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THIRD EDITION

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NEUROLOGICAL SURGERY

A Comprehensive Reference Guide to the Diagnosis and Management of Neurosurgical Problems

THIRD EDITION

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Cephalic Pain; Dorsal Rhizotomy and Dorsal Root Ganglionectomy; Cordotomy by Open Operative Techniques

Contents

volume 6

chapter 132

Cranial and intracranial bacterial infections

Infection may be introduced into the central nervous system in several ways: (1) direct inoculation following penetrating cranial trauma or operation, (2) direct extension through the skull and meninges from an adjacent infective focus such as the middle ear or mastoid air cells, and (3) hematogenous spread. Hematogenous spread of organisms may be via transcranial venous pathways from an adjacent extracranial focus of infection (e.g., in the paranasal sinuses) or through arterial dissemination (e.g., in meningitis due to *Haemophilus influenzae* or metastatic brain abscess). In each case, the likely offending organisms differ and the pathophysiology of the infective process varies. These differences will be discussed individually in the following sections on specific intracranial infections. However, there are certain natural defense mechanisms that share a common role in attempting to contain all of these infective processes.

Host Defenses*

Except in the case of direct inoculation of the infective organism, the development of infection in the central nervous system indicates a failure of the natural host defenses to contain the organism and exclude it from the nervous system. These defenses fall into four categories: cell-mediated immunity, humorally mediated immunity, neutrophil function, and the reticuloendothelial or mononuclear phagocytic system. Experience with immunosuppressed patients suggests that those with deficiencies in cell-mediated immunity are most likely to develop central nervous system infections with predominantly intracellular organisms. *Listeria monocytogenes, Mycobacterium tuberculosis, Toxoplasma gondii, Cryptococcus neoformans, Aspergillus* species, and *Nocardia asteroides* are among the organisms seen in these patients. This category of patients includes those receiving daily corticosteroid therapy, those with lymphoma, those having undergone organ transplantation, and those with acquired immunodeficiency syndrome (AIDS). Deficiencies in humoral immunity are frequently associated with multiple myeloma, chronic lymphocytic leukemia, and Hodgkin's disease, especially after intensive chemotherapy and radiotherapy. These patients appear to be at unusual risk for infections caused by encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Where the neutrophil population is quantitatively or qualitatively insufficient (generally when the absolute neutrophil count is less than 1000 cells per cu mm), fungal disorders and infections caused by *Pseudomonas aeruginosa* become a significant problem. Finally, patients whose reticuloendothelial system is damaged cannot produce sufficient immunoglobulin-M opsonizing antibodies to facilitate the phagocytosis of invading organisms by the reduced number of mononuclear phagocytes. Patients who have undergone splenectomy and do not possess immunity to a given organism are susceptible to

*See references 3 and 116.

S. J. Haines, T. Mampalam, M. L. Rosenblum, and M. G. Nagib

fulminant sepsis, especially from encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.

When one or more of these primary host defenses are inadequate, there is an increased risk of central nervous system infection. As indicated earlier, the definition of primary host defense inadequacy suggests that certain organisms are more likely than others to be causing the infection. When the primary host defenses function normally, it is still possible to overwhelm them and establish central nervous system infection.

A second line of defense is the physical barrier represented by the membranes separating the central nervous system from the rest of the body. In the case of direct extension from an infective process outside the central nervous system, the dura and arachnoid represent important physical barriers that are seldom breached.[102] The protective nature of the arachnoid is attested to by the relative rarity of subdural empyema in most forms of bacterial meningitis. When arterial bacteremia is the mechanism of inoculation, the physical barrier is only that of the capillary wall and basement membrane of the choroid plexus. Some experimental studies appear to document that choroid plexitis is the initial phase of central nervous system infection in meningitis that follows bacteremia, although other studies suggest that the first phase is retrograde infection from the dural venous sinuses.[123, 132]

Once bacteria have invaded the central nervous system, each of the previously mentioned primary host defenses remains active within this system, although at very much reduced levels. Understanding of cell-mediated immunity in the central nervous system is very limited. Humorally mediated immunity within the central nervous system is evaluated primarily by measurement of immunoglobulins in the cerebrospinal fluid. Normally these levels are extremely low, although they do rise somewhat during meningitis.[50] Antibody synthesis within the cerebrospinal fluid has been demonstrated in certain central nervous system infections.[125] The levels remain substantially lower than those in serum and support the concept of the central nervous system as a relatively immunodeficient locus. Neutrophils are known to enter the cerebrospinal fluid during meningitis, and this is indeed one of the hallmarks of typical bacterial meningitis. Because of deficient opsonization and probably because of other unknown factors, neutrophil phagocytosis of bacteria is relatively inefficient in the cerebrospinal fluid. The precise role of neutrophils in defending the central nervous system against infection remains unclear. There is some degree of mononuclear phagocytosis within the central nervous system, but this is substantially less active in this location than elsewhere in the body.[6] It seems clear, therefore, that the central nervous system can accurately be viewed as a relatively immunocompromised location and that once the primary host defenses have been breached and central nervous system infection is established the addition of other methods of eradicating infection is very important.

Antibiotics and the Central Nervous System

The structural characteristics of the central nervous systems capillaries create a relative barrier to the entry of hydrophilic drