of specific forms of encephalitis have not been formally defined. However, different forms of encephalitis often produce distinctive MRI patterns that may provide clues suggestive of particular agents that can guide more definitive confirmatory tests (Fig. 2). Temporal lobe and limbic abnormalities are seen in HSV and HHV6 encephalitis, whereas subependymal enhancement occurs with CMV ventriculitis. An MRI often reveals multi-focal hemorrhagic infarctions and demyelinating lesions in cases of VZV vasculopathy [54]. Predominant demyelination on MRI is suggestive of progressive multi-focal leukoence-

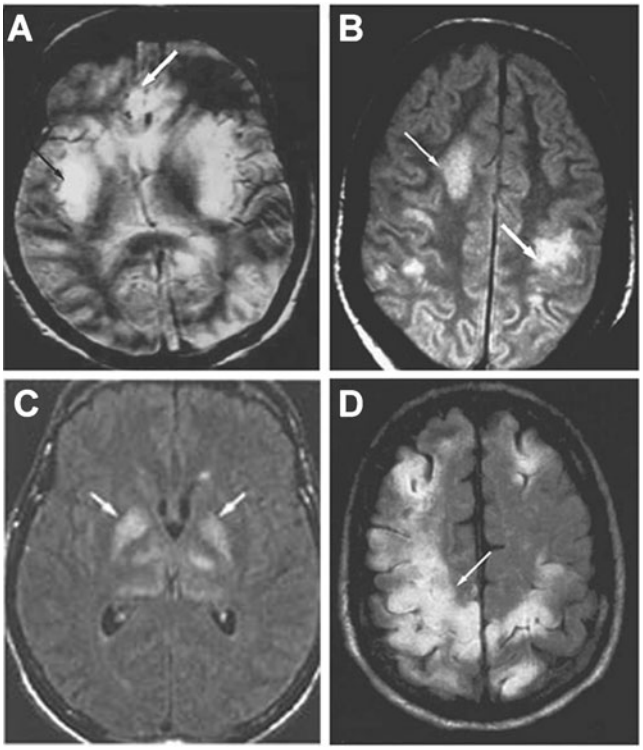

Fig. 2 Typical magnetic resonance imaging (MRI) changes associated with viral encephalitis. (**A**) Herpes simplex virus type 1 encephalitis with increased T2-weighted signal in bilateral temporal lobes. Increased signal does not extend beyond the insular cortex (black arrow), but does involve the cingulate gyrus (white arrow). (**B**) Varicella-zoster virus vasculopathy on proton-density MRI scan with multiple areas of infarction in both hemispheres (arrows). (**C**) West Nile virus encephalitis with increased signal on FLAIR MRI of the basal ganglia (arrows). (**D**) Enterovirus encephalitis with increased signal intensity on FLAIR MRI in both hemispheres in posterior cerebral hemisphere (arrow). (Adapted from Beckham and Tyler. Encephalitis, 7th ed. Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases. Churchill Livinstone, Elsevier 2010:1248)

phalopthay (PML) caused by JC virus infection or ADEM. PML lesions typically do not enhance in severely immunocompromised patients, whereas MRI lesions associated with ADEM show similar characteristics, acutely enhance, and then become nonenhancing with time.

In HSV encephalitis, MRI is significantly more sensitive than CT, revealing temporal lobe abnormalities in 90% of PCR-proven HSV cases [55]. There were 79% of patients with HSV encephalitis that had abnormalities on their initial CT scan, but 100% of the 17 patients whose CT scan was initially normal and who had repeat scans had abnormalities an average of 5 days later [55, 56]. There were 89% of patients with HSV encephalitis who exhibited MRI abnormalities of the temporal lobe, and 36% also had frontal involvement. Only 9% of patients with herpes simplex encephalitis (HSE) had an MRI with abnormalities exclusively outside the frontotemporal area. In 57% of HSE patients, the abnormalities were predominantly unilateral [11]. Characteristic MRI changes occur early in the course of HSE and include high-signal intensity lesions on T2-weighted and FLAIR images involving the medial and inferior temporal lobes with extension into the insula. MRI abnormalities can also include the orbitofrontal gyri and inferomedial frontal lobes [56, 57]. Diffusion-weighted imaging abnormalities may antedate and be more extensive than abnormalities seen on T2 and FLAIR sequences.

