Review Article

Current concepts of bacterial infections of the central nervous system

Bacterial meningitis and bacterial brain abscess

GLENDA GARVEY, M.D.
College of Physicians and Surgeons of Columbia University, New York, New York

Investigative work continues to provide guidance toward more rational management of bacterial meningitis and bacterial brain abscess. An increased understanding of the host's response in cases of bacterial meningitis has established that diffusibility of an antibiotic into the cerebrospinal fluid (CSF) is necessary, but is not sufficient for microbial cure. The antibiotic must also have a bactericidal effect on the pathogen. Meningitis after neurosurgery may be caused by Gram-negative aerobic bacilli. In some of these cases the newer cephalosporin antibiotics may be a useful advance. Meningitis complicating ventricular CSF shunts presents a paradigm for the problem of eradicating foreign body-related infections. Studies of the interaction of the host, the organism, and the shunt material offer some explanation for the limited efficacy of antibiotics observed in this setting. There have been advances in microbial definition of bacterial brain abscess. The identification of Bacteroides fragilis as a pathogen in certain brain abscesses has established a role for a newly available antibiotic, metronidazole. The study of the pathological distinction between cerebritis and frank abscess is clarifying two clinical characteristics of brain abscess: the limited success of antibiotic treatment and the increase in intracranial pressure. Computerized tomography has offered a valuable clinical "look" at brain abscesses; however, there are still problems in correlating the scan images with the evolving pathological process.

KEY WORDS • brain abscess • bacterial meningitis • infection • steroid therapy • cerebrospinal fluid shunt • antibiotic therapy

THE clinical goals of rapid diagnosis and consistently successful treatment of bacterial infections involving the central nervous system (CNS) remain elusive. Efforts to achieve these goals have focused investigation on the interaction between the microorganism and the host defenses within the sanctuary of the brain, with particular emphasis on bacterial meningitis and cerebral shunt infections. Recent findings have redefined principles of antibiotic selection and management. Progress in precise microbiological analysis in cases of bacterial brain abscess has permitted refinement of antibiotic use, but understanding of the pathophysiology of bacterial abscess formation in the brain — the nature, sequence, and timing of the inflammatory response — remains imperfect. Attempts to correlate pathological findings with computerized tomography (CT) scans, have forced reevaluation of the roles of surgery and antibiotics in the management of brain abscess.

Bacterial Meningitis

Mechanism of Bacterial Infection

The interaction between bacteria and host defenses that results in meningitis is still not fully defined. It has been observed clinically that certain bacteria are more likely to attack the meninges and establish infection than others. This meningeal "tropism" may in part be
determined by surface characteristics of the organism. Compatible receptors on the membranes of the meningeal cells and the capsular surface of the bacteria have been postulated as contributory factors.

Analysis of the host defenses available in the cerebrospinal fluid (CSF) before and after bacterial invasion has identified at least two major mechanisms available to the host for clearance of bacteria. One clearance system requires a high-affinity or type-specific antibody and an intact classical complement system for opsonization, and the presence of competent polymorphonuclear cells for phagocytosis. The second system functions prominently in the immunologically suppressed host, opsonizing the organism with the interaction of low-affinity or nonspecific antibody and the alternate complement pathway. Depending on the particular organism, clearance by this system may occur in the absence of polymorphonuclear cells.

Analysis of normal CSF has demonstrated markedly low or absent levels of complement and opsonic proteins. The CSF therefore represents an immunological "vacuum," essentially devoid of factors needed for bacterial clearance.

Once bacteria attack and invade the meninges, lack of complement and opsonic protein in this "closed sanctuary" may provide them with a grace period. Initially, the bacteria are relatively free to multiply unrestrained, despite the presence of newly recruited polymorphonuclear cells. The components and timing of the immunological response after bacterial invasion have been studied. Slow targeting of polymorphonuclear cells into the CSF and the lack of serum-specific antibody available for diffusion during the inflammatory response are factors that increase the likelihood that bacterial infection will be established.

**Antibiotic Selection**

Based on these studies, principles of antibiotic selection for use in the setting of bacterial meningitis have been refined. The intricate layering of cell lipid membranes as well as possible extracellular and intracellular transport mechanisms create a selective barrier between the intravascular space and the CSF. Similar, although not identical, components constitute the barrier between the intravascular space and parenchymal brain tissue. Passage through these barriers is restricted by, among other factors, the relative lipid solubility, pH-determined ionization, and molecular structure of the particular antibiotic chosen. The inflammatory response increases the diffusion of some antibiotics and not others. Animal models and clinical studies have established a spectrum of antibiotic access from the blood into the CSF which can reasonably be considered relevant for access to brain tissue as well (Table 1).

Investigative work has demonstrated that the CSF represents a relative immunological vacuum, and supports the clinical observation that antibiotic diffusion into the CSF alone is not sufficient. The antibiotic must be able to achieve levels within the CSF that are bactericidal to the particular pathogen.

The classification of antibiotic activity as bacteriostatic or bactericidal depends on several factors. In the laboratory, the inhibitory effect can be defined by the highest dilution of the antibiotic that prevents visible turbidity after culture of a known inoculum in tubes of nutrient broth after 18 hours. Bactericidal effect defines the concentration of antibiotic that kills more than 99% of the bacterial population after subculture of the visibly clear tubes for 24 hours. Clinically, the level of antibiotic that is bactericidal must be considered in the context of concentration achievable in the relevant body fluid. The impression derived from clinical experience is that if an antibiotic can achieve levels that are only bacteriostatic to the organism, complete eradication of bacteria must depend on competent host phagocytosis. Antibiotics that can achieve bactericidal levels against the specific bacteria within the relevant body fluid may accomplish bacterial killing in the relative absence of host clearance mechanisms. The deficiency of complement and opsonic proteins in the CSF would therefore suggest that the best chance for microbial cure in meningitis would be offered by the use of an antibiotic that diffused into the CSF in levels bactericidal for the specific pathogen.

**Table 1**

<table>
<thead>
<tr>
<th>Antibiotic access to cerebrospinal fluid</th>
<th>Good: With &amp; Without Meningeal Inflammation</th>
<th>Good: With Meningeal Inflammation</th>
<th>Fair to Poor</th>
<th>None</th>
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<tbody>
<tr>
<td>chloramphenicol</td>
<td>penicillins</td>
<td>cephalosporins</td>
<td>polymixin</td>
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<td>metronidazole</td>
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<td>cephalothin</td>
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<td>&quot;3rd generation&quot;</td>
<td>ampicillin</td>
<td>cefoxitin</td>
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<tr>
<td>cephalosporins:</td>
<td>methicillin</td>
<td>aminoglycosides</td>
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<tr>
<td>moxalactam</td>
<td>oxacillin</td>
<td>gentamicin</td>
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<td>cefotaxime</td>
<td>nafcillin</td>
<td>tobramycin</td>
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<tr>
<td>trimethoprim/sulfur</td>
<td>carbencillin</td>
<td>amikacin</td>
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<td></td>
<td>ticarcillin</td>
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<td>rifampin</td>
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<td>trimethoprim/sulfur</td>
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<td>vancomycin</td>
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As noted by Rahal and Simberkoff, chloramphenicol, a favored antibiotic for use in meningitis, demonstrates the clinical relevance of these principles of antibiotic selection. Chloramphenicol diffuses well into the CSF, particularly when inflammation is present. Levels in the CSF that are bactericidal for Streptococcus pneumoniae, Neisseria meningitides, and Haemophilus influenzae are usually easily achievable. However, for some Gram-negative enteric bacilli, such as Escherichia coli and Klebsiella, bacteriostatic levels are achievable, but lethal or bactericidal levels often are not. Therefore, chloramphenicol may be recognized as an appropriate choice for use in the penicillin-allergic patient with S. pneumoniae meningitis, for example; however, it may not be relied on for treatment of meningitis caused by Gram-negative enteric bacilli. Indeed, clinical experience supports this construct. Microbial cure is dependably achieved in cases of S. pneumoniae meningitis managed with chloramphenicol, but relapse and development of resistance can occur during treatment for Gram-negative enteric bacilli.

Investigative work on host defenses within the CSF and antibiotic access have special relevance to two clinical problems: meningitis after neurological surgery, and meningitis complicating cerebral ventricular shunts.

**Postneurosurgical Meningitis**

The bacteria most frequently isolated in meningitis occurring in the early period after neurological surgery include the Staphylococci — usually S. aureus but also S. epidermidis. However, gram-negative aerobic bacilli are major pathogens in this setting. The principal reservoirs for these bacteria include intraoperative contamination with organisms carried into the field on sponges from the hands and faces of the surgical staff as well as from the patient’s skin. These are the predominant sources for the staphylococcal species. A second major reservoir is local wound infection, particularly in association with irrigation systems, and surgical drains, such as the Hemovac. The organisms found in local wound infection are predominantly the Gram-negative enteric bacilli including the Enterobacteraceae — especially E. coli, Klebsiella, Citrobacter, and Serratia, as well as Morganella, Pseudomonas, and Acinetobacter. These organisms are able to survive and multiply in aqueous environments such as pressure-transducer fluid and irrigation fluids.

