seroprevalence in some areas reaching 10%.[207] A report of a Jamestown Canyon virus infection in Montana underscores continued low-level transmission in the northern continental United States.[208] La Crosse virus causes infection predominantly in children (mean age, 7.5 years). Symptoms of encephalitis include fever, headache, vomiting in 70%, seizures in 46%, and altered mental status in 42%.[206] Focal neurologic signs include hemiparesis, aphasia, dysarthria, and chorea. About 10% of patients develop increased ICP, and rarely cerebral herniation can occur.[206] Jamestown Canyon virus has similar clinical features.

CSF analysis reveals a lymphocytic pleocytosis of 600 cells/mm^3, normal glucose level, and an increased protein level in 30% of patients.[206] Peripheral leukocytosis and hyponatremia secondary to SIADH are common. IgM detection in the CSF or a fourfold increase in paired sera for IgG is considered diagnostic for infection.

No antiviral therapy currently exists for the California encephalitis group of viruses, and no vaccine is available. Mortality from La Crosse encephalitis is approximately 1% to 3%, and most survivors return to normal function.[204,206] Ribavirin treatment for La Crosse encephalitis in children is not recommended owing to problems with pharmacokinetics, toxicity at higher doses, and penetration into the CNS.[209] Predictors of a poor outcome include hyponatremia, persistently elevated body temperature, and a GCS score less than 13.[205,210]

Japanese Encephalitis

JEV was initially isolated in Japan in 1935. JEV causes infections across all of Asia, the western Pacific region, and parts of Australia. JEV is the most important cause of viral encephalitis in the world, causing 68,000 cases and 13,000 to 20,000 deaths annually.[211] The virus is transmitted naturally in an enzootic cycle among birds, pigs, and other vertebrate hosts by the *Culex tritaeniorhynchus* mosquito and other *Culex* spp. Similar to other flaviviruses, humans are incidental hosts that become infected when encountering the enzootic cycle. In rural areas where JEV is endemic, it is predominantly a disease of children, in whom seroprevalence approaches 100%, but only 1 in 300 exposures results in clinical disease.[211] Several reports also highlight the importance of JEV in returning travelers from endemic regions.[212,213]

After a 1- to 2-week incubation period, symptomatic patients develop a nonspecific febrile illness followed by neurologic symptoms of altered consciousness and seizures in 85% of children and 10% of adults.[214,215] Subtle focal seizures, such as twitching of an eyebrow or finger, can be important clinical findings in JEV infection.[211] Similar to other flaviviruses, in patients with JEV, movement disorders occur in 25% and are characterized by parkinsonism, dystonia, jaw dystonias, opisthotonus, choreoathetosis, orofacial dyskinesia, myoclonic movements, and opsoclonus-myoclonus.[211,215,216] Other focal neurologic findings include CN palsies, upper motor neuron weakness, and a lower motor neuron syndrome of acute flaccid paralysis.

CSF shows an elevated opening pressure in 50% of patients. The characteristic CSF profile is lymphocytic pleocytosis, normal glucose level, and mildly elevated protein level. MRI is often normal but may reveal high T2-weighted signal intensity in the thalami, basal ganglia, midbrain, brainstem, and occasionally spinal cord.[217,218] Diagnosis is confirmed with IgM capture ELISA in the CSF or with amplification of viral nucleic acid from CSF or brain tissue by PCR.[219–222] The sensitivity of commercial IgM ELISAs in CSF ranges from 65% to 69%, with specificities of 89% to 100%.[223]

The mortality rate in hospitalized patients ranges from 20% to 30%, and 50% of survivors have severe neurologic sequelae. Poor prognostic signs include altered level of consciousness, multiple seizures, increased ICP, isolation of virus in the CSF, and low titer of JEV–specific immunoglobulins in the CSF.[211–215,224] In a study of 118 cases of JEV in Malaysia from 1997 to 2005, the mortality rate was 8%, and 57% of survivors experienced moderate-to-severe long-term neurologic sequelae.[225] Predictors of long-term poor outcome included a GCS score of 8 or lower or two or more witnessed seizures.

No therapy for JEV has been proven efficacious in randomized controlled clinical trials. Prevention is the primary strategy to control JEV infection. Personal protection with insect repellents, mosquito avoidance, and mosquito population control programs are important approaches. The most effective prevention to date is vaccination. Two JEV vaccines are licensed in the United States. A mouse brain–derived, formalin-inactivated vaccine (JE-MB) showed efficacy in a randomized double-blind trial in Thailand and is approved in the United States for use in individuals older than 1 year. Production of JE-MB was discontinued in 2006, and remaining vaccine is reserved for use in children 1 to 16 years of age[227] (see Chapter 153). An inactivated Vero cell culture–derived vaccine (JE-VC) was approved for use in the United States in 2009 for individuals 17 years of age and older.[227] A live-attenuated vaccine developed in hamster kidney cells (SA14-14-2) is used in China, and several other vaccines are either currently in use (chimeric JEV–yellow fever 17D vaccine) or in development.[174,228]

Influenza

Influenza A is known to be associated with immune-mediated neurologic complications such as Guillain-Barré syndrome or transverse myelitis. The overall role of influenza as a cause of CNS disease has been difficult to ascertain. Less commonly, influenza has been associated with encephalitis in children and young adults. During the influenza A (H1N1) pandemic in 2009, influenza was associated with encephalitis and neurologic complications. In a study of 506 children hospitalized with H1N1, 1.4% ($n = 7$) of patients presented with encephalitis, and 5 of the patients with encephalitis had a preexisting medical condition.[229] When seizures are included, the incidence of neurologic complications associated with H1N1 influenza increases to 9.7%. Severe influenza in children and young adults with underlying neurologic or neurodevelopmental conditions has occurred in smaller outbreaks.[230]

Patients often present with typical influenza symptoms during the winter and spring months. Symptoms include fever; respiratory abnormalities (cough, coryza, wheezing, labored breathing); nausea; and diarrhea. Patients with severe influenza develop increased work of breathing, and neurologic involvement can be characterized by altered mental status, seizures, or focal neurologic signs. The diagnosis is commonly made on the basis of the association of the rapid influenza diagnostic test (RIDT) or positive RT-PCR studies on respiratory samples. CSF may show evidence of a pleocytosis with normal glucose and protein levels, but PCR studies for influenza are often negative.[231] It is unclear whether CNS complications associated with influenza are a result of direct neuroinvasion or secondary to immune-mediated mechanisms.[231]

Although the efficacy of antiviral therapy in neurologic complications associated with influenza has not been established in clinical trials, it would be prudent to administer antiviral therapy as early as possible, and ideally within 48 hours of symptom onset.[230] Antiviral therapy for influenza should be started regardless of vaccination status and is often initiated with other empirical antibiotic therapy (such as acyclovir), pending results of the clinical investigation. As therapy for influenza, oseltamivir (75 mg by mouth twice daily for patients > 40 kg) has been recommended for at least 10 days (https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm) (also see Chapter 165).

Colorado Tick Fever Virus (See Chapter 149)

Colorado tick fever virus belongs to the family Reoviridae. It is transmitted by the wood tick *Dermacentor andersoni* mainly in the western mountain regions of the United States and Canada above 4000 feet in elevation.[232] An enzootic infection cycle exists between small mammals, such as ground squirrels, marmots, or chipmunks, and *D. andersoni*. When infected, the tick is infected for life (transstadially) throughout the three main stages of development—larval, nymphal, and adult. Humans are exposed to the habitat of *D. andersoni* during summer months and are dead-end hosts.

A history of tick bite is obtained in approximately 90% of patients, and the incubation period is 0 to 14 days (mean, 3 days).[232] Patients develop abrupt onset of fever, chills, generalized myalgias, severe headache, hyperesthetic skin, and severe malaise. Gastrointestinal symptoms such as nausea, vomiting, or diarrhea may be present. About 15% of patients develop a maculopapular or petechial rash. Other physical findings include pharyngitis, mild lymphadenopathy, or mild splenomegaly. In 50% of patients, fever resolves after 2 days and then recurs in the biphasic or "saddleback" pattern.[232] After convalescence, patients older than age 30 may have persistent fatigue for 3 weeks.

Complications such as encephalitis or meningitis predominantly occur in children in about 5% to 10% of the cases. Colorado tick fever virus is rarely fatal.[233] In these patients, neurologic signs and symptoms include nuchal rigidity, photophobia, and mild altered mental status.

The diagnosis of Colorado tick fever virus infection is usually made through IgM capture ELISA, neutralization, or complement fixation.[234] There is no established treatment for Colorado tick fever virus. Most patients recover, although rare deaths have been reported as a result of intravascular coagulopathy after Colorado tick fever virus infection.[233]

Enteroviruses

Enteroviruses comprise more than 70 different viruses in the Picornaviridae family. They can be grouped into polioviruses, coxsackieviruses A and B, echoviruses, and numbered enteroviruses. Enteroviruses cause more than 80% of meningitis cases and also cause more severe neurologic diseases such as encephalitis. Enterovirus infections in the CNS have been reviewed[235] (see Chapters 170–172).

Poliovirus

In 1988 the World Health Assembly started the Global Polio Eradication Initiative, resulting in a decrease from more than 350,000 cases of poliovirus in 1988 to 223 cases in 2012. In 2017 there were only 20 cases of wild-type polio (all type 1) reported worldwide (12 in Afghanistan and 8 in Pakistan); 86 cases of polio associated with circulating vaccine-derived poliovirus strains occurred in 2017 (74 in Syria and 12 in Congo). Poliovirus is transmitted by fecal-to-oral contact and by pharyngeal spread during epidemics. Symptomatic poliovirus infection results in meningitis in 8% of cases and paralytic disease in 1% of all cases. After an incubation period of 1 to 2 weeks, patients develop fever, headache, meningismus, altered mental status, and seizures (in children and infants). Asymmetrical flaccid paralysis, diaphragm paralysis, and CN palsies may follow.

CSF evaluation reveals polymorphonuclear cells early followed by a shift to lymphocytes after several days, elevated protein level (100–300 mg/dL), and normal glucose level. Diagnosis is made with CSF RT-PCR. Treatment for poliovirus infection is supportive. The last large outbreak of poliovirus in the Western Hemisphere occurred in 2000, when 19 cases in the Dominican Republic were reported; the cases were due to a circulating recombinant poliovirus derived from the polio type 1 strain in the oral polio vaccine, rather than wild-type virus. As of 2000, the Advisory Committee on Immunization Practices has recommended the use of inactivated polio vaccine in the United States for the entire primary immunization series (see Chapter 171). Trivalent, live-attenuated (Sabin) vaccine is still used in endemic areas of poliovirus infection.

Nonpoliovirus Enteroviruses

Nonpolio enteroviruses cause a wide spectrum of disease in the CNS, including aseptic meningitis, encephalitis, acute poliomyelitis, acute cerebellar ataxia, optic neuritis, and cranial neuritis (see Chapter 172). In neonates, encephalitis is a complication of an overwhelming sepsis-like syndrome with 10% mortality. Enteroviruses may cause encephalitis, particularly in patients with hypogammaglobulinemia and neonates. In an analysis of the CEP, enteroviruses were responsible for 4.6% of encephalitis cases.[236] This is likely an underestimate, however, based on the referral bias inherent in the design of the study. Of the 73 patients diagnosed with confirmed enterovirus encephalitis, 23% were adults who often presented with mild symptoms and altered consciousness (46%), including rare cases of coma (5%) or personality changes (5%).[236] In 2014, enterovirus D-68 emerged as a major cause of acute upper respiratory infections in children. This outbreak was also associated with a dramatic upsurge in cases of polio-like acute flaccid myelitis (AFM) in children[237] resulting in 120 CDC-confirmed cases in children from 34 states. AFM appears to be following an alternating-year pattern; in 2015, cases returned to baseline levels (21 cases, 16 states), only to rise again in 2016 when 144 cases were reported from 37 states and then fall in 2017 (17 cases). Although the role of enterovirus D-68 in the upsurge in AFM cases has not been definitively proven, accumulating epidemiologic and virologic evidence increasingly suggests a potential causal role.

Enterovirus encephalitis occurs during the summer months from June to October. MRI has a variable sensitivity for enteroviral encephalitis; some studies can show increased T2-weighted signal intensity of both cerebral hemispheres with associated edema (see Fig. 89.3D). In the CEP, cases of enterovirus encephalitis were diagnosed with RT-PCR of the CSF, and serotyping was available for 20 cases, with echovirus 30 being the most common strain isolated, followed by enterovirus 71, echovirus 18, and coxsackieviruses.[236] Enterovirus 71 can produce more severe disease, with cases of focal and generalized encephalitis reported.[238,239] Cases of enterovirus 71 encephalitis have been associated with a syndrome of shock, pulmonary edema, and extensive brainstem injury (rhombencephalitis) linked to neurogenic pulmonary edema in some cases. In the CEP, two of the four deaths from enteroviruses were due to enterovirus 71, and the other two enteroviruses were not serotyped.[236]

Currently, no specific antiviral therapy is approved for the treatment of enterovirus infections. Various serotypes have been associated with variable sensitivity to pleconaril, an experimental drug.[240] However, clinical outcome data are insufficient to recommend its use in patients with enterovirus encephalitis, and its development has been halted.

Rabies Virus

Rabies virus belongs to a family of RNA viruses called Rhabdoviridae, genus *Lyssavirus*. It is most commonly transmitted to humans through the saliva of an infected animal after a bite (see Chapter 163). In 2012 there was no evidence of dog-to-dog transmission of rabies in the United States and Puerto Rico, and no human infections have been attributed to a dog bite in the United States.[241] Dogs that become infected in the United States are infected with rabies from wildlife. Approximately 93% of the rabies detected in the United States is found in animal wildlife, such as raccoons, bats, skunks, and foxes.[241] In contrast, canine rabies is enzootic in the dog population in many developing countries, and travelers to these countries can be at risk for exposure to rabies from domestic and feral dogs.[242,243] In Bali, 104 cases of human rabies were reviewed and 92% had a history of a dog bite.[243] In the United States, human cases of rabies are rare. Most human cases of rabies have followed bat exposure[244]; however, one patient who died of undiagnosed rabies in 2004 was subsequently found to have rabies only after organs were transplanted from this patient into four individuals, resulting in clinical rabies and death of all recipients.[245]

After a bite wound, rabies virus from infected saliva invades motor and sensory nerves. Neurologic disease is preceded by an incubation period that ranges from 7 days to more than 6 years, with a median incubation of 1 to 2 months.[246,247] The virus moves centripetally from the periphery to the dorsal root ganglia and the spinal cord using fast axoplasmic transport,[248–250] resulting in nerve dysfunction manifesting as a prodrome of neuropathic pain. When rabies has invaded the nerve cell body in the spinal cord, acute neurologic symptoms evolve into encephalitis.

Patients present with a syndrome of hyperactivity (furious rabies) in 80% of the cases, characterized by hydrophobia and aerophobia owing to spasms of the pharyngeal and nuchal muscles triggered by swallow attempts or other types of stimuli.[251] These spasms increase in frequency and are followed by agitation, hallucinations, autonomic hyperactivity, and seizures. Body temperature may be as high as 107°F. Paralytic (dumb rabies) presentations constitute 20% of cases and are characterized by paresthesias, weakness, and flaccid paralysis in the bitten limb. Diagnosis should be considered in any patient with altered consciousness and an exposure history or travel to an endemic area. Diagnosis is made with immunohistochemical staining for rabies antigen from a skin biopsy specimen in the region of the hairline at the neck.[251] Recent development of a reverse-transcription heminested PCR test on skin biopsy specimens demonstrated a sensitivity of greater than or equal to 98% and a specificity of 100%.[252] Other diagnostic methods include examination of corneal smears for rabies antigen and intracerebral inoculation of mice with patient saliva. Detection of rabies virus neutralizing antibodies in the CSF or serum is diagnostic in unimmunized patients, but antibody detection tests can lack sensitivity.

Infected patients should be isolated because body fluids can contain high titers of active virus. Treatment of rabies virus infection is largely supportive and results in a uniformly fatal outcome. One case of survival after rabies virus infection was reported in a 15-year-old girl after treatment with coma induction and EEG burst suppression using midazolam and ketamine supplemented with barbiturates and benzodiazepines.[253] Antiviral therapy included IV ribavirin (33 mg/kg load and then 16 mg/kg every 6 hours) and enteral amantadine (200 mg/day).[253] Despite this case of survival with treatment of rabies virus infection, several failures have been reported.[254]

The mainstay of rabies treatment is PEP. Wounds should be cleansed with soap and water followed by povidone-iodine. Human diploid cell rabies vaccine, rabies vaccine adsorbed, or purified chick embryo vaccine should be administered intramuscularly.[255] In 2010, new CDC recommendations for rabies PEP included vaccination on days 0, 3, 7, and 14 but no dose at day 28 as previously instructed.[256] Previously vaccinated individuals are still given vaccine on days 0 and 3. In addition to vaccination, PEP includes human rabies immunoglobulin, 20 IU/kg, administered as soon as possible after the exposure, up to 7 days after the first dose of vaccine. As much of the dose as possible should be administered at the bite wound site, and any remaining dose should be administered intramuscularly in the same limb, but distant to the vaccination site. Using the CDC- and World Health Organization–recommended rabies PEP regimen, a study of 110 rabies-exposed travelers found that only 14% received human rabies immunoglobulin and that antibody levels afterward were less than 0.5 IU/mL in 6.7% of travelers who received four doses of vaccine.[257] Thus follow-up antibody titers at day 21 after rabies PEP vaccination may be useful.[257] If the animal that caused the bite wound is available, healthy animals should be quarantined and observed for clinical illness over a 10-day period. If the animal is ill, it should be euthanized and the brain should be analyzed by the local health department for evidence of rabies infection.

Measles Virus

Measles virus remains an important cause of morbidity and mortality throughout the world (see Chapter 160).[258] In approximately 0.1% of cases, measles virus can cause an acute postinfectious measles encephalitis resulting in a 20% mortality.[246] Measles virus can also cause a chronic infection in neurons that results in subacute sclerosing panencephalitis (SSPE) or measles inclusion body encephalitis.[246,259] Measles inclusion body encephalitis is a rare and uniformly fatal condition that causes disease in young patients with defective cellular immunity.[259,260] SSPE is a slowly progressive disorder characterized by seizures, deterioration of cognitive and motor function, myoclonic movements, and death. It occurs 5 to 15 years after initial measles infection, which usually occurs in children younger than 2 years.[261] Immunization has reduced the incidence of SSPE more than 90% in developed countries; however, the rate of SSPE is 21 per 1 million population in India.[261,262] When SSPE occurs in adults, the mean age is 25 years and most patients have an undocumented or negative vaccination history for measles.

Initial symptoms may be subtle and include intellectual deterioration and behavioral changes.[261] These symptoms progress to myoclonic jerks, ataxia, dystonia, and generalized or partial seizures.[261,262] Ocular and visual symptoms occur in 10% to 50% of patients and precede neurologic disease by several years. Ocular symptoms include cortical blindness, chorioretinitis, and optic atrophy.[263,264] CSF examination findings are usually normal with a markedly increased immunoglobulin level. Neuroimaging findings are generally limited, but MRI may reveal high signal intensity on T2-weighted images in the white matter, particularly the occipital subcortical white matter, with near-uniform sparing of gray matter.

SSPE has a rapidly progressive course in adults.[265] A small, single uncontrolled trial suggested that treatment with oral inosine pranobex (Isoprinosine) and interferon-α may be effective for adult-onset SSPE,[266] but in general no adequate therapy is currently available for the treatment of SSPE.

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The complete reference list is available online at Expert Consult.

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90 Brain Abscess

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SHORT VIEW SUMMARY

Definition

- Brain abscess is a focal, intracerebral infection that begins as a localized area of cerebritis and develops into a collection of pus surrounded by a well-vascularized capsule.

Epidemiology

- Brain abscess accounts for approximately 0.4 to 0.9 cases per 100,000 people per year, with higher rates in immunocompromised patients.
- In most pediatric and adult series, a male predominance exists (a ratio of 2:1 to 3:1) with a median age of 30 to 40 years, although age distribution varies depending on the predisposing condition leading to formation of brain abscess.
- The incidence of brain abscess is also affected by the general health of the population. In one study of 973 patients from one tertiary hospital in South Africa from 1983 to 2002, the incidence declined during the study period as a result of improvements in socioeconomic standards and availability of health care services.
- The incidence of otogenic abscesses has decreased, whereas the incidence of posttraumatic and postoperative brain abscesses has increased.

Microbiology

- Streptococci (aerobic, anaerobic, and microaerophilic) are the bacteria most commonly cultured from patients with bacterial brain abscess, and they are frequently isolated in mixed infections (30%–60% of cases).
- *Staphylococcus aureus* accounts for 10%–20% of isolates, usually in patients with cranial trauma or infective endocarditis, and it is often isolated in pure culture; cases caused by community-associated methicillin-resistant *S. aureus* strains have been reported.
- Attention to proper culture techniques has increased the isolation of anaerobes from brain abscesses with *Bacteroides* and *Prevotella* spp., isolated in 20%–40% of patients, often in mixed culture.
- Enteric gram-negative bacilli (e.g., *Proteus* spp., *Escherichia coli, Klebsiella* spp., and *Pseudomonas* spp.) are isolated in 23%–33% of patients, often in patients with otitic foci of infection, patients with septicemia, patients who have had neurosurgical procedures, or patients who are immunocompromised.
- Immunocompromised patients with brain abscess have a distinct microbiology: toxoplasmosis and tuberculosis in patients with advanced human immunodeficiency virus (HIV) infection; *Aspergillus* and *Candida* in patients with hematologic malignancies; and *Listeria, Nocardia,* various fungi, and *Toxoplasma* in solid-organ transplant recipients and other patients with compromised cellular immunity.
- Nocardial brain abscess may occur as an isolated central nervous system (CNS) lesion or as part of a disseminated infection in association with pulmonary or cutaneous disease.

Diagnosis

- Magnetic resonance imaging is the imaging modality of choice in the evaluation of a patient suspected to have this disorder.
- The combined use of proton magnetic resonance spectroscopy, diffusion-weighted imaging, and diffusion tensor imaging has been shown to improve the specificity of diagnosis of focal ring–enhancing lesions and differentiate brain abscess from other cystic lesions of the brain including tumors.
- A major advance in the use of computed tomography (CT) in patients with suspected brain abscess is the ability to perform stereotactic CT-guided aspiration to facilitate microbiologic diagnosis and to guide antimicrobial therapy; at the time of aspiration, specimens should be sent for Gram stain, routine aerobic and anaerobic cultures, and cultures for mycobacteria and fungi.

Therapy

- When abscess material has been obtained for microbiologic and histopathologic studies, empirical antimicrobial therapy should be initiated on the basis of the patient's predisposing conditions and the presumed pathogenesis of abscess formation (see Table 90.3).
- In HIV-infected patients with CNS mass lesions, the initial approach to management is different because of the high likelihood of the diagnosis of toxoplasmic encephalitis.
- Antimicrobial therapy with high-dose intravenous agents has traditionally been administered for 6 to 8 weeks in patients with bacterial brain abscesses.
- Surgical management is required in most patients with bacterial brain abscess for optimal therapy. The best candidates for medical therapy appear to be patients with a small abscess (≤2.5 cm), with good clinical condition (Glasgow Coma Scale score >12), and with a well-known etiology.
- Surgical aspiration or removal of all abscesses larger than 2.5 cm in diameter combined with a 6-week or longer course of intravenous antimicrobial therapy, along with response on follow-up neuroimaging, should result in a cure rate of more than 90% in patients with bacterial brain abscess.
- The optimal therapy for fungal brain abscess usually requires a combined medical and surgical approach; immunocompromised patients have a high mortality rate despite surgery and antifungal therapy.

Brain abscess is a focal, intracerebral infection that begins as a localized area of cerebritis and develops into a collection of pus surrounded by a well-vascularized capsule.[1] Brain abscess was an almost uniformly fatal disease before the late 1800s, when surgical techniques (i.e., drainage) led to cure in selected patients. Further advances in the management of brain abscess were made after the introduction of antimicrobial therapy and stereotactic brain biopsy and aspiration techniques. In this chapter, the common bacterial, fungal, and protozoal causes of brain abscess are reviewed, and the clinical presentation, diagnosis, and approach to management are emphasized.

EPIDEMIOLOGY AND ETIOLOGY

Brain abscess is one of the most serious complications of head and neck infections. Estimates reveal the incidence of brain abscess to be approximately 0.4 to 0.9 cases per 100,000 population, with higher rates in immunocompromised patients.[2,3] In a 14-year epidemiologic review of 6027 cases in Taiwan, the overall incidence was 1.8 cases per 100,000 person-years and increased with age (0.58 per 100,000 person-years in individuals 0–14 years of age and 4.67 per 100,000 person-years in individuals older than 60 years).[4] In most pediatric and adult series, a male predominance exists (ratio of 2:1 to 3:1) with a median age of

30 to 40 years, although the age distribution varies depending on the predisposing condition leading to the formation of brain abscess. When the abscess is related to a focus in the paranasal sinuses, most patients are 10 to 30 years of age; when the abscess is from an otitic focus, patients are younger than 20 or older than 40 years.[2] The incidence of brain abscess is also affected by the general health of the population. In one study of 973 patients from one tertiary hospital in South Africa from 1983 to 2002,[5] the incidence declined during the study period as a result of improvements in socioeconomic standards and availability of health care services. In that series, the mean age was 24 years, and three-fourths of patients were men; predisposing conditions were otorhinogenic (38.6%), traumatic (32.8%), pulmonary (7%), cryptogenic (4.6%), postsurgical (3.2%), meningitic (2.8%), cardiac (2.7%), and other (8.6%). Overall, about 25% of cases of brain abscess occur in children, most in the 4- to 7-year age group; they usually originate from an otitic focus or in patients with cyanotic congenital heart disease. However, in a series of 27 children with bacterial brain abscess, sinusitis, meningitis, and traumatic brain injury were the most common predisposing conditions.[6] Brain abscess is extremely rare in patients younger than 2 years. Brain abscess is a rare complication after cranial operations, seen in 0.2% of 1587 operations in one report.[7] The predisposing conditions for brain abscess have changed in recent years; over the past 10 to 15 years, the incidence of otogenic abscesses decreased, whereas the incidence of posttraumatic and postoperative brain abscesses increased.[8] In more recent series, there has been an increase in the number of cases seen in immunocompromised hosts. In these patients, hematogenous dissemination is the more common pathogenesis rather than extension from a contiguous focus of infection.

The outcome in patients with brain abscess in terms of both mortality and long-term sequelae has steadily improved.[3,9] Recent mortality rates have ranged from 0% to 24%,[2] with improvement likely attributed to the availability of more effective antimicrobial regimens (e.g., the addition of metronidazole), new surgical techniques, and, most importantly, the availability of computed tomography (CT). Data from the University of California in San Francisco showed a decrease in the overall mortality rate from 44% during the 3 years before availability of CT to 0% for the 3 years after the introduction of CT in 1977,[10] principally related to early diagnosis and an accurate method of postoperative follow-up with CT. In a retrospective analysis of 620 cases of brain abscess from China over a 62-year period,[11] mortality decreased from 22.8% in 1952 to 6.3% in 2014, likely due to improvements in neurosurgical techniques, cranial imaging, and antimicrobial regimens. However, in more general series, mortality ranged from 8% to 25%.[5,12,13–18]

The incidence of neurologic sequelae in patients who survive a brain abscess ranges from 20% to 70%. In one study of factors influencing the outcome in 39 cases of bacterial brain abscess, the prognosis was primarily determined by the rapidity of progression of the disease before hospitalization and the patient's mental status on admission.[12] Poor prognostic factors have included poor Glasgow Coma Scale score and the presence of underlying diseases (e.g., immunodeficiency, malignancy, hematologic disorders) and other comorbid conditions. In one study of 142 patients with brain abscess, Glasgow Coma Scale score greater than 12 and no evidence of sepsis were associated with a more favorable outcome.[16] In other series, outcome has been related to the approach to management. In one review of 80 surgically treated brain abscesses in 59 patients,[19] immunosuppression, hematogenous spread, and advanced age were predictors of poor outcome. In another series of 973 patients with brain abscess from South Africa,[5] 97% of whom underwent surgical drainage, predictors of mortality included cerebral infarction, ventriculitis, coma, hydrocephalus, dilated pupils, bilateral abscesses, multiple abscesses, human immunodeficiency virus (HIV) coinfection, papilledema, and neurologic deterioration. In a 22-year retrospective study of 31 patients who underwent nonoperative management of bacterial brain abscess, the overall mortality rate was 48%; the Glasgow Coma Scale score at presentation, septic shock, and neck stiffness were risk factors for poor outcome.[20] Early recognition of predisposing conditions is important for improving the outcome in brain abscess. In patients with bacterial brain abscess complicated by intraventricular rupture, mortality rates are much higher, ranging from 27% to 85%.[21]

TABLE 90.1 Predisposing Conditions and Microbiology of Brain Abscess

PREDISPOSING CONDITION	USUAL MICROBIAL ISOLATES
Otitis media or mastoiditis	Streptococci (anaerobic or aerobic), *Bacteroides* and *Prevotella* spp., Enterobacteriaceae
Sinusitis (frontoethmoid or sphenoid)	Streptococci, *Bacteroides* spp., Enterobacteriaceae, *Staphylococcus aureus, Haemophilus* spp.
Dental infection	Mixed *Fusobacterium, Prevotella, Actinomyces,* and *Bacteroides* spp., streptococci
Penetrating trauma or postneurosurgical	*S. aureus,* streptococci, Enterobacteriaceae, *Clostridium* spp.
Lung abscess, empyema, bronchiectasis	*Fusobacterium, Actinomyces, Bacteroides,* and *Prevotella* spp., streptococci, *Nocardia* spp.
Bacterial endocarditis	*S. aureus*, streptococci
Congenital heart disease	Streptococci, *Haemophilus* spp.
Neutropenia	Aerobic gram-negative bacilli, *Aspergillus* spp., Mucorales, *Candida* spp., *Scedosporium* spp.
Transplantation	*Aspergillus* spp., *Candida* spp., Mucorales, *Scedosporium* spp., Enterobacteriaceae, *Listeria monocytogenes*, *Nocardia* spp., *Toxoplasma gondii, Mycobacterium tuberculosis*
HIV infection	*T. gondii, Nocardia* spp., *Mycobacterium* spp., *Listeria monocytogenes, Cryptococcus neoformans*

When the microorganisms likely to be responsible for causing brain abscesses are evaluated, the isolation frequency depends on the predisposing condition (Table 90.1).[2,14,22] Improved microbiologic culture techniques, particularly for anaerobes, have had a significant impact on the awareness of microorganisms that are found in brain abscesses. In addition, immunocompromised patients with brain abscess have a distinct microbiology.[2,3] This includes *Toxoplasma* and *Mycobacterium tuberculosis* in patients with advanced HIV infection; *Aspergillus* and *Candida* in patients with hematologic malignancies; and *Listeria, Nocardia,* various fungi, and *Toxoplasma* in solid-organ transplant recipients and other patients with compromised cellular immunity.[23] The common bacteria, fungi, protozoa, and helminths that can produce brain abscess are reviewed next.

Bacterial Brain Abscess

Streptococci (aerobic, anaerobic, and microaerophilic) are the bacteria most commonly cultured from patients with bacterial brain abscess, and they are frequently isolated in mixed infections (30%–60% of cases).[2,14] These bacteria, especially the *Streptococcus anginosus (milleri)* group *(Streptococcus anginosus, Streptococcus constellatus,* and *Streptococcus intermedius)*, normally reside in the oral cavity, appendix, and female genital tract, and they have a proclivity for abscess formation (see Chapter 203). Although streptococcal brain abscesses are seen most often in patients with oropharyngeal infections or infective endocarditis, they are also isolated after neurosurgical or other medical procedures.[24]

Staphylococcus aureus generally accounts for 10% to 20% of isolates, usually in patients with cranial trauma or infective endocarditis, and it is often isolated in pure culture; cases caused by community-associated methicillin-resistant *S. aureus* strains have been reported.[25] The attention to proper culture techniques has increased the isolation of anaerobes from brain abscesses with *Bacteroides* and *Prevotella* spp., isolated in 20% to 40% of patients, often in mixed culture.[2,3] Enteric gram-negative bacilli (e.g., *Proteus* spp., *Escherichia coli, Klebsiella* spp., and *Pseudomonas* spp.) are isolated in approximately 23% to 33% of cases, often in patients

with otitic foci of infection, patients with septicemia, patients who have had neurosurgical procedures, or patients who are immunocompromised. At one center, *Klebsiella* was the most prevalent pathogen (usually associated with hematogenous dissemination or postneurosurgical states),[26,27] followed by *Proteus* and *Enterobacter* spp.[28] Multiple organisms are cultured in 14% to 28% of cases in patients with positive culture results.[2,13–16] The incidence of negative cultures has ranged from 0% to 43% in selected series,[2,13–17,29,30] with the frequency often correlating with prior use of antimicrobial therapy.

In one review and meta-analysis of 123 studies including 9699 patients with brain abscess, streptococci were the most commonly cultured bacteria (34% of cases), followed by staphylococci (18% of cases) and enteric gram-negative bacteria (15% of cases).[31] Almost one-fourth of cases were polymicrobial. Of note, 32% of cases had negative cultures, possibly reflecting prior use of antimicrobial therapy and limitations of diverse diagnostic microbial methodology over the 8 decades of the meta-analysis. As whole-genome sequencing and targeted-genome sequencing move into diagnostic microbiology laboratories, a larger range of microbial pathogens in brain abscesses is going to be encountered, including more fastidious organisms (see below).[32] How that will impact therapy is yet to be determined.

Other bacterial pathogens may be isolated from brain abscesses in selected patients or from immunocompromised patients. Although *Haemophilus influenzae, Streptococcus pneumoniae,* and *Listeria monocytogenes* are common etiologic agents of bacterial meningitis, they are rarely isolated from patients with pyogenic brain abscesses (<1% of cases).[33–36] However, these organisms may be seen in patients with bacterial meningitis complicated by cerebritis resulting in abscess formation during the clinical course.[37] Brain abscess accounts for about 10% of central nervous system (CNS) infections caused by *L. monocytogenes.*[35,38] *Listeria* brain abscess is usually seen in immunocompromised patients. In a review of 39 cases of *Listeria* brain abscess, 85% of the patients had significant underlying conditions (including leukemia, lymphoma, HIV infection, and various conditions requiring corticosteroids or other immunosuppression), and disease was often associated with concomitant meningitis (38% of cases) and bacteremia (86% of cases).[36] In contrast, although meningitis caused by facultative gram-negative organisms (e.g., *Citrobacter koseri [Citrobacter diversus], Proteus* spp., *Serratia marcescens, Enterobacter* spp.) is infrequent, it is associated with concomitant brain abscess in more than 75% of cases[1,39–41]; children with bacteremia or meningitis caused by these organisms should be evaluated for the possibility of brain abscess.

Salmonella spp. have rarely been reported to cause brain abscess, usually after bacteremia in the presence of some compromise of the reticuloendothelial system.[42] Cerebral abscesses may also be a complication of infection with *Burkholderia pseudomallei.*[43] Actinomycosis of the CNS may manifest as brain abscess, usually secondary to hematogenous spread from a primary infection in the lung, abdomen, or pelvis, although contiguous spread from foci of infection in the ears, paranasal sinuses, or cervicofacial regions may occur; actinomycotic brain abscess should be considered in patients with head trauma, previous surgery, and otorhinolaryngeal infections who present with a long duration of neurologic symptoms and no fever.[44] Nocardial brain abscess may occur as an isolated CNS lesion or as part of a disseminated infection in association with pulmonary or cutaneous disease.[1] This organism is most often isolated in patients with defects in cell-mediated immunity (in patients receiving corticosteroid therapy, in organ transplant recipients, in patients infected with HIV, and in patients with neoplastic disease),[45,46] although 50% of patients with nocardiosis have no readily identifiable underlying immune compromise. In most series of organ transplant recipients with *Nocardia* infection,[46–48] use of trimethoprim-sulfamethoxazole at the dose administered for prophylaxis against *Pneumocystis jirovecii* was not shown to offer adequate protection against nocardiosis. Cases of nocardial brain abscess have also been seen in pregnant patients.[49]

Mycobacteria may also cause focal CNS lesions.[1,2] *M. tuberculosis* may cause tuberculomas (single or multiple, characterized by granulomatous inflammation with caseating necrosis) or "true" brain abscesses, which are similar to pyogenic abscesses (i.e., an encapsulated collection of pus, instead of granulomatous inflammation) and require drainage[50,51]; although tuberculomas are more common, some publications fail to make the distinction between these two entities.[52] Cases have been reported in patients with HIV infection and after solid-organ transplantation,[53–55] although tuberculous brain abscess can be seen in immunocompetent and immunocompromised hosts.[56] In a series of 715 cases of brain abscess in India from 1999 to 2006, 60% of patients had infection with *M. tuberculosis*[8]; this contrasts with a meta-analysis that found only 42 cases of tuberculosis among 9699 cases of brain abscess.[31] A prospective case series from India of 93 patients with intracranial tuberculosis found tuberculoma to be 10 times more common than abscess[57]; in this series, only one-third of patients had abnormalities on chest radiograph. Nontuberculous mycobacteria are found much less frequently, although there are well-documented cases of *Mycobacterium kansasii* brain abscess in patients with AIDS.[58,59] Cases of brain abscess caused by *Mycobacterium avium* complex have also been described in HIV-infected patients,[60,61] sometimes appearing as part of immune reconstitution inflammatory syndrome.[62]

Fungal Brain Abscess

The incidence of fungal brain abscess has increased as a result of the prevalent administration of immunosuppressive agents, broad-spectrum antimicrobial therapy, and corticosteroids.[63,64,65] However, some fungi exhibit neurotropism and can infect apparently immunocompetent hosts.[66] The risk of CNS infections in immunocompromised hosts is often defined by the immunocompromised state. Neutropenia and hematopoietic stem cell transplantation predispose mainly to *Candida, Aspergillus,* and other opportunistic molds such as the Mucorales, *Scedosporium,* and *Paecilomyces*. Solid-organ transplantation predisposes to *Candida* and *Aspergillus* as well as dematiaceous molds. HIV predisposes to *Cryptococcus*. Finally, some primary immunodeficiencies may have specific susceptibilities (e.g., chronic granulomatous disease for *Aspergillus* and *Paecilomyces lilacinus [Purpureocillium lilacinum]* and CARD9 deficiency for CNS candidiasis).

The diagnosis of fungal brain abscess is often unexpected, and many cases are not discovered until autopsy. In autopsy studies, *Candida* spp. have emerged as the most prevalent etiologic agents; neuropathologic lesions include microabscesses, macroabscesses, noncaseating granulomas, and diffuse glial nodules. Risk factors for invasive *Candida* infection include the use of corticosteroids, broad-spectrum antimicrobial therapy, and hyperalimentation. Disease is also seen in premature infants; in patients with malignancy, neutropenia, chronic granulomatous disease, diabetes mellitus, or thermal injuries; and in patients with a central venous catheter in place.[65,67] However, several other pathogenic fungi should be considered in the differential diagnosis of fungal brain abscess, particularly in immunosuppressed patients.

Cases of intracranial infection caused by *Aspergillus* spp. have been reported worldwide, with most cases occurring in adults. Cerebral aspergillosis is reported in 10% to 20% of all cases of invasive aspergillosis; the brain is rarely the only site of infection.[68] The lungs are the usual site of primary infection, and intracranial seeding occurs during dissemination of the organism or by direct extension from an area anatomically adjacent to the brain (e.g., the paranasal sinuses).[65] Most cases of invasive aspergillosis are found in neutropenic patients who have an underlying hematologic malignancy. Other risk groups include patients with hepatic disease, Cushing syndrome, diabetes mellitus, chronic granulomatous disease, or HIV infection; injection drug users; postcraniotomy patients; organ transplant recipients; recipients of allogeneic bone marrow and stem cell transplants; and patients receiving long-term corticosteroid therapy.[63,68,69] *Aspergillus* brain abscess has been reported in patients with primary CNS lymphoma receiving the tyrosine kinase inhibitor ibrutinib,[70] but this potential risk factor awaits confirmation.

Mucormycosis (zygomycosis) is one of the most acute, fulminant fungal infections known. Many predisposing conditions to mucormycosis have been described including diabetes mellitus (70% of cases) usually in association with acidosis, acidemia from profound systemic illnesses (e.g., sepsis, severe dehydration, severe diarrhea, chronic renal failure), hematologic neoplasms, renal transplantation, injection drug use, and the use of deferoxamine.[65,71,72] Mucormycosis has emerged as an important invasive fungal infection in solid-organ and hematopoietic stem cell

transplantation recipients[73]; 10% to 15% of hematopoietic stem cell transplant recipients with mucormycosis have CNS involvement, most frequently in the context of dissemination. Less than 5% of cases involve normal hosts. CNS disease may result from direct extension of the rhinocerebral form of mucormycosis, by open head trauma or by hematogenous dissemination. The order Mucorales includes many species that have caused brain lesions (see Chapter 258), with *Rhizopus arrhizus (Rhizopus oryzae)* being one of the most common.

Infection with *Scedosporium* spp. *(Scedosporium apiospermum* and *Scedosporium prolificans* [now *Lomentospora prolificans*]*)* may cause CNS disease in normal and immunocompromised hosts (e.g., patients with neutropenia or cellular immunodeficiency).[65,74–78] *S. apiospermum* is the asexual form of *Pseudallescheria boydii* and may enter the CNS by direct trauma, by hematogenous dissemination from a pulmonary route, by direct extension from infected sinuses, or perhaps by way of an intravenous catheter. One case was observed in a patient who underwent extracorporeal membrane oxygenation.[79] Brain abscess is the usual CNS manifestation, although meningitis and ventriculitis have also been reported. There is an association between near drowning in polluted water and subsequent illness, resulting from the presence of the pathogen in contaminated water and manure.

Many of the etiologic agents of fungal meningitis may also cause brain abscess (e.g., *Cryptococcus neoformans, Coccidioides* spp., *Histoplasma capsulatum,* and *Blastomyces dermatitidis* as well as *Fusarium* spp.)[65,80]; the epidemiologic and etiologic characteristics of these organisms are described in other chapters of this book. Many of the melanized, or dematiaceous, fungi have also been reported to cause brain abscess including *Cladophialophora bantiana, Bipolaris hawaiiensis, Bipolaris spicifera, Exophiala dermatitidis (Wangiella dermatitidis), Ochroconis gallopava (Dactylaria constricta* var. *gallopava), Chaetomium strumarium, Curvularia pallescens, Rhinocladiella mackenziei, Fonsecaea monophora,* and *Acrophialophora fusispora*.[65,81–85] More than half of published cases were in patients with no risk factors or immunodeficiency; no specific exposures were associated with onset of infection, although most cases seem to occur in rural areas.[83]

Protozoal and Helminthic Brain Abscess

Several protozoa and helminths have been reported to produce brain abscess[1,2,86,87,88,89] including *Trypanosoma cruzi, Entamoeba histolytica, Schistosoma* spp., and *Paragonimus* spp. In addition, free-living amebas (*Naegleria* spp., *Acanthamoeba* spp., and *Balamuthia* spp.) are preferentially neurotropic. Neurocysticercosis, caused by the larval form of *Taenia solium,* is a major cause of brain lesions in the developing world.[90,91] *Echinococcus granulosus* and *Echinococcus multilocularis* can rarely involve the brain and manifest as ring-enhancing lesions. The epidemiologic features and approach to diagnosis and management of these and other protozoa and helminths are discussed in other chapters of this book.

Toxoplasma gondii is the most common protozoal cause of brain abscess.[88,92] The incidence of human infection caused by *T. gondii* depends on dietary habits (especially the amount of meat consumed and whether eaten rare, raw, or well done), the number of stray cats living in close proximity to humans (as infected cats may shed millions of oocysts in their feces), climatic conditions (moderate temperatures and high humidity favor oocyst survival in soil), and overall level of sanitation and hygiene. *T. gondii* infection of the CNS appears in various syndromes but is usually associated with the development of intracerebral mass lesions or encephalitis in immunocompromised hosts, although cases of CNS toxoplasmosis have been rarely described in presumptively immunocompetent persons.

The number of cases of CNS toxoplasmosis has increased dramatically since 1981, specifically in patients with HIV infection, most commonly in patients with $CD4^+$ lymphocyte counts <50/cells mm^3.[88,92–95] Studies before the advent of antiretroviral therapy estimated that 5% to 47% of patients latently infected with *T. gondii* would develop CNS disease.[96] The use of trimethoprim-sulfamethoxazole prophylaxis of *P. jirovecii* pneumonia and antiretroviral therapy has substantially decreased the incidence of *Toxoplasma* encephalitis.[97,98]

CNS toxoplasmosis can be seen after allogeneic hematopoietic stem cell transplantation,[88,92,99] particularly in patients with increased immunosuppression because of graft-versus-host disease or T-cell depletion and in recipients of cord blood. Solid-organ transplant recipients are also at risk. Disease in organ transplant recipients not only occurs secondary to reactivation but may also occur after the transfer of infected cysts in the allograft, most commonly in heart transplant recipients. CNS toxoplasmosis is less common in patients with other immunocompromised states.

PATHOGENESIS AND PATHOPHYSIOLOGY

Pathogenesis

Microorganisms can reach the brain by several different mechanisms (see Table 90.1).[1,2,13–18,29,33] The most common pathogenic mechanism of brain abscess formation is spread from a contiguous focus of infection, most often in the middle ear, mastoid cells, or paranasal sinuses. Brain abscess occurring secondary to otitis media is usually localized to the temporal lobe or the cerebellum. Compared with earlier reports, more recent series have shown a decrease in the number of cases secondary to otitis media and an increase in cases after neurosurgery and trauma.[18] If antimicrobial therapy of otitis is neglected, however, there is an increased risk for intracranial complications. Paranasal sinusitis continues to be an important condition predisposing to brain abscess. The frontal lobe is the predominant abscess site, although when brain abscess complicates sphenoid sinusitis, the temporal lobe or sella turcica is usually involved. Dental infections are a less common cause of brain abscess[100,101]; infections of molar teeth seem most often to be the inciting factor. The frontal lobe is the usual site of the abscess after dental infection, but temporal lobe extension has also been reported.

A second mechanism of brain abscess formation is hematogenous dissemination to the brain from a distant focus of infection. These abscesses are usually multiple and multiloculated, and they have a higher mortality rate than abscesses that arise secondary to contiguous foci of infection.[2] The most common sources of initial infection in adults are chronic pyogenic lung diseases, especially lung abscess, bronchiectasis, empyema, and cystic fibrosis. Brain abscess may also occur hematogenously from wound and skin infections, osteomyelitis, pelvic infection, cholecystitis, and other intraabdominal infections. Another predisposing factor leading to hematogenously acquired brain abscess is cyanotic congenital heart disease,[102–104] which accounts for 5% to 15% of all brain abscess cases, with higher percentages in some pediatric series. These are most commonly seen in patients with tetralogy of Fallot or transposition of the great vessels. Brain abscess is rare after bacterial endocarditis (<5% of cases in most series),[105,106] despite the presence of continuous bacteremia; one recent study found brain abscess in 14 of 198 critically ill patients with infective endocarditis.[107]

Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) is a predisposing factor for brain abscess (occurring in about 1% of patients) and is almost always observed in patients with coexisting pulmonary arteriovenous malformations, perhaps by allowing septic emboli to cross the pulmonary circulation without capillary filtration or by bacterial seeding of an ischemic portion of the brain after paradoxical sterile emboli.[108–111] The risk for developing brain abscesses in patients with hereditary hemorrhagic telangiectasia ranges from 5% to 9% and is 1000 times greater than in the general population. In a study of 445 consecutive patients with CT-confirmed pulmonary arteriovenous malformations (including 403 with hereditary hemorrhagic telangiectasia), 37 (8.3%) had a cerebral abscess[112]; 29 of the 37 patients had no pulmonary arteriovenous malformation diagnosed before the abscess, suggesting that these abnormalities may account for a significant proportion of cases of cerebral abscess in immunocompetent patients. Brain abscesses have also developed after esophageal dilation and after sclerosing therapy for esophageal varices.[113–115]

Trauma is a third pathogenic mechanism in the development of brain abscess. Brain abscess occurs secondary to an open cranial fracture with dural breach or as a result of neurosurgery or a foreign-body injury.[116] Four cases of brain abscess were reported in patients with malignant gliomas after craniotomy. These patients were treated with carmustine wafers (Gliadel wafers),[117] which are placed locally in the tumor bed and release carmustine after they undergo hydrolysis. The wafers may serve as a nidus for subsequent infection.

The incidence of brain abscess formation after head trauma ranges from 3% to 17% in military populations, where it is usually secondary to retained bone fragments or contamination of initially "sterile" missile sites with bacteria from skin, clothes, and the environment.[118] In a study of 160 war missile penetrating craniocerebral injuries in Croatia, in which 21 skull base injuries were treated surgically,[119] the authors did not attempt to remove all retained metallic or bone fragments but only the accessible ones. Retained foreign bodies did not seem to increase the infection rate except in cases with an in-driven cluster of bone fragments or cerebrospinal fluid (CSF) leak; three cases of brain abscess were seen, for which repeat surgery was required. These findings were confirmed in another retrospective study from Croatia in 88 patients with missile brain wounds in which only accessible bone and metallic fragments were removed during intracranial débridement[120]; there were nine cases of brain abscess, and retained fragments were not responsible for an increased rate of infection. In another study of 43 patients who survived low-velocity missile injuries of the brain during military conflicts and who had retained intracranial fragments,[121] suppurative sequelae were seen in 6 patients, and 2 of these patients progressed to brain abscess. Traumatic predisposing conditions to brain abscess in the civilian population (incidence of 2.5%–10.9% after trauma) include compound depressed skull fractures; dog bites; rooster pecking; horse bites; tongue piercing; and, especially in children, injury from lawn darts and pencil tips.[122–125] Nosocomial brain abscess has also been reported after halo pin insertion,[126] after electrode insertion to localize seizure foci,[127] and after placement of deep brain stimulation hardware[128] and intracranial pressure monitors.[129]

Brain abscess is cryptogenic in 10% to 35% of patients.[2,22] Patent foramen ovale has been suggested as a possible predisposing condition in patients with cryptogenic brain abscess,[130] although this report of two patients did not establish patent foramen ovale as a definitive risk factor.

Natural History of Infection

Several animal models have been used to examine the pathophysiologic consequences and temporal course of brain abscesses after the initiation of infection. A canine model was used to define the pathologic stages of brain abscess formation after the inoculation of α-hemolytic streptococci.[131] On the basis of detailed histologic evaluation, four stages of brain abscess evolution were defined: early cerebritis (days 1–3), late cerebritis (days 4–9), early capsule formation (days 10–13), and late capsule formation (day 14 and later after initial inoculation). Although these stages are arbitrary, they are useful in classification and in comparing organisms with regard to their virulence in the production of brain abscess. The early cerebritis stage is characterized by an acute inflammatory infiltrate with visible bacteria on Gram stain and marked edema surrounding the lesion. The center of the lesion becomes necrotic during the late cerebritis stage, and macrophages and fibroblasts begin to invade the periphery. With early capsule formation, the necrotic center begins to decrease in size, with simultaneous development of a collagenous capsule that is less prominent on the ventricular side of the lesion; cerebral edema also starts to regress during this stage. In this canine model, the collagen capsule was complete circumferentially by the end of the second week and then increased in density and thickness.

Similar neuropathologic findings have been observed in a model of experimental anaerobic brain abscess,[132] although capsule formation could not be divided into early and late stages because of delayed encapsulation. A subsequent study revealed that *S. aureus* was more virulent than the α-hemolytic streptococci in brain abscess formation[133]; the amount of necrosis, the total area of involvement after staphylococcal challenge, the course of infection as it progressed toward resolution, the time for the abscess to reach a stable size, and the time to contain the necrotic region with a collagenous capsule all were greater after inoculation of *S. aureus*. Capsule formation was less prominent on the ventricular than on the cortical surface in these studies,[131–133] perhaps because differences in vascularity between cortical gray matter and white matter allowed greater fibroblast proliferation on the cortical side of the abscess; this may explain the tendency for brain abscesses to rupture into the ventricular system, rather than into the subarachnoid space.

An alternative hypothesis was supported in an experimental rat model after inoculation of *E. coli*.[134] It was suggested in this study that brain abscesses tended to rupture intraventricularly because the infectious process is directed along the major white matter tracts (areas of low tissue resistance) rather than as a result of asymmetrical collagen deposition. The importance of virulence factor production in development of brain abscess was shown by the inability of heat-inactivated *S. aureus* to induce proinflammatory cytokine or chemokine expression in an experimental murine model[135]; α-toxin was identified as a key virulence factor for survival of *S. aureus* in the brain and the subsequent development of brain abscess.

CLINICAL PRESENTATION

The clinical course of brain abscess ranges from indolent to fulminant.[a] Most clinical manifestations (Table 90.2) are not due to the systemic signs of infection, but rather to the size and location of a space-occupying lesion within the brain and the virulence of the infecting microorganism. Headache is the most common presenting symptom and is observed in 70% to 75% of patients. The headache may be moderate to severe and hemicranial or generalized, but it lacks particularly distinguishing features, accounting for frequent delays in diagnosis. Sudden worsening of the headache, accompanied by a new onset of meningismus, may signify rupture of the abscess into the ventricular space[136]; this complication is often associated with a high mortality rate (85% in some series). The classic triad of headache, fever, and focal neurologic deficit is present in only about 20% of patients with brain abscess on admission.[137]

In a study of 33 consecutive patients with intraventricular rupture of brain abscess, severe headaches and signs of meningeal irritation were prominent before rupture, with a rapidly deteriorating clinical condition developing within 10 days after the signs of meningeal irritation[138]; CT performed before rupture showed localized enhancement of the ventricular wall adjacent to the abscess, most likely because capsule formation was more complete on the cortical side than on the ventricular side of the abscess. In another study, intraventricular rupture was more likely if the abscess was deep seated, multiloculated, and in close proximity to the ventricular wall[21]; a reduction of 1 mm in the distance between the ventricle and the abscess increased the rupture rate by 10%. In addition, the clinical presentation of brain abscess in an immunocompromised patient may be masked by the diminished inflammatory response.[63,64]

The location of the brain abscess defines the clinical presentation.[2,13–18,29,33] Patients with a frontal lobe abscess often present with headache, drowsiness, inattention, deterioration of mental status, hemiparesis with unilateral motor signs, and a motor speech disorder. The clinical presentation of cerebellar abscesses includes ataxia, nystagmus, vomiting, and dysmetria. Temporal lobe abscesses may cause ipsilateral headache and aphasia if the lesion is in the dominant

TABLE 90.2 Common Symptoms and Signs in Brain Abscess

SYMPTOM OR SIGN	FREQUENCY (%)
Headache	49–97
Mental status changes	28–91
Focal neurologic deficits	20–66
Fever	32–79
Triad of headache, fever, and focal deficit	<50
Seizures	13–35
Nausea and vomiting	27–85
Nuchal rigidity	5–52
Papilledema	9–51

[a]The clinical presentation varies depending on size and location of the abscess.
Data from references 1, 2, 5, 12, 22, 29, and 33.

[a]References 1–3, 12–18, 21, 22, 29, 31, 33.

hemisphere; a visual field defect (e.g., an upper homonymous quadrantanopia) may be the only presenting sign of a temporal lobe abscess. Abscesses of the brainstem usually manifest with facial weakness, fever, headache, hemiparesis, dysphagia, and vomiting.[139,140] The classic findings of a well-defined brainstem syndrome are frequently lacking in patients with brainstem abscesses because the abscess is likely to extend longitudinally along fiber tracts, rather than expanding transversely.[1]

Certain pathogens may lead to the development of specific clinical characteristics after CNS infection. In patients with nocardial brain abscess, the presentation is generally nonspecific, with fever, headache, and focal deficits determined by the site and size of the lesion.[45,46,141] The clinical suspicion of nocardial brain abscess may be increased by the presence of pulmonary, skin, or muscle lesions, which are present concurrently in many, but not all, cases. All patients with pulmonary nocardiosis should undergo evaluation to exclude CNS disease. In HIV-infected patients with tuberculous brain abscess, seizures, headache, altered consciousness, and hemiparesis are prominent presenting symptoms.[55]

Patients with *Aspergillus* brain abscess most commonly manifest signs of a stroke syndrome (secondary to ischemia or intracerebral hemorrhage or both) referable to the involved area of brain.[65] Headache, encephalopathy, and seizures may also occur. Fever is an inconsistent feature, and signs of meningeal irritation are rare. Patients who are severely immunocompromised usually present with nonspecific findings (i.e., alteration in mental status or seizures or both) shortly before death, whereas patients who are less immunocompromised are more likely to have headache and focal neurologic deficits.[68] Patients with *Aspergillus* brain abscess commonly have evidence of aspergillosis involving other organ systems.

Rhinocerebral mucormycosis initially manifests with symptoms referable to the eyes or sinuses including headache (often unilateral), facial pain, diplopia, lacrimation, and nasal stuffiness or epistaxis[65,72]; fever is usual. As the infection spreads to contiguous structures, necrotic lesions appear in the turbinates, nose, paranasal skin, or hard palate. Chemosis, proptosis, and external ophthalmoplegia may occur. Cranial nerve abnormalities are common (including cranial nerves II–VII, IX, and X), and blindness may occur as a result of invasion of the cavernous sinus, ophthalmic artery, and orbit. Thrombosis is a striking feature of this disease because the organism has a proclivity for blood vessel invasion. Focal neurologic deficits such as hemiparesis, seizures, or monocular blindness suggest far-advanced disease. With further progression, invasion of the internal carotid artery in the cavernous sinus can occur, accompanied by metastatic lesions in the frontoparietal cortex and deepening coma. Among patients with nonrhinocerebral brain abscess caused by Mucorales, fever, headache, or focal neurologic deficits were present in more than half of the patients. In one review of 22 cases,[71] 50% of the patients were injection drug users, and the basal ganglia were the most commonly involved CNS site (83% of patients).

Brain abscess caused by *S. apiospermum* tends to occur in immunocompromised patients or in patients 15 to 30 days after an episode of near drowning.[75,76] Brain abscesses can be located in the cerebrum, cerebellum, or brainstem; clinical presentations include seizures, altered consciousness, headache, meningeal irritation, focal neurologic deficits, abnormal behavior, and aphasia. The clinical manifestations of CNS disease caused by *Cryptococcus, Histoplasma, Coccidioides, Candida,* and other fungal pathogens depend on the intracranial location of the abscess. In one review, nearly one-third of bone marrow transplant recipients with brain abscess caused by *Candida* spp. had no signs or symptoms[64]; these infections were commonly diagnosed at postmortem examination.