CT is almost invariably normal early in WNV and other arbovirus infections in the CNS. The MRI abnormalities are less frequent in cases of WNV than those that have been reported for HSV encephalitis. In 2 series involving a total of 34 patients, initial MRI studies were normal in approximately one-third of patients. MRI abnormalities associated with WNV encephalitis included areas of increased T2 and FLAIR and low T1 signal that involved the basal ganglia, thalamus, and brainstem [58, 59]. The MRI imaging abnormalities in WNV infection are generally distinct from those seen in HSV encephalitis, although in 1 series approximately 20% of patients had abnormalities limited to the mesial temporal lobes [59]. Some patients with WNV infection only have meningeal enhancement or abnormalities that are only seen on diffusion-weighted imaging. Patients with JEV have MRI abnormalities similar to those reported for WNV. In a recent study, MRI was more sensitive than CT for JEV infections, showing abnormalities in >90% of adults and children [60]. The most commonly involved areas were the thalamus (88%), basal ganglia (41-54%) and brainstem, but some patients can have medial temporal lesions resembling those seen in HSV encephalitis [60–62]. Patients infected with enterovirus 71 may demonstrate increased T2 and FLAIR signal intensity in the midbrain, pons, and medulla.

CSF Profile

CSF examination forms an essential part of the diagnosis of encephalitis and should be performed in all patients unless absolutely contraindicated [38]. The most typical CSF profile in patients with viral encephalitis is a CSF pleocytosis with a predominance of lymphocytes, a normal glucose, and an elevated protein. In cases of *Flavivirus* infection, particularly WNV, neutrophils may predominate, which is also a finding reported with Eastern equine encephalitis [50]. In 1 large series, the median percentage of neutrophils in patients with WNV encephalitis was 45%, and 37% of cases had a neutrophil predominance [50]. By contrast, patients with HSV encephalitis, typically have 5 to 24% neutrophils [11, 63, 64].

The magnitude of CSF pleocytosis varies greatly in different forms of encephalitis. In the classic studies of biopsy proven HSV encephalitis by the Collaborative Antiviral Study Group (CASG), patients with HSV encephalitis had a median CSF WBC count of 130 cells/cubic

millimeter; and 68% of patients had between 50 to 500 cells [65]. There were 4% of patients who had <5 cells/cubic millimeter, and only 8% had >500 cells/cubic millimeter. Similar CSF profiles were noted in a study of CSF PCR-proven HSV encephalitis. In that study, no patient with HSV encephalitis had <5 cells/cubic millimeter, and 69% of HSE patients had between 50 and 500 cells/cubic millimeter [55]. In a large series of cases with serologically proven WNV encephalitis, the mean CSF cell count was 227 cells/cubic millimeter (95% CI 133–321) [50]. Although pathologic evaluation of HSV encephalitis often demonstrates the presence of hemorrhagic necrosis, CSF red blood cell counts do not differ significantly between patients with biopsy proven HSV encephalitis and nonherpetic encephalitis [12, 65]. Glucose concentrations are normal in >95% of patients with encephalitis due to HSV and *Flaviviruses* (WNV, SLE) but may be low in some cases of CMV, mumps, and Eastern equine encephalitis infection.

CSF PCR and Antibody Studies

For some neuroinvasive viruses, PCR of the CSF has high sensitivity and specificity, making it the diagnostic study of choice for identifying a specific viral etiology. For example, HSV PCR in the CSF has a sensitivity of 98% and a specificity of 94% [66]. The sensitivity of PCR for detection of HSV encephalitis varies with the timing of the study. In the California Encephalitis Project, 3 patients with negative CSF HSV PCR tests performed within 72 hours of symptom onset had positive tests 4 to 7 days later [67]. CSF HSV PCR sensitivity declines as a function of duration of antiviral therapy with 98% of studies remaining positive in patients treated for 7 days or less, followed by a decrease in sensitivity with ongoing treatment to 47% at 8 to 14 days, and 21% after 15 days of antiviral treatment [66]. Using quantitative PCR, acyclovir-treated patients had negative PCR results 19±6 days (range, 9–28 days) after initiating acyclovir therapy [68].