Antibiotics that fulfill the principles for treatment of meningitis are available for staphylococcal organisms if they are sensitive to the penicillinase-resistance antibiotics. “Methicillin-resistant” S. aureus and S. epidermidis organisms that are resistant to beta-lactam antibiotics may be associated with meningitis after neurological surgery. In this instance, choice of an antibiotic is severely limited. Vancomycin alone or with rifampin has been recommended.

Many antibiotics are now available to treat systemic infections caused by enteric Gram-negative bacilli. However, two problems limit their availability for treating meningitis: 1) most of these antibiotics are unable to diffuse into the CSF in bactericidal concentrations; and 2) in many instances, these organisms may have developed resistance to antibiotics, particularly if they are hospital-acquired. Until recently, the only reliable agents in regard to bacterial sensitivity have been the aminoglycoside antibiotics — gentamicin, tobramycin, and amikacin. Resistance to these agents has developed. The risk of toxicity, both nephrotoxicity and ototoxicity, of these agents is significant. Nonetheless, these agents have remained almost by default the mainstay for treatment of Gram-negative bacillary meningitis. When the aminoglycosides are administered systemically, their access into the CSF is markedly limited, so intrathecal administration in addition to standard systemic dosing has been required. Evaluation of levels achieved in the CSF and study of the dynamics of CSF flow have established that introduction of an aminoglycoside into the lumbar space cannot achieve significant levels of the drug over the convexities of the brain or within the ventricular system. In some adults in whom ventriculitis may not be a component of the meningitis, the use of intralumbar aminoglycosides has been successful. However, microbial cure is not achieved reliably, and arachnoiditis has been described as a complication of administration. Efforts to introduce the drug directly into the ventricle by frequent ventricular taps in infants or through an implanted reservoir have been fraught with complications, including cerebral parenchymal injury and superinfection with resistant organisms.

The availability of the “third generation” cephalosporin antibiotics represents a significant advance in the treatment of this clinical problem. Moxalactam (Moxam) and cefotaxime (Claforan) are two of these agents that have been studied in connection with Gram-negative bacillary meningitis. Both drugs have excellent activity against many Gram-negative bacilli and easily achieve bactericidal levels within the CSF when given systemically. The efficacy of moxalactam in meningitis is essentially limited to H. influenzae and certain enteric Gram-negative bacilli including E. coli, Klebsiella and some Proteus infections. The drug is without reliable activity against Enterobacter and has no activity against Pseudomonas bacteria. Cefotaxime has essentially the same spectrum of activity, but also offers some activity against Streptococci, but not Group D Streptococci. Specific sensitivity testing of the E. coli, Klebsiella, and Proteus species against these drugs must always be performed. Sensitivity of the organism cannot be assumed, particularly in cases of hospital-acquired Gram-negative bacillary meningitis.

**Meningitis in Ventricular Shunting**

There have been significant advances in the design and materials used in ventricular shunting. Although the incidence is decreasing, infection remains a persist-
ent problem. The majority of infections occur in the early postoperative period: 70% within the first 2 months, 78% within 4 months after surgery. Late infections many months to years after placement do occur, more commonly with ventriculoperitoneal than with ventriculoperitoneal shunts.

The bacteria most frequently isolated are *Staphylococci* — *S. epidermidis* probably more commonly than *S. aureus*, as well as diphtheroids and *Bacillus* species. These organisms are part of normal skin flora and routes of infection include contamination of the apparatus at the time of placement. The organisms are transmitted from skin or nasal droplets of the surgical staff or the patient's scalp. In the immediate postoperative period, scalp wounds or follicular abscesses in association with sutures may provide the nidus for deeper infection and involvement of the shunt.

Gram-negative bacilli are also isolated in shunt infections. Reservoirs for these organisms include bowel flora, particularly in cases of subclinical or clinical peritonitis associated with early placement of ventriculoperitoneal shunts. Gram-negative bacilli may also be introduced through irrigation fluids or through ventricular drains placed prior to shunt surgery.

