

REVIEW ARTICLE

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Brain Abscess

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DESPITE ADVANCES IN IMAGING TECHNIQUES, LABORATORY DIAGNOSTICS, surgical interventions, and antimicrobial treatment, brain abscess remains a challenging clinical problem with substantial case fatality rates. Brain abscess can be caused by bacteria, mycobacteria, fungi, or parasites (protozoa and helminths), and the reported incidence ranges from 0.4 to 0.9 cases per 100,000 population.^{1,2} Rates are increased in immunosuppressed patients.³

PATHOGENESIS AND EPIDEMIOLOGY

In most patients, brain abscess results from predisposing factors, such as underlying disease (e.g., infection with the human immunodeficiency virus [HIV]), a history of treatment with immunosuppressive drugs, disruption of the natural protective barriers surrounding the brain (e.g., due to an operative procedure, trauma, mastoiditis, sinusitis, or dental infection), or a systemic source of infection (e.g., endocarditis or bacteremia).⁴ Bacteria enter the brain through contiguous spread in about half of cases and through hematogenous dissemination in about one third of cases, with unknown mechanisms accounting for the remaining cases (Fig. 1).⁴

Pathogenic mechanisms of infection are dependent on predisposing conditions. Severe immunocompromise, resulting from immunosuppressive therapy in patients who have undergone solid-organ or hematopoietic stem-cell transplantation³ or from HIV infection,⁵ is often associated with tuberculosis or nonbacterial causes of infection, such as fungi or parasites. HIV infection is associated with brain abscess caused by *Toxoplasma gondii*,⁵ but HIV infection also predisposes patients to infection with *Mycobacterium tuberculosis*.⁶ Patients who have received solid-organ transplants are at risk not only for nocardial brain abscess but also for fungal abscess (e.g., resulting from infection by aspergillus or candida species). Fungi are responsible for up to 90% of cerebral abscesses among recipients of solid-organ transplants.^{3,7}

Abscess formation may occur after neurosurgical procedures or head trauma. In these cases, infection is often caused by skin-colonizing bacteria, such as *Staphylococcus aureus* and *S. epidermidis*, or gram-negative bacilli.⁸ Brain abscess due to contiguous spread from parameningeal foci of infection (e.g., the middle ears, mastoids, and sinuses) is frequently caused by streptococcus species,⁴ but staphylococcal and polymicrobial abscesses (including those caused by anaerobes and gram-negative bacilli) also occur.⁹

The hematogenous spread of bacteria is associated with underlying cardiac disease (e.g., endocarditis or congenital heart defects), pulmonary disease (e.g., arteriovenous fistulas),¹⁰ or distant foci of infection (primarily the skin, paranasal sinuses, and teeth).⁴ Staphylococcus and streptococcus species are often identified in brain abscesses after hematogenous spread.⁴ The microbial flora of brain abscesses resulting from paranasal sinus or dental infection are often polymicrobial.⁹

The first stage of brain abscess is early cerebritis,¹¹ which may lead to a perivascular inflammatory response surrounding the necrotic center, with increased edema in the surrounding white matter. Subsequently, the necrotic center reaches its