PCR detection of VZV DNA has a specificity of >95%, but the sensitivity is ≤30% in some studies [69]. In cases of VZV CNS vasculopathy, CSF should also be tested for intrathecal synthesis of VZV specific antibody (IgM and IgG CSF/serum ratio), as these studies are complementary to PCR and may be positive when PCR tests are negative [69]. In a recent study, CSF VZV specific IgG was detected in 100% (14/14) of cases, but PCR was positive in only 28% [69].

PCR for EBV DNA in the CSF can be a valuable addition to the evaluation of a patient with viral encephalitis [70]. However, the results must be correlated with the clinical presentation, imaging, and serology results, because latently positive mononuclear cells in the CSF can produce false-positive results. False-positive PCR results are possible for much of the same reasons in patients suspected of HIV or HHV6 encephalitis, because infiltrating lymphocytes may act as a reservoir for viral reactivation and are not representative of primary infection.

CSF PCR is extremely specific (>95%) for the diagnosis of progressive multifocal leukoencephalopathy (PML) in immunocompromised patients with appropriate clinical and radiographic findings. However, the sensitivity of CSF JCV PCR may be as low as 50 to 80%, with lower values seen in more immunocompetent patients who likely have lower viral loads. Higher CSF JC viral loads correlate with worse outcomes in patients with PML [71]. Antibody testing for JC virus in serum or CSF is of little use in the diagnosis of PML, as 55 to 85% of individuals are seropositive in serum by adult life. In patients with intact capacity to mount antibody responses, such as those at risk for PML due to treatment with the lymphocyte migration inhibitor natalizumab, all reported cases of PML to date have been seropositive for JC virus at diagnosis, and the results of negative JC virus serology would provide an argument against the diagnosis. However, in patients with diminished humoral immunity, such as those with acquired immune deficiency syndrome (AIDS), or receiving immunosuppressive agents that blunt antibody responses, such as the anti-CD20 monoclonal antibody rituximab, the absence of JCV seropositivity does not exclude the possibility of PML. Demonstration of intrathecal synthesis of JC virus-specific antibody has been reported to have a sensitivity of 78% and a specificity of 97% for diagnosis of PML, but intrathecal antibody synthesis is not generally detectable until 2 to 3 weeks after onset of the illness [72].

In the case of *Flaviviruses* including WNV, CSF PCR is less sensitive (57-70%) compared to detection of CSF IgM antibodies for diagnosis of a neuroinvasive disease [73]. An exception may occur in the immunocompromised patient, such as a bone marrow and solid organ transplant recipient who has a prolonged, high titer viremia, and can have positive serum, and/or CSF PCR studies when antibody tests are negative or seroconversion is delayed [74, 75]. CSF IgM WNV antibodies are diagnostic of both acute WNV infection and neuroinvasive disease; their presence is indicative of intrathecal synthesis because IgM molecules cross the blood-brain-barrier poorly due to their large size. CSF IgM antibodies are found in approximately 80% of patients with WNV neuroinvasive disease within a week of onset of symptoms, rising at the rate of approximately 10% per day after symptom onset [76].

EEG

EEGs in patients with viral encephalitis are frequently abnormal, but the results only rarely provide a clue to a specific etiological diagnosis. The most common abnor-

mality is the presence of generalized slowing [77]. Focal EEG abnormalities, most commonly involving the temporal lobes, are seen in 75 to 80% of patients with HSV encephalitis [65, 78]. Common abnormalities include the presence of frontotemporal slowing, temporal sharp activity, and/or spike activity, and periodic lateralizing epileptiform discharges at a rate of 2 to 3 Hz. None of these patterns is diagnostic of HSV encephalitis. EEG abnormalities have been reported in approximately 60 to 90% of patients with WNV encephalitis. The most common finding is the presence of diffuse irregular slow waves, although it has been suggested that the presence of anteriorly predominant slowing may suggest the diagnosis [79]. Triphasic slow waves, generally considered more characteristic of metabolic encephalopathies, have also been reported in WNV encephalitis [80].

Management

The clinical status of patients with encephalitis can deteriorate rapidly; therefore, patients should be closely monitored in an intensive care unit or equivalent setting. Viral encephalitis caused by arboviruses or herpes viruses does not require patient isolation for infection control. Respiratory or contact isolation should be considered in cases of encephalitis of unknown etiology or in patients with possible bacterial meningitis or a skin rash. Universal precautions should be applied to handling all body fluids, including CSF, blood, saliva, and respiratory secretions, and stool and urine, as their potential infectivity varies with the inciting pathogen.

Patients with encephalitis can experience autonomic dysfunction, resulting in hypotension or cardiac arrhythmias, and also patients should have close monitoring of blood pressure and electrocardiogram testing until clinically stable. If the airway is compromised due to alterations in consciousness, then intubation should be considered to protect the airway and prevent aspiration. If clinically indicated, empiric antimicrobial agents should be initiated in patients with suspected bacterial infection or bacterial meningitis.

Patients with encephalitis may develop increased intracranial pressure. Patients with potential signs of increased ICP, such as decreased level of consciousness, papilledema, or cerebral edema often require continuous intracranial pressure monitoring. Clinical trials studying the role of steroids in encephalitis patients are not conclusive and further studies are needed; however, in cases of encephalitis with increased ICP, corticosteroids may be used to treat cerebral edema [77, 81, 82]. Additional measures to acutely diminish increased ICP include hyperventilation and intravenous mannitol administration.

Patients with certain types of encephalitis are likely to be at increased risk of seizures, and seizures can contribute to transiently increased ICP. The value of prophylactic anticonvulsant therapy in patients with encephalitis is uncertain. Patients with seizures are generally treated urgently with lorazepam or diazepam followed by maintenance therapy with intravenous fosphenytoin. Patients may require continuous electrocardiographic monitoring as clinical observation in obtunded patients may not reliably detect seizures.

In cases of suspected encephalitis, empiric acyclovir therapy (30 mg/kg intravenously per day divided into 3 doses) should be started as soon as possible and continued until HSV encephalitis is ruled out by appropriate testing or an alternative diagnosis is established. A delay in empiric acyclovir therapy for suspected HSV encephalitis is associated with an increased risk of death and severe disability [11]. In a recent retrospective review of 184 patients with HSV encephalitis, 37% of patients received acyclovir late in the hospitalization (>1 day after admission) [44]. Late administration of acyclovir was associated with severe underlying disease, alcohol abuse, atypical CSF features (<10 WBCs), and a delay of >1 day in neuroimaging [44].

Bacterial Brain Abscess

Brain abscess is one of the most serious complications of a head and neck infection. The incidence in non-HIV patients was estimated at 0.3 to 1.3 cases per 100,000 people per year [83]. In a recent retrospective analysis of 973 patients with brain abscess in South Africa, Oto-rhino sources of infection (38%) were the most common, followed by traumatic (32%), pulmonary (7%), and cryptogenic (4%). Operative drainage of abscesses >2.5 cm in diameter and antibiotic therapy resulted in a mortality rate of 13%, a poor outcome in 5%, and a good outcome in 81% of patients [84]. These outcomes are similar in other retrospective studies in Europe and Asia [6, 85, 86].