The clinical manifestations of CNS toxoplasmosis in immunocompromised patients are variable, ranging from an insidious process evolving over several weeks to acute onset with a confusional state; the initial symptoms and signs may be focal or nonfocal or both.[88,92] *T. gondii* has a predilection to localize in the basal ganglia and brainstem, producing extrapyramidal symptoms resembling those of Parkinson disease. Generally, patients who present with nonfocal abnormalities develop signs of focal neurologic disease as the infection progresses, although some patients develop a diffuse, rapidly fatal encephalopathic process. Nonfocal evidence of neurologic dysfunction may predominate including generalized weakness, headache, confusion, lethargy, alteration of mental status, personality changes, and coma. CNS toxoplasmosis may also manifest differently depending on the risk group. Infection in transplant recipients is often diffuse, disseminated disease. Localizing neurologic signs tend to occur late in the course of infection or not at all in transplant recipients. In patients with underlying malignancies (e.g., Hodgkin disease), the presentation of toxoplasmic encephalitis is evenly distributed between focal and nonfocal manifestations of encephalitis.

Patients with AIDS and toxoplasmic encephalitis often present subacutely with nonspecific symptoms such as neuropsychiatric complaints, headache, disorientation, confusion, and lethargy progressing over 2 to 8 weeks; associated fever and weight loss are also common.[92–94,96] Patients develop clinical evidence of focal CNS mass lesions with ataxia, aphasia, hemiparesis, visual field loss, and vomiting or a more generalized encephalitis with increasing confusion, dementia, and stupor; seizures are common and may be the presenting clinical manifestation of CNS toxoplasmosis in patients with AIDS.

DIAGNOSIS

CT has revolutionized the diagnosis of brain abscess. Before the advent of CT, delays in diagnosis contributed significantly to the high morbidity and mortality in patients with brain abscess. The characteristic CT appearance of brain abscess is a hypodense center with a peripheral uniform ring enhancement after the injection of contrast material; this is surrounded by a variable hypodense area of brain edema (Fig. 90.1).[142] Other CT findings include nodular enhancement and areas of low attenuation without enhancement; the latter is observed during the early cerebritis stage before abscess formation. As the abscess progresses, contrast enhancement is observed. When the abscess becomes encapsulated in the later stages, contrast material no longer differentiates the lucent center, and the CT appearance is similar to the early cerebritis stage. CT is also useful for following the course of brain abscess, although after aspiration, improvement in the CT appearance may not be seen for 5 weeks or longer.

Magnetic resonance imaging (MRI) is now the first imaging choice in the evaluation of a patient with suspected brain abscess. MRI is more sensitive than CT and offers significant advantages in the early detection of cerebritis, including greater contrast between cerebral edema and adjacent brain, more conspicuous spread of inflammation into the ventricles and subarachnoid space, and earlier detection of satellite lesions (Fig. 90.2).[142] On T1-weighted images, the abscess capsule often appears as a discrete rim that is isointense to mildly hyperintense. Contrast enhancement with the paramagnetic agent gadolinium diethylenetriamine pentaacetic acid provides the added advantage of clearly differentiating the central abscess, the surrounding enhancing rim, and the cerebral edema surrounding the abscess.

On T1-weighted images, enhancement of the abscess capsule occurs. On T2-weighted images, the zone of edema that surrounds the abscess is one of marked high signal intensity; the capsule now appears as a well-defined hypointense rim at the margin of the abscess. Therapy with corticosteroids can decrease enhancement seen with CT and MRI. The addition of functional MRI sequences provides more information. The combined use of fluid-attenuated inversion recovery imaging, proton magnetic resonance spectroscopy (MRS), diffusion-weighted imaging (DWI) with measurement of an apparent diffusion coefficient, and diffusion tensor imaging has been shown to improve the specificity of the diagnosis of focal ring–enhancing lesions and to differentiate brain abscess from other cystic lesions of the brain including tumors.[2,143,144] Although the sensitivity and specificity of these techniques is not 100%, restriction of diffusion (hyperintense on DWI, low values on apparent diffusion coefficient map) is characteristic of pyogenic abscesses (Fig. 90.3).[145] Abscess is distinguished from rim-enhancing tumors by demonstrating amino acids within the contents of the cysts, a finding that is essentially diagnostic of the presence of activated polymorphonuclear leukocytes. Proton MRS can differentiate necrotic or cystic tumors and cerebral abscesses; in combination with DWI, it can significantly increase the diagnostic accuracy of conventional MRI with a sensitivity of 72% to 96% and a specificity of 86% to 96%.[144] Succinate and acetate peaks on proton MRS, observed only in anaerobic infections

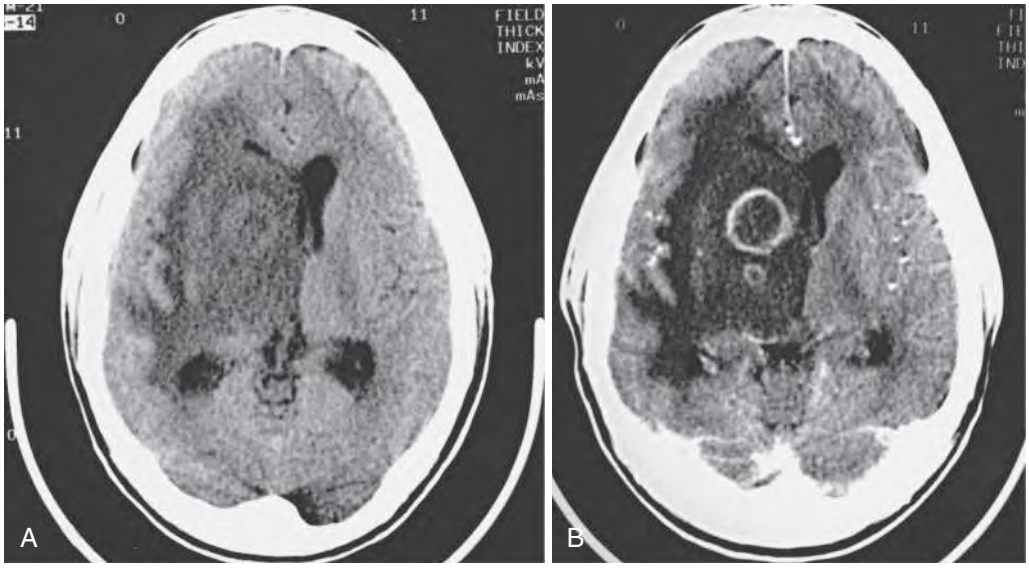

FIG. 90.1 Computed tomography (CT) of the head reveals a large rounded area of low attenuation in the right lentiform nucleus, compression of the horn of the right lateral ventricle, and a shift to the left with vasogenic edema. (A) Unenhanced CT scan reveals increased signal within the center of the area of low attenuation. (B) After intravenous administration of a contrast agent, there is ring enhancement of the abscess and evidence of a smaller satellite lesion.

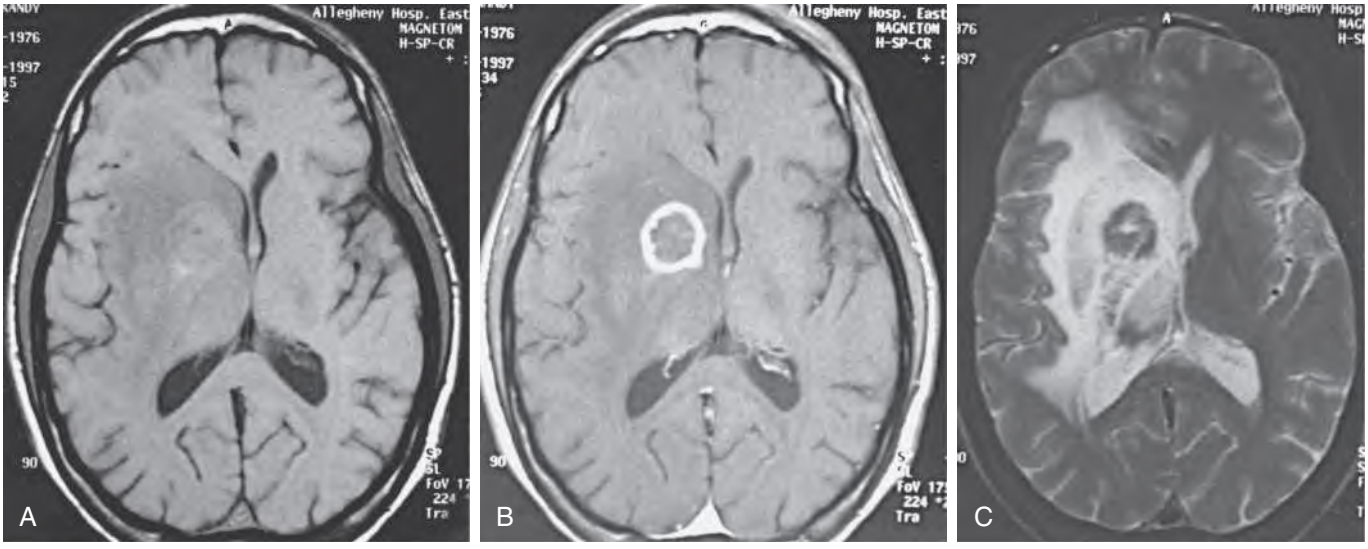

FIG. 90.2 Magnetic resonance imaging of the brain (same patient as shown in Fig. 90.1) reveals 2-cm, round, ring-enhancing lesion in right lentiform nucleus with associated vasogenic edema and midline shift to the left. (A) T1-weighted image reveals ill-defined area of low attenuation. (B) T1-weighted image after administration of gadolinium reveals ring enhancement of the abscess. (C) T2-weighted image shows hypointensity of rim of abscess with large area of high signal intensity consistent with cerebral edema.

due to glycolysis and subsequent fermentation, can be used to further differentiate anaerobic from aerobic metabolism.[144] Although the presence of amino acids in proton MRS is a sensitive marker of pyogenic abscess, its absence does not exclude a pyogenic etiology.[146]

CT and MRI are also quite sensitive in defining lesions in patients with fungal brain abscess; these modalities are not specific, although some exceptions do exist. The finding of a cerebral infarct in a patient with risk factors for invasive aspergillosis should suggest that diagnosis.[65] The areas of infarction typically develop into either single or multiple abscesses involving the cerebrum (usually frontal or temporal lobes) or cerebellum. In immunosuppressed patients with CNS aspergillosis, there is little or no contrast enhancement with MRI.[69] In patients with rhinocerebral mucormycosis, CT and MRI may show characteristic changes including sinus opacification, erosion of bone, and obliteration of deep fascial planes. Frontal lobe involvement in mucormycosis may show little or no ring enhancement; the lack of contrast enhancement is a poor prognostic sign because it indicates failure of host defense mechanisms to isolate or encapsulate the offending organism. Cavernous sinus involvement may be seen on MRI.

CT and MRI are extremely useful in the diagnosis of CNS toxoplasmosis.[92,93] The characteristic CT appearance (seen in 90% of patients) is rounded isodense or hypodense lesions with ring enhancement after the administration of contrast material; homogeneous enhancement or no enhancement can also be seen. The eccentric target sign in a T1 postcontrast image is particularly suggestive of toxoplasmosis. There are multiple lesions in 70% to 80% of cases, often involving the corticomedullary junction and the basal ganglia, although any part of the CNS may be involved. Marked edema and a mass effect are also frequently observed. A double-dose, delayed-contrast study may be a more sensitive method for delineating the true extent of disease. CT usually underestimates the number of lesions documented pathologically at autopsy. MRI has a greater sensitivity than CT and has detected lesions in patients

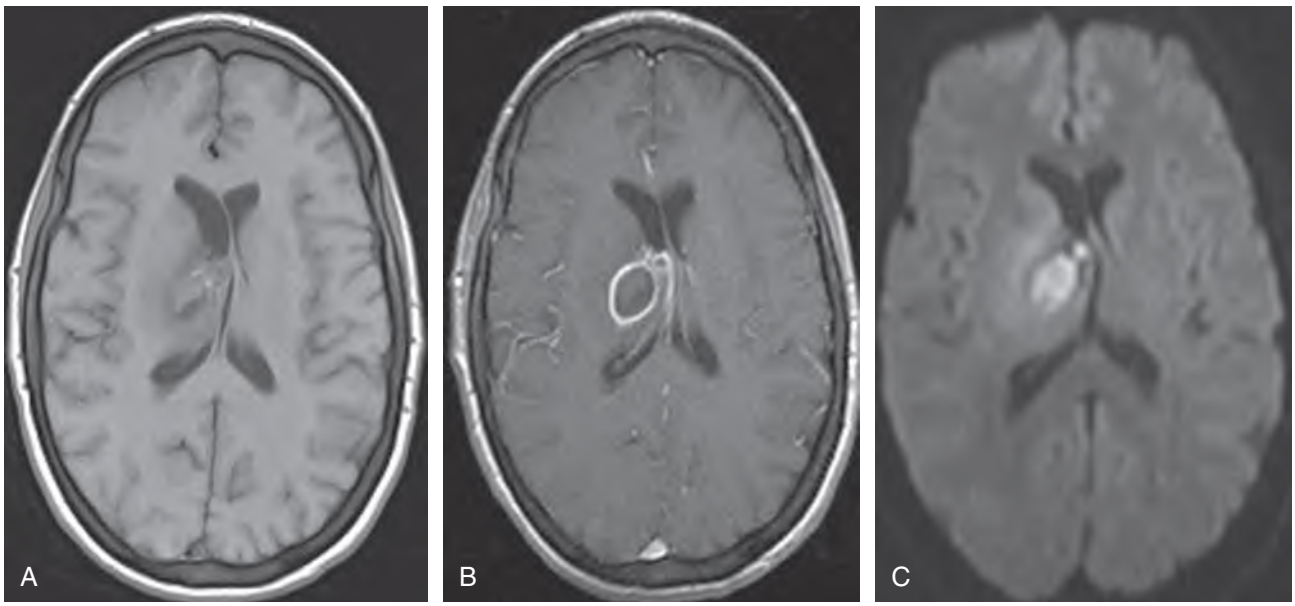

FIG. 90.3 Magnetic resonance imaging of the brain reveals a 3 × 1.7 cm bilobed peripherally enhancing, centrally restricted brain abscess located within the right thalamus. (A) T1-weighted image. (B) T1-weighted image after administration of gadolinium reveals ring enhancement of the abscess. (C) Diffusion-weighted imaging reveals marked hypersignal, a finding consistent with pyogenic brain abscess.

with active toxoplasmic encephalitis whose CT scans were normal. MRI should be performed in patients with AIDS and neurologic symptoms in whom CT shows no abnormality (or only cerebral atrophy). CT and MRI also may be useful in following the response to therapy because most patients show radiographic evidence of improvement within 10 to 14 days of initiation of anti-*Toxoplasma* therapy.[95,147]

The characteristic radiographic appearance of CNS toxoplasmosis in patients with AIDS, combined with its high prevalence, has been used to postpone the need for brain biopsy to establish a definitive diagnosis. The differential diagnosis of localized intraparenchymal brain lesions in patients with AIDS primarily also includes CNS lymphoma; progressive multifocal leukoencephalopathy; and, less commonly, tuberculosis, cryptococcoma, chagoma, and pyogenic brain abscess, the last mentioned usually in injection drug users or in the presence of another focus of infection. In patients with AIDS, because toxoplasmic encephalitis occurs as a result of a recrudescence of a latent infection,[93,94] the presence of anti-*Toxoplasma* immunoglobulin G (IgG) antibody can almost uniformly be shown before the development of the encephalitis. More than 97% of patients with AIDS and toxoplasmic encephalitis have serum IgG antibody titers against *T. gondii* ranging from 1:8 to more than 1:1024[92]; the predictive value of a positive serologic result in patients with characteristic abnormalities on radiographic studies may be 80% in the United States.[93,148] In contrast, in a retrospective review of 115 patients with AIDS and CNS toxoplasmosis at San Francisco General Hospital between 1981 and 1990, 4 of 18 patients with pathologically confirmed disease had undetectable anti-*Toxoplasma* IgG antibody by an indirect immunofluorescence assay.[95] Despite these conflicting data, many physicians in the United States initiate a therapeutic trial of anti-*Toxoplasma* chemotherapy in a patient with AIDS who is seropositive for *T. gondii* and has characteristic neuroradiographic abnormalities.[149] This is generally a valid approach in patients with AIDS and presumed CNS toxoplasmosis (see Chapter 278). Follow-up imaging in 2 weeks is obtained to decide whether a biopsy is necessary. Several meta-analyses suggest that brain biopsy is safe and effective and frequently results in a change in management in patients with AIDS and intracranial lesions when imaging studies are not characteristic for a specific diagnosis.[150,151]

CSF polymerase chain reaction (PCR) assay has also been used as a diagnostic test for toxoplasmic encephalitis; CSF PCR assay has a specificity of 96% to 100% but a sensitivity of only about 50% in the diagnosis of CNS toxoplasmosis.[96] Although the results from different reported studies vary, it seems clear that a positive PCR result in blood or CSF is very strong evidence in favor of the diagnosis of toxoplasmic encephalitis, whereas a negative result does not exclude the diagnosis.[152–154]

A major advance in the use of CT in patients with suspected brain abscess is the ability to perform stereotactic CT-guided aspiration to facilitate microbiologic diagnosis and to guide antimicrobial therapy. Ultrasound-guided aspiration, via transdural insonation, has also been performed through a single bur hole and showed excellent abscess visualization in 10 patients in one study,[155] although aspiration by CT guidance is generally the preferred method. Aspiration during the cerebritis stage may be complicated by hemorrhage.

At the time of aspiration, specimens should be sent for Gram stain, routine aerobic and anaerobic cultures, and cultures for mycobacteria and fungi. In patients with a likely bacterial brain abscess, 16S ribosomal RNA gene sequencing and amplification may serve as an important adjunctive tool in patients with negative culture results but who have histopathologic and Gram stain findings suggestive of a bacterial abscess[156–159]; this technique may provide a definitive etiologic diagnosis allowing for targeted antimicrobial therapy, although more studies are needed. In another study, use of multiple 16S ribosomal DNA sequencing was found to dramatically increase the number of infectious agents identified in cerebral abscesses.[160] These data were confirmed in a subsequent study in which metagenomic analysis from 71 patients identified 71 taxa that had not been previously identified, including 37 that are yet uncultured[161]; the major source of these agents was the sinuses and dental flora, and they were found in polymicrobial specimens. However, the importance of many of these pathogens in patients with brain abscess is unclear.[162] In addition, archaea-targeted PCR sequencing and metagenomics has demonstrated that methanogens (i.e., antibiotic-resistant anaerobic archaea that escape routine detection in clinical microbiology laboratories) belong to the anaerobic community responsible for brain abscess,[163] suggesting that medical treatment of brain abscess should incorporate agents (e.g., imidazole derivatives) active against these microorganisms, although more data are needed. Special stains such as acid-fast stains for mycobacteria, modified acid-fast stains for *Nocardia,* and other special stains (e.g., mucicarmine or Fontana-Masson for *Cryptococcus,* methenamine silver for fungi) should also be used to aid in making an etiologic diagnosis.

Aspergillus spp. manifest as septate hyphae in tissue sections with acute-angle, dichotomous branching. Biopsy specimens of cerebral lesions in mucormycosis usually show broad, irregular diameter hyphae; right-angle branching; and a lack of septa. *S. apiospermum, L. prolificans,*

and *Fusarium* hyphae cannot be distinguished reliably from *Aspergillus* spp. Hyphae of melanized, or dematiaceous, fungi in the brain may be brownish on hematoxylin and eosin stain and usually brown on Fontana-Masson stain and tend to have swollen and constricted areas in the hyphae, but they are not reliably distinguished from other molds. In patients with CNS toxoplasmosis,[92] diagnosis may require specialized immunohistochemical techniques (peroxidase-antiperoxidase) to detect the organisms or its antigens. Pseudocysts and tachyzoites, which are easily identifiable by histopathologic stains, may not be found in the center of the necrotic lesion and are best identified at the periphery of the lesion or within normal brain tissue. The immunofluorescence technique that uses monoclonal anti-*Toxoplasma* antibodies on brain touch preparations is a sensitive test for rapid diagnosis.

INITIAL MANAGEMENT OF THE PATIENT WITH BRAIN ABSCESS

The initial approach to a patient with a suspected brain abscess is a multidisciplinary one and should include evaluation by a neuroradiologist, a neurosurgeon, and an infectious diseases specialist using the following steps[1,2,31,137,164]:

1. MRI or contrast CT should be performed to verify the suspicion of brain abscess; if confirmed, plans for aspiration or surgery should be made (see below).
2. Obtain ancillary studies in an attempt to establish an etiologic diagnosis. These include blood cultures, which may have a yield of up to 28%; CSF analysis (if neuroimaging findings do not indicate risk of brain herniation with lumbar puncture), which may have utility for some conditions in the differential diagnosis, particularly in immunocompromised patients; and CT of the chest, especially in immunocompromised patients in whom there may also be involvement with the same pathogen (e.g., *Nocardia* or *Aspergillus*).
3. If single or multiple ring-enhancing lesions are found, the patient should undergo surgery. All lesions greater than 2.5 cm in diameter should be excised or stereotactically aspirated, and specimens should be sent to the microbiology and pathology laboratories (discussed earlier). For abscesses in the early cerebritis stage, or when the abscesses are 2.5 cm in diameter or less, the largest lesion should be aspirated for diagnosis and identification of the organism.
4. When abscess material has been obtained for microbiologic and histopathologic studies, empirical antimicrobial therapy should be initiated on the basis of the patient's predisposing conditions and the presumed pathogenesis of abscess formation (Table 90.3). If a primary source of infection outside the CNS is recognized as potentially having led to formation of the brain abscess, empirical antimicrobial therapy can be begun on the basis of microbiologic studies from the other source (e.g., positive blood cultures in a patient with infective endocarditis).
5. Therapy with corticosteroids should be initiated in patients with significant edema and an associated mass effect that is causing increased intracranial pressure or a predisposition to transtentorial herniation. Phenytoin should be considered to prevent seizures during early stages of therapy.

The empirical approach to antimicrobial therapy for bacterial brain abscess should take into account the frequency of isolation of certain organisms.[2] Because of the high rate of isolation of streptococci (particularly the *S. anginosus [milleri]* group) from brain abscesses of various causes, high-dose intravenous penicillin G or another drug (e.g., a third-generation cephalosporin, either cefotaxime or ceftriaxone) active against this organism should be included in the initial therapeutic regimen. Penicillin G is also active against most anaerobic species with the notable exception of *Bacteroides fragilis,* which may be isolated in a high percentage of cases of brain abscess; metronidazole should be included in the initial regimen when this organism is suspected. Metronidazole has bactericidal activity against *B. fragilis* and *Prevotella melaninogenica* and attains high concentrations in brain abscess pus, and its entry into cerebral abscesses is not affected by concomitant corticosteroid therapy.[165] The combination of metronidazole plus a third-generation cephalosporin is a common regimen used in more recent series.[18]

TABLE 90.3 Empirical Antimicrobial Therapy for Bacterial Brain Abscess

PREDISPOSING CONDITION	ANTIMICROBIAL REGIMEN
Otitis media or mastoiditis	Metronidazole + third-generation cephalosporin[a]
Sinusitis (frontoethmoid or sphenoid)	Metronidazole + third-generation cephalosporin[a,b]
Dental infection	Metronidazole + third-generation cephalosporin[a]
Penetrating trauma or postneurosurgical	Vancomycin + third-generation or fourth-generation cephalosporin[a,c]
Lung abscess, empyema, bronchiectasis	Third-generation cephalosporin[a] + metronidazole + sulfonamide[d]
Bacterial endocarditis	Vancomycin[e]
Congenital heart disease	Third-generation cephalosporin[a]
Unknown	Vancomycin + metronidazole + third-generation or fourth-generation cephalosporin[a,c]

[a]Cefotaxime or ceftriaxone; the fourth-generation cephalosporin cefepime may also be used.
[b]Add vancomycin when infection caused by methicillin-resistant *Staphylococcus aureus* is suspected.
[c]Use ceftazidime or cefepime as the cephalosporin if *Pseudomonas aeruginosa* is suspected.
[d]Trimethoprim-sulfamethoxazole; include if *Nocardia* spp. is suspected.
[e]Additional agents should be added based on other likely microbiologic etiologies.

When *S. aureus* is considered a likely pathogen (e.g., after cranial trauma or after neurosurgery), vancomycin should be used, but therapy should be changed to nafcillin if methicillin-sensitive organisms are isolated.[166] Because an increase in community-acquired methicillin-resistant *S. aureus* has been observed in recent years, vancomycin should be used empirically when *S. aureus* brain abscess is suspected or proven[25,167] until in vitro susceptibility testing is performed. Use of ceftaroline in brain abscess remains undefined. If *P. aeruginosa* is a likely infecting pathogen, ceftazidime or cefepime is the agent of choice. In patients with a bacterial brain abscess of unclear pathogenesis, empirical therapy with vancomycin, metronidazole, and a third-generation or fourth-generation cephalosporin (cefotaxime or ceftriaxone, or ceftazidime or cefepime if *P. aeruginosa* is suspected) is recommended pending culture results.

The initial empirical antimicrobial approach to immunocompromised patients is not evidence based but focuses on pathogens historically associated with specific immune defects of the patient. In transplant recipients (both solid-organ and hematopoietic stem cell transplants), *Nocardia* and fungal infections are additional considerations, so the combination of high-dose meropenem (which will cover most *Nocardia,* anaerobes, and gram-negative bacilli, including *Pseudomonas,* and possibly *Listeria*) plus voriconazole and vancomycin (until infection with methicillin-resistant *S. aureus* has been excluded) would be chosen by many experts. In patients with hematologic malignancies in whom neutropenia is the main risk factor, appropriate coverage for fungal infections is needed, and combination therapy with voriconazole and an amphotericin B preparation may be considered; the antifungal prophylaxis that the patient was receiving (if any) should be taken into consideration when choosing an empirical antifungal regimen. A very unusual but characteristic distinct syndrome of bacteremia, meningitis, and brain abscess caused by *Bacillus cereus* have been described in patients receiving high-dose chemotherapy for acute leukemia, sometimes with thrombosis and hemorrhage,[168–170] and addition of vancomycin should be considered in the empirical regimen in the appropriate clinical setting.

In HIV-infected patients with CNS mass lesions, the initial approach to management is different because of the high likelihood of the diagnosis of toxoplasmic encephalitis.[93,171] For patients with large lesions showing

a mass effect and threatening impending herniation, open biopsy with decompression is the standard. In HIV-infected patients with multiple ring-enhancing lesions on contrast-enhanced CT or MRI and positive anti-*Toxoplasma* IgG serologic tests, empirical therapy for toxoplasmic encephalitis should be initiated (Table 90.4); clinical and radiographic improvement should be observed within 10 to 14 days in 95% of patients with toxoplasmic encephalitis (see above).[96,147] A strategy for the management of suspected *Toxoplasma* CNS lesions in HIV-infected patients is presented in Chapter 278.

THERAPY

When the infecting pathogen is isolated, antimicrobial agents can be modified for optimal therapy. Recommendations for standard therapy, with alternative agents, are provided in Table 90.4. Table 90.5 lists dosages of these agents used for CNS infections. In this section the principles of antimicrobial use and surgical therapy for bacterial and fungal brain abscesses are reviewed. The therapeutic approach to toxoplasmic encephalitis is discussed in Chapter 278.

Bacterial Brain Abscess

Antimicrobial Therapy

No randomized controlled trials have evaluated the efficacy of different antimicrobial agents in the treatment of bacterial brain abscess. The antimicrobial agents used to treat bacterial brain abscess should be able to penetrate into the abscess cavity and should have in vitro activity against the pathogens isolated.[1,2] The few studies that have addressed the penetration of antimicrobial agents into brain abscess fluid have included limited numbers of patients. Concentrations of penicillin G have been measured in brain abscess pus but were detected consistently only if the daily dosage in adults exceeded 24 million units; in some cases, penicillin G may be inactivated in pus, with the result that bacteria can still be cultured despite adequate penicillin concentrations. Limited data are available on the penetration of the semisynthetic penicillins (e.g., nafcillin, oxacillin) into brain abscesses, although some studies suggest that concentrations of these drugs in brain abscess fluid are variable.