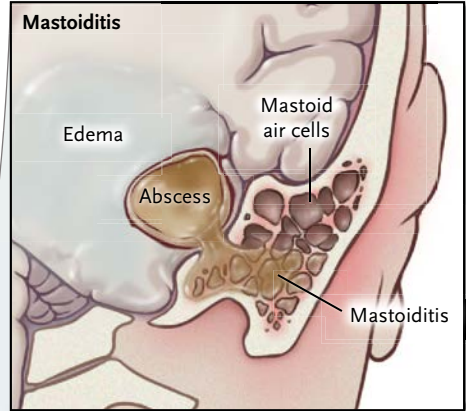
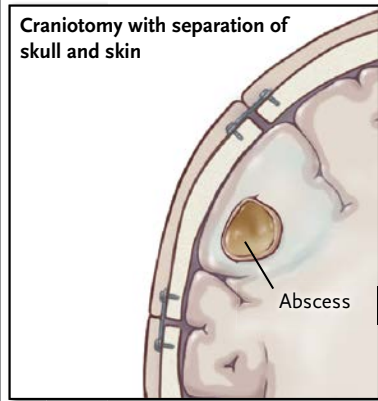
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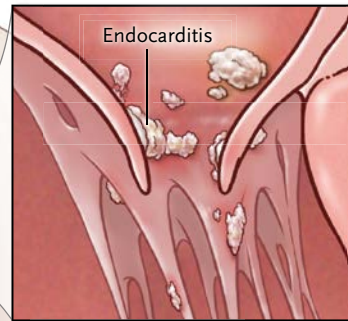
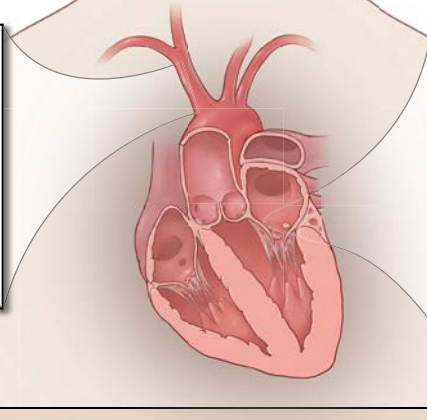
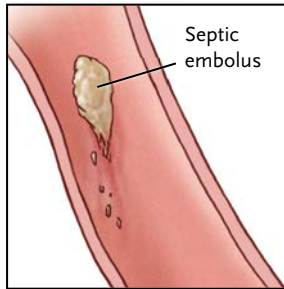
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A Sources of abscess formation



Hematogenous spread



B Stereotactic aspiration of subcortical abscess

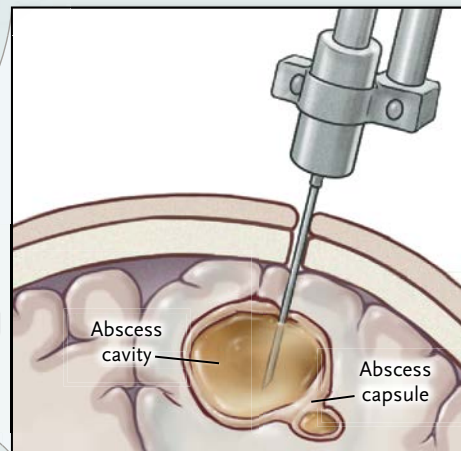
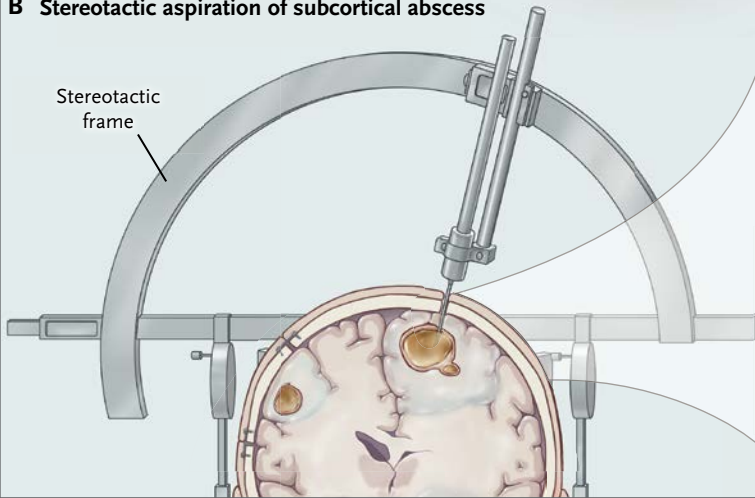


Figure 1 (facing page). Pathogenic Mechanisms of Brain-Abscess Formation and Stereotactic Aspiration.

Bacterial invasion of the brain leading to abscess formation may be due to the direct spread from contiguous foci of infection, such as the site of craniotomy or mastoiditis, or to hematogenous spread from pulmonary or cardiac foci of infection (Panel A). Minimally invasive aspiration may be achieved by means of a stereotactic frame (Panel B).

maximum size and a capsule is formed through the accumulation of fibroblasts and neovascularization. The capsule thickens with an abundance of reactive collagen, but inflammation and edema extend beyond the capsule. The histopathological features of brain abscess are shown in Figure 2.