Patients with brain abscess typically present with 1 or more symptoms including fever, headache, altered level of consciousness, or focal neurological signs, including seizures, poor balance, dysphagia, or focal sensorimotor deficits [85]. The presentation varies based on the size and location of the abscess. Identifying associated infections such as otitis, mastoiditis, or sinusitis can provide important clues as to where an abscess may be located and the likely underlying causative organisms. Radiological investigation with CT or MRI is the primary diagnostic modality, and lumbar puncture is not recommended because it carries a risk of brain herniation and is not diagnostic in the majority of cases. A CT of the brain with contrast allows

differentiation of an abscess with a hypodense center surrounded by smooth, regular thin-walled capsules with areas of ring enhancement [87]. MRI imaging is the modality of choice in patients with suspected brain abscess. MRI results are variable and change with the stage of the abscess, which allows for better differentiation between stages of abscess formation that are amenable to abscess drainage, and allows for determination of associated edema, spread of inflammation into ventricles and the subarachnoid space, and allows early detection of satellite lesions [83, 87]. On T1-weighted nonenhanced images, the capsule of the abscess is a thin-walled ring isointense to the brain and hypointense on T2-weighted images [87]. With gadolinium administration, the abscess shows ring or multi-loculated enhancement.

The microbiology of a brain abscess is often associated with the underlying predisposing condition. In general, streptococci are most commonly cultured from patients with bacterial brain abscess and are commonly associated with mixed bacterial infections with other bacteria, including anaerobic Gram-negative rods in as many as 60% of the cases [88]. The *Streptococcus anginosus* (milleri) group include *S. anginosus*, *S. constellatus*, and *S. intermedius*, and particularly prone to produce abscesses following oropharyngeal or sinus infection, or bacterial endocarditis [89]. Other common organisms associated with bacterial brain abscess include *Staphylococcus aureus* associated with endocarditis or trauma and anaerobes, such as *Bacteroides* species often found in a mixed culture. Gram-negative rods, such as *Proteus sp.* or *Pseudomonas spp.* are often associated with otitis, mastoiditis, or postoperative neurosurgical procedures [90]. Organisms that cause bacterial meningitis do not typically cause brain abscess. Brain abscess accounts for approximately 10% of the infections in the CNS caused by *Listeria monocytogenes*, and are typically found in immunocompromised patients [91].

Management of Bacterial Brain Abscess

Appropriate management of brain abscess requires a multidisciplinary approach between the treating physician, neuroradiologist, neurosurgeon, and infectious disease specialists. Following diagnosis of brain abscess by MRI or CT scan, empiric antibiotic therapy should be initiated. These patients often undergo evaluation for bacterial meningitis, as well, at initial presentation, and may receive empiric antibiotic therapy prior to neuroimaging. Initial management of brain abscess requires empiric antibiotic therapy based on the likely source of infection (Table 3) and neurosurgical drainage of the abscess. Lesions greater than 2.5 cm are stereotactically aspirated by CT guidance or less commonly excised. All specimens should be sent for microbiology and pathology for diagnosis. For abscess in early cerebritis stages or when abscesses are less than 2.5 cm in diameter, the largest lesion may be aspirated for diagnosis.

Table 3 Empiric Therapy for Brain Abscess Based on Contiguous Infection*

Contiguous Infection	Site of Abscess	Causative Pathogens	Antimicrobial Therapy
Otogenic infection	Temporoparietal lobe and cerebellus	Strep. species, bacteroides, enterobacteriaceae, pseudomonas	Ceftazidime or cefepime plus metronidazole
Paranasal sinusitis	Frontal lobes	Streptococcus species, peptostreptococcus species, bacteroides, fusobacterium	Third-generation cephalosporin plus mentronidazole
Haematogenous spread	Parietal, frontal, or temporal lobes	Source of primary infection:	
		1) Endocarditis: S. viridans, S. aureus, enteroccocus	Vancomycin, third-generation cephalosporin, metronidazole
		2) Intra-abdominal infection: Gram- negative bacilli, enterococcus, anaerobes	Vancomycin, third-generation cephalosporin, metronidazole or vancomycin and meropenem
		3) Pulmonary infection: strep species, anaerobes, fusobacterium	Third-generation cephalosporin and metronidazole
		4) Urinary tract infection: Gram-negative bacilli	Third-generation cephalosporin and metronidazole
Penetrating trauma		Staph. aureus, coagulase-negative staph., clostridium species, aerobic gram-negative bacilli, bacteroides species	Vancomycin, third-generation cephalosporin and metronidazole
Postoperative		Staph. aureus, coagulase-negative staph., enterobacteriaceae, pseudomonas species, anaerobes	Vancomycin, cefepime, and metronidazole, or vancomycin plus meropenem