Metronidazole has excellent in vitro activity against strict anaerobes, making it an important agent for the treatment of patients with brain abscess.[165] Its excellent pharmacokinetic profile (i.e., good oral absorption and penetration into brain abscess cavities) has made metronidazole a more attractive antianaerobic agent than chloramphenicol for therapy of brain abscess. However, metronidazole must always be used in combination with an antimicrobial agent effective against streptococci because polymicrobial infections are common in patients with brain abscesses. Vancomycin has also been shown to have excellent concentrations in brain abscess fluid after prolonged therapy. In one study,

TABLE 90.4 Antimicrobial Therapy for Brain Abscess

ORGANISM	STANDARD THERAPY	ALTERNATIVE THERAPIES
Bacteria		
Actinomyces spp.[b]	Penicillin G	Clindamycin
Bacteroides fragilis[b]	Metronidazole	Clindamycin
Enterobacteriaceae[b]	Third-generation cephalosporin[c]	Aztreonam, trimethoprim-sulfamethoxazole, fluoroquinolone, meropenem
Fusobacterium spp.[b]	Metronidazole	Clindamycin, meropenem
Haemophilus spp.[b]	Third-generation cephalosporin[c]	Aztreonam, trimethoprim-sulfamethoxazole
Listeria monocytogenes	Ampicillin or penicillin G[d]	Trimethoprim-sulfamethoxazole
Mycobacterium tuberculosis	Isoniazid + rifampin + pyrazinamide + ethambutol	
Nocardia spp.	Trimethoprim-sulfamethoxazole or sulfadiazine	Minocycline, imipenem, meropenem, third-generation cephalosporin,[c] amikacin, linezolid
Prevotella melaninogenica[b]	Metronidazole	Clindamycin, meropenem
Pseudomonas aeruginosa	Ceftazidime or cefepime	Aztreonam, fluoroquinolone, meropenem
Staphylococcus aureus Methicillin-sensitive Methicillin-resistant	 Nafcillin or oxacillin Vancomycin	 Vancomycin Trimethoprim-sulfamethoxazole
Streptococcus anginosus (milleri) group, other streptococci[b]	Penicillin G	Third-generation cephalosporin,[c] vancomycin
Fungi		
Aspergillus spp.	Voriconazole	Liposomal amphotericin B, amphotericin B lipid complex, amphotericin B deoxycholate, itraconazole,[e] posaconazole[e]
Candida spp.	Liposomal amphotericin B,[f] amphotericin B lipid complex,[f] amphotericin B deoxycholate[f]	Fluconazole, voriconazole
Cryptococcus neoformans	Amphotericin B deoxycholate,[f] liposomal amphotericin B,[f] amphotericin B lipid complex[f]	Fluconazole
Mucorales	Liposomal amphotericin B, amphotericin B lipid complex, amphotericin B deoxycholate	Posaconazole,[e] isavuconazole[e]
Scedosporium apiospermum	Voriconazole	Itraconazole,[e] posaconazole[e]
Protozoa		
Toxoplasma gondii	Pyrimethamine + sulfadiazine	Pyrimethamine + clindamycin; trimethoprim-sulfamethoxazole; pyrimethamine + azithromycin, clarithromycin, atovaquone, or dapsone

[a]Choice of specific antimicrobial agents for standard therapy, or consideration of alternative therapies, should be based on in vitro susceptibility testing for pathogens for which testing can be performed.
[b]Depending on the pathogenesis of bacterial brain abscess (see text), these bacteria may be isolated as part of a mixed infection.
[c]Cefotaxime or ceftriaxone.
[d]Addition of an aminoglycoside should be considered.
[e]Consider for use in salvage therapy in nonresponding patients or in patients intolerant of amphotericin B–based therapies.
[f]Addition of flucytosine may be considered.

TABLE 90.5 Recommended Dosages of Antimicrobial Agents for Central Nervous System Infections in Adults

ANTIMICROBIAL AGENT	TOTAL DAILY DOSAGE	DOSING INTERVAL (h)	ANTIMICROBIAL AGENT	TOTAL DAILY DOSAGE	DOSING INTERVAL (h)
Amikacin[b]	15 mg/kg	8	Isoniazid[d]	300 mg	24
Amphotericin B deoxycholate	0.6–1.0 mg/kg[c]	24	Itraconazole	400–800 mg	12
Amphotericin B lipid complex	5 mg/kg	24	Linezolid	1200 mg	12
Ampicillin	12 g	4	Liposomal amphotericin B	5–7.5 mg/kg	24
Atovaquone[d]	3000 mg	6	Meropenem	6 g	8
Azithromycin	1200–1500 mg	24	Metronidazole	30 mg/kg	6
Aztreonam	6–8 g	6–8	Nafcillin	12 g	4
Cefepime	6 g	8	Oxacillin	12 g	4
Cefotaxime	8–12 g	4–6	Penicillin	24 million U	4
Ceftazidime	6 g	8	Posaconazole[g]	300 mg	24
Ceftriaxone	4 g	12	Pyrazinamide[d]	15–30 mg/kg	24
Ciprofloxacin	800–1200 mg	8–12	Pyrimethamine[d,h]	25–100 mg	24
Clindamycin	2400–4800 mg	6	Rifampin[d]	600 mg	24
Dapsone[d]	100 mg	24	Sulfadiazine[d]	4–6 g	6
Ethambutol[d]	15 mg/kg	24	Tobramycin[b]	5 mg/kg	8
Fluconazole	400–800 mg	24	Trimethoprim-sulfamethoxazole[i]	10–20 mg/kg	6–12
Flucytosine[d,e]	100 mg/kg	6	Vancomycin[j]	30–45 mg/kg	8–12
Gentamicin[b]	5 mg/kg	8	Voriconazole[k]	8 mg/kg	12
Isavuconazole[f]	200 mg	24			

[a]Patients with normal renal and hepatic function; unless indicated, intravenous mode of administration used.
[b]Need to monitor peak and trough serum concentrations.
[c]Dosages up to 1.5 mg/kg/day may be used for aspergillosis or mucormycosis.
[d]Dosage for oral administration.
[e]Maintain serum concentrations of 50–100 µg/mL.
[f]Isavuconazole is available commercially as isavuconazonium sulfate, the prodrug of isavuconazole. The drug requires IV loading dose of 372 mg of isavuconazonium (equivalent to 200 mg of isavuconazole) every 8 hours for 6 doses, followed by dosing every 24 hours.
[g]IV loading dose of 300 mg every 12 hours for 2 doses. There are limited clinical data on the use of newer formulations (i.e., IV and delayed-release tablets) of posaconazole in the management of fungal central nervous system infections, but these formulations have improved pharmacokinetic properties and are recommended. The oral suspension of posaconazole (200 mg every 6 hours initially, then 400 mg every 12 hours) has been successfully used in isolated cases.
[h]Higher dosages used in patients with AIDS and toxoplasmic encephalitis; load with 100–200 mg.
[i]Dosage based on trimethoprim component; higher dose used for *Nocardia* brain abscess.
[j]Adjust dosage based on trough serum concentration; maintain at 15–20 µg/mL.
[k]IV loading dose of 6 mg/kg IV every 12 hours for two doses; maintain serum trough concentrations of 2–5 µg/mL.

simultaneous measurement of vancomycin concentrations in serum and brain abscess fluid was obtained 1 hour after a 500-mg dose[166]; vancomycin concentrations obtained before and during operative removal of the brain abscess were 15 µg/mL and 18 µg/mL, respectively, with a simultaneous serum vancomycin concentration of 21 µg/mL.

The third-generation cephalosporins are attractive agents for the treatment of brain abscess because of their good CNS penetration and excellent in vitro activity against many of the pathogens isolated from bacterial brain abscesses. When cefotaxime was given in higher doses than usually recommended (3 g every 8 hours), brain abscess concentrations of cefotaxime and its active metabolite, desacetylcefotaxime, were greater than the minimal inhibitory concentrations of most gram-positive and gram-negative organisms against which cefotaxime is used systemically. When combined with metronidazole and used in conjunction with surgical excision, high doses of cefotaxime also have been effective clinically in the treatment of brain abscess.[172] Ceftriaxone and ceftazidime have been used in the treatment of brain abscess,[173,174] although only a few patients have been studied. Ampicillin-sulbactam has also been shown to successfully treat brain abscesses[175]; intracavitary concentrations were variable but adequate in most cases.

Imipenem has been used successfully to treat pyogenic and nocardial brain abscesses,[176,177] although the use of imipenem has been associated with an increased risk for seizures, limiting its usefulness in patients with CNS mass lesions. Meropenem, a carbapenem antimicrobial agent similar to imipenem, was successful in one case of an *Enterobacter cloacae* brain abscess,[178] suggesting that this agent may be useful in cases of brain abscess, especially when caused by resistant pathogens. Usage of doripenem in brain abscess is as yet undefined. In an 11-year retrospective, nonrandomized study comparing intravenous cefotaxime and metronidazole with intravenous meropenem or imipenem monotherapy, treatment with meropenem was associated with a significantly lower mortality rate and a lower seizure rate compared with imipenem.[179] The fluoroquinolones have good CNS penetration and have been used anecdotally in the treatment of patients with brain abscess,[180] although further data are needed to determine the efficacy of the fluoroquinolones for the treatment of brain abscess.

Antimicrobial therapy with high-dose intravenous agents has traditionally been administered for 6 to 8 weeks in patients with bacterial brain abscesses.[1,2,22] This is often followed by oral antimicrobial therapy for 2 to 3 months if an appropriate agent or agents are available, although the efficacy and necessity of this approach have not been established. Biweekly neuroimaging for up to 3 months is also suggested to monitor for abscess reexpansion or failure to resolve.[22,164] The combination of surgical aspiration or removal of all abscesses larger than 2.5 cm in diameter with a 6-week or longer course of intravenous antimicrobial therapy along with improvement on follow-up neuroimaging should result in a cure rate of more than 90%.[8] Patients should be followed with neuroimaging until the abscess has completely resolved; if the abscess enlarges after 2 weeks of antimicrobial therapy or fails to resolve after 3 to 4 weeks, further surgical aspiration or excision should be performed.

Shorter courses (3–4 weeks) of antimicrobial therapy may be adequate for patients who have undergone surgical excision of the abscess. Surgical therapy (i.e., excision or aspiration) is often required for the optimal management of brain abscess (discussed later), although certain subsets of patients may be treated with antimicrobial therapy alone.[140,181–183] These subsets include patients with medical conditions that increase the risk of surgery, multiple abscesses, abscesses in a deep or dominant location, concomitant meningitis or ependymitis, early abscess reduction with clinical improvement after antimicrobial therapy, and abscess size smaller than 3 cm. In one series, no abscess larger than 2.5 cm resolved without surgical therapy.[181] The best candidates for medical therapy appear to be patients with a small abscess (≤2.5 cm), in good clinical condition (Glasgow Coma Scale score >12), and with a well-known etiology.[184] However, surgery should be considered in patients in whom the clinical condition is worsening or in patients without clinical or radiologic improvement within 1 to 2 weeks.

Patients treated with antimicrobial therapy alone may require prolonged (up to 12 weeks) courses of parenteral treatment and must receive careful clinical and radiographic follow-up. The Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy recommends intravenous therapy for 1 to 2 weeks for bacterial brain abscess, after which time, depending on the clinical response, change to an appropriate oral regimen can be considered.[185] This approach has been used in several series,[18,186,187] although it cannot be considered standard therapy in most patients with bacterial brain abscess. The ability of MRI and DWI to track resolution of the abscess has proved very useful in identifying patients with bacterial brain abscess who may need only 2 weeks of postoperative intravenous antibiotics.[188]

When a brain abscess caused by *Nocardia* is suspected or proved, the sulfonamides, with or without trimethoprim, are recommended as first-line therapy,[46,189,190] although treatment failures have been reported.[191] Alternative agents include minocycline, amikacin, imipenem, third-generation cephalosporins, and linezolid, which are among the most active agents against *Nocardia* in vitro.[192–194] However, the taxonomy of *Nocardia* has changed considerably over the past decade, so it is recommended to use molecular methods for identification, and in vitro susceptibility testing should ideally be performed by a reference laboratory.[195] Also, in vitro activity does not always correlate with clinical efficacy. Combination therapies have been studied,[196–200] and combination regimens containing third-generation cephalosporins or imipenem along with a sulfonamide or amikacin should be considered for immunocompromised patients or patients in whom therapy fails.[1,201] Of note, 100% of *Nocardia* isolates are susceptible to linezolid. In addition, linezolid was shown to be efficacious in two patients with multiple *Nocardia* brain abscesses,[202] although therapy was changed in one patient as a result of an adverse effect from linezolid. One patient was successfully treated with unexpectedly low doses of linezolid along with therapeutic drug monitoring for optimization of drug exposure.[203] Tedizolid is also active in vitro against all isolates of *Nocardia*[204]; it may be less myelosuppressive than linezolid and has been successfully used for 6 months in a patient with *Nocardia farcinica* brain abscess without toxicity,[205] although more data are needed, as the CNS penetration of tedizolid is less than linezolid. Brain abscess caused by *N. farcinica*, a species highly resistant to various antimicrobial agents, has also been successfully treated with moxifloxacin either alone or in combination with another agent.[206–208] The European experience with *Nocardia* infections after solid-organ transplantation suggests that 40% of cases of CNS involvement may be asymptomatic, confirms the increased virulence of *N. farcinica*, and fails to show any advantage of combination therapy over monotherapy.[48,209] The duration of antimicrobial therapy for nocardial brain abscess ranges from 3 to 12 months.[46,210] Therapy in immunosuppressed patients should probably be continued for 1 year,[141] with careful follow-up to monitor for relapse.

The therapy for tuberculous brain abscess is similar to that for tuberculosis in other locations. However, treatment is more complex for patients with tuberculous brain abscess caused by multidrug-resistant and extremely drug-resistant strains. Because published reports on tuberculous brain abscess consist mainly of case reports and case series, overall mortality rates are not well defined.[55]

Surgical Therapy

Most patients with bacterial brain abscess require surgical management for optimal therapy. The two procedures available are aspiration of the abscess after bur hole placement and complete excision after craniotomy.[22,30,33,211] No prospective trial comparing the two procedures has ever been performed, although in a series of 142 patients with brain abscess, no significant differences in outcome were observed in patients treated with excision, craniotomy with drainage, or stereotactic drainage.[17] However, in one retrospective review of 47 studies from the years 1990–2008, patients who underwent aspiration had a mortality rate of 6.6% compared with 12.7% in patients who underwent surgical excision.[212] In contrast, a meta-analysis of more recent series found that for encapsulated abscesses in noneloquent areas of the brain, excision resulted in improved neurologic status at 1 month, lower reoperation rate, and shortened duration of hospital stay and antimicrobial duration.[213] The choice of procedure must be individualized for each patient. Aspiration may be performed by a stereotactic procedure using CT or MRI guidance, which affords the surgeon rapid, accurate, and safe access to virtually any intracranial point, including areas located in deep critical regions of the CNS (e.g., brainstem, cerebellum, or diencephalic structures adjacent to the ventricles)[174,214–218]; aspiration can also be used for swift relief of increased intracranial pressure.

Complete excision by craniotomy is now infrequently performed because of the development of aspiration and closed drainage techniques described previously, but it may be required in patients with multiloculated abscesses (for whom aspiration techniques have failed), abscesses containing gas, or abscesses that fail to resolve. Posttraumatic abscesses containing foreign bodies or retained bone fragments usually require excision to prevent recurrence, as do abscesses resulting from fistulous communications and abscesses localized to one lobe but contiguous to a primary focus.[22] Excision of abscesses in the cerebellar area has also been recommended, although in recent years bur hole aspiration has emerged as a satisfactory method of drainage[8]; drainage is important because precipitous neurologic deterioration can occur in the relatively smaller volume of the posterior fossa in the presence of disproportionate edema, especially in children.[219] In one retrospective review, there was a lower mortality in the excision group.[220] Patients with cerebellar abscesses that demonstrate mass effect, effacement, or displacement of the fourth ventricle in the setting of overt or incipient hydrocephalus should also have CSF diversion with placement of an external ventricular drain[5,8]; the presence of a periventricular lucency (transependymal flow) is an absolute indication for immediate ventricular drainage regardless of the level of consciousness.

Craniotomy with total excision is difficult in cases of nocardial brain abscess because these abscesses are usually multiloculated.[141] In one review of 11 patients with nocardial brain abscess,[221] aspiration alone (which was repeated as clinically indicated) was a safe, efficacious treatment for 9 patients. In another series of three patients with nocardial brain abscess, cure was achieved only after neurosurgical enucleation,[222] suggesting that an aggressive approach should be used. In patients with tuberculous brain abscess, an early surgical procedure is mandatory to establish the diagnosis and improve the efficacy of antituberculous therapy[56]; procedures include stereotactic-guided aspiration, simple puncture, continuous drainage, and repeated aspiration through bur holes. In patients with intraventricular rupture of a purulent brain abscess who have dilated ventricles and ventriculitis, ventricular drainage combined with the administration of appropriate intravenous or intrathecal antimicrobial agents, or both, is recommended[21,138]; urgent craniotomy and abscess drainage with or without lavage of the ventricular system has also been suggested, although the optimal approach has not been clarified.

Fungal Brain Abscess

The optimal therapy for fungal brain abscess usually requires a combined medical and surgical approach; surgery involves either excision or drainage of the abscess. Therapy for fungal brain abscess in immunocompromised patients carries a high mortality rate, however, despite surgery and antifungal therapy.[223] Nevertheless, early recognition of this infection can lead to a successful outcome, especially if leukocyte counts return to normal or if the dosages of immunosuppressive agents can be reduced.[1] The mainstay of medical therapy for candidal brain

abscess is an amphotericin B preparation plus 5-flucytosine.[65,224] The lipid formulations of amphotericin B are preferred for CNS infections, with fluconazole suggested for step-down therapy.[225] The efficacy of fluconazole in the treatment of *Candida* brain abscess has not been evaluated, although one case report in a premature infant with *Candida albicans* brain abscess showed a decrease in abscess size after the addition of fluconazole to amphotericin B plus 5-flucytosine.[226] Echinocandins do not cross the blood-brain barrier, and cases of brain abscesses have developed during treatment of *Candida* endocarditis with caspofungin.[227]

The antifungal therapy of choice for *Aspergillus* brain abscess was previously amphotericin B deoxycholate (0.8–1.25 mg/kg/day); doses up to 1.5 mg/kg/day have been used, depending on the clinical response.[228] However, its efficacy was notoriously low.[229] Voriconazole is now the drug of choice in patients with *Aspergillus* brain abscess.[223,230] In one review of voriconazole in the treatment of invasive aspergillosis that included 19 patients with cerebral disease, 3 (16%) patients had a partial response to treatment,[231] although the response rate in more recent studies is approximately 35%.[69,230] Combination therapy (voriconazole, combined with either caspofungin or liposomal amphotericin B) has also been advocated.[232–234] Posaconazole has poor penetration into the CNS, although there are reports of efficacy in CNS aspergillosis.[235] There are no current reports of CNS aspergillosis treated with isavuconazole.

Mucormycosis also should be treated with amphotericin B deoxycholate or one of its lipid formulations, along with correction of underlying metabolic derangements and aggressive surgical débridement.[65,72,223,236,237] Some data have suggested that the lipid formulations of amphotericin B resulted in higher recovery rates than amphotericin B deoxycholate in patients with mucormycosis and hematologic diseases or solid-organ transplantation, leading to a recommendation for use of a lipid formulation, usually liposomal amphotericin B, as first-line therapy.[73] The role of surgery in the treatment of cerebral mucormycosis cannot be overemphasized. Because of their propensity for invading blood vessels, the Mucorales cause extensive tissue infarction, impairing the delivery of antifungal agents to the site of infection. Surgery is often the only modality that may effectively eliminate the invading microorganisms. Amphotericin B has also been applied topically in the orbital cavities in patients with rhinocerebral mucormycosis,[237] although it is unclear if this is beneficial. Posaconazole or isavuconazole may be considered as follow-up therapy in patients who have already responded to amphotericin B–based therapies.[238] Given the relatively low penetration of posaconazole into the CNS, we recommend use of delayed-release tablets or the intravenous formulation as well as measuring serum concentrations of this agent, although there are limited clinical data on the use of these new formulations in the treatment of fungal CNS infections. Hyperbaric oxygen therapy has been reported to be a useful adjunct in cerebral mucormycosis,[239,240] although no prospective, controlled trials have been done to assess its efficacy adequately.

For *Scedosporium* brain abscess, surgical drainage is the cornerstone of effective therapy.[75] The organism shows in vitro resistance to amphotericin B. Based on clinical experience and the absence of good alternative agents, voriconazole is now the antifungal agent of choice for treatment of *S. apiospermum* brain abscess.[241] In one review of the use of voriconazole, which included 21 patients with CNS disease caused by *Scedosporium*, 43% had a therapeutic response.[242] There is a case report of successful use of posaconazole in the treatment of *S. apiospermum* brain abscess.[243] *L. prolificans (S. prolificans)* is a mold usually resistant to all antifungal agents; the combination of voriconazole and terbinafine was successful in one patient with chronic granulomatous disease and a brain abscess caused by this pathogen.[244]

Some dematiaceous fungi are often isolated from brain abscesses in immunocompromised and immunocompetent patients. Some, such as *Cladophialophora bantiana, Rhinocladiella mackenziei,* and *Exophiala dermatitidis,* seem to have a special tropism for the CNS. Complete excision of brain abscess caused by these fungi whenever feasible is associated with better outcomes than aspiration or partial excision.[83] However, the outcome remains poor, with an overall mortality of greater than 70%. Because these infections are uncommon, there are not good data on the antifungal agent of choice. Voriconazole, posaconazole, and itraconazole usually have in vitro activity, and the combination of amphotericin B and flucytosine shows synergism in vitro.[245] Of the azole antifungal agents, most experience is with itraconazole, but there are reported cases of successful treatment with posaconazole.[246,247] The reports of successful outcomes of these infections usually involve surgical incision and drainage (sometimes repeatedly) and a combination of antifungal agents.[66,248]

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The complete reference list is available online at Expert Consult.

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91 Subdural Empyema, Epidural Abscess, and Suppurative Intracranial Thrombophlebitis

Allan R. Tunkel

SHORT VIEW SUMMARY

Definition
- *Subdural empyema* refers to a collection of pus between the dura and arachnoid.
- *Epidural abscess* is a localized collection of pus between the dura mater and overlying skull or vertebral column.
- *Suppurative intracranial thrombophlebitis* includes dural venous sinus thrombosis and suppuration, most commonly septic cavernous sinus thrombosis.

Epidemiology
- The most common conditions predisposing to cranial subdural empyema are otorhinologic infections, especially of the paranasal sinuses, which are affected in 40% to 80% of cases. Spinal subdural empyema originates hematogenously.
- About 0.2 to 2 per 10,000 hospitalized patients have spinal epidural abscess, with most cases usually secondary to extension from vertebral osteomyelitis. More recent series reveal an incidence of up to 8.0 cases per 10,000 admissions, with patients more likely to have experienced at least one previous health care visit or to have received antimicrobials within 30 days of admission; to have comorbidities of injection drug use, alcohol abuse, and obesity; and to harbor coinfection at a noncontiguous site.
- Septic cavernous thrombosis usually originates in sphenoid and ethmoid sinusitis.

Microbiology
- A number of bacterial species have been isolated in patients with cranial subdural empyema, including aerobic streptococci, staphylococci, aerobic gram-negative bacilli, and anaerobic streptococci and other anaerobes.
- *Staphylococcus aureus* is the most common etiologic agent in patients with spinal epidural abscess.
- Staphylococci and streptococci are the usual bacteria causing septic cavernous sinus thrombosis.

Diagnosis
- Epidural spinal abscess should be suspected in patients with back pain, fever, and pain on percussion over the spine. Weakness or other long-tract signs are present initially in half of the cases. Magnetic resonance imaging (MRI) with gadolinium enhancement is the diagnostic procedure of choice in patients with subdural empyema and epidural abscess.
- Septic cavernous sinus thrombosis should be suspected in patients with headache, fever, and diplopia. Unilateral facial pain, decreased vision, or ptosis may also be seen. The noninvasive diagnostic procedure of choice in patients with suppurative intracranial thrombophlebitis is MRI and magnetic resonance venography; computed tomography venography is done in patients unable to undergo MRI.

Therapy
- Subdural empyema is a medical and surgical emergency. The goals of surgery are to achieve adequate decompression of the brain and completely evacuate the empyema; based on retrospective outcome data, craniotomy is the surgical procedure of choice.
- The principles of therapy for spinal epidural abscess are prompt laminectomy and surgical decompression in patients with neurologic dysfunction, drainage of the abscess, and 4 to 8 weeks of intravenous antimicrobial therapy, selected on the basis of culture and susceptibility testing. Antimicrobial therapy alone can be considered in patients with localized pain and radicular symptoms without long-tract findings, but frequent neurologic examinations and serial MRI studies should be performed to demonstrate resolution of the abscess. The risk of this approach is that rapid progression in the absence of surgery can cause permanent paraplegia.
- Empirical antimicrobial therapy for suppurative intracranial thrombophlebitis is usually vancomycin, metronidazole, and a third- or fourth-generation cephalosporin; anticoagulation should also be used in patients with septic cavernous sinus thrombosis unless there are contraindications.

SUBDURAL EMPYEMA

Epidemiology and Etiology

Subdural empyema refers to a collection of pus in the space between the dura and arachnoid. It accounts for 15% to 20% of all localized intracranial infections. Before the advent of antimicrobial therapy, the disease was essentially fatal (almost 100% mortality), but with current methods of diagnosis and treatment, mortality rates are approximately 10% to 20%.[1–5] The most common conditions predisposing to cranial subdural empyema are otorhinologic infections, especially of the paranasal sinuses, which are affected in 40% to 80% of patients[1,2,4–7]; this percentage may even be higher in children.[8–10] In contrast, in one 20-year review of 31 children with subdural empyema, only about 10% had a prior otorhinolaryngeal infection; about 20% had developed subdural empyema after head trauma or neurosurgery.[11] However, in another systematic review of intracranial complications of pediatric sinusitis that included 16 studies involving 180 patients,[12] the most common intracranial complication was subdural empyema, accounting for 49% of intracranial complications. The pathogenesis of cranial subdural empyema involves spread of the infection to the subdural space via valveless emissary veins in association with thrombophlebitis or via extension of osteomyelitis of the skull with accompanying epidural abscess. Once the infection reaches the subdural space, it can spread without interruption over the convexities of the brain. The mastoid and middle ear are the source in 10% to 20% of patients, especially in geographic areas where cases of otitis media are not treated promptly with antimicrobial therapy. Other predisposing conditions in patients with subdural empyema include skull trauma, neurosurgical procedures, and infection of a preexisting subdural hematoma[4,5,13–16] which may occur as a result of hematogenous dissemination from a distant infection.[17] The infection is metastatic in about 5% of cases, principally from a pulmonary source. Rare predisposing factors include cranial traction devices, nasal surgery, ethmoidectomy, and nasal polypectomy,[4] and the presence of multimodal intracranial monitoring devices.[18] In one series of patients with infratentorial empyema,[19] cases tended to cluster in the spring and summer months, with disease seen more commonly in males than females (65% vs. 35%). In infants with subdural empyema, meningitis is an important predisposing condition.[20] Subdural empyema occurs in about 2% to 10% of infants with bacterial meningitis,[5] presumably secondary to infection of an initially sterile subdural effusion. However, *Haemophilus influenzae* type b immunization has decreased the incidence of bacterial meningitis in

infants and children (see Chapter 87), and cranial subdural empyema is now more commonly seen in teens and young adults.[21]

A number of bacterial species have been isolated in patients with cranial subdural empyema,[3–6,22] including aerobic streptococci (25%–45% of cases), staphylococci (10%–15% of cases), aerobic gram-negative bacilli (3%–10% of cases), and anaerobic streptococci and other anaerobes (33% to as much as 100% in some small series in which careful culturing was performed). Polymicrobial infections are common. These organisms make up the microbial flora that is frequently isolated from patients with chronic sinusitis or cranial abscess. Postoperative and posttraumatic infections are more commonly caused by staphylococci and aerobic gram-negative bacilli. Unusual pathogens include *Salmonella* species[23,24] and *Cutibacterium (Propionibacterium) acnes*.[25–27] The latter microorganism has been isolated after trauma, neurosurgical procedures, or use of prosthetic material such as dural allografts, a material no longer used. In two series, 17%[5] and 21%[4] of samples taken from patients with cranial subdural empyema were sterile, although operative cultures have been reported to be sterile in 7% to 53% of cases.[7] In patients with bacterial meningitis who develop focal neurologic deficits, the diagnosis of cranial subdural empyema should be considered, particularly in those with group A streptococcal meningitis or with preceding otitis or sinusitis.[28] Subdural empyema is a rare complication of meningococcal meningitis, primarily affecting infants or very young children.[29] Cranial subdural empyema caused by *Mycobacterium tuberculosis*[30,31] and *Candida* species[32] has also been reported.

Spinal subdural empyema is a rare condition that usually occurs secondary to metastatic infection from a distant site,[33,34] although cases have been reported after epidural steroid injection.[35] The most frequent microbial isolate is *Staphylococcus aureus,* with streptococci, coagulase-negative staphylococci, and gram-negative bacilli found less frequently.[36]

Clinical Features

The clinical presentation of cranial subdural empyema can be rapidly progressive, with symptoms and signs secondary to the presence of increased intracranial pressure, meningeal irritation, or focal cortical inflammation.[1–5,7,36] This acute presentation of subdural empyema is seen most often in patients with contiguous spread of infection; the diagnosis should be considered in patients with acute bacterial sinusitis in combination with severe intractable headache, varying degrees of altered level of consciousness, focal neurologic deficits, signs of meningeal irritation, or a combination of these.[37,38] Fever higher than 39°C is present in most cases. Headache, which may be localized to the infected sinus or ear, is a prominent complaint and becomes generalized as the infection progresses. Vomiting is common as intracranial pressure increases. Altered mental status (i.e., drowsiness and disorientation), which progresses to obtundation or coma if the infection is not treated, is seen in more than two-thirds of patients. However, the triad of fever, headache, and altered mental status may be less commonly seen in children than in adults.[10] Focal neurologic signs appear in 24 to 48 hours and progress rapidly, with eventual involvement of the entire cerebral hemisphere. The most common focal signs are hemiparesis and hemiplegia; ocular palsies, dysphasia, homonymous hemianopsia, dilated pupils, and cerebellar signs have all been reported. However, in one study, no focal signs were observed in 41% of 699 patients with cranial subdural empyema.[5] One-third of patients in this series also presented with subgaleal abscesses, suggesting that the infection had spread from the calvaria across the dura. Seizures (either focal or generalized) are seen in 25% to 80% of cases.[7] Signs of meningeal irritation are present in approximately 80% of patients, although fewer have the Kernig or Brudzinski sign. In untreated patients, there is rapid neurologic deterioration with signs of increased intracranial pressure and cerebral herniation, although papilledema develops in less than 50% of cases. This fulminant presentation, however, may not be seen in patients who have subdural empyema after cranial surgery or trauma, those who have received prior antimicrobial therapy, those with infected subdural hematomas, or those with infections metastatic to the subdural space. In one review of 55 patients with traumatic cranial subdural empyema,[16] headache (84% of cases), fever (69% of cases), and neck stiffness (65% of cases) were the most common clinical features, and the mean time from initial trauma to presentation was 19 days (range, 4–60 days). In patients with infratentorial empyema, clinical features are usually nonspecific, with the triad of fever, headache, and vomiting being the most common symptoms[19]; cerebellar signs, which could localize the lesion to the posterior fossa, were elicited in only 40% of cases. In subdural empyema of infancy (which occurs in patients with bacterial meningitis), persistent fever, declining neurologic status, seizures, or some combination of these is most frequently observed.[21]

The clinical presentation of spinal subdural empyema is usually one of radicular pain and symptoms of spinal cord compression, which may occur at multiple levels.[34,36,39] The clinical presentation is difficult to distinguish from that of spinal epidural abscess, although tenderness on palpation is said to be a feature of epidural abscess and not subdural empyema (see later discussion).