CLINICAL MANIFESTATIONS

The most frequent clinical manifestation of brain abscess is headache; fever and altered level of consciousness are frequently absent.⁴ Neurologic signs depend on the site of the abscess and can be subtle for days to weeks. Behavioral changes may occur in patients with abscesses in the frontal or right temporal lobes. Patients with abscesses in the brain stem or cerebellum may present with cranial-nerve palsy, gait disorder, or either headache or altered mental status owing to hydrocephalus.¹² Up to 25% of patients present with seizures.⁴ Clinical manifestations become more evident as the abscess grows larger and the surrounding edema increases, but these symptoms and signs may be difficult to recognize because of sedation or the nature of the underlying neurologic disease.⁸ Patients with hematogenous spread of bacteria may present with symptoms of the underlying infection.¹³ The differential diagnosis includes a range of neurologic and infectious diseases, such as brain tumors, stroke, bacterial meningitis, epidural abscess, and subdural empyema. Primary central nervous system lymphoma is part of the differential diagnosis in patients infected with HIV.

DIAGNOSTIC MEASURES

Cranial imaging should be performed in all patients with suspected brain abscess. Computed tomographic (CT) scanning with contrast enhancement provides a rapid means of detecting

the size, number, and localization of abscesses. Magnetic resonance imaging (MRI), combined with diffusion-weighted and apparent-diffusion-coefficient images, is a valuable diagnostic tool in differentiating brain abscess from primary, cystic, or necrotic tumors (Fig. 3). One prospective study involving 115 patients with 147 cystic brain lesions, which included 97 patients with brain abscess, showed that diffusion-weighted imaging had a sensitivity and specificity for the differentiation of brain abscesses from primary or metastatic cancers of 96% (positive predictive value, 98%; negative predictive value, 92%).¹⁴ The use of proton nuclear magnetic resonance (¹H NMR) spectroscopy for the differentiation of brain abscess from cerebral tumors or metastasis has been studied, but the specificity and sensitivity were only marginally higher with the combination of diffusion-

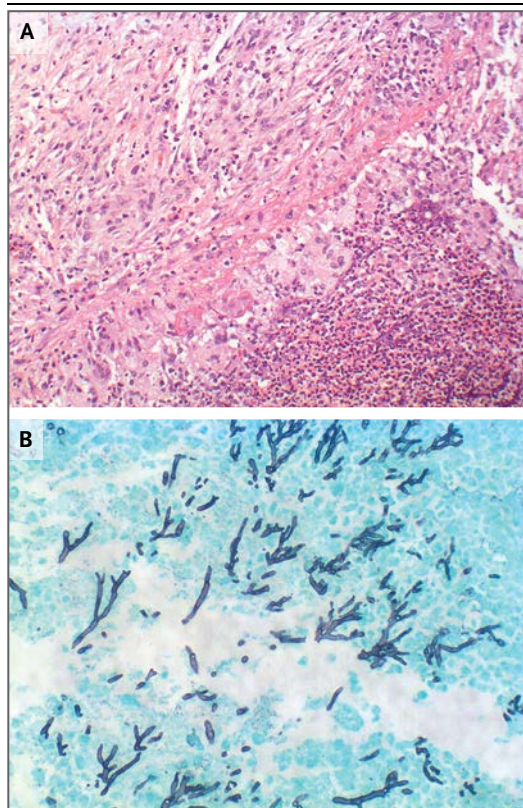


Figure 2. Pathological Findings for Fungal Abscess.

In Panel A, staining of a biopsy specimen with hematoxylin and eosin reveals an abscess with collections of neutrophils (prominent in the lower right corner) and macrophages within gliotic brain tissue. Staining with Gomori methenamine silver highlights the presence of fungal organisms (black) (Panel B).

weighted imaging and ^1H NMR spectroscopy than with diffusion-weighted imaging alone.¹⁵

Cultures of blood and cerebrospinal fluid iden-

tify the causative pathogen in approximately one quarter of patients.⁴ Cultures of cerebrospinal fluid may be valuable in patients with coexisting

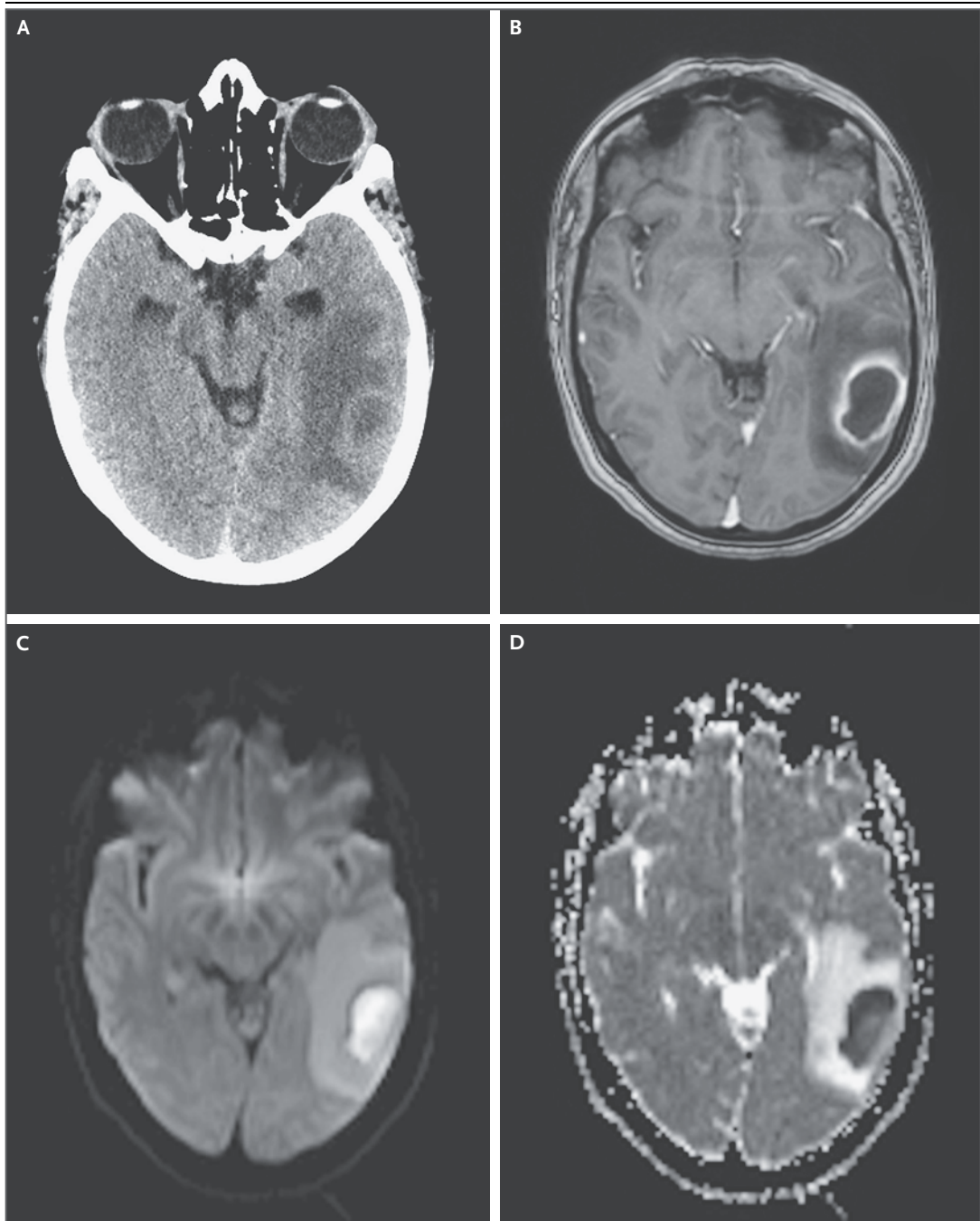


Figure 3. Imaging Studies of Brain Abscess.

An axial CT image of the cranium (Panel A) shows left parietal abscess characterized by a hypodense center, an iso-dense ring, and a surrounding hypodense zone that is consistent with edema. A T_1 -weighted MRI scan obtained after the administration of gadolinium (Panel B) shows a hypointense necrotic center with pus, ring-shaped enhancement of the abscess wall, and a hypointense zone of edema surrounding the abscess. Diffusion-weighted MRI shows a hyperintense signal within the abscess (Panel C), which is hypointense on apparent-diffusion-coefficient imaging (Panel D).

meningitis.¹⁶ However, the risk of brain herniation must be considered in these patients. Lumbar puncture should be performed only when there is clinical suspicion of meningitis or abscess rupture into the ventricular system and when there are no contraindications for lumbar puncture, such as brain shift on cranial imaging or coagulation disorders. Underlying dental, paranasal sinus, ear, and skin foci of infection should be cultured; surgical removal of these foci may be required.

NEUROSURGICAL MANAGEMENT

Neurosurgery is imperative for the identification of the causative pathogen, if it has not been determined otherwise, and, in selected patients, for the purpose of reducing the size of the abscess. With the use of modern stereotactic neurosurgical techniques, almost any brain abscess that measures at least 1 cm in diameter is amenable to stereotactic aspiration, regardless of location (Fig. 1). Stereotactic navigation systems can be used for abscess drainage,¹⁷ and images obtained with volumetric CT or MRI can be used to build a three-dimensional reconstruction of the patient's brain. Careful trajectory planning can then be optimized from the point of brain entry to the abscess to avoid "eloquent" brain tissue (i.e., areas of the brain that are critical for important functions such as speech, movement, sensation, and vision).

Stereotactic aspiration of the purulent center should be performed for the purposes of diagnosis and decompression unless it is contraindicated because of the suspected organism type or the patient's clinical condition. If brain imaging does not show a central cavity in the abscess, careful consideration should be given to the choice between performing a stereotactic biopsy of the area of presumed cerebritis and administering empirical antimicrobial treatment with follow-up cranial imaging. In HIV-infected patients with probable toxoplasmosis, presumptive therapy may be justified in the absence of a tissue-based diagnosis when tests for antitoxoplasma IgG antibodies are positive. In rare cases, surgery is withheld because poor health status or coexisting conditions would increase the surgical risk. If stereotactic navigation is not available, intraoperative ultrasonography can be performed through a burr hole or small craniotomy in order to direct abscess drainage, but this approach

is not recommended for small abscesses in deep brain locations.¹⁸

Diagnostic aspiration should be aimed at achieving maximal drainage of the abscess. Continuous drainage, made possible by placing a catheter into the abscess cavity, has been advocated as a means of decreasing reoperation rates, but this technique is not routinely recommended.¹⁹ Some experts advise postoperative administration of antimicrobial agents directly into the abscess cavity through the drainage catheter, since antimicrobial penetration into the abscess cavity after systemic administration can be limited, but there are few data on the risks and benefits of this approach and it is not routinely recommended. Total resection was recommended up to 20 years ago, but it now has a limited role, given the improvements in medical and minimally invasive neurosurgical management. Nevertheless, if an abscess is superficial and is not located in eloquent brain tissue, resection, rather than drainage, should be considered, particularly when there is suspicion of fungal or tuberculous infection or of branching bacteria (e.g., actinomyces or nocardia species).

If the causative pathogen has been identified, the indication for aspirating the abscess depends on its size and location, the patient's clinical condition, and the likelihood of achieving meaningful decompression through aspiration. In a small case series,²⁰ treatment was prone to failure when therapy consisted of antimicrobial agents alone. An abscess size of more than 2.5 cm in diameter has been recommended as an indication for neurosurgical intervention,²¹ but data from comparative studies are lacking, and this size cannot be regarded as a definitive indication for aspiration. In patients with multiple small brain abscesses, the largest abscess should be aspirated for diagnostic purposes; the decision to aspirate other abscesses should be made on the basis of their size, the extent of surrounding edema, the patient's symptoms, and the response to antimicrobial treatment. For patients in whom the abscess causes brain shift, leading to brain herniation, neurosurgical intervention may be indicated irrespective of the abscess size. If an abscess is abutting but has not yet ruptured into the ventricular system, drainage should be considered to prevent rupture of the abscess and resulting ventriculitis.

Microbiologic evaluation of cerebrospinal fluid, blood, or aspirate from the abscess should in-

clude Gram's staining and aerobic and anaerobic cultures.²² In immunocompromised patients and patients with risk factors such as a history of pulmonary tuberculosis or opportunistic infection, smears and cultures should be obtained for mycobacteria, nocardia species, and fungi, and a polymerase-chain-reaction (PCR) assay for *T. gondii* should be performed. If a bacterial brain abscess is strongly suspected but the culture results are negative, PCR-based 16S ribosomal DNA sequencing may provide a definitive etiologic diagnosis, allowing for targeted antimicrobial therapy.²³ When this test was performed on aspirates from brain abscesses in 71 patients, 30 (42%) of whom had positive cultures, bacterial DNA was detected in 59 patients (83%).⁹ The investigators identified 80 different bacterial taxa, 44 of which had not been described previously in brain abscesses, including 37 that have not been reported to be cultured.⁹ Although these data are indicative of the bacterial diversity within brain abscesses, it is unclear whether all these species are involved in the pathogenesis of abscesses and warrant treatment.²⁴

ANTIMICROBIAL THERAPY

A delay in the initiation of antimicrobial therapy can result in a poor outcome, as indicated by a retrospective study in which the median interval between diagnosis and the start of antimicrobial therapy was 2 days.²⁵ The investigators concluded that antimicrobial therapy should be started when there is clinical suspicion of a brain abscess. Because the administration of antimicrobial agents before stereotactic aspiration of the abscess may reduce the yield of bacterial cultures, it is reasonable to postpone the therapy until after neurosurgery has been performed, but only if the disease is not severe, the patient's condition is clinically stable, and surgery can be performed within a few hours. Caution is warranted with this approach, since the abscess may progress rapidly and unexpectedly, irrespective of the initial level of disease severity.

The choice of initial antimicrobial therapy should be based on the organisms that are the most likely cause of the disease, as determined on the basis of the mechanisms of infection and the patient's predisposing condition, on patterns of antimicrobial susceptibility, and on the ability

of the antimicrobial agent to penetrate the abscess (Tables 1 and 2). After organ transplantation, patients should receive empirical treatment with a third-generation cephalosporin (ceftriaxone or cefotaxime) plus metronidazole for bacterial brain abscess, trimethoprim-sulfamethoxazole or sulfadiazine for infection with nocardia species, and voriconazole for infection with fungal species, especially aspergillus.²⁶ In the initial treatment of HIV-infected patients, the addition of an agent that targets toxoplasmosis (pyrimethamine plus sulfadiazine) is recommended, but only for those with positive test results for antitoxoplasma IgG antibodies.⁵ Treatment for tuberculosis (isoniazid, rifampin, pyrazinamide, and ethambutol)²⁷ should be considered in patients with HIV infection and in patients who are immigrants from or have traveled in areas of the world where tuberculosis is endemic and who have known risk factors for tuberculosis, pending further diagnostic evaluation.⁵

Empirical treatment for patients who have undergone neurosurgical procedures or have sustained head trauma with skull fractures consists of vancomycin plus a third- or fourth-generation cephalosporin (i.e., cefepime) and metronidazole. For patients with contiguous spread from a parameingeal focus of infection and no history of neurosurgery, empirical treatment consists of ceftriaxone or cefotaxime combined with metronidazole. Vancomycin should be added if staphylococcal infection is also suspected. Meropenem may be considered as alternative empirical treatment in patients with contraindications to therapy with cephalosporins or metronidazole. A retrospective Spanish study showed similar outcomes for patients treated with cefotaxime plus metronidazole and those treated with meropenem.²⁸ In patients with brain abscess due to hematogenous spread, treatment consists of a third-generation cephalosporin combined with metronidazole to cover anaerobes; vancomycin should be added to treat potential staphylococcal infection, pending organism identification and the results of in vitro susceptibility testing.

Once the infecting pathogen has been isolated, antimicrobial agents can be modified to achieve the most effective therapy (Table 2). A dilemma arises when only a single pathogen is identified in blood cultures. Since 27% of brain abscesses are polymicrobial,⁴ broad-spectrum antimicrobial

Table 1. Predisposing Conditions and Microbial Isolates in Patients with Brain Abscess.*

Predisposing Condition	Common Microbial Isolates
Immunocompromise	
HIV infection	<i>Toxoplasma gondii</i> , nocardia and mycobacterium species, <i>Listeria monocytogenes</i> , <i>Cryptococcus neoformans</i>
Neutropenia	Aerobic gram-negative bacilli, aspergillus species, Mucorales, candida and scedosporium species
Transplantation	Aspergillus and candida species, Mucorales, scedosporium species, Enterobacteriaceae, nocardia species, <i>T. gondii</i> , <i>Mycobacterium tuberculosis</i>
Contiguous spread of bacteria	
Penetrating trauma or neurosurgery	<i>Staphylococcus aureus</i> , <i>S. epidermidis</i> , streptococcus species (anaerobic and aerobic), Enterobacteriaceae, clostridium species†
Otitis media or mastoiditis	Streptococcus species (anaerobic and aerobic), bacteroides and prevotella species, Enterobacteriaceae†
Paranasal sinusitis	Streptococcus species (anaerobic and aerobic), bacteroides species, Enterobacteriaceae, <i>S. aureus</i> , haemophilus species†
Hematogenous spread of bacteria	
Lung abscess, empyema, bronchiectasis	Fusobacterium, actinomyces, bacteroides, prevotella, nocardia, streptococcus species
Bacterial endocarditis	<i>S. aureus</i> , streptococcus species
Congenital heart disease	Streptococcus and haemophilus species
Dental infection	Mixed infection with fusobacterium, prevotella, actinomyces, bacteroides, and streptococcus species (anaerobic and aerobic)

* HIV denotes human immunodeficiency virus.