Management of ventricular shunt infections remains controversial. Bayston and Penny have documented a "slime" or mucoid substance formed in association with *S. epidermidis* colonization of shunt material. Recent studies of the initial adherence of bacteria to solid surfaces have investigated several catheters of diverse polymer composition. It was observed that *S. epidermidis* was able to grow, proliferate, and colonize these catheters in a broth free of nutrients. Scanning electron microscopy of the catheter surfaces demonstrated areas of erosion in association with the colonies of *S. epidermidis*. The significance of these findings is not clear. Additives within the polymer may be used as nutrients by the bacteria. In this study, the same slime-like material was noted in association with the colonization of the catheters.

In a study of foreign-body infection, Zimmerli, et al., used as their model rigid tissue cages of polymer — polymethacrylate and polytetrafluorethylene implanted subcutaneously into the flanks of guinea pigs. It was noted that the polymorphonuclear cells that surrounded these cages were relatively inefficient in phagocyte function when compared to polymorphonuclear cells in the blood and peritoneal fluid. Inoculation of small numbers of a low-virulence *S. aureus* (strain Wood 46) established infection rapidly. Over time, effective opsonization of these organisms around the cages diminished. One construct suggested by these observations is that some component of the foreign material may interfere with cell function of the surrounding polymorphonuclear cells. Initial adherence of bacteria is therefore relatively unhindered. Once attached, the *Staphylococci* elaborate a substance — the "slime" — that then may function as a barrier to opsonization and antibiotic activity.

This investigative work supports the clinical observation that antibiotic treatment alone is rarely successful in the management of shunt infections. When antibiotics alone are used, it is recommended that CSF levels are assayed to assure bactericidal concentrations of the chosen antibiotic against the infecting organism. This concept is derived from antibiotic management of endocarditis. Once the antibiotic is begun, achievement of serum bactericidal levels of 1:8 dilution or greater of an aliquot of the patient's serum cultured with a standard inoculum of the patient's organism has been associated with a lower relapse rate.

Attempts at antibiotic treatment may be necessary when loss of access makes shunt replacement difficult. However, the likelihood of success remains low. Clinical experience as well as investigative work fully support the recommendation that a combination of appropriate antibiotics with removal of the entire shunt apparatus, including the valve and the ventricular limb (not just the systemic limb), should constitute initial management of shunt infection. This regimen carries the best likelihood of cure.

The timing of antibiotic administration in relation to shunt removal and replacement has been best studied in a review of *S. epidermidis* infections of ventriculoperitoneal shunts. Nicholas, et al., found that, in the absence of a scalp wound near the intended site of shunt replacement and if the CSF is sterile at the time of replacement, the entire shunt may be removed and a new shunt replaced in the same operative procedure. Antibiotics are then continued for a minimum of 2 weeks.

When organisms other than *S. epidermidis* are involved, recommendations may include a two-stage procedure. The first stage requires administration of appropriate antibiotics and then removal of the complete shunt apparatus. Antibiotic treatment is then continued with or without ventricular drainage as dictated by the patient's tolerance. The second stage includes replacement of the shunt and completion of the antibiotic course. The ideal interval between shunt removal and shunt replacement is not known. The risk of secondary bacterial contamination in association with prolonged ventricular drainage or frequent ventricular taps is real. It is difficult to assess the proper time interval that will assure sterilization of the CSF without increasing the risk of superinfection.

**Bacterial Brain Abscess**

*Nature and Bacteriology*

After antibiotics became available the assumption was made that the morbidity and mortality rates associated with bacterial brain abscess would decline rapidly. However, it is only in the past 10 to 15 years that outcome has improved significantly. Meticulous, discriminating microbiological studies, facilitated by improved techniques for anaerobic cultures, and a growing understanding of the inflammatory changes associated
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with bacterial infection of the brain parenchyma have been two factors accounting for these advances.

The most common identifiable clinical settings associated with brain abscess include a contiguous focus of infection, such as chronic sinusitis, chronic otitis, or cranial trauma (either surgical or accidental), and metastatic infection, as in bacterial endocarditis. Cyanotic congenital heart disease and chronic pulmonary disease are underlying conditions that are associated with brain abscess.\(^1,5,36,42\) The increased risk may be the result of local cerebral damage secondary to hypoxemia. These areas of hypoxic change may be permissive loci for seeding during bacteremic episodes. Bacteremia may be more frequent when not "filtered" by the lung in heart disease, as in cases of right heart shunting, or in patients with suppuration of the lung. In most recent series of bacterial abscess the classical sources and risk factors are often lacking, and single idiopathic abscesses constitute a major category.