Diagnosis

The diagnosis of cranial subdural empyema should be considered for any patient who presents with meningeal signs and a focal neurologic deficit.[1–4,5] A lumbar puncture with cerebrospinal fluid (CSF) analysis is contraindicated because of the risk of cerebral herniation. In one large series,[5] 280 patients with cranial subdural empyema underwent lumbar puncture; 33 patients were thought to have experienced neurologic deterioration as a direct result of this procedure, with 3 unnecessary deaths. In patients in whom a lumbar puncture has been done, CSF findings have been nonspecific and have included an elevated opening pressure; neutrophilic pleocytosis (although in up to 40% of patients there may be a mononuclear pleocytosis); and an increased CSF protein concentration.[36] CSF Gram stain and cultures are negative unless the course is complicated by the presence of bacterial meningitis. Cranial radiographs may show evidence of concurrent sinusitis or osteomyelitis, but they are not useful in establishing the diagnosis of subdural empyema.

Diagnostic procedures for cranial subdural empyema include either computed tomography (CT) with contrast or magnetic resonance imaging (MRI).[1,7,34,36] The typical CT appearance is that of a crescentic or elliptic area of hypodensity below the cranial vault or adjacent to the falx cerebri; loculations may also be seen. Depending on the extent of disease, there may be an associated mass effect with displacement of midline structures. After the administration of intravenous contrast, a fine, intense line of enhancement can be visualized between the subdural collection and the cerebral cortex. MRI provides better clarity of morphologic detail and may reveal the presence of a subdural empyema not seen on CT; it is particularly helpful in detecting subdural empyemas located at the base of the brain, along the falx cerebri, or in the posterior fossa. MRI can also be used to differentiate extraaxial empyemas from most sterile effusions and subdural hematomas. Diffusion-weighted images and apparent diffusion coefficient images add to the diagnostic value of MRI; in patients with subdural empyema, there is consistently restricted diffusion (high signal) with corresponding low signal on apparent diffusion coefficient images.[40] Based on these differences, MRI is now considered the diagnostic procedure of choice for cranial subdural empyema (Fig. 91.1). Both CT and MRI are also useful for demonstrating sinusitis and otitis. MRI is the diagnostic procedure of choice for spinal subdural empyema[36,41] because it is better than CT in defining the extent of the lesion.

Management and Outcome

Subdural empyema is a medical emergency, and its treatment optimally requires a combined medical and surgical approach. Surgery (i.e., drainage) is necessary because antimicrobial agents alone do not reliably sterilize the empyema. Cultures (aerobic and anaerobic) of purulent material are necessary to guide the use of specific antimicrobial agents, and surgical decompression is useful for controlling increased intracranial pressure. Once purulent material has been aspirated via craniotomy or, less optimally, by burr hole placement, antimicrobial therapy should be initiated based on Gram stain results and on the likely predisposing factor that led to the development of the subdural empyema. If *S. aureus* is a suspected pathogen, vancomycin should be used empirically but changed to nafcillin if the organism is found to be methicillin susceptible and the patient is not allergic to penicillin. Linezolid has been successfully

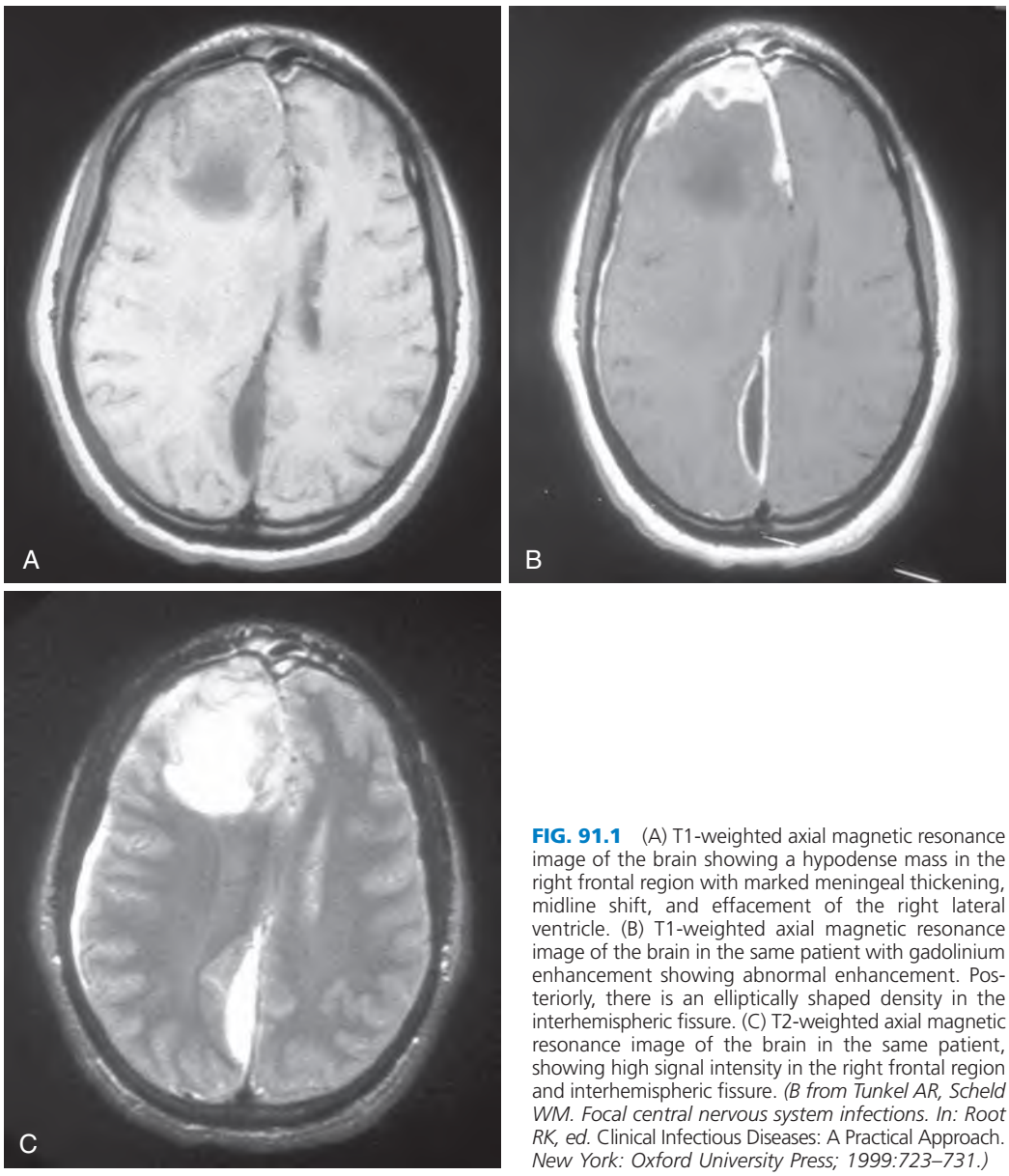

FIG. 91.1 (A) T1-weighted axial magnetic resonance image of the brain showing a hypodense mass in the right frontal region with marked meningeal thickening, midline shift, and effacement of the right lateral ventricle. (B) T1-weighted axial magnetic resonance image of the brain in the same patient with gadolinium enhancement showing abnormal enhancement. Posteriorly, there is an elliptically shaped density in the interhemispheric fissure. (C) T2-weighted axial magnetic resonance image of the brain in the same patient, showing high signal intensity in the right frontal region and interhemispheric fissure. *(B from Tunkel AR, Scheld WM. Focal central nervous system infections. In: Root RK, ed.* Clinical Infectious Diseases: A Practical Approach. *New York: Oxford University Press; 1999:723–731.)*

used in isolated cases of subdural empyema caused by streptococci[42] and can be considered for patients with subdural empyema caused by gram-positive bacteria in whom conventional therapy fails. Metronidazole is recommended if anaerobes are suspected. For infection likely caused by aerobic gram-negative bacilli, empirical therapy with cefepime, ceftazidime, or meropenem is appropriate, pending microorganism identification and in vitro susceptibility testing. Metronidazole is not necessary for antianaerobic activity if meropenem is used. Dosage information for these agents can be found in Chapter 90. Depending on the clinical response, parenteral antimicrobial therapy should be continued for 3 to 4 weeks after drainage, although there are no firm data to support a specific duration of antimicrobial therapy in patients with subdural empyema; longer periods of intravenous and perhaps oral therapy may be required if the patient has accompanying osteomyelitis. There have been anecdotal cases in which cranial subdural empyema was treated with antimicrobial therapy alone. This approach may be appropriate in patients with minimal or no impairment of consciousness, no major neurologic deficit, limited extension of the empyema without midline shift, and early improvement with antimicrobial therapy alone.[4,21] However, these selected patients need careful clinical and radiographic monitoring and probably longer courses of antimicrobial therapy.

The goals of surgical therapy in cranial subdural empyema are to achieve adequate decompression of the brain and to completely evacuate the empyema. The optimal surgical approach in patients with cranial subdural empyema (drainage via craniotomy or burr holes) is controversial.[1,21,36,43] Some studies have demonstrated a lower mortality rate in patients who have undergone craniotomy, although it may be that a larger number of patients treated with burr hole drainage were more ill and had a greater surgical risk. Use of burr holes with irrigation may be more efficacious for drainage in the early stages of subdural empyema when the pus is liquid,[44,45] allowing easier aspiration. If drainage is accomplished via burr holes, multiple burr holes may be necessary to allow extensive irrigation. When the pus becomes thickened and loculated as the disease progresses, these patients should undergo craniotomy. However, craniotomy may be essential for posterior fossa subdural empyema or if drainage is inadequate after burr holes.

If craniotomy is performed, wide exposure is necessary to allow adequate exploration of all areas where the empyema is suspected (Fig. 91.2). The neurosurgeon may also elect to leave drains or catheters in the subdural space, although this may increase the subsequent risk of nosocomial infections. In one report,[46] the efficacy of craniotomy versus CT-guided burr hole or craniectomy drainage was analyzed during the periods 1983 to 1987 (189 patients) and 1988 to 1997 (509 patients).

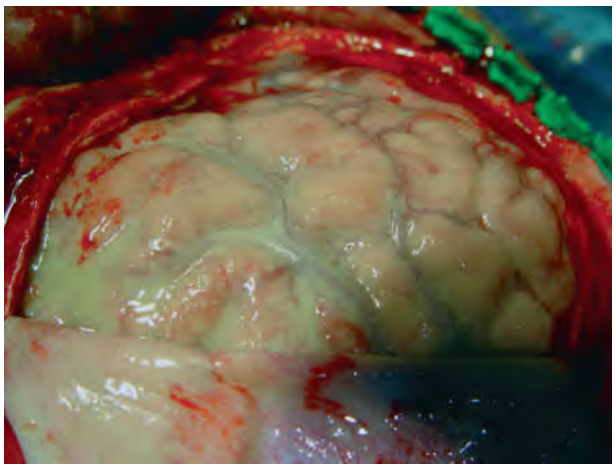

FIG. 91.2 Operative photograph of a patient with cranial subdural empyema revealing extensive purulent material over the cerebrum. *(Courtesy Alan R. Turtz, MD, Cooper University Hospital, Camden, NJ.)*

At operation, the empyema collections were sometimes found to be more loculated, tenacious, and extensive than indicated by neuroimaging studies. Based on this experience, craniotomy became the preferred method of drainage for these authors beginning in 1988. A significant improvement in outcome was demonstrated between the 1983 to 1987 study period (good outcome in 71.4% of patients) and the 1988 to 1997 period (good outcome in 86.1%; $P = .001$). Analysis of the entire database (1983 through 1997) revealed that the mortality rates were higher for patients treated only with drainage via burr holes (23.3%) compared with those who underwent craniectomies (11.5%) or craniotomies (8.4%). Patients with multiple burr holes or craniectomy drainage not only required more frequent operations to drain recurrent or remaining pus but also exhibited higher mortality rates and poorer outcomes. The authors recommended limited procedures (i.e., burr hole drainage or craniectomy) only for patients with septic shock, patients with localized parafalcine collections, and children with subdural empyemas secondary to meningitis (because there is usually no brain swelling and the pus is thin). These data were confirmed in another study of 90 patients with intracranial subdural empyema in which patients with a cranial bone opening procedure had a better result in terms of clinical improvement and clearance of the empyema on CT images[47]; reoperation was more frequent among patients who had undergone burr hole surgery. Regardless of the initial surgical approach, several studies have shown that a number of patients require reoperation; in one study, reoperation was required in half of those patients treated with burr hole drainage and one-fifth of those initially treated with craniotomy.[48] Surgical correction of the antecedent otorhinologic infection may also be required.

In the modern era, survival rates among patients with cranial subdural empyema are greater than 90% for those who are awake and alert at presentation but less than 50% for those who are unresponsive to pain at presentation.[36] Furthermore, 10% to 44% of patients may experience permanent neurologic deficits.[4,21] Cranial subdural empyemas may also be complicated by septic venous thrombosis, localized cerebritis, and cerebral abscesses. In a review that included 65 patients with supratentorial empyema and 27 patients with infratentorial empyema,[49] mortality rates were 10.8% and 3.7%, respectively; the lower mortality in those with infratentorial empyema supports the importance of early surgery, effective management of hydrocephalus, and adequate antimicrobial therapy.[19]

In patients with spinal subdural empyema, empirical antimicrobial therapy should be directed against staphylococci, streptococci, and aerobic gram-negative bacilli,[36] with adjustments based on culture results. Laminectomy is also necessary for drainage of the infection.

EPIDURAL ABSCESS

Epidemiology and Etiology

Epidural abscess is a localized collection of pus between the dura mater and the overlying skull or vertebral column. Because cranial epidural abscess can cross the cranial dura along emissary veins, an accompanying subdural empyema is often present.[1] Therefore the bacterial etiology and pathogenesis of cranial epidural abscess are usually identical to those described earlier for cranial subdural empyema, with the initial focus usually in the paranasal sinuses, middle ear, or mastoid cells; 60% to 90% of cases are associated with sinusitis and otitis, and complications are more common in children, adolescents, and young adults.[50] Cranial epidural abscess may also occur after trauma, fetal scalp monitoring, halo pin penetration, and recent intracranial, transnasal, or transmastoid surgical procedures.[15,20,50,51]

About 0.2 to 2 per 10,000 hospitalized patients have been previously reported to have spinal epidural abscess, with apparent increases in incidence likely from rises in the number of injection drug users and use of therapeutic spinal interventions.[50] In a recent study of 162 cases of spinal epidural abscess in adults, the incidence increased from 2.5 to 8.0 cases per 10,000 admissions from 2005 to 2015.[52] Compared with 88 control subjects, patients were significantly more likely to have experienced at least one previous health care visit or to have received antimicrobials within 30 days of admission; to have comorbidities of injection drug use, alcohol abuse, and obesity; and to harbor coinfection at a noncontiguous site. However, in another retrospective review of 101 cases from 2004 to 2014, the incidence was 5.1 cases per 10,000 admissions, with no significant change during the study period[53]; an identifiable underlying risk factor was identified in 84% of patients, most likely diabetes mellitus and injection drug use. Spinal epidural abscess usually occurs secondary to hematogenous dissemination from foci elsewhere in the body to the epidural space or by extension from local infection.[54–67] Most patients have one or more predisposing conditions, a spinal abnormality or intervention, or a local or systemic source of infection.[65] Bacteremia may be an important predisposing factor because the incidence of spinal epidural abscess is increased in patients who use injection drugs[68,69] and in those who have intravenous catheters or infective endocarditis. Diabetes mellitus also appears to be an important risk factor; it has been identified in up to 50% of patients.[57,59,62,70] Other predisposing factors include immunosuppressive therapy, human immunodeficiency virus infection, malignancy, renal insufficiency, and alcoholism. Hematogenous spread occurs in 25% to 50% of cases, secondary to infections of the skin (e.g., furuncles, cellulitis, infected acne), urinary tract infections, periodontal abscesses, pharyngitis, pneumonia, or mastoiditis. Mild blunt spinal trauma (a history elicited from 15%–35% of patients) may provide a devitalized site that is susceptible to transient bacteremia, although it is unclear whether this represents a true risk factor for the subsequent development of spinal epidural abscess. A primary source of infection is not identified in 20% to 40% of patients.[54–57,66] Infection of the epidural space has also been reported after penetrating injuries, extension of decubitus ulcers or paraspinal abscesses, back surgery, lumbar puncture, CT-guided needle biopsies, and administration of epidural anesthesia or analgesia.[70–75]

Many cranial epidural abscesses are polymicrobial in origin and include anaerobic gram-positive cocci, staphylococci, streptococci, and anaerobic gram-negative bacilli.[50] Anaerobic organisms are identified in cultures from many sinusitis-associated intracranial epidural abscesses.

The infecting microorganism in most (50%–90%) of the patients with spinal epidural abscess is *S. aureus*[54–67,70,76–78]; the proportion of cases caused by a methicillin-resistant strain has increased in recent years,[65] representing 41% of cases in one series[78] and 31% and 27% of *S. aureus* isolates in other studies.[52,53] Other isolates include aerobic and anaerobic streptococci (8%–17% of cases) and aerobic gram-negative bacilli (10%–17% of cases), especially *Escherichia coli* and *Pseudomonas aeruginosa*; *Pseudomonas* spp. are more commonly isolated from injection drug users.[50] In recent case series, investigators have noted an increased incidence of aerobic gram-negative bacilli, streptococci, and anaerobes. In one series from Taiwan, 28.5% of 42 cases of adult spinal epidural abscess were caused by gram-negative bacilli.[79] More than one microorganism is isolated in about 5% to 10% of cases.[54,57,58,69] Isolation of coagulase-negative staphylococci is associated with spinal procedures such as placement of catheters for analgesia, glucocorticoid injections, and surgery.[65] In addition to numerous case reports of patients with spinal epidural abscess caused by other bacteria, epidural infection can also be caused by *Nocardia* and *Actinomyces* spp.[80–82] and *M. tuberculosis*[83];

M. tuberculosis is a more common cause of spinal epidural abscess in regions with rising numbers of immunocompromised patients.[50] Fungi have also been isolated in patients with spinal epidural abscess.[58,84–86] Cases of *Exserohilum rostratum* epidural abscess were reported in association with contaminated epidural or paraspinal glucocorticoid injections of preservative-free methylprednisolone from a single compounding pharmacy (see Chapter 268).[87] Meningitis occurred in some cases either through the contaminated injection into the meninges or transdural spread from an epidural infection.

Clinical Features

The clinical presentation in patients with cranial epidural abscess may be insidious and overshadowed by the primary focus of infection (i.e., sinusitis or otitis media).[1,21,58] Fever and headache are the usual complaints, but the patient may otherwise feel well (leading to a delay in diagnosis) unless the clinical course is complicated (e.g., by development of subdural empyema, brain abscess, or meningitis). This insidious presentation occurs because the dura is closely opposed to the inner surface of the cranium, so the abscess usually enlarges too slowly to produce a sudden onset of major neurologic deficits (in contrast to the presentation in patients with cranial subdural empyema) unless there is deeper intracranial extension. Eventually, focal neurologic signs and seizures (either focal or generalized) may develop. About 45% of patients also have periorbital cellulitis or frontal edema.[50] In the untreated patient, papilledema and other signs of increased intracranial pressure develop as the abscess enlarges. Otitis media and mastoiditis can spread along the temporal bone to the petrous pyramid (petrositis) and cause a cranial epidural abscess, resulting in Gradenigo syndrome, which is characterized by involvement of cranial nerves V and VI, with unilateral facial pain and weakness of the lateral rectus muscle.[88]

The clinical findings in patients with spinal epidural abscess may develop within hours to days (usually after hematogenous seeding), or the course may be more chronic, over weeks to months (usually in association with vertebral osteomyelitis or another contiguous focus of infection).[54–66,89] The presentation in most patients with spinal epidural abscess progresses through the following four clinical stages: (1) backache and focal vertebral pain, with tenderness on percussion; (2) nerve root pain, manifesting with radiculopathy, paresthesias, or both; (3) spinal cord dysfunction, characterized by defects of motor, sensory, or sphincter function; and (4) paraplegia. It is important to note that the exact mechanism by which the epidural abscess causes neurologic injury is not totally clear. The widespread belief is that it is a combination of direct mechanical compression by an expanding abscess, with or without associated vascular damage that may be a consequence of compression of the intrinsic circulation of the spinal cord or local arteritis from the infection.[39,65,90,91] Pain is the most consistent symptom (70%–90% of cases) and is usually accompanied by local tenderness at the affected level. Fever is reported in 60% to 70% of patients, although it was noted in only 32% of patients in one study.[59] The specific neurologic signs depend on the level of spinal cord involvement. Because the neurologic manifestations are usually reversible before complete paralysis occurs, emergency imaging studies and intervention are necessary if the diagnosis is being considered (see later discussion). The classic triad of back pain, fever, and neurologic deficits is seen in the minority (8%–37%) of patients.[39,52,53,65,91] Patients with tuberculous spinal epidural abscess have a more insidious course than those with nontuberculous spinal epidural abscess owing to the slow proliferation of *M. tuberculosis* compared with the rapid proliferation of pathogens in nontuberculous disease.[50]

Diagnosis

MRI (with gadolinium enhancement) is the diagnostic procedure of choice for cranial epidural abscess. It demonstrates a superficial, circumscribed area of diminished intensity with pachymeningeal enhancement. The possibility of adjacent subdural empyema or other intracranial infection can also be assessed.[1,58] CT scanning may be used to image bone or if MRI is not available. MRI is superior to CT in the identification and delineation of the collections; gadolinium enhancement helps in diagnosis by showing a thickened dural surface, which helps to differentiate epidural abscesses from sterile effusions and hematomas, which may occur in patients after trauma or cranial surgery. Cranial epidural abscess can cross the midline of the brain, which helps to differentiate it from subdural empyema, and most do not involve the subjacent brain parenchyma.[50]

MRI is also the diagnostic procedure of choice in cases of suspected spinal epidural abscess (Figs. 91.3 and 91.4).[58–60,62,65,66,76] MRI is recommended over CT because it can better depict the spinal cord and epidural space in both sagittal and transverse sections and can also be used to identify accompanying osteomyelitis, intramedullary spinal cord lesions, and diskitis. The epidural mass may be isointense or hypointense on T1-weighted images and hyperintense on T2-weighted images. Gadolinium enhancement typically demonstrates linear enhancement surrounding nonenhancing purulent or necrotic matter. The enhancement may be either homogeneous or heterogeneous in the stage of epidural

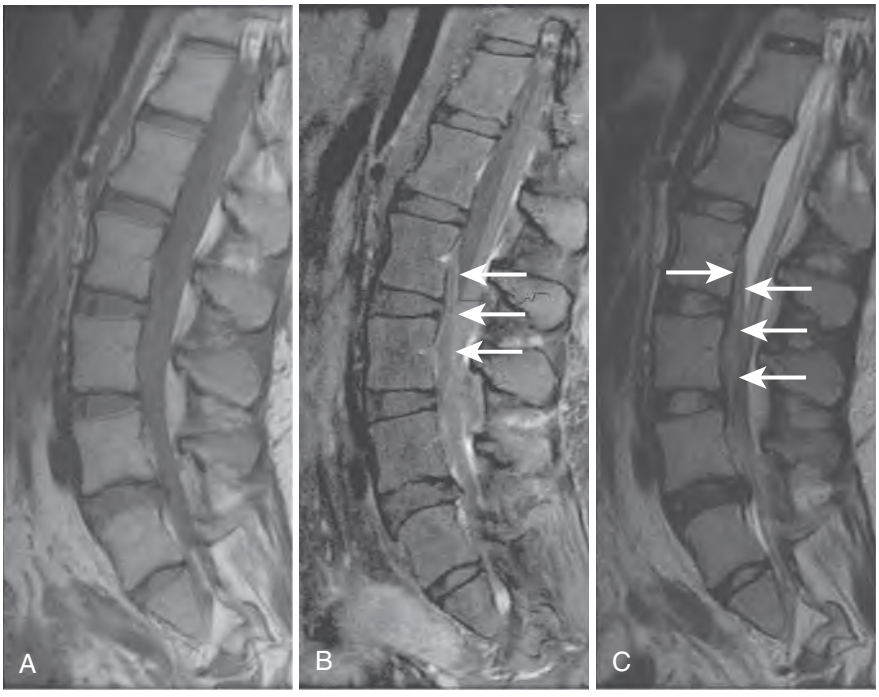

FIG. 91.3 Precontrast (A) and postcontrast (B) T1-weighted sagittal images demonstrating rim-enhancing soft tissue in the ventral and dural epidural space *(arrows),* consistent with epidural abscess. (C) T2-weighted sagittal image demonstrating compression of the thecal sac *(arrows). (Courtesy Stanley Lu, MD, Monmouth Medical Center, Long Branch, NJ.)*

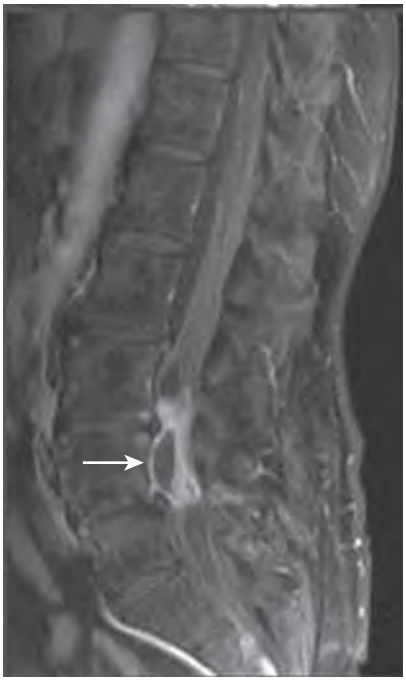

FIG. 91.4 Magnetic resonance image of spine with arrow pointing to fungal epidural abscess after injection of contaminated corticosteroid.

plexus engorgement or phlegmon or peripherally with central fluid signal in the mature stage of a centrally pus-filled abscess.[92] MRI can also enable ready assessment of the response to therapy (see later discussion). CT myelography may be performed if MRI is unavailable or contraindicated.