† The Enterobacteriaceae include *Escherichia coli* and enterobacter, klebsiella, proteus, and salmonella species.

therapy is advised until the results of culture of the abscess itself are known or until repeated aerobic and anaerobic cultures from blood or other sites of infection show no other pathogen. However, if the pathogenesis of infection is from a contiguous site, broad-spectrum antimicrobial therapy should be used to cover multiple pathogens (including anaerobes), even if no other infectious agents have been isolated. Brain abscess due to infection with multidrug-resistant gram-negative bacilli has been described after neurosurgical procedures or complicated head trauma.²⁹ Fungal brain abscesses are notoriously unresponsive to antimicrobial treatment, although in one study, the introduction of voriconazole therapy resulted in decreased mortality (65%, as compared with 91% for historical controls).²⁶

The duration of intravenous antimicrobial therapy in patients with bacterial brain abscess has traditionally been 6 to 8 weeks.²² Prolonged treatment with metronidazole has been associated with neuropathy.³⁰ However, in one study, peripheral neuropathies improved in all patients after metro-

nidazole was stopped.³⁰ The Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy recommended only 1 to 2 weeks of intravenous therapy for patients with bacterial brain abscess and stated that after such treatment, and depending on the clinical response, a change to an appropriate oral regimen can be considered.³¹ This approach has been used successfully in selected patients^{32,33} but is not considered to be standard therapy. An oral treatment regimen in these patients consisted of metronidazole, ciprofloxacin, and amoxicillin.³³

Important criteria for evaluating treatment are the neurologic condition of the patient and abscess size on cranial imaging. Cranial imaging should be performed immediately if there is clinical deterioration, after 1 to 2 weeks if there is no improvement, and on a biweekly basis for up to 3 months until clinical recovery is evident.¹⁹ Indications for further neurosurgery are clinical deterioration with an increasing abscess size on cranial imaging, despite the use of antimicrobial therapy.

Table 2. Antimicrobial Therapy in Patients with Brain Abscess.

Treatment	Therapy*
Empirical treatment	
Standard	Cefotaxime or ceftriaxone plus metronidazole; alternatively, meropenem (add vancomycin if infecting pathogen may be <i>Staphylococcus aureus</i> , pending organism identification and in vitro susceptibility testing)
For transplant recipients	Cefotaxime or ceftriaxone plus metronidazole, voriconazole, and trimethoprim-sulfamethoxazole or sulfadiazine
For patients with HIV infection	Cefotaxime or ceftriaxone plus metronidazole, pyrimethamine, and sulfadiazine; consider isoniazid, rifampin, pyrazinamide, and ethambutol to cover possible tuberculosis infection
Treatment based on isolated pathogen	
Bacteria†	
Actinomyces species‡	Penicillin G
<i>Bacteroides fragilis</i> ‡	Metronidazole
Enterobacteriaceae‡	Cefotaxime or ceftriaxone
<i>Fusobacterium</i> species‡	Metronidazole
<i>Haemophilus</i> species‡	Cefotaxime or ceftriaxone
<i>Listeria monocytogenes</i>	Ampicillin or penicillin G§
<i>Mycobacterium tuberculosis</i>	Isoniazid, rifampin, pyrazinamide, and ethambutol
<i>Nocardia</i> species	Trimethoprim-sulfamethoxazole or sulfadiazine
<i>Prevotella melaninogenica</i> ‡	Metronidazole
<i>Pseudomonas aeruginosa</i>	Ceftazidime or ceftipime¶
<i>S. aureus</i>	
Methicillin-sensitive	Nafcillin or oxacillin
Methicillin-resistant	Vancomycin
<i>Streptococcus anginosus</i> group, other streptococcal species‡	Penicillin G
Fungi	
<i>Aspergillus</i> species	Voriconazole
<i>Candida</i> species	Amphotericin B preparation¶¶
<i>Cryptococcus neoformans</i>	Amphotericin B preparation¶¶
Mucorales	Amphotericin B preparation
<i>Scedosporium apiospermum</i>	Voriconazole
Protozoa	
<i>T. gondii</i>	Pyrimethamine plus sulfadiazine