The bacteriology of brain abscess can be defined in relation to the presumed etiology and/or predisposing underlying disease. The definition of the bacterial spectrum, however, has required the development of techniques permitting isolation and identification. \(Streptococci\) have long been recognized as the predominant bacteria isolated. However, over 50% of culture results in some series in the past were "sterile." When improved anaerobic culture techniques became available, the incidence of positive cultures in this condition increased. Heineman and Braude\(^1,5\) presented work that suggested that many, although not all, of the abscesses thought to be sterile may have been caused by anaerobic organisms, particularly anaerobic \(Streptococci\) and \(Bacteroides\) species. Meticulous culture techniques have been used by de Louvois, et al.,\(^10\) resulting in a major advance in definition of the bacterial spectrum in brain abscesses. These studies confirmed that \(Streptococci\), with a predominance of \(S.\) \(millerii\), a viridens group of \(Streptococcus\), was the most common isolate in brain abscesses of all origins. \(Streptococcus\) was a prominent single pathogen in abscesses not located in the temporal lobe. \(Staphylococcus aureus\) was isolated particularly in cases resulting from trauma.

De Louvois, et al.,\(^10\) also emphasized the importance of Gram-negative aerobic bacilli. \(Haemophilus\) species were isolated alone or as part of mixed flora, particularly in cases of chronic sinusitis. The \(Enterobacteraceae\), especially \(E.\) \(coli\), and \(Proteus\) species, were often found in mixed cultures of posttraumatic or postneurosurgical abscesses, or of abscesses associated with chronic otitis.\(^10\)

Most significantly, Gram-negative anaerobic bacilli, particularly \(Bacteroides fragilis\), were identified as important pathogens in brain abscess. They were isolated predominantly in mixed cultures of temporal lobe abscesses associated with chronic otitis, and somewhat less commonly in abscesses associated with sinusitis.\(^10,11,15\) The recognition of \(Bacteroides fragilis\) has been critically important.\(^10,11,15\) Until recently, the outcome of otic brain abscesses has seemed least improved by the availability of antibiotics.\(^1\) The antibiotics used in these past series have included penicillin and chloramphenicol. Both of these agents diffuse into brain tissue, but sensitivity of \(Bacteroides fragilis\) to penicillin is unreliable, and neither antibiotic is reliably bactericidal for the organism. Metronidazole (Flagyl) is a newly available antibiotic that diffuses well into the CSF and brain tissue. It achieves levels that are rapidly bactericidal to \(Bacteroides\), specifically \(B.\) \(fragilis\).\(^34,48\) Its use in the management of otogenic brain abscess, in conjunction with another antibiotic such as penicillin for aerobic and anaerobic organisms for which metronidazole is not active, has demonstrated superior response.\(^1,13,16\)

Antibiotics alone, even if chosen for bactericidal effect on correctly identified organisms, and for diffusibility into brain tissue, have in general been ineffective in improving the morbidity and mortality rates associated with frank brain abscess. Investigative work on the inflammatory changes associated with bacterial infection of the brain has established a distinction between bacterial cerebritis and formal brain abscess. This distinction is useful in considering the role of antibiotics in these cases.

Results in animal experiments support the likelihood that, for initial bacterial invasion of brain parenchyma to occur, there must be preexisting or concomitant injury such as arterial or venous occlusion or trauma.\(^25\) Once bacteria have established infection, there is recruitment of acute inflammatory cells and secondary alteration of vascular endothelial permeability. Aggregation of polymorphonuclear cells and extravasation of protein containing fluid occurs. The sequence of response proceeds with recruitment of macrophages, ongoing phagocytosis of bacteria, and increasing local edema.\(^25,30,47\) There is increasing proliferation of vascular mesenchymal cells, polymorphonuclear cells, macrophages, microglial cells, and reactive astrocytes. These cells form a zone of granulation tissue. A thin capsule of fibroblasts and reticular fibers gradually develops, surrounding the area of intense inflammatory reaction.\(^30,45\) Perifocal edema increases, and there is an increase in total brain water.\(^47\) As the capsule matures peripherally, a core of active inflammatory cells, necrotic debris, and microorganisms develops within the center of the infected area of brain. The early stages of this infection have been referred to as cerebritis. The later stage, characterized by a complete capsule and central necrosis is the pathological equivalent of brain abscess. The speed of evolution from cerebritis to brain abscess is determined by many factors, including the inherent virulence of the particular bacterial organism(s), the inoculum size, as well as the availability and responsiveness of the local and systemic immune defenses.