Management and Outcome

The management of cranial epidural abscess requires a combined medical and surgical approach. Empirical antimicrobial therapy, after cultures have been obtained, for cranial epidural abscess is similar to that for cranial subdural empyema (see earlier discussion); therapy is usually continued for 3 to 6 weeks after surgical drainage or longer (6–8 weeks) if osteomyelitis is present.[21] Surgical drainage is also required; craniotomy or craniectomy is generally preferred over burr hole placement or aspiration of purulent material through the scalp.[1,15,21]

The principles of therapy for spinal epidural abscess are prompt surgical decompression, drainage of the abscess, and long-term antimicrobial therapy.[50,54–66] Empirical antimicrobial therapy for spinal epidural abscess, initiated after cultures have been obtained, must include a first-line antistaphylococcal agent (i.e., vancomycin pending organism identification and in vitro susceptibility testing) plus coverage for aerobic gram-negative bacilli (e.g., cefepime, ceftazidime, meropenem), especially for any patient with a history of spinal procedure or injection drug use. Once the infecting pathogen has been identified (through cultures of surgical drainage fluid, CT-guided aspiration specimens, or blood), antimicrobial therapy can be modified based on the results of in vitro susceptibility testing. Duration of antimicrobial therapy is usually 4 to 6 weeks; 6 to 8 weeks are recommended in patients with contiguous osteomyelitis because one study suggested that relapse was less likely in patients who received at least 8 weeks of antimicrobial therapy[93]; in some centers, further oral antimicrobial courses of 1 to 2 months are given.[50] Patients with tuberculous spondylitis and spinal epidural abscess must receive antituberculous therapy; a 12-month course has been recommended for patients with spinal epidural abscess.[50]

Patients with spinal epidural abscess and neurologic dysfunction require surgical drainage with decompression and drainage performed as a surgical emergency to minimize the likelihood of permanent neurologic sequelae.[54–66] Depending on location and extent of the epidural abscess, the surgical approaches include laminectomy, hemilaminectomy, or interlaminar fenestration.[66] Primary microsurgery with decompression at the site of maximal cord compression, with abscess and/or granulation tissue removal, has also been used successfully.[94] CT-guided aspiration can be used for culture if emergent surgery is delayed but is ineffective for drainage because of loculations in the pus. Endoscopic drainage has been used in a few cases. There have been no randomized, prospective trials that have compared the efficacy of antimicrobial therapy plus surgery with that of antimicrobial therapy alone in patients with spinal epidural abscess. However, in one literature review of 38 patients with spinal epidural abscess treated with antimicrobial therapy alone,[95] 23 patients recovered, 2 died, 1 worsened, and 12 remained the same or improved. In contrast, a retrospective analysis of 57 cases of spinal epidural abscess revealed that patients could be treated safely and effectively with prolonged intravenous antimicrobial therapy alone or in combination with percutaneous needle aspiration for culture irrespective of the neurologic abnormality at the time of presentation,[96] although the numbers of patients in each of the outcome subgroups were small. In another retrospective study of 52 patients with no evidence of systemic sepsis and with neurologic examination findings that were normal or stable (defined as radiculopathy or signs of partial cord compression present for more than 72 hours before admission and without deterioration),[97] 24 of 29 patients treated with medical therapy alone had a good or excellent neurologic outcome. Based on these studies, it would appear that antimicrobial therapy alone can be considered in patients who have localized pain or radicular symptoms without long-tract findings. However, these patients require frequent neurologic examinations and serial MRI studies to demonstrate resolution of the abscess. In addition, delayed surgery runs a high risk of rapid progression to permanent paraplegia,[91,98,99] and neurologic deterioration has been demonstrated in a substantial number of patients even while they were receiving appropriate antimicrobial therapy.[50,55,57,65,95] A number of studies have demonstrated that in many patients initially treated with only antimicrobial therapy, medical management failed and surgical intervention was required (ranging from 10% to 75%),[100–103] and some studies have raised concerns that patients treated initially with medical therapy and who later underwent surgery were weaker when compared with their findings at initial presentation.[100,101,104]

Emergency surgical decompression remains the procedure of choice and certainly should be performed in any patient with increasing neurologic deficit, persistent severe pain, or increasing fever or peripheral white blood cell count.[105] Surgery is not likely to be a viable therapeutic option in patients who have experienced complete paralysis for longer than 24 to 36 hours,[57,65] although some experts would perform surgical therapy in patients if complete paralysis has lasted less than 72 hours,[61] and surgical therapy may be required to treat the epidural infection and control sepsis. Nonsurgical management may also be appropriate for patients with panspinal infection or in those with a high surgical risk.[65] In one retrospective series of 104 patients with a diagnosis of spinal epidural abscess over a 10-year period, there were no statistically significant differences between the groups managed with or without surgery, although 30.6% of patients with a dorsal spinal epidural abscess were paraplegic or quadriplegic compared with only 7.3% of those with a ventral spinal epidural abscess ($P = .003$),[106] suggesting that the anatomy of the spinal epidural abscess might play a role in determining the treatment plan.[99]

In patients with cranial epidural abscess, factors associated with good outcomes are young age, absence of encephalopathy or severe neurologic deficit at presentation, and lack of comorbid conditions.[50] Poor prognosis is linked to herniation, delayed neuroimaging, and low clinical suspicion with early development of encephalopathy.

Mortality rates for spinal epidural abscess ranged from 5% to 32% in recent series.[a] Irreversible paralysis continues to affect 4% to 22% of patients.[53,65] The final neurologic outcome in patients with spinal epidural abscess is related to the severity of neurologic impairment before initiation of appropriate therapy.[57–60,65,66,70,107] Complete recovery with return of full neurologic function is most likely if neurologic signs are present for less than 24 hours before initiation of therapy; complete recovery is less likely if symptoms persist longer than 36 to 48 hours. A worse

[a]References 52, 53, 56, 57, 59, 60, 62, 69, 94.

outcome has been observed in patients with multiple medical problems, increasing age (older than 50 years), previous spinal surgery, cervical or thoracic abscess location, sepsis at presentation, leukocytosis (>14,000/mm^3 at admission), thrombocytopenia (<100,000/mm^3), elevated serum C-reactive protein (CRP) concentrations during the second postoperative week, isolation of methicillin-resistant staphylococci, and degree of thecal sac compression (>50% spinal canal involvement).[50,59,70,78] In one review of spinal epidural abscess in patients on hemodialysis, there was a higher mortality rate and patients were less likely to improve neurologically when compared with nonhemodialysis patients.[108] In a study of spinal epidural abscess patients undergoing surgical drainage along with antimicrobial therapy, leukocytosis, elevated CRP, poor glycemic control, and motor deficits at the time of operation were all found to have a strong influence on motor function improvement after surgical treatment.[109] The final neurologic outcome and functional capacity should be assessed at least 1 year after treatment because, until then, patients may continue to regain some neurologic function.[65]

SUPPURATIVE INTRACRANIAL THROMBOPHLEBITIS

Epidemiology and Etiology

Suppurative intracranial thrombophlebitis includes both venous thrombosis and suppuration. It may begin within veins or venous sinuses, or it may occur after infection of the paranasal sinuses, middle ear, mastoid, face, or oropharynx.[110–112] Additional vessels may be involved by propagation or discontinuous spread. Suppurative thrombophlebitis also occurs in association with epidural abscess, subdural empyema, or bacterial meningitis. Occasionally, there is metastatic spread from a distant site of infection.

The development of septic intracranial venous sinus thrombosis depends on the close proximity of various structures to the dural venous sinuses. The usual predisposing condition for septic cavernous sinus thrombosis is paranasal sinusitis (especially of the ethmoid or sphenoid sinuses).[110,111,113,114] Infections of the face and mouth are less commonly the primary sources of infection in the antimicrobial era. Otitis media and mastoiditis are infections that are associated with lateral (transverse) sinus thrombosis[110,115–119] and infection of the superior and inferior petrosal sinuses; the lateral sinus is a more common site of thrombosis in children.[120] Infections of the face, scalp, subdural space, epidural space, and meninges are associated with septic thrombophlebitis of the superior sagittal sinus. In all these infections, the likely microorganisms depend on the associated primary condition. The most important infecting microorganism in septic cavernous sinus thrombosis is *S. aureus,* which is isolated in 60% to 70% of patients.[110,113,114] Streptococci, especially the *Streptococcus anginosus* group *(Streptococcus milleri)*, are also important agents.[121,122] However, the likely infecting bacterial pathogens depend on the pathogenesis of infection: staphylococci, streptococci, gram-negative bacilli, and anaerobes if the antecedent condition is sinusitis, and predominantly *S. aureus* in the case of facial infections. *S. aureus,* streptococci, and *E. coli* are commonly reported as pathogens in patients with lateral sinus thrombosis,[110,116] although in one study, *Fusobacterium necrophorum* was the microorganism isolated in four of six children with lateral sinus thrombosis.[117] In another study of patients with lateral sinus thrombosis secondary to chronic ear infection,[116] all patients had mixed infections, and *Bacteroides fragilis* was isolated in five of six patients. Lateral sinus thrombosis complicating mastoiditis continues to be a problem in the postantibiotic era.[118] Venous sinus thrombosis may also be seen in patients with rhinocerebral mucormycosis[123] or invasive aspergillosis.[124]

Clinical Features

The clinical findings in patients with suppurative intracranial thrombophlebitis depend on the sinus involved and the presence of concomitant central nervous system infection (e.g., meningitis, brain abscess, subdural empyema).[110,111] The two cavernous sinuses are positioned on either side of the sella turcica; they are connected by anterior and posterior intercavernous sinuses that encircle the pituitary gland.[113,114] The horizontal segment of the internal carotid artery and cranial nerve VI run through the lumen, and cranial nerves III and IV and the ophthalmic and maxillary branches of cranial nerve V run through the outside layers of the lateral walls of the cavernous sinuses (Fig. 91.5). The clinical manifestations may relate to damage to the nerves that traverse the cavernous sinuses. The most common symptoms in patients with septic cavernous sinus thrombosis are headache, fever, and diplopia[110,122]; headache is more common if the antecedent condition is sinusitis rather than a facial infection. Other symptoms include blurred vision, facial pain, and ptosis.[121,122] Signs include fever (present in >90% of patients), proptosis, chemosis, periorbital edema, and weakness of the extraocular muscles (secondary to involvement of cranial nerves III, IV, and VI).[110,111,113,114] Because cranial nerve VI is the only cranial nerve that traverses the interior of the cavernous sinus, a lateral gaze palsy may be an early neurologic finding. Papilledema or venous engorgement is observed in 65% of patients, and a change in mental status in 55%. Meningismus is present in up to 40% of patients, usually secondary to retrograde spread of the thrombophlebitis. Less than 50% of patients have dilated or sluggishly reactive pupils, decreased visual acuity (which may progress to blindness), and dysfunction of cranial nerve V. As infection spreads to the opposite cavernous sinus through the intercavernous sinuses, findings are duplicated in the opposite eye, usually within 24 to 48 hours after the initial unilateral periorbital edema. Carotid artery inflammation and cortical vein thrombophlebitis are particularly serious complications of septic cavernous sinus thrombosis because they carry the risk of cerebral hemorrhagic infarction.[110,114]

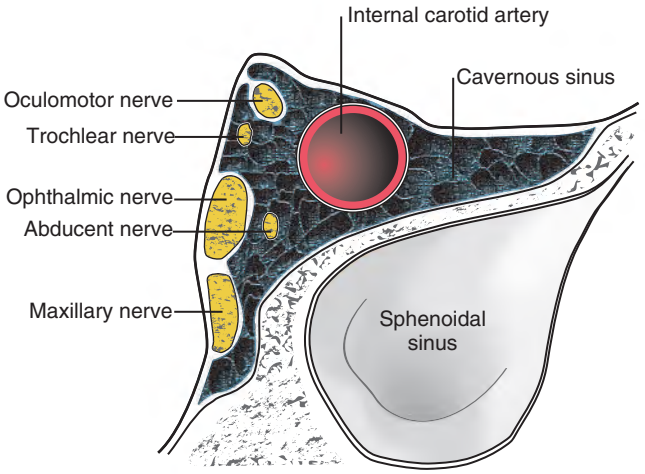

FIG. 91.5 **Oblique section through the cavernous sinus.**

Persons with septic cavernous sinus thrombosis may present with either acute or chronic illness.[110,111] In the acute presentation (usually secondary to facial infection), the time between primary infection and cavernous sinus thrombosis is short (usually <1 week), and the patient presents in a significantly toxic state, with rapid development of the signs and symptoms described earlier; there is also rapid progression to bilateral eye signs. In contrast, in the more indolent form of cavernous sinus thrombosis, which usually occurs secondary to dental infection, otitis media, or paranasal sinusitis, the orbital manifestations are often unimpressive and involvement of the contralateral eye is a late and inconsistent finding.

The presentation in patients with septic lateral sinus thrombosis is typically more gradual, and patients complain predominantly of headache (>80% of cases); photophobia, earache, vomiting, and vertigo may also occur because otitis media is a common predisposing condition.[110,116–118,125,126] Fever and abnormal ear findings are observed in most patients (79% and 98%, respectively), and palsy of cranial nerve VI, facial pain and altered facial sensation, papilledema, mastoid tenderness, and nuchal rigidity may also be present. Posterior auricular swelling and pain (Griesinger sign) are present in almost 50% of cases; a common complication is otitic hydrocephalus. In one study of 13 patients, the majority exhibited cranial neuropathies and raised intracranial pressure.[127]

The triad of suppurative otitis, cranial nerve VI palsy, and cranial nerve V irritation resulting in retro-orbital and temporoparietal pain (Gradenigo syndrome), which suggests the presence of inflammation along the petrous part of the temporal bone, should also raise the suspicion of lateral (transverse and sigmoid) sinus thrombosis.[128] Inflammation can spread from the petrous bone to the cavernous sinus.

Thrombosis of the superior sagittal sinus produces an abnormal mental status, motor deficits, nuchal rigidity, and papilledema.[110] Seizures occur in more than half of these patients. The majority of cases occur in the setting of bacterial meningitis, in which the onset may be fulminant. Patients with sinusitis as a predisposing condition tend to have a subacute onset of symptoms.

Diagnosis

Laboratory studies are usually nonspecific in suppurative intracranial thrombophlebitis.[110,111] Lumbar puncture demonstrates a mild pleocytosis (mononuclear, neutrophilic, or mixed) and an elevated CSF protein concentration (consistent with a parameningeal focus of infection), although there may be findings of frank meningitis in patients with septic thrombosis of the superior sagittal sinus, and the causative microorganism may be isolated on culture of CSF. Blood cultures may be positive, especially in patients with a rapidly progressive course. Chest radiographs may reveal evidence of septic pulmonary emboli after propagation of the thrombus into the inferior petrosal sinus and jugular vein. Sinus radiographs may document involvement of the paranasal sinuses, although conventional radiographs are inferior to CT or MRI in the detection of sphenoid sinusitis.

The noninvasive diagnostic procedures of choice for suppurative intracranial thrombophlebitis are MRI (Figs. 91.6 to 91.8) and magnetic resonance venography.[36,128,129] In septic cavernous sinus thrombosis, the lateral wall of the cavernous sinus bulges laterally, a subdural empyema may be adjacent laterally, the superior ophthalmic vein may be distended and thrombosed, the carotid artery is narrowed in the siphon, and cerebral thrombosis from emboli may be found. The flow void signal, a dark area on gadolinium-enhanced T1 weighting, is absent in a thrombosed vessel (see Fig. 91.6). Magnetic resonance venography is extremely useful in showing detailed venous anatomy and demonstrating an area of decreased or absent signal in the area of the thrombus.[128] In patients unable to undergo MRI, CT venography appears to have a degree of sensitivity and specificity equaling that of magnetic resonance venography.[128,129] High-resolution CT (with and without intravenous contrast) with a slice thickness of 3 mm or less may also show findings of venous sinus thrombosis.[130] In patients with septic cavernous sinus thrombosis, CT usually reveals unilateral or bilateral multiple irregular filling defects in the enhancing cavernous sinus, with or without orbital inflammatory change, or enlargement or expansion of the cavernous sinus with lateral wall flattening or convexity rather than the normal concavity. An additional benefit of both MRI and CT is the ability to fully evaluate the paranasal sinuses and to provide information concerning subdural and epidural infection, cerebral infarction, cerebritis, hemorrhage, and cerebral edema.

Management and Outcome

Selection of appropriate antimicrobial therapy for suppurative intracranial thrombophlebitis depends on the antecedent clinical condition; the likely microorganisms are similar to those observed in cranial subdural empyema and cranial epidural abscess (see earlier discussions). If the antecedent clinical condition is paranasal sinusitis, empirical antimicrobial therapy should be directed toward staphylococci, streptococci, aerobic gram-negative bacilli, and anaerobes. In septic cavernous sinus thrombosis, an antistaphylococcal agent should always be included because of the high likelihood of isolation of *S. aureus*. Vancomycin is recommended empirically, pending results of in vitro susceptibility testing. An appropriate empirical regimen is vancomycin, metronidazole, and a third- or fourth-generation cephalosporin, pending culture results and in vitro susceptibility testing. Intravenous antimicrobial therapy is usually continued for at least 3 to 4 weeks, but the duration needs to be individualized depending on the clinical response. The role of corticosteroids is not well established in the management of septic cerebral venous thrombosis; although they may help in decreasing inflammation and swelling, this use is not well supported by evidence.[129]

Surgery may also be necessary for optimal treatment of septic intracranial thrombophlebitis.[110,111,113,114] Surgical therapy for infected sinuses is necessary if antimicrobial therapy alone is ineffective; this is especially important in patients with cavernous sinus thrombosis secondary to sphenoid sinusitis. In fact, some authors have recommended operative intervention for all patients who develop cavernous sinus thrombosis as a complication of sinusitis. Mastoid surgery is an important adjunct in patients with septic lateral sinus thrombosis,

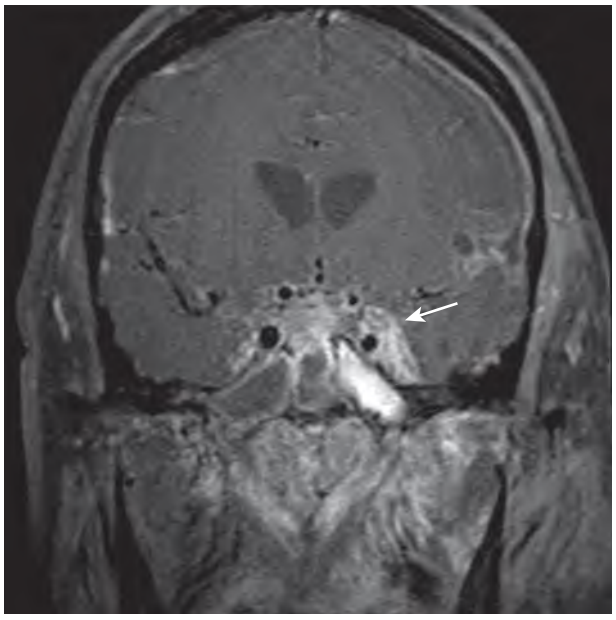

FIG. 91.6 Magnetic resonance image of cavernous sinus thrombosis. Arrow points to contrast-enhanced cavernous sinus with a dark circle of a flowing carotid artery (flow void signal). The dark white area below is the inflamed sphenoid sinusitis, which caused the cavernous sinus thrombosis.

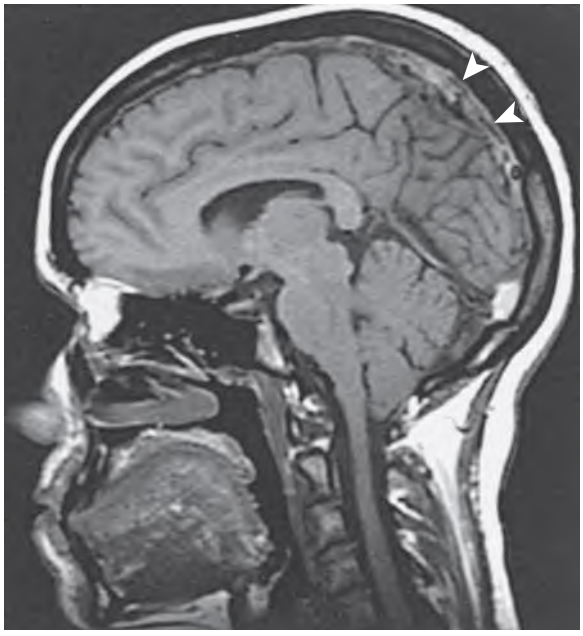

FIG. 91.7 Magnetic resonance image of superior sagittal sinus thrombosis. There is increased signal with the vessel on the T2-weighted image *(arrowheads)*, indicating the presence of thrombus. *(Courtesy Dr. Wayne Davis, University of Utah.)*

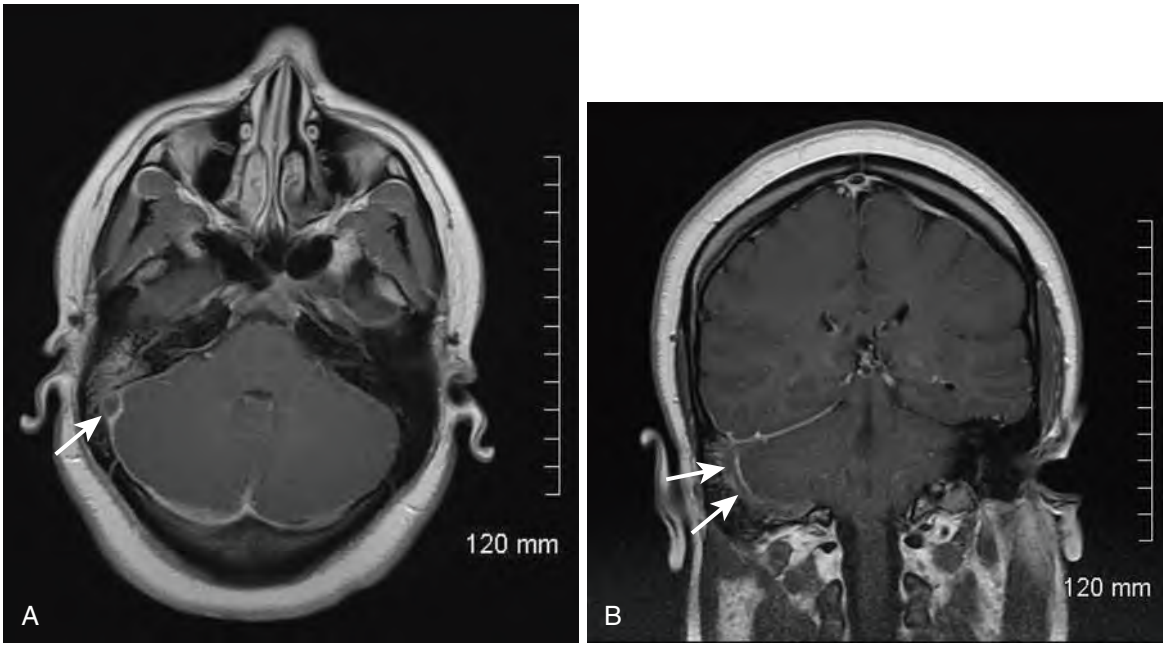

FIG. 91.8 Gadolinium-enhanced T1-weighted images in the axial (A) and coronal (B) planes demonstrating extensive filling defects of the right sigmoid sinus *(arrows)* representing thrombosis and associated with adjacent right mastoiditis. *(Courtesy Stanley Lu, MD, Monmouth Medical Center, Long Branch, NJ.)*

although the extent of mastoid surgery and the management of the thrombosed sinus remain controversial.[118,125,126,131–134] Internal jugular vein ligation has been used for lateral sinus vein thrombosis, more commonly in the preantibiotic era,[116,131,132] but the efficacy of this procedure is poorly defined and it is not part of routine management. Some authors have recommended ligation of the internal jugular vein for patients who develop septic embolization despite antimicrobial therapy and surgical drainage.[117,133,135] Surgical therapy may also be required for other infections (e.g., dental abscesses, complicating brain abscess, subdural empyema).

Although anticoagulation is recommended in patients with aseptic cerebral venous thrombosis,[136–138] the use of anticoagulation in suppurative intracranial thrombophlebitis is controversial. There is support in the literature for the use of anticoagulation (i.e., low-molecular-weight heparin) to prevent the spread of the thrombus from the cavernous sinus to other dural venous sinuses and cerebral veins.[110,111,113,114] Retrospective evidence indicates that anticoagulation, in combination with antimicrobial therapy, reduces mortality and is most beneficial if given early (within 7 days after hospitalization) in the treatment of cavernous sinus thrombosis.[110,139] In a recent review of patients with cavernous sinus thrombosis, anticoagulation was mentioned in the management of 41 of 88 patients[140]; compared with patients who did not undergo anticoagulatation, a considerably greater number of patients made a full recovery (53.6% vs. 32%) and fewer patients died (12% vs. 28%), although there was no difference in morbidity. However, it must be recognized that anticoagulation carries the risk of intracranial hemorrhage from sites of cortical venous infarction or from sites on the intracavernous walls of the carotid artery. Some authors have not recommended anticoagulation in patients with septic lateral sinus or superior sagittal sinus thrombosis because of the high number of venous hemorrhagic infarcts observed postmortem[110]; most of these infections can also be controlled with antimicrobial therapy and surgery, and the use of anticoagulation has not been shown to be beneficial.[131,132] However, in one study of 7 patients with lateral sinus thrombosis, 6 of whom received anticoagulation for an average of 24 months, only 1 had a complication of epistaxis, which resolved with pressure.[126] In another study of patients with lateral sinus thrombosis, anticoagulants were used in 4 patients with thrombus progression into the internal jugular vein and transverse sinuses without evidence of complications.[119] Despite these findings, most authors agree that there is no place for anticoagulation in the management of septic lateral sinus thrombosis.[133] In the absence of prospective data, anticoagulation should be considered in the treatment of septic cavernous sinus thrombosis unless there are contraindications or documented hemorrhagic intracranial complications on neuroimaging studies. Some practitioners use anticoagulation in cavernous sinus thrombosis only as an adjunct to antimicrobial therapy in patients with a deteriorating clinical condition.[114] The duration of anticoagulation has varied from 2 weeks to several months; some have continued anticoagulation until complete thrombus resolution has been documented on neuroimaging studies.

Before the availability of antimicrobial therapy, suppurative intracranial thrombophlebitis carried a mortality rate of 80% to 100%. Since 1940, mortality rates have ranged from 0% to 16% in patients with septic lateral sinus thrombosis[116] and from 13% to 30% in patients with septic cavernous sinus thrombosis,[110,113] although in one series of 14 pediatric patients with septic cavernous sinus thrombosis, 79% died despite parenteral antimicrobial therapy.[141] Mortality in septic sagittal sinus thrombosis is much higher, reported as 78% in one review.[110] Among patients who survive their episode of septic cavernous sinus thrombosis, up to 50% are left with long-term cranial nerve deficits,[110,114] although they may continue to improve for several months after completion of therapy. Partial or complete visual loss is seen in 7% to 22% of patients. Patients should be observed for several months after completion of antimicrobial therapy because isolated relapses have been documented within 6 weeks after apparent clinical resolution, and intracranial abscesses have been demonstrated as long as 8 months later.[114]

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The complete reference list is available online at Expert Consult.

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92 Cerebrospinal Fluid Shunt and Drain Infections

Adarsh Bhimraj and Allan R. Tunkel

SHORT VIEW SUMMARY

Definition

- Ventriculoperitoneal (VP) shunt infections can be either superficial, involving the skin and soft tissue adjacent to the shunt valve, reservoir, or tubing, or it can be a deeper infection, involving the cerebral ventricles proximally or the peritoneum distally.
- Cerebrospinal fluid (CSF) drain infections can be subcutaneous tunnel infections, catheter exit site infections, or ventriculitis.

Epidemiology

- The case incidence of CSF shunt infection (i.e., the occurrence of infection in any given patient) has ranged from 5% to 41%, although usually it is 4% to 17%.
- The operative incidence (i.e., the occurrence of infection per procedure) has ranged from 2.8% to 14%, although usually it is less than 6%.
- In patients with external ventricular drains, the incidence of ventriculitis ranges from 10.6 to 11.4 per 1000 catheter-days.

Microbiology

- Staphylococcal species account for the majority of isolates in patients with CSF shunt infections, with *Staphylococcus epidermidis* most frequently isolated (47%–64% of infections), followed by *Staphylococcus aureus* (12%–29% of infections).
- The most common isolated gram-negative species are *Escherichia coli, Klebsiella, Proteus*, and *Pseudomonas*; cases of *Acinetobacter* meningitis have also been reported in patients with VP shunts.
- In recent years an increasing prevalence of diphtheroids, principally *Cutibacterium acnes* (formerly *Propionibacterium acnes*) has been found in CSF shunt infections.

Diagnosis

- The diagnosis is established by either direct culture of the CSF obtained by shunt aspiration or by culture of the proximal shunt components if the shunt is explanted.
- CSF culture from the shunt, reservoir, or drain is the most important test to establish the diagnosis of infection; CSF aerobic and anaerobic cultures should be obtained and held for 7 to 10 days to detect fastidious organisms.
- In patients with lumbar drains or externalized ventricular drains, definite infection is defined as a positive CSF culture (obtained from the ventricular or lumbar catheter) associated with CSF pleocytosis.

Therapy

- The principles of antimicrobial therapy for CSF shunt infections are generally the same as those for acute bacterial meningitis; the agent selected must penetrate the central nervous system and attain adequate CSF concentrations.
- Empirical therapy with intravenous (IV) vancomycin plus either cefepime, ceftazidime, or meropenem is appropriate.
- Optimal therapy of an infected CSF shunt is an initial IV antimicrobial, followed by removal of all components of the infected shunt, insertion of a fresh ventricular catheter, and a period of external drainage with continued systemic antibiotics until the drain culture is negative. Later the drain is removed and a new shunt is placed.
- Direct instillation of antimicrobial agents into the lateral ventricle or, in the case of lumbar shunts, into the lumbar thecal sac may be necessary in patients with shunt infections that are difficult to eradicate with IV antimicrobial therapy and shunt removal or when the patient is unable to undergo shunt replacement. Antimicrobials in the absence of shunt removal are seldom effective.

Prevention

- There is evidence to support the use of periprocedural prophylactic antimicrobial administration for patients undergoing CSF shunt insertion and placement of external ventricular drains.
- Use of antimicrobial-impregnated CSF shunts and CSF drains appears to be safe and possibly effective in prevention of ventriculitis. Detailed operating room procedures have been advocated to decrease postoperative infections.
- Use of a standardized protocol and reducing variation by adherence to a common protocol are effective at reducing CSF shunt and CSF drain infection rates.

In the United States hydrocephalus accounts for approximately 70,000 annual hospital admissions[1] and is treated by diverting the cerebrospinal fluid (CSF) either to another body cavity (via CSF shunt) or externally (via CSF drain). CSF shunts are considered to be permanent catheters in which the proximal end of the shunt is in the cerebral ventricle, an intracranial cyst, or the lumbar subarachnoid space; the distal end usually terminates in the peritoneal, pleural, or vascular space (Fig. 92.1). Most neurosurgeons prefer the peritoneal cavity as the shunt terminus (i.e., a ventriculoperitoneal [VP] shunt) rather than the vascular space (ventriculoatrial shunt) because VP shunts require fewer revisions, are easier to place and revise, and have fewer serious complications.[2] Part of the system (as a separate integrated component) is a pressure-regulating valve that is usually placed just outside the skull or as an integral part of the distal tubing.[4] Reservoirs for intermittent percutaneous access can also be added to the system or incorporated into the valve assembly. Additional hardware includes antisiphon valves and various connectors, allowing interconnection of more than one catheter or device. Programmable valves that can change the opening pressure by means of an external magnet are often used but may need to be reset after a magnetic resonance imaging (MRI) scan.