* The preferred daily doses of antimicrobial agents in adults with normal renal and hepatic function are as follows (with intravenous administration advised unless otherwise specified): cefotaxime, 2 g every 4 to 6 hours; ceftriaxone, 2 g every 12 hours; metronidazole 500 mg every 6 to 8 hours; meropenem, 2 g every 8 hours; vancomycin, 15 mg per kilogram of body weight every 8 to 12 hours to maintain a serum trough level of 15 to 20 µg per milliliter; penicillin G, 2–4 million units every 4 hours (or a continuous infusion of 12–24 million units daily); ampicillin, 2 g every 4 hours; isoniazid, 300 mg every 24 hours (oral); rifampin, 600 mg every 24 hours (oral); pyrazinamide, 15 to 30 mg per kilogram every 24 hours (oral); ethambutol, 15 mg per kilogram every 24 hours (oral); trimethoprim-sulfamethoxazole, 10 to 20 mg of trimethoprim plus 50 to 100 mg of sulfamethoxazole per kilogram per day, administered in two to four divided doses; sulfadiazine, 1 to 1.5 g every 6 hours (oral); ceftazidime, 2 g every 8 hours; ceftipime 2 g every 8 hours; nafcillin, 2 g every 4 hours; oxacillin, 2 g every 4 hours; voriconazole, 4 mg per kilogram every 12 hours after a loading dose of 6 mg per kilogram every 12 hours for two doses; amphotericin B deoxycholate, 0.6 to 1.0 mg per kilogram every 24 hours with doses of up to 1.5 mg per kilogram for patients with aspergillosis or mucormycosis; amphotericin B lipid complex, 5 mg per kilogram every 24 hours; liposomal amphotericin B, 5 to 7.5 mg per kilogram every 24 hours; pyrimethamine, 25 to 75 mg every 24 hours (oral); and sulfadiazine, 1 to 1.5 g every 6 hours (oral).

† The specific agent of choice depends on the results of in vitro susceptibility testing.

‡ These bacteria may be isolated as part of a mixed infection, and combination therapy may be needed.

§ An aminoglycoside should also be considered (e.g., 1.7 mg of gentamicin per kilogram every 8 hours).

¶ The addition of 25 mg of flucytosine per kilogram every 6 hours should be considered; serum trough levels of 50 to 100 µg of flucytosine per milliliter should be maintained.

COMPLICATIONS AND OUTCOME

For patients with a decline in consciousness, immediate brain imaging is indicated to detect hydrocephalus or impending brain herniation. Abscess rupture into the ventricular system results in ventriculitis, often leading to hydrocephalus, and is associated with high mortality (ranging from 27 to 85%). In patients with rupture, placement of an external ventricular catheter provides a means of draining and sampling cerebrospinal fluid and monitoring intracranial pressure, as well as providing a direct route for the administration of intraventricular antibiotics, if needed.³⁴ Hydrocephalus is also common in patients with abscesses in the posterior fossa.³⁵ A decline in consciousness may also be caused by seizures or status epilepticus.³⁶ Randomized studies of the use of prophylactic antiepileptic drugs in patients with brain abscess have not been performed. In one study involving patients with brain tumors, preventive treatment with antiseizure drugs was not associated with decreased seizure rates.³⁷ Anticonvulsant treatment is not routinely indicated in patients with brain abscess.

Focal neurologic deficits may develop in response to abscess growth or surrounding edema.

Adjunctive glucocorticoid therapy may reduce cerebral edema and is used in about half of patients with brain abscess.⁴ Since data from randomized studies are lacking and glucocorticoids may reduce passage of antimicrobial agents into the central nervous system, their use should be limited to patients with profound edema that is likely to lead to cerebral herniation. Hyperbaric oxygen has been described as an adjunctive treatment but only in small case series, and it cannot be regarded as routine.³⁸

The outcome for patients with brain abscess has improved over the past 50 years, following improvements in cranial imaging techniques, the use of antimicrobial treatment regimens, and the introduction of minimally invasive neurosurgical procedures.⁴ Mortality has declined from 40% in 1960 to 15% in the past decade.⁴ Currently, 70% of patients with brain abscess have a good outcome, with no or minimal neurologic sequelae,⁴ although data on functional and neuropsychological evaluation after brain abscess are lacking.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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