*Adapted from Lu, et al. Strategies for the management of bacterial brain abscess. J Clin Neuroscience 2006;13:979–985

Associated infections including endocarditis, sinusitis, or mastoiditis should also be evaluated for surgical intervention to remove a continued focus of seeding to the CNS. Empiric antibiotic therapy should include ceftriaxone (2 g intravenously daily) and metronidazole (500 mg intravenously every 6 h) for most cases. Changes in empiric antibiotic therapy should be considered based on the underlying infections, including vancomycin for the risk of methicillin-resistant Staphylococcus aureus (MRSA) or use of carbapenems, such as meropenem in cases of postsurgical brain abscess with an increased risk of resistant Gram-negative rod infection. Duration of therapy is dependent on the site of infection, adequacy of drainage, organism involved, and the underlying health status of the patient. In general, patients with bacterial brain abscess require at least 4 weeks of antibiotic therapy and may require a course as long as 8 weeks of parenteral antibiotic therapy. Follow-up neuroimaging and close patient follow-up to the response of therapy are critical to the appropriate treatment of a brain abscess.

Cranial Subdural Empyema

Cranial subdural empyema (SDE) presents as a focal, loculated suppuration between the dura mater and the arachnoid [92]. Symptom onset is usually very rapid with initial complaints of fever and headache that follow recent craniofacial infection (otitis or sinusitis) or trauma [92]. Patients develop meningeal irritation, increased intracranial pressure, focal neurological signs or symptoms, altered consciousness, and seizures [93]. Causative organisms are dependent on the original sight of infection. In cases of craniofacial infection, *S. anginosus* group with or without associated anaerobic organisms are common etiologic bacteria followed by *Staphylococcus sp*. and Gram-negative organisms associated with otogenic sources [92, 93]. Postsurgical SE is commonly associated with *S. aureus* infection in as many as 46% of cases [92]. Other hospital acquired Gram-negative rods, including *Pseudomonas sp.* and *Klebsiella pneumoniae* contribute significantly, as well to iatrogenic SE, and should be considered when empiric therapy is initiated.

As with brain abscess, MRI is the preferred imaging modality to diagnosis SE, and the CT scan is less sensitive, especially in cases of posterior fossa involvement. CSF examination is not recommended because the infection is localized and encapsulated, such that CSF examination often provides little useful diagnostic information and may increase the risk of cerebral herniation.

Treatment of SE is a medical emergency and requires a combined surgical and medical approach. The optimum therapy for SE involves surgical drainage and antibiotic therapy based on Gram stain and cultures obtained at the time of the drainage procedure. Empiric antibiotic therapy should be initiated based on suspected organisms and the underlying risk factor for development of SE. The goals of surgical therapy for cranial SE is to decompress the brain and evacuate the empyema. A recent study showed improved outcomes in patients with craniotomy [94], but the specific approach (burr hole *vs* craniotomy) to achieve decompression and evacuation is controversial [92]. Once diagnostic material is obtained for cultures, empiric antibiotic therapy should be initiated based on the Gram stain and the underlying risk for infection. Vancomycin is often included in empiric therapy as *S. aureus* is a common pathogen. If *S. aureus* is found to be methacillin-sensitive, then nafcillin is the treatment of choice in a nonpenicillin allergic patient. Metronidazole therapy is also recommended as empiric therapy if anaerobic organisms are suspected. For infections likely caused by aerobic Gram-negative bacilli, empiric therapy with cefepime or meropenem is indicated pending finalized culture and sensitivity results. With appropriate management, mortality rates are 10% in patients with good mental status at presentation, but mortality increases to 50% in patients that present later in infection with significant changes in mental status or semi-comatose state [95, 96]. Thus, early and emergent intervention is vital to improve outcomes in patients with subdural empyema.

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