CSF drains are temporary catheters that divert the fluid externally.[2,5] The proximal end is either in the cerebral ventricle (ventricular drain) (see Fig. 92.1) or in the lumbar subarachnoid space (lumbar drain). Ventricular drains are also useful for the temporary management of patients with elevated intracranial pressure secondary to acute hydrocephalus caused by intracranial hemorrhage, neoplasms obstructing the CSF circulation, or trauma. Ventricular drains are usually tunneled, in which a subcutaneous tract is created between the bur hole and the catheter exit site. Lumbar drains are used in patients with CSF leaks after neurosurgery. The distal end of the catheter is connected to a collecting system, which has a drip chamber, sampling and injection ports (used to obtain CSF and inject medications), and a collection bag.[2,5] The drip chamber is positioned so that the drop-forming end is a certain distance, such as 10 cm, above the right atrium or, in recumbent

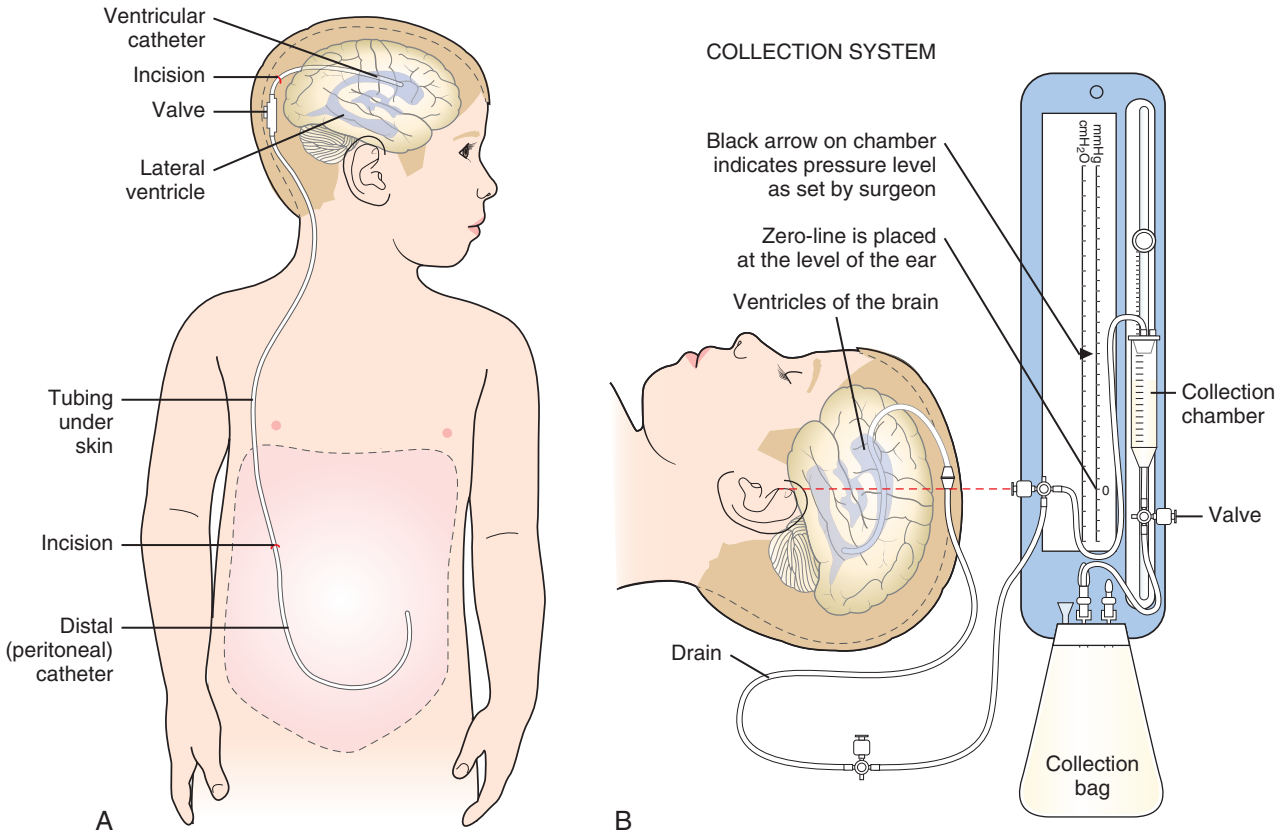

FIG. 92.1 (A) Ventricular shunt for hydrocephalus. (B) Typical arrangement of external ventricular drain.

patients, above the external auditory canal (see Fig. 92.1). Overdraining can result in a subdural effusion, possibly rupturing a small blood vessel crossing the pia arachnoid.

Both CSF shunts and CSF drains are prone to infection. VP shunt infections can be either superficial, involving the skin and soft tissue adjacent to the shunt valve or reservoir, or can be a deeper infection involving the cerebral ventricles proximally or the peritoneum distally. Ulceration of skin over the shunt valve can introduce air or organisms into the lateral ventricle. CSF drain infections can be tunnel infections, catheter exit site infections, or ventriculitis. In the following sections, we review the epidemiology, etiology, clinical features, and management approach to CSF shunt and CSF drain infections.

EPIDEMIOLOGY

The case incidence of CSF shunt infection (i.e., the occurrence of infection in any given patient) has ranged from 5% to 41% in various series,[2] although the incidence is usually in the range of 4% to 17%.[6–13] The operative incidence (i.e., the occurrence of infection per procedure) has ranged from 2.8% to 14%,[2] although most series have generally reported operative infection rates of less than 6%.[14–16] In four prospective, randomized trials in pediatric patients with CSF shunt placement or shunt revision, infection rates ranged from 8% to 11%.[17–20] In another large retrospective review of 1173 children shunted for hydrocephalus from 1985 to 2004, 158 patients presented with a total of 190 episodes of shunt infection, for a case incidence of 13.6% and an operative incidence of 5.9%.[12] In a study by the Canadian Nosocomial Infection Surveillance Program in patients with CSF shunt-associated infections, the infection rate was 4.1% during the first year after placement.[21] In another large study of cases reported to the Pediatric Health Information System longitudinal administrative database from 41 children's hospitals, which included 7071 children with uncomplicated CSF shunt placements between January 1, 2001 and December 31, 2005, the unadjusted 24-month CSF shunt infection rate was 11.7% per patient and 7.2% per procedure.[22]

TABLE 92.1 Factors Associated With an Increased Risk of Cerebrospinal Fluid Shunt Infection

Premature birth
Younger age
Previous shunt infection
Cause of hydrocephalus[b]
Experience of the neurosurgeon
Number of people traversing the operating theater
Exposure to perforated surgical gloves[c]
Intraoperative use of the neuroendoscope
Length of the shunt procedure
Insertion of catheter below T7 in ventriculoatrial shunting[d]
Patient skin preparation
Shaving of skin
Exposure of large areas of patient's skin during the procedure
Shunt revision[e]

[a]Not all studies have found all these factors to be associated with an increased risk of cerebrospinal fluid shunt infection.
[b]Purulent meningitis, hemorrhage, myelomeningocele.
[c]Double gloving when handling implantable devices may reduce the risk of infection.
[d]Presence of foreign-body irritation on the tricuspid valve, with thrombus formation and subsequent infection during bacteremia.
[e]The risk may be especially high in patients undergoing three or more revisions.

A number of factors have been reported to be associated with an increased risk of CSF shunt infection (Table 92.1). Children are more likely than adults to acquire shunt infection. In one study that included 7071 children,[22] factors associated with infection were young age, female sex, African-American race, public insurance, etiology of intraventricular hemorrhage, respiratory complex clinical condition, subsequent revision procedure, hospital volume, and surgeon case volume. A higher case incidence rate may be related to the infection rate with succeeding shunt revisions.[23] The infection rate may be especially high in those undergoing three or more revisions,[24] although that has not been observed in all studies.[9] In patients undergoing revision after treatment for an

infected CSF shunt, the operative incidence of infection is considerably higher (12%–26%).[25,26] The same microorganism has been cultured at least one-half to two-thirds of the time, suggesting that the initial infection was not adequately treated. Premature birth, previous shunt infection, and intraoperative use of the neuroendoscope were identified as independent risk factors in a recent study of patients with VP shunt infections.[27] In a study of 675 children who had an initial CSF shunt infection (treated by shunt removal/new shunt placement, externalization, nonsurgical management, or removal with no shunt placement), the 6-month reinfection rate was 14.8%, and the median time to infection was 21 days[28]; reinfection was associated with nonsurgical management.

In a large meta-analysis of 35 studies of patients with CSF drains, which yielded 752 infections from 66,706 catheter-days of observation, the overall pooled incidence of external ventricular drain-related CSF infection was 11.4 per 1000 catheter-days (95% confidence interval [CI], 9.3 to 13.5); for high-quality studies, the incidence was 10.6 per 1000 catheter-days (95% CI, 8.3 to 13).[29] Factors associated with an increased risk of infection are intraventricular hemorrhage, subarachnoid hemorrhage, cranial fracture with CSF leak, catheter irrigation, craniotomy, and duration of catheterization. Although controversy exists regarding the relationship between the duration of catheterization and risk of infection, most studies consider extended catheter duration, usually exceeding 5 days, to be an important risk factor for subsequent infection.[5] In a recent prospective multicenter cohort study of external ventricular drain (EVD) insertions in the United Kingdom and Ireland, the 30-day EVD infection rate was 9.3%; a regression analysis in the same study showed that duration of EVD placement and frequent CSF sampling were independently associated with an increased risk of ventriculitis.[30]

ETIOLOGY

The etiologic agents causing both CSF shunt and CSF drain infections are fairly similar; the most common microorganisms are those that colonize the scalp and skin of the back, or those that are present in the health care environment. The etiologic agents identified in CSF shunt infections are shown in Table 92.2.[2,13,31,32] Staphylococcal species account for the majority of isolates in patients with CSF shunt infections, with *Staphylococcus epidermidis* most frequently isolated (47%–64% of infections), followed by *Staphylococcus aureus* (12%–29% of infections). The most common isolated gram-negative microorganisms are *Escherichia coli, Klebsiella, Proteus*, and *Pseudomonas*; cases of *Acinetobacter* meningitis have also been reported in patients with VP shunts.[33–35] The usual etiologic agents of community-acquired bacterial meningitis (i.e., *Haemophilus influenzae, Streptococcus pneumoniae*, and *Neisseria meningitidis)* are only isolated in approximately 5% of CSF shunt infections. In 10% to 15% of cases more than one microorganism is isolated, usually including a *Staphylococcus* strain or *E. coli.* In recent years an increasing prevalence of diphtheroids, particularly *Cutibacterium acnes* (formerly *Propionibacterium acnes)* has been found in CSF shunt infections. However, it may be that the incidence is not increasing but, rather, that the etiologic diagnosis was not made because isolation of these organisms was not considered to be significant, or adequate culture techniques (i.e., anaerobic culture and prolonged incubation) were not used.[32,36] Fungal shunt infections are rare, although the frequency of *Candida* shunt infections has increased in recent years (ranging from 6%–17% in one review).[37] Fungal shunt infections may be seen in patients receiving broad-spectrum antimicrobial therapy, corticosteroids, and hyperalimentation; in those with indwelling intravascular catheters; or in those who are immunocompromised. A previous ventricular shunt may also increase the risk of subsequent *Candida* meningitis.[38]

Different microorganisms may be isolated depending on the type of shunt. Shunts terminating in the peritoneal cavity may have a greater risk of infection with gram-negative organisms[23,39]; mixed infections may be seen when the catheter has perforated a hollow viscus.[40,41] Although some investigators have found an increased prevalence of gram-negative shunt infections in patients with a peritoneal termination,[42] others have found no difference in the bacterial spectrum in those with VP or ventriculoatrial shunts.[43]

In patients with VP shunt-related peritonitis and pseudocysts, the pathogenic organisms are mostly gram positives, especially *Staphylococcus* spp., and this might be from transcutaneous spread along the distal catheter, rather than from gut perforation[44,45] (Fig. 92.2).

Lumboperitoneal shunts have distributions of infecting organisms similar to those originating in the ventricles.[42,43] Gram-positive cocci account for the majority of cases of ventriculitis associated with CSF drains, but infections caused by gram-negative bacilli, gram-positive bacilli, fungi, and antimicrobial-resistant bacteria have also been described.[5,46] At certain institutions the incidence of gram-negative CSF drain ventriculitis was higher. In an Australian study gram-negative infections accounted for 71% of the cases, with 48% caused by *Acinetobacter* spp.[47] Similarly, in a study from Singapore, 50% of the infections were caused by *Acinetobacter* spp.[48] These studies emphasize the importance of considering local or institutional microbiology and antibiograms in choosing empirical antimicrobial therapy.

PATHOGENESIS

There are four mechanisms by which CSF shunts may become infected.[2] The first mechanism is retrograde infection from the distal end of the shunt from a peritonitis, although this is rare. For example, bowel perforation can lead to distal catheter contamination. Retrograde infection is the most likely mechanism of infection of CSF drains. Microorganisms may enter the device by tracking from the exit site alongside the device, gaining access to the fluid column that drains CSF, or they may be introduced from flushing the tubing to maintain tubular function.

The second mechanism is through the skin, such as inserting a needle into the reservoir or the shunt to culture the CSF or assess patency, injecting drug into a ventricular reservoir, and after breakdown

TABLE 92.2 Bacterial Etiologic Agents in Cerebrospinal Fluid Shunt Infections

ETIOLOGIC AGENT	INCIDENCE (%)
Staphylococci[a]	55–95
Gram-negative bacteria	6–20
Streptococci	8–10
Diphtheroids[b]	1–14
Anaerobes	6
Mixed cultures	10–15

[a]The majority are caused by coagulase-negative staphylococci.
[b]Including *Cutibacterium acnes,* formerly *Propionibacterium acnes.*

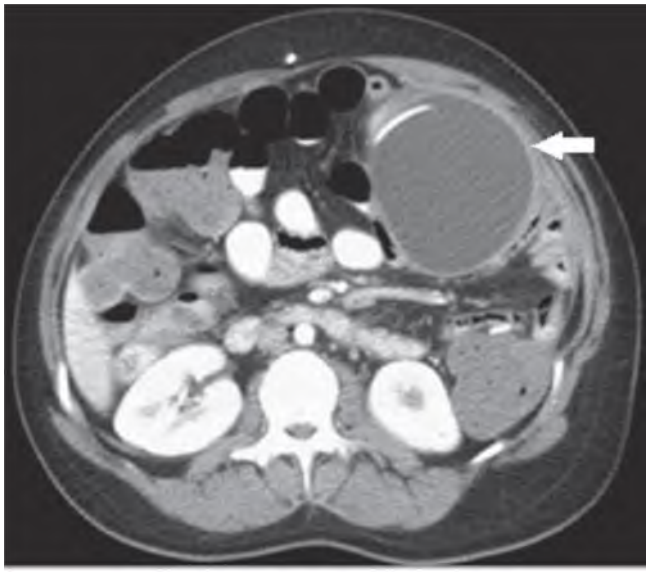

FIG. 92.2 Infected ventriculoperitoneal shunt–related pseudocyst (white arrow points to pseudocyst). *(From Gayer G, Lubner MG, Bhalla S, Pickhardt PJ. Imaging of abdominal and pelvic surgical and postprocedural foreign bodies.* Radiol Clin North Am. *2014;52:991–1027.)*

of the skin overlying the shunt.[2] The infection may be surgically acquired (i.e., when the incision fails to heal) or because the patient scratches the open wound, often seen in infants and small children. In premature infants with thin skin or in debilitated or immobile patients, a decubitus ulcer may develop over the shunt. Infection of tissues near the shunt site may also lead to direct inoculation of microorganisms.

A third mechanism is hematogenous seeding. Patients with ventriculoatrial shunts who have a foreign body (i.e., the catheter) in the vascular system are at continued risk of infection from bacteremia (with a retrograde infection). The susceptibility of nonvascular shunts to an infection that is spread hematogenously is less clear, although the likelihood is very low.

The fourth and most frequent mechanism is colonization of the shunt at the time of surgery.[2] This mechanism is suggested by the timing of most shunt infections, usually within the first month of operation, and by the microorganisms that are isolated. In one study in adults with CSF shunt-associated infections, 62% occurred within the first month after shunt surgery, and 72% were acquired intraoperatively.[13] At the time of implantation, direct exposure and handling of the shunt can allow bacterial contamination. One prospective observational study identified holes in the surgical gloves, combined with digital shunt handling by the surgical team, as a possible risk factor.[25] Instituting the practice of double gloving led to a reduction in shunt infection rates compared with historical controls.[49] However, in multiple studies using surveillance culture techniques, less than 50% of the microorganisms cultured from the wound or infected shunt could be traced directly to the patient,[2,40,50] suggesting that there are other factors that affect colonization and subsequent CSF shunt infection. Another study found that, in 13 shunt infections that occurred out of 108 shunt placements, only one CSF shunt infection had an isolate that was similar to the perioperative surgical site culture,[51] suggesting that contamination at the time of surgery may be an uncommon cause of shunt infection.

CLINICAL FEATURES

The clinical features of CSF shunt infection can be quite variable and depend on the pathogenesis of infection, organism virulence, and type of shunt.[2,13,24,42,43] Unlike the organisms that cause community-acquired bacterial meningitis, those causing CSF catheter-associated ventriculitis, such as coagulase-negative staphylococci and *C. acnes*, are indolent, evoke minimal inflammation, and are usually pathogenic in the presence of prosthetic material. Often, there may only be minimal ventriculitis without meningeal involvement, or only mechanical blockage as a result of biofilm formation in or on the catheter.[52,53] Therefore the clinical symptoms of meningitis may be absent and the clinical presentation more subtle, with a longer duration of symptoms. The most frequent symptoms in patients with CSF shunt infection are headache, nausea, lethargy, and change in mental status, seen in as many as 65% of infected patients; these symptoms occur as a result of shunt malfunction secondary to the infection. Fever is reported in as few as 14% to as many as 92% of cases, so the absence of fever cannot exclude the possibility of infection, although fever is typically present in the majority of patients. Pain, often related to infection at the peritoneal or pleural endings of the shunt, may be absent in as many as 60% of infections.

Symptoms and signs of a CSF shunt infection may be referable to either the proximal or distal portion of the shunt. Infection beginning in the proximal portion of the shunt (i.e., the catheter within the CSF space) results in meningitis or ventriculitis in approximately 30% of cases and may cause shunt obstruction or decreased function.[2,23,43] Rarely, intracranial empyemas and abscesses may occur secondary to a poorly treated infection, in the presence of retained hardware, or in patients with external monitors.

Symptoms of infection referable to the distal portion of the shunt are more specific to terminus location.[2,23] Infected shunts that terminate in the pleural or peritoneal space may lead to an inflammatory response in the absorbing tissue (i.e., pleuritis or peritonitis). In patients with infected VP shunts, symptoms of peritonitis appear as the peritoneal inflammation becomes more severe, and fever, anorexia, and other signs and symptoms of an acute abdomen develop. With low-virulence organisms, localizing signs of peritonitis may be confined to abdominal tenderness and/or guarding. In the peritoneal cavity host defense mechanisms attempt to limit the infection, often resulting in the encystment of the shunt catheter, fluid buildup within the pseudocyst, and loculation of pockets of fluid within the abdomen. These fluid collections can grow quite large because deposited CSF is not absorbed within the pseudocyst. Partial or complete shunt obstruction may result.

Infected ventriculoatrial shunts lead to bacteremia, which may occur secondary to infected CSF directly entering the bloodstream, resulting from an infected thrombus or atrial mural vegetation at the end of the vascular catheter, or represent true bacterial endocarditis. However, the clinical presentation of an infected vascular shunt is usually nonspecific, with fever and lethargy often seen. One unique complication of a chronic vascular shunt is shunt nephritis,[2,10,23,43] which is observed in 4% to 14% of patients with infected ventriculoatrial shunts. The majority of isolated bacteria in patients with shunt nephritis are usually coagulase-negative staphylococci, although diphtheroids and other pathogens have been isolated. The pathogenesis of shunt nephritis is similar to that of subacute bacterial endocarditis, with deposition of immunoglobulin M and G antigen-antibody complexes in the renal glomeruli. The complement system is activated, with subsequent depletion of circulating complement factors C3 and C4. Failure to detect this condition can lead to permanent renal failure. Treatment usually, but not always, leads to resolution of the renal dysfunction.

Some shunt infections, however, are insidious and cause few or no symptoms, perhaps only an intermittent low-grade fever or general malaise. The patient may present with an unexplained occlusion of an open-ended peritoneal catheter or failure of peritoneal CSF absorption. Therefore the clinician must consider the possibility of CSF shunt infection in these patients and institute an appropriate diagnostic workup (see later).

Lumbar or ventricular drains become infected from organisms introduced through the drainage system or through the skin site.[2,54,55] Infections are more frequent with CSF drains than CSF shunts and may be caused by hospital flora. The change in mental status that occurs in patients in whom meningitis or ventriculitis develops may be difficult to distinguish from the impaired level of consciousness that is a manifestation of the patient's underlying disease. In patients with CSF drain-related ventriculitis, symptoms and signs are not very useful. The underlying reason for drain placement, such as subarachnoid hemorrhage or tumor, can also cause a similar neurologic presentation, and these patients are often unresponsive in the intensive care unit and unable to report symptoms. Fever that occurs in these patients may also be from other sources of infection.

DIAGNOSIS

The diagnosis of CSF shunt and CSF drain infections is difficult because changes in CSF parameters may be subtle, especially with indolent organisms,[2,13] thus making it hard to determine if the abnormalities are related to infection or secondary to underlying reason for catheter placement, such as hydrocephalous from intracranial hemorrhage or a result of neurosurgery itself.[56,57] In patients with suspected CSF shunt ventriculitis the diagnosis is established by either direct culture of the CSF obtained by shunt aspiration or by culture of the proximal shunt components if the shunt is explanted.[2,43] To obtain fluid from a ventricular shunt, there must be a reservoir that can be tapped. These reservoirs are typically located in an easily accessible subcutaneous location. After sterile preparation the reservoir is percutaneously punctured; most shunts should not be punctured with anything larger than a 25-gauge needle. Introduction of infection is a possible, albeit low, risk of this procedure. In a pediatric study with 266 children who underwent 542 shunt aspirations, there was no evidence of shunt infection; one patient developed an infection after a shunt tap, but there was redness over the shunt tract at the time of the aspiration.[58]

In patients with infected ventricular shunts, the microbiologic yield is greater when CSF is obtained from a shunt aspiration than from a lumbar puncture.[13] Direct aspiration of the shunt yielded a positive culture in 91% to 92% of cases, whereas CSF culture from a lumbar puncture was positive in only 45% to 67% of cases.[13,59]

Once obtained, CSF should be sent for cell count with differential, chemistries (glucose and protein), Gram stain, and aerobic and anaerobic cultures.[2] Although high white blood cell (WBC) counts correlate with

the presence of infection, infection may be present even in patients with normal CSF WBC counts. CSF WBC counts and lactate concentrations were normal in approximately 20% of episodes in one study of adults with shunt-associated infection.[13] CSF eosinophilia (>8% of the differential count) has been associated with an indolent infection.[60] The cell count may be obscured by recent neurosurgery or intraventricular hemorrhage, which can cause an inflammatory reaction, so-called chemical meningitis.[56] Attention should also be paid to the site of CSF sampling because the CSF WBC count in samples obtained by shunt aspiration or from ventricular fluid tends to be lower than when CSF is obtained after lumbar puncture.[13] A negative result of a CSF Gram stain does not exclude the likelihood of infection.

CSF culture from the shunt reservoir is the most important test to establish the diagnosis of infection.[32] The culture will usually be positive in patients with an infected device even when there is no pleocytosis or alteration in CSF chemistries. CSF cultures may require several days to weeks of incubation before they can be called negative, especially for slowly growing organisms such as *C. acnes*, or the results may be confounded in patients who have received previous antimicrobial therapy. On occasion, shunts may be tapped for evaluation of function in patients with no clinical evidence of infection and may be found to be culture positive. In this situation contamination may be responsible for the positive culture, but true infection must be strongly considered. The shunt should be retapped, and a positive culture with the same microorganism is usually indicative of true infection.[2]

In patients with external ventricular drains and lumbar drains, the diagnosis of ventriculitis is more difficult than in patients with CSF shunts, as chemical meningitis and contamination of cultures during CSF collection is more frequent. The diagnostic conundrum relates to the degree of CSF pleocytosis or CSF hypoglycorrhachia that is consistent with an infectious ventriculitis and not a chemical meningitis resulting from hemorrhage or neurosurgery, as there is a considerable overlap in CSF parameters between these two entities. Although CSF lactate has been suggested as one parameter that may be a useful indicator of bacterial meningitis in CSF obtained via lumbar puncture, a recent study demonstrated that CSF lactate alone is not a reliable indicator of bacterial ventriculitis in patients with external ventricular drains.[61] In contrast, another study found CSF lactate to be a good marker for external drain-related infections.[62] More data are needed.

Another conundrum relates to the finding of a single positive CSF culture, which may be a contaminant or a true pathogen; abnormal CSF WBC counts and CSF glucose concentrations are often seen in these patients with chemical meningitis. The published literature on CSF drain-related ventriculitis is also plagued with the lack of clear diagnostic criteria, with a multitude of heterogeneous definitions. One study found 16 unique definitions in the published literature; when the definitions were applied to the test cohort, the frequency of infection ranged from 22% to 94% (median, 61% with an interquartile range of 56%–74%).[63] With that caveat, a definite infection can be defined as a positive CSF culture for a pathogenic organism (obtained from the ventricular or lumbar catheter) associated with significant CSF pleocytosis or CSF hypoglycorrhachia.[5,54,64] Progressively decreasing CSF glucose and increasing CSF pleocytosis on serial CSF analyses, in the absence of positive CSF cultures or positive Gram stain, characterizes a suspected infection in the absence of another etiology. A contaminating microorganism is defined as an isolated positive CSF culture and/or positive Gram stain with a normal CSF cell count, CSF glucose, and CSF protein. Normal protein in the ventricular CSF is less than 20 mg/dL, lower than in lumbar CSF.

In the absence of clinical evidence of a CSF shunt infection, routine cultures of shunt components, when shunts are removed for other indications, should not be done.[2] In one study of 174 shunt revisions, 19 patients had positive shunt component cultures without signs of infection (i.e., asymptomatic bacteriologic shunt contamination), only one of which was treated with antimicrobial therapy.[65] There was no increase in the risk of shunt malfunction in this group when compared with other patients with CSF shunts in the database at their institution.

Polymerase chain reaction (PCR) assay has been evaluated to detect the presence of bacterial DNA in CSF from patients with external ventricular drains and VP shunts. In one study that used PCR to detect gram-positive bacteria in 86 specimens, 42 were culture negative but PCR positive.[66] There were no positive culture results in patients with a negative CSF PCR, suggesting that a negative result is predictive of the absence of infection. More studies are needed, however, before routine use of PCR can be recommended in this setting.[2]

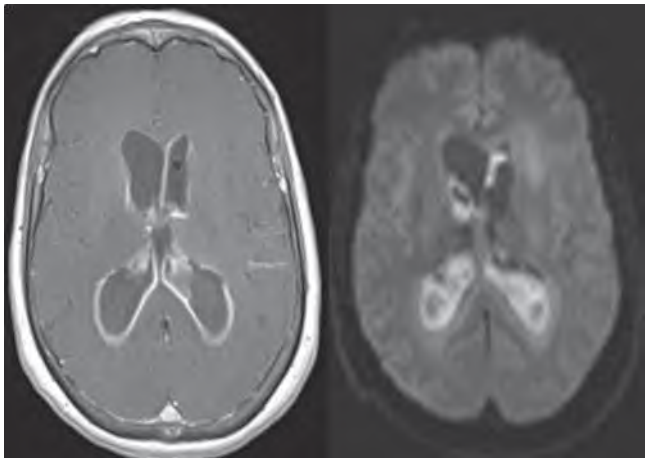

FIG. 92.3 Intraventricular empyema. *Left*, T1 post-contrast image showing ependymal enhancement of the occipital horns of lateral ventricles. *Right*, Areas of restricted diffusion in both the occipital horns of the lateral ventricles suggestive of purulent material.

In patients with ventriculoatrial shunts, blood cultures should also be performed because bacteremia is invariably present in patients with infected ventriculoatrial shunts (positive blood cultures in >90% of cases).[2] This contrasts with infections in other types of CSF shunts in which the incidence of negative blood cultures approaches 80%.[43]

The diagnosis of CSF shunt infection may be more difficult to establish when the distal portion of the VP shunt is infected.[2] The shunt tap may be normal with negative cultures if a retrograde infection has not yet developed in the patient. VP shunts with distal occlusion but no symptoms or signs of infection should be investigated for possible infection at the time of revision. A computed tomography or ultrasound scan of the abdomen may identify CSF loculations at the shunt terminus (see Fig. 92.2). Although some free fluid in the pleural or peritoneal cavities is normal, it should not be confused with the larger volumes and cysts seen with infection at the shunt terminus.