Management of Brain Abscess

Two observations are particularly relevant to the management of brain abscess: the development of an
encapsulated focus with a central core of purulence, and the altered endothelial permeability and secondary increase in perifocal and total brain water. Antibiotics with appropriate features, including specific protein and lipid-binding characteristics, can diffuse into the area of inflammatory response to the bacterial insult. The milieu of cerebritis, rich in capillaries and inflammatory cells but without necrosis, should permit antibiotics to remain active. In contrast, animal models and clinical studies have demonstrated that once an abscess has formed, bacteria persist within the central core. These bacteria can be isolated, despite access of appropriate antibiotics measurable within the abscess. The intensely acid environment associated with the necrotic debris may decrease or eliminate antimicrobial action. Antibiotics at this stage may be important adjuncts for the treatment of advancing areas of cerebritis, but cannot be relied upon to sterilize organisms within the necrotic core. Despite antibiotic treatment, the microorganisms can persist in this area and continue to elaborate substances toxic to brain tissue.

The second observation of importance for management is the recognition of increased vascular permeability early in the inflammatory response. This change in permeability causes accumulation of interstitial fluid both around the focus and throughout uninfected portions of the brain. This diffuse change in water content of the brain in the presence of a relatively small focus of infection has been noted in animal studies, confirmed by clinical experience, and must be considered to be characteristic of brain abscess.

**Diagnosis**

These studies of the inflammatory changes in the brain in response to bacterial infection have implications for appropriate management. Early diagnosis of the infection must be the goal before the establishment of a core of necrosis that may be inaccessible to antibiotic effect and before increased brain water exceeds the plasticity of the brain. It is important to consider this diagnosis when a patient first presents with fever, even if low-grade, and altered neurological status, particularly in a permissive clinical setting associated with brain abscess. However, clinical signs and symptoms themselves are not helpful in the distinction between cerebritis and frank abscess. In one series, it was noted that an interval of greater than 2 weeks between onset of signs or symptoms and presentation correlated at surgery with a fully formed abscess.

The role of CT scanning in distinguishing cerebritis from cerebral abscess is still being defined. Since CT scans may "lag" days behind established intraparenchymal infection, they cannot be used to rule out the diagnosis if an initial study is negative. However, the appearance of a lesion with a surrounding ring that enhances with contrast material had been considered compatible with frank abscess formation. It is now recognized that this ring of enhancement does not represent a "capsule" but rather the "halo" of contrast material released into areas of altered vascular permeability surrounding the focus. This ring may therefore appear in stages of cerebritis before an actual capsule has formed. Evidence suggests that a relatively faint inhomogeneous enhancing ring with a surrounding area of hypoattenuation correlates with cerebritis, while a homogeneous ring correlates more reliably with firm capsule formation. Animal studies suggest that an increasing diameter of the surrounding hypolucency area or of the enhancing ring is characteristic of cerebritis. Stabilization and decrease in ring diameter correlated with abscess formation. The use of sequential CT scans may aid in this determination. The tempo of evolution as shown by CT scan is quite variable: the interval between findings suggesting an early stage of infection and a late stage may vary from only hours to days.

Once the diagnosis of an intraparenchymal focal bacterial infection has been secured, antibiotics must be selected with attention to the available culture results and to the likely pathogens in the particular setting. The antibiotics must be those capable of diffusing into brain tissue and bactericidal to the likely bacteria. Very few studies of antibiotic use and diffusion into brain tissue are available. At present, those antibiotics determined to diffuse well into the CSF should be selected until further information is available.

**Steroid Therapy**

The threat to the patient's life in the presence of bacterial brain infection is the effect of the expanding mass, not the septic nature of this lesion. The pressure within the expanding core of the abscess may result in rupture. When it does occur, rupture is often medial into the ventricle. Pathological study confirms that abscesses develop most commonly at the corticomedullary junction. The abscess capsule forms asymmetrically around the inflammatory mass. Characteristically, the capsule is thinnest at the medullary margin and is most substantial at the cortical margin. A difference in vascularity of these areas has also been noted. There may be inadequate vascular adventitial cells and fibroblasts for dense capsule formation in the white matter of the medial portion of the capsule.