Neuroimaging studies are not useful in identifying CSF shunt infection but may show evidence of shunt malfunction and should be performed to evaluate ventricular size before initiating surgical treatment.[2] In acute shunt obstruction, extravasation of CSF from the lateral cerebral ventricles into contiguous cerebral cortex may occur. If there has been prior neurosurgery, imaging may detect the presence of potentially contaminated extraneous catheters from previous surgical procedures in either the brain or abdomen. Rarely, a subdural empyema or brain abscess may be the first indication of a shunt infection. In CSF drain-related infections that are refractory to intravenous (IV) and intraventricular therapy, MRI of the brain, with and without contrast and with diffusion-weighted imaging, is helpful in detecting intraventricular empyema, which often needs surgical drainage in addition to antimicrobial therapy (Fig. 92.3).[67,68]

THERAPY

Numerous methods for treating CSF shunt infections have been reported, but no randomized, prospective studies have been done to evaluate different antimicrobial therapies.[2,69] The therapeutic approach to an infected CSF shunt must take into account the need for a functioning device during or after treatment. For example, in patients with noncommunicating hydrocephalus and persistent infection, shunt removal and an endoscopic third ventriculostomy have been advocated in children[70]; even if the endoscopic third ventriculostomy fails, the VP shunt inserted after failure appears to have better longevity than if the VP shunt is inserted without first performing the ventriculostomy.[71] Factors to be considered in the therapy of an infected CSF shunt include the selection

of antimicrobial therapy, timing of hardware removal, timing of shunt replacement, and duration of antimicrobial therapy. These therapeutic approaches, however, have not been standardized in published studies, and there is wide variation in clinical practice.[72]

Antimicrobial Therapy

The principles of antimicrobial therapy for CSF shunt infections are generally the same as those for acute bacterial meningitis (see Chapter 87 for antimicrobial choice and dosing recommendations)[2,73]; the agent selected must penetrate the central nervous system and attain adequate CSF concentrations. However, because the organisms that cause CSF shunt infections often form biofilms, into which antimicrobial agents do not penetrate well, drug therapy may be problematic for patients when the catheter is not removed. If CSF pleocytosis is present, antimicrobial therapy should be initiated after appropriate cultures are obtained but before culture results are available. The most likely microorganisms associated with CSF shunt and CSF drain infections are coagulase-negative staphylococci (especially *S. epidermidis*), *S. aureus, C. acnes*, and gram-negative bacilli (including *Pseudomonas aeruginosa*). Empirical therapy with IV vancomycin plus either cefepime, ceftazidime, or meropenem is appropriate.[2,73] The empirical choice to treat a presumptive gram-negative pathogen should be based on the local antimicrobial resistance patterns of these pathogens. Therapy can then be modified once an organism is isolated and in vitro susceptibility results are available. If staphylococci are isolated and the organism is methicillin susceptible, therapy should be changed to either nafcillin or oxacillin. The addition of rifampin to an antistaphylococcal agent may augment treatment,[74] especially if the infected catheter is retained. One patient with an *S. epidermidis* VP shunt infection[75] and another with an *Enterococcus faecalis* VP shunt infection[76] were cured with shunt removal and IV linezolid, although linezolid cannot be considered as first-line therapy for this infection. Daptomycin, combined with rifampin, has also been successfully used in patients with infections of CSF shunts caused by gram-positive pathogens.[77] In one study of six neurosurgical patients with indwelling external CSF shunts and suspected meningitis or ventriculitis,[78] a single dose of daptomycin (10 mg/kg) led to an overall CSF penetration of 0.8%; when corrected for protein binding, the overall CSF penetration was 11.5%. An IV amphotericin B preparation (usually liposomal amphotericin B), often combined with 5-flucytosine, is recommended for *Candida* shunt infection[2]; once the patient shows clinical improvement, a change of therapy to fluconazole may be considered if the isolated species is susceptible.

Intraventricular and Intrathecal Antimicrobial Therapy

Direct instillation of antimicrobials into the lateral ventricles (via a ventricular drain or a ventricular access device such as an Ommaya reservoir) or the lumbar subarachnoid space (via a lumbar drain) may be necessary in patients with shunt or drain infections that are difficult to eradicate with IV antimicrobial therapy or when the patient is unable to undergo the surgical components of therapy (see later).[2,79] This route of administration bypasses the blood-CSF barrier, with controlled delivery of the antimicrobial agent to the site of infection. No antimicrobial agent has been approved by the US Food and Drug Administration for intraventricular use. However, intraventricular antimicrobial therapy has been recommended as an option for patients in whom the infection responds poorly to systemic antimicrobial therapy alone.[2] A recent systematic review sponsored by the American Association of Neurological Surgeons/Congress of Neurological Surgeons noted insufficient evidence to recommend their use in pediatric shunt infections,[80] although other studies suggest benefit. There have been several studies on the pharmacokinetics (PK), safety, and efficacy of intraventricular antimicrobial therapy, especially in adults[81–87]; CSF sterility and normalization of CSF parameters were achieved sooner with intraventricular and IV use when compared with IV use alone. A randomized trial in 10 patients with staphylococcal ventriculitis showed that much higher CSF concentrations were achieved with intraventricular vancomycin when compared with IV therapy.[88] In another study of 34 patients with persistently positive CSF cultures despite antimicrobial treatment, those who received intraventricular or lumbar intrathecal antimicrobials achieved CSF sterilization within 24 hours in 50% of patients and within 48 hours in an additional 18% of patients[89]; only 3 patients had adverse effects, all of which were clinically insignificant. The clinical outcome of patients, as assessed by the modified Rankin Scale, improved in 50% and stayed unchanged in 29%. In another study on infections in patients with CSF diversion devices, 25 patients received intraventricular and systemic antimicrobials, and 23 received systemic antimicrobials alone; the mean times to CSF sterilization and normalization of CSF microscopy were significantly shorter for the intraventricular group ($P < .05$ and $P < .005$, respectively), as was duration of hospital stay ($P < .002$) and required length of systemic antimicrobial therapy ($P < .001$).[90] However, use of intraventricular antimicrobial agents was not recommended in infants based on data in a Cochrane Review[91]; one clinical trial found a three times higher relative risk of mortality for infants with gram-negative meningitis who were treated with intraventricular gentamicin and IV antimicrobials when compared with IV therapy alone, although one-half of the infants in the intraventricular gentamicin group had received only one dose, raising doubts about the exact cause of death.

Antimicrobial agents administered by the intraventricular or intrathecal route should be preservative free. When administered through a ventricular drain, the drain should be clamped for 15 to 60 minutes to allow the antimicrobial solution to equilibrate in the CSF before opening the drain.[92] In treating VP shunt ventriculitis, administration of the antimicrobials through the shunt reservoir may also result in the agent draining into the peritoneal cavity; to avoid this issue, antimicrobials can be administered via a ventricular access device separate from the shunt reservoir.[93]

There are limited studies published on antimicrobial CSF PK/pharmacodynamics (PD); that is, the relationship between intraventricular and intrathecal antimicrobial dose and frequency of administration with CSF concentrations or CSF sterilization and normalization of CSF inflammatory parameters. There is a dire need for such studies, but use of intraventricular therapy should generally be based on sound general PK/PD principles. At this time, intraventricular therapy should be reserved for organisms with high minimum inhibitory concentrations (MICs) in which use of IV antimicrobials cannot achieve the desired CSF PK/PD targets based on pathogen and MIC or in patients with clinical failure with use of IV antimicrobials (defined as persistent CSF cultures on IV therapy). The recommended doses of antimicrobial agents for intraventricular use, based on limited studies, has been outlined in Table 92.3, with adjustments of dose and dosing interval based on the ability of the agent to achieve adequate CSF concentrations.[2,73] Determining the correct dosing regimen is challenging as the CSF concentrations obtained for the same intraventricular dose in PK studies have been highly variable, probably because of the differences among patients in either the volume of distribution, ventricular size, or variable CSF clearance as a result of CSF drainage.[81–86,91] A consensus guideline by the British Society for Antimicrobial Chemotherapy Working Party on Infections in Neurosurgery has recommended that the initial dose of an intraventricular antimicrobial be based on ventricular volume.[94] The recommended dose of vancomycin is 5 mg in patients with slit ventricles, 10 mg in patients with normal-sized ventricles, and 15 to 20 mg in patients with enlarged ventricles; using the same rationale, the initial dosing of an aminoglycoside can also be tailored to ventricular size. The same working party recommended that the frequency of dosing be based on the daily volume of CSF drainage: once-daily dosing if CSF drainage is greater than 100 mL/day, every other day if the drainage is 50 to 100 mL/day, and every third day if drainage is less than 50 mL/day. This approach, though pragmatic, has not been empirically validated in clinical studies. Another approach is to base dosing on monitoring of CSF drug concentrations. However, there are very few studies that have evaluated CSF therapeutic drug monitoring and, given the variable CSF clearance of an antimicrobial agent, it is difficult to determine when to obtain CSF to measure peak and trough drug concentrations. A CSF drug concentration can be obtained 24 hours after administration of the first dose that can be presumed to be the trough CSF concentration. The trough CSF concentration divided by the minimal inhibitory concentration of the agent for the isolated bacterial pathogen is termed the *inhibitory quotient*, which should exceed 10 to 20 for consistent CSF sterilization.[2,73] Although not standardized, this approach is

TABLE 92.3 Antimicrobial Agents Administered by the Intraventricular Route

ANTIMICROBIAL AGENT	DAILY INTRAVENTRICULAR DOSE
Vancomycin	5–20 mg[b]
Gentamicin	1–8 mg[c]
Tobramycin	5–20 mg
Amikacin	5–50 mg[d]
Polymyxin B	5 mg[e]
Colistin[f]	10 mg
Teicoplanin	5–40 mg[g]
Quinupristin/dalfopristin	2–5 mg
Daptomycin	2–5 mg[h]
Amphotericin B	0.01–0.5 mg in 2 mL of 5% dextrose in water[i]

[a]There are no specific data that define the exact dose of intraventricular antimicrobial agents that should be used in cerebrospinal fluid shunt and drain infections; see text for details of specific studies.
[b]Most studies have used a 10- or 20-mg dose.
[c]Four to 8 mg in adults and 1–2 mg in infants and children.
[d]Thirty milligrams daily is the usual intraventricular dose.
[e]Dose of 2 mg/day in children.
[f]Formulated as colistimethate sodium.
[g]Five to 20 mg every 24–48 hours used in one study.[98]
[h]One study used 10 mg every day for 2 days and 10 mg every 48 hours[99]; another study used 5 or 10 mg every 72 hours.[100]
[i]Dose for *Candida* shunt infection. Not usually necessary but may be needed if removal of the device is too risky or the patient has not responded to systemic antifungal therapy.

reasonable to ensure that adequate CSF concentrations of these agents are obtained.

Although there are methodologic limitations in published studies, intraventricular vancomycin was shown to be safe and efficacious in a recent systematic review in adults.[83] Indeed, combined intraventricular and IV use may improve CSF vancomycin concentrations without side effects.[95] Intraventricular aminoglycosides were also shown to be effective[81,85]; in one study, there were no relapses when intraventricular gentamicin was combined with IV meropenem in patients with neurosurgical gram-negative bacillary ventriculitis and meningitis.[85] In another study of treatment of 34 consecutive shunt infections in 30 children, high-dose intraventricular antimicrobial therapy sterilized CSF cultures in 100% of 26 children who were treated for 3 days or more.[96] IV and intraventricular quinupristin/dalfopristin has been used successfully to treat a patient with ventriculostomy-related meningitis caused by vancomycin-resistant *Enterococcus faecium*.[97] Teicoplanin, a glycopeptide antimicrobial agent not currently licensed in the United States, was also found to be successful after intraventricular administration in seven patients with staphylococcal neurosurgical shunt infections.[98] Intraventricular daptomycin was successfully used in individual case reports in patients with CSF shunt and CSF drain infections caused by methicillin-resistant coagulase-negative staphylococci and resistant enterococci.[99–102] Intraventricular colistin, usually formulated as colistimethate sodium, and polymyxin B have been used in the treatment of gram-negative ventriculitis and meningitis,[79,103–105] but these agents should be reserved for patients with infections caused by multidrug-resistant gram-negative bacteria or in those failing therapy with standard IV agents. Colistimethate is biologically inactive before hydrolytic cleavage into free colistin, unlike polymyxin B, so the latter is preferable. Penicillins and cephalosporins should not be given by the intrathecal route because they have been associated with significant neurotoxicity, especially seizures.[79]

Shunt Removal

The approaches to the treatment of CSF shunt infections in the published literature have included antimicrobial therapy with or without shunt removal.[2,23,42,43,106] There has only been one prospective, randomized trial of three different approaches to management of infected CSF shunts in 30 children, all of whom received antimicrobial therapy[107]; not removing the shunt led to a 30% cure, one-stage shunt replacement led to a 90% cure, and two-stage shunt replacement led to a cure in 100% of patients. In early attempts to treat CSF shunt infections, IV and/or intraventricular antimicrobial agents were used exclusively to avoid additional operations and to maintain CSF diversion during treatment. Success with this approach, however, was low (34%–36%) and carried a high mortality rate.[39,108] In addition, the instillation of antimicrobial agents into CSF often required a lengthy hospitalization, and the frequency of an adverse outcome was unacceptably high. The ability of many of these organisms to adhere to prostheses and survive antimicrobial therapy likely precluded optimal treatment in situ. However, in one observational study of treatment with systemic and intraventricular antimicrobial agents (instilled via a separate ventricular access device), 84% of 43 patients were cured, with a 92% success rate for infections caused by bacteria other than *S. aureus*,[93] suggesting that conservative management may be appropriate for selected patients with CSF shunt infections caused by less virulent microorganisms, such as coagulase-negative staphylococci. Similar results have been achieved in patients with CSF shunt infections caused by *C. acnes*.

Combining the removal of shunt hardware with immediate shunt replacement and IV antimicrobial therapy cures approximately 65% to 75% of patients with shunt infections,[39,108] although the failure and reinfection rates still remain quite significant with this approach. The other option is shunt removal with delayed replacement (to treat the infection with antimicrobial therapy in the absence of any foreign devices), although this approach leaves untreated the reason for the initial shunt placement.[109]

The most successful approach to treatment of a CSF shunt infection is systemic antimicrobial use with removal of all components of the infected shunt, followed by insertion of a ventricular drain. When the drainage cultures are negative, the drain is removed and a new CSF shunt placed (see later).[2,72] The ventriculitis of shunt infections appears to clear more quickly with external drainage. The presence of a drainage catheter also allows monitoring of CSF parameters, including cultures, and allows administration of intraventricular antimicrobial therapy, if necessary. Ventricular drainage also allows continued treatment of the underlying hydrocephalus and avoids the complications associated with only shunt removal. With this approach, treatment success is usually greater than 85%.[2,31,39,108] In one recent retrospective, observational study of 86 episodes in patients with VP shunt infections and who were 12 years or older, 6 episodes were treated with only antibiotics, and 80 episodes were treated with strategies that combined antimicrobial therapy with surgical treatment—either two-stage shunt replacement, one-stage shunt replacement, or shunt removal without replacement.[110] Administration of antibiotics with a two-stage shunt replacement was the most successful strategy, with a cure rate of 89% and CSF sterilization rate of 95%, indicating that this approach remains the optimal approach to patients with VP shunt infection.

The greatest risk of the external ventricular drain is that of secondary infection.[2,5,111] A longer duration of the drain appears to increase the risk, although prophylactic catheter exchange performed every 5 days does not significantly decrease the likelihood of CSF infection.[112,113] In one randomized, controlled trial with 103 patients who required external ventricular drains for more than 5 days,[113] the CSF infection rate was 7.8% for the group that underwent catheter exchange every 5 days and 3.8% for the no-change group ($P = .5$), suggesting that a single external ventricular drain can be used for as long as clinically indicated unless a change is necessary because of CSF infection or catheter malfunction. Attention to maintaining a sterile, closed system with avoidance of injections into the system and surveillance of the draining CSF will usually keep this risk to less than 5%. In the treatment of infection caused by an external ventricular drain, removal of the drain is an important adjunctive measure.[2]

Duration of Antimicrobial Therapy and Shunt Reimplantation

The duration of antimicrobial therapy for CSF shunt infections is not completely defined and is dependent on the isolated microorganism, the extent of infection as defined by cultures obtained after

externalization, and occasionally CSF findings.[2] Once the infected CSF shunt has been removed, the optimal timing of shunt reimplantation has not been studied. Early placement may increase the risk of relapse, but a delay in reimplantation may increase the risk of secondary infection of the external ventricular drain. The timing of reimplantation should be individualized based on the isolated organism, severity of ventriculitis, and improvement of CSF parameters and CSF sterilization in response to antimicrobial therapy. In patients with shunt infection caused by coagulase-negative staphylococci and with normal CSF findings, the presence of negative CSF cultures for 48 hours after externalization generally confirms that removal of the hardware effected a cure and the patient can be reshunted on the third day after removal. If a coagulase-negative *Staphylococcus* was isolated in association with CSF abnormalities (i.e., CSF pleocytosis, abnormal chemistries), a true infection was likely present. If repeat cultures are negative, 7 days of antimicrobial therapy are usually recommended before reshunting, but if repeat cultures are positive, antimicrobial treatment is continued until CSF cultures remain negative for 7 to 10 consecutive days before a new CSF shunt is placed. This approach is also recommended for infection caused by *C. acnes*.[32] For shunt infections caused by *S. aureus* or gram-negative bacilli, 10 days of antimicrobial therapy with negative cultures are recommended before reshunting.[2,73,114] Some experts also suggest that consideration be given to a 3-day period off antimicrobial therapy to verify clearing of the infection before shunt reimplantation, although this observation period is generally not recommended.[2,73] It is important to note, however, that these recommendations have not been rigorously studied, and some patients may require a longer duration of antimicrobial therapy before a new CSF shunt is placed. Furthermore, significant variations have been observed in the duration of antimicrobial therapy in patients with CSF shunt infections.[26,72] Careful follow-up after reimplantation is also critical to ensure that the patient has been cured. Regardless of the manner of treatment, CSF shunt infection can recur. In one study[26] the recurrence rate was 26%, with two-thirds of cases caused by the same microorganism; the recurrence rate in patients with *S. epidermidis* shunt infection was 29%. A major risk factor for recurrence was a history of shunt infection within the preceding 6 months. In one recent study in children, risk factors for reinfection were complex shunts (i.e., multiple shunts placed or any single shunt with multiple catheters together), an atrial shunt, any complication after the first infection (e.g., shunt malfunction, hemorrhage, or CSF leak), or intermittent negative cultures (defined as positive CSF cultures that clear and then return over the course of treatment).[115]

Surgical Management of Ventriculoperitoneal Shunt–Related Peritoneal Pseudocyst

Abdominal peritoneal pseudocyst at the distal terminus of the VP shunt is a rare complication, with very limited studies on its management.[45,116,117] Based on limited studies, we recommend externalization of the distal catheter and, if the pseudocyst is still present, drainage of the pseudocyst and removal of at least the distal components of the VP shunt tubing and reimplantation with repositioning of the distal catheter in a different location.

Surgical Management of Intraventricular Empyema

Intraventricular empyema is more commonly seen in patients with gram-negative ventriculitis, usually does not resolve with only IV and/or intraventricular therapy, and often requires surgical drainage. Open craniotomy can be performed for drainage, but less invasive neuroendoscopic approaches have been shown to be safe and successful in small studies.[67,68]

PREVENTION

There have been few systematic studies on specific surgical techniques to minimize the possibility of infection in patients undergoing CSF shunt placement. Much of what is recommended is based on the described risk factors for shunt infection (see Table 92.1).[2] In one prospective, randomized controlled trial in 61 patients undergoing 84 shunt procedures, the shunt infection rate was reduced in those getting antimicrobial sutures (4.3% vs. 21%; $P = .038$),[118] although there was a high rate of infection in the control group. There is some weak evidence that double gloving may decrease CSF shunt infection rates,[49] and good surgical techniques[119] and adherence to infection control measures are important. In patients with external ventricular drains, adherence to a checklist for insertion that included hand hygiene, appropriate skin preparation with povidone iodine, allowing the skin preparation to completely dry before insertion, use of all five maximal sterile barriers (sterile gloves, sterile gown, cap, mask, and large sterile drape), and adherence to the policy for external ventricular drain maintenance led to a decline in infection rates from 16 per 1000 external ventricular drain catheter days to 4.5 per 1000 catheter days[120]; this infection rate further decreased to 1.3 per 1000 catheter days. Initiation of this protocol eventually resulted in no infections over a 25-month period. Other studied interventions are detailed in the following sections.

Antimicrobial Prophylaxis

There is evidence to support the use of periprocedural prophylactic antimicrobial administration for patients undergoing CSF shunt insertion and placement of external ventricular drains.[2] Although no prospective, randomized trials of periprocedural prophylactic antibiotics for CSF shunt placement have been adequately powered to clearly establish efficacy, several meta-analyses have concluded that this approach decreases infection rates by approximately 50%.[121,122] A Cochrane Database Review indicated that the odds ratio for decreased infection was 0.52 (95% CI, 0.36 to 0.74).[123] The antimicrobial agent should be given before incision to achieve adequate tissue concentrations and continued for as long as 24 hours postoperatively.

Although the use of periprocedural prophylactic antibiotics for placement of external ventricular drains is also generally accepted, the use of prophylactic prolonged systemic antimicrobials for the duration of external CSF drainage is more controversial.[2] One study noted that the infection rate was 3.8% in those who received prophylactic antibiotics for the duration of placement of the external ventricular drain and 4.0% for those who received only periprocedural antibiotics,[124] suggesting that prophylactic antibiotics throughout drainage did not significantly decrease the rate of ventriculitis and might select for emergence of resistant organisms. In contrast, another study demonstrated the benefit of prophylactic antibiotics (2.6% CSF infection rate vs. 10.6% in those who only received periprocedural antibiotics; $P = .001$),[125] although the infections in those receiving prophylactic antimicrobials were caused by more drug-resistant virulent pathogens and the mortality rate was higher (66% vs. 41%). In a pooled estimate of nine studies, the CSF infection rate was 8.1% in those who received periprocedural antibiotics and 5.3% in those who received antibiotics for the duration of external drainage,[5] leading to a recommendation to maintain prophylactic antibiotics in all patients while the external ventricular drain is in place, although this is not the practice in all centers. In a more recent systematic review that pooled data from two randomized controlled trials and four observational studies,[126] there was a reduced relative risk (RR) of 0.45 with use of prophylactic prolonged systemic antimicrobials; although there were significant methodologic limitations and heterogenicity in the pooled studies, the definitions of ventriculitis were variable, the type and dose of antimicrobials were different, adverse effects were not well studied, and most of the studies were retrospective and prone to bias. In light of these findings, and also based on the availability of a safer efficacious alternative (i.e., antimicrobial-impregnated catheters; see later), we do not favor use of prophylactic prolonged systemic antimicrobials for prevention of infection in patients with external ventricular drains.

Antimicrobial-Impregnated Catheters

Antimicrobial-impregnated catheters for external ventricular drains and CSF shunts have been under development for several decades and more recently have been introduced into clinical practice. They are typically impregnated with either minocycline or clindamycin, combined with rifampin. In one prospective, randomized trial of 110 patients who underwent placement of CSF shunts impregnated with clindamycin and rifampin, there was a decrease in infection rate from 16.6% to 6%,[127] although the study was hampered by a small number of patients

TABLE 92.4 Individual Components of a Standardized Protocol for Cerebrospinal Fluid Shunt Insertion

Sign on operating room door to minimize traffic[a]
Patient position of operative site away from door[a]
Antimicrobial agents received before incision
Hair clipped, not shaved[a]
ChloraPrep (chlorhexidine) applied by or approved by attending physician
Wait 3 minutes to allow ChloraPrep to dry
Proper hand-washing technique by all team members
Double gloving by all team members
Ioban use (a sterile, adhesive, antimicrobial plastic surgical drape through which the incision can be made)
Vancomycin/gentamicin injection into shunt reservoir[a]
Dressing

[a]Features not included in revised protocol, which included antimicrobial-impregnated catheters (see text for details).[138]

From Kestle JRW, Riva-Cambrin J, Wellons JC 3rd, et al. A standardized protocol to reduce cerebrospinal fluid shunt infection: the Hydrocephalus Clinical Research Network Quality Improvement Initiative. J Neurosurg Pediatr. *2011;8:22–29.*

TABLE 92.5 External Ventricular Drain Infection Control Protocol

External Ventricular Drain Placement

- Physician washes/cleanses hands with alcohol-based solution
- Broad clipping of hair with sufficient room to place a medium-sized adherent transparent dressing film using coarse and fine clippers
- Single dose of antibiotic (e.g., cefazolin) is given before incision
- No prophylactic antibiotics are given after the single pre-incision dose
- Chlorhexidine skin preparation before draping
- Full sterile draping of patient's head and body
- Physician wears cap, mask, sterile gown, and sterile gloves
- All staff in room wear cap and mask
- Repeat chlorhexidine skin preparation after draping
- Rifampin/minocycline-coated ventricular catheter is placed
- Catheter is tunneled approximately 3–5 cm from insertion site

Dressing

- Catheter is secured in question-mark pattern using surgical staples
- Benzoin tincture is applied to skin and allowed to fully dry
- Chlorhexidine-eluting patch is applied over catheter exit site
- Medium-sized adherent transparent dressing film is applied
- Secure borders of dressing film with sterile adhesive strips
- No routine dressing changes; change for dressing compromise only

External Ventricular Drain Manipulation

- All staff in room wear cap and mask
- Three-way stopcock of access port is turned to 45 degrees ("off" to all directions)
- Access port and surrounding tubing are submerged in isopropyl alcohol
- Physician dons cap, mask, sterile gown, and sterile gloves
- Access port and surrounding tubing are cleaned with chlorhexidine
- Port cap is removed and discarded
- Luer fitting inside of port is cleaned (multiple times) with chlorhexidine
- Luer fitting inside of port is rinsed (multiple times) with sterile, preservative-free normal saline
- Cerebrospinal fluid draw or flush is performed with strict sterile technique
- New sterile port cap is applied

From Flint AC, Rao V, Renda NC, et al. A simple protocol to prevent external ventricular drain infections. Neurosurgery. *2013;72:993–999.*

and a high infection rate in the control group. Other noncontrolled studies in patients with CSF shunts have led to mixed results, some supporting[128,129] and others disputing[130,131] these findings. In a meta-analysis of pooled data from 12 studies comparing antimicrobial-impregnated with non–antimicrobial-impregnated VP shunts, there was a statistically significant decrease in infections in patients who had received antimicrobial-impregnated shunts (RR, 0.37; $P < .0001$).[132] In another systematic literature review of 5613 shunt procedures, use of antimicrobial-impregnated shunt catheters was associated with a decreased risk of shunt infection (3.3% vs. 7.2%; $P < .00001$),[133] with significant differences in both children and adults; use did not appear to be associated with emergence of antimicrobial-resistant infections. Use of antimicrobial-impregnated shunts has not only reduced the incidence of CSF shunt infections but also resulted in significant hospital cost savings.[134] In one study that compared the effectiveness of antimicrobial-impregnated shunt catheters in 12,589 consecutive cases from 287 hospital systems in pediatric and adult patients with hydrocephalus, there was a significant reduction in infection in both pediatric patients (2.6% vs. 7.1%; $P < .01$) and adults (2.2% vs. 3.6%; $P = .02$) who received antimicrobial-impregnated catheters, a reduction that was demonstrated regardless of hospital size, annual shunt procedure volume, hospital location, or patient risk factors.[135]

Similar results have been noted in patients who received antimicrobial-impregnated external ventricular drains. A prospective, randomized trial of 306 patients who had placement of external ventricular drains impregnated with minocycline and rifampin showed a decrease in the CSF infection rate from 9.4% to 1.3%.[136] Pooled data from five studies in one meta-analysis showed a statistically significant benefit for antimicrobial-impregnated external ventricular drains (RR, 0.31; $P = .009$).[132] Therefore use of antimicrobial-impregnated CSF shunts and CSF drains appears to be safe and effective in prevention of ventriculitis,[2] although prospective, randomized controlled trials are needed to firmly confirm their benefits.

Combined Interventions

Many of the studies on prevention of CSF shunt infections detailed earlier have examined single interventions to determine effects on infection rates. However, use of "practice bundles" may also be valuable in development of standardized protocols for insertion of CSF shunts.[2] The Hydrocephalus Clinical Research Network undertook an initiative in which centers agreed to develop an 11-step protocol to try to reduce CSF shunt infection rates (Table 92.4); this was a collaboration of pediatric neurosurgical centers and included all children getting shunts or revisions.[137] The initiative involved 21 surgeons and included 1571 procedures in 1004 children. Overall protocol compliance was about 75%, and another 20% followed 10 of the 11 steps. The Network infection rate decreased from 8.8% before the protocol to 5.7% while using the protocol (RR reduction, 36%; $P = .0028$), indicating that use of a standardized protocol and reducing variation by adherence to a common protocol are effective at reducing CSF shunt infection rates. Only proper hand-washing technique by all team members emerged as an independent predictor of decreased infection rates; factors associated with increased infection were use of BioGlide catheters and use of antiseptic cream by any members of the surgical team. The Hydrocephalus Clinical Research Network has subsequently published results of a revised procedure, with results from January 2012 through September 30, 2013.[138] To simplify the protocol, injection of vancomycin and gentamicin into the shunt reservoir was eliminated, as was orientation of the surgical field in respect to the operating room door, placing a sign on the operating room door, or requiring hair clipping rather than shaving. Antibiotic-impregnated catheters were used for the shunts, unlike the prior protocol. A total of 1935 procedures were performed on 1670 patients in eight centers; revisions constituted 1193 (62%) of these procedures. The infection rate was 6.0%, similar to 5.7% with the prior protocol. The role of antibiotic impregnated catheters in the new protocol could not be determined.

Similarly, in patients requiring placement of an external ventricular drain after a simple infection control protocol (Table 92.5) reduced ventriculitis rates from 6.3% in the baseline period to 0.8% in the first 3 years of the protocol period.[139] In a 4-year follow-up the authors reported a further decrease in the ventriculitis rate to 0%.[140]

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The complete reference list is available online at Expert Consult.

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