A more frequent complication of the pressure effect of the abscess is progressive diffuse increase in brain water. Increasing intracranial pressure (ICP) and abrupt herniation remain the major causes of morbidity and mortality. Control of life-threatening pressure changes is the basis for management of brain abscesses. Steroids have been considered as one means of controlling increased ICP. Steroids appear to decrease endothelial permeability of the vessels associated with the inflammatory reaction around the abscess, and may reduce the magnitude of change in brain water. This effect on inflammation, however, may also result in decreased diffusion of antibiotics into the infected focus,
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as has been recorded in cases of resolving meningitis,14 which could reduce the antibiotic effect on the infection.30 The use of steroids in this setting therefore remains controversial. Quartey, et al.,30 in rabbit experiments, used dexamethasone 24 or 72 hours after the initiation of brain infection, in conjunction with appropriate antibiotics. In their model, steroid therapy was associated with increased necrosis, persistence of organisms, and elimination of capsule formation. On the other hand, work by Wallenfang, et al.,47 in cats demonstrated a favorable effect of dexamethasone in reducing potentially catastrophic brain edema without compromising the formation of the capsule. In this model, the dexamethasone was started 7 days after induction of infection. The clinical relevance of these animal studies is difficult to assess. Beller, et al.,5 noted a higher mortality rate in patients treated with steroids. However, a 15-year review by Alderson, et al.,1 suggested that the increased use of steroids was possibly related to improved survival rates. The appropriate dosing regimen for steroids, the proper timing, and the relative adverse effects on microbial treatment remain undefined.

Surgical Treatment

The timing of surgical intervention remains difficult and debated. Awaiting serial CT scan evidence of abscess stabilization to ensure encapsulation places the patient at high risk for intraventricular rupture or abrupt herniation. A recent series from Newcastle-upon-Tyne reviewed the mortality figures in 90 consecutive cases of brain abscess treated from 1964 through 1978.1 A decrease in mortality rate was noted sequentially in each 5-year period: 42% to 21% to 9.7%. This careful review correlated improved survival times in the first 10 years primarily with earlier surgical intervention. There was a definite shortening of the interval between admission and primary excision of the abscess, particularly for the Grade B patients—those who were drowsy and disoriented, but responding to commands. This trend preceded any contribution to more rapid or reliable diagnosis afforded by the newly available CT scanner, and represented a willingness to pursue a more aggressive surgical approach. The decline in mortality rates was also correlated with recognition of Bacteroides fragilis as a pathogen, particularly in otogenic abscesses, and the availability of metronidazole, as well as with the more consistent use of steroids. These factors were analyzed and found to be of importance but of less significance than earlier surgical intervention, particularly in the first 10 years of the series.

There are circumstances in which surgical intervention may not be feasible. A group of these “high risk” patients was reported by Rosenblum, et al.35 Their series included patients with surgically inaccessible lesions, multiple abscesses, active meningitis, or ventricular shunts in place, and patients who were markedly debilitated by other underlying diseases. All of these patients had lesions visible on CT scanning that were compatible with bacterial foci, although the distinction between early stages of infection and the later stage of abscess formation could not be and was not made. These patients were all managed only with prolonged appropriate antibiotics, for at least 6 weeks. Those who responded successfully had small lesions (mean 1.7 cm or less), and were classified neurologically on presentation as either Grade I (alert) or Grade II (lethargic). Other series of successful outcome with antibiotic treatment alone have been reported with documentation by CT scanning. What cannot be confirmed is the initial pathological stage of inflammation at initiation of antibiotic treatment.18 A CT scan can reveal a lesion that represents a small area of cerebritis, which can be treated effectively before central necrosis occurs; this prompt treatment may be one explanation for successful medical management of these CT-apparent brain “abscesses.”

Scanning techniques are not yet available to permit both earlier diagnosis and definition of the stage of inflammatory response of the infected focus. The use of serial CT scans for assessment of the success of medical treatment may also have limitations; however, a better understanding of CT findings during treatment is available.27 It is now well acknowledged that if concomitant steroids are used along with antibiotics the contrast-enhancing ring may diminish and even disappear.49 This effect of steroid therapy should not shorten the duration of antibiotics or decrease vigilance and consideration of surgical intervention. It is now also recognized that with tapering of steroids the enhancing ring may reappear or increase in density. The pathological significance of the reappearance of enhancement is not clear.49

Conclusions

The host’s immune response within the CSF and brain parenchyma in bacterial meningitis and bacterial brain abscess remains incompletely understood. However, present knowledge has allowed more intelligent use of antibiotics in these diseases. Newer antibiotics with access to CSF and brain tissue at bactericidal levels permit killing of certain bacteria previously impervious to available antibiotics. Specifically, the newer cephalosporin-related antibiotics are useful in the treatment of some Gram-negative aerobic bacilli that are important causes of meningitis and brain abscess in certain set-
tings. Metronidazole is invaluable as a bactericidal drug for *Bacteroides fragilis*, now recognized as a major pathogen in certain brain abscesses. However, with these advances in understanding and application has come recognition of the limitations of antibiotic therapy. Microbial persistence remains a particular problem in infection involving foreign material and in frank brain abscess. The failure to achieve microbial cure with antibiotics alone in these cases forces continuing evaluation of the role of surgery in the management of these infections, and encourages efforts at earlier diagnosis and prevention of infection.

Techniques that permit rapid diagnosis of bacterial meningitis are available. Some provide early nonspecific markers of bacterial infection (for example, the limulus lysate gelation technique). Other methods permit identification of a specific pathogen in advance of obtaining culture results (for example, counterimmunoelectrophoresis). The limulus lysate test is based on the observation that a lysate prepared from amebocytes of the horseshoe crab, *Limulus polyphemus*, undergoes gelation in the presence of endotoxin. It was anticipated that this test might be useful in screening blood for early detection of Gram-negative bacteremia, but the test proved too sensitive in this setting: factors in blood other than endotoxin caused gelation. However, gelation of the amebocyte lysate by CSF offers an indication, before culture results are available, that Gram-negative aerobic bacterial meningitis may be present. The test is not specific, and cultures must be relied upon for confirmation and identification.

Counterimmunoelectrophoresis is a technique that has proved useful for early, specific diagnosis of bacterial meningitis, particularly in patients who have received previous antibiotic therapy. Counterimmunoelectrophoresis is a modification of the agar gel diffusion technique. Prepared antibody and an aliquot of the CSF to be tested are placed in opposed agar wells. An electric current is passed through the agar substrate. The negatively charged antigen, if present in the CSF, will migrate toward the anode. The antibody globulin migrates toward the cathode. Movement in the presence of the current is more rapid than by simple diffusion. Bands of confluence may identify a specific bacterial antigen present in the aliquot of CSF within 30 to 90 minutes. At present, antibodies prepared to the capsular antigens of *H. influenzae*, *N. meningitidis* Groups A, B, and C, *S. pneumoniae* and *S. agalactiae* are available. False-negative results do occur, particularly with *N. meningitidis* Group B and some types of *S. pneumoniae*. Nonetheless, this technique has been helpful in early diagnosis of spontaneously occurring meningitis in which *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* are common pathogens. However, these organisms are rarely causes of meningitis in the post-neurosurgical setting or of meningitis complicating shunt infection. At present, therefore, counterimmunoelectrophoresis is not usually helpful for early specific identification in these conditions, and bacterial culture remains the only reliable technique.

Difficulty in rapid specific diagnosis of meningitis occurring in the patient after neurosurgery or with a ventricular shunt has increased efforts at prevention. Epidemiological studies of modes of transmission and simple techniques of handwashing have been important in control of meningitis following neurological surgery. The use of antibiotic-incorporated polymers for ventricular shunts is being investigated in efforts to decrease the incidence of early-onset shunt-related meningitis. Recommendations by the American Heart Association for antibiotic prophylaxis in the placement of prosthetic heart valves during procedures associated with bacteremia may be advisable to prevent late infection in patients with cerebral ventricular shunts.

Prevention of brain abscess may well not be possible in most circumstances. Availability of earlier and more aggressive antibiotic treatment of ear and sinus infections, however, may have reduced the incidence of associated brain abscesses. A continued decrease in mortality resulting from brain abscesses at present seems dependent on the development of more sensitive techniques to diagnose the infection in its earliest stages. Perhaps nuclear magnetic resonance will be useful here.

New antibiotics with improved access and an appropriately focused spectrum for these CNS infections will become available. Techniques for earlier diagnosis and more accurate monitoring of response to treatment will be developed. Most important, investigation in animal models and clinical correlations are in progress that will provide information about normal host responses within the meninges and the brain. These studies should permit a better understanding of these "old" infections and a refinement of our concepts of management, diagnosis, and prevention.

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Address reprint requests to: Glenda Garvey, M.D., College of Physicians and Surgeons of Columbia University, 630 West 168th Street, New York, New York 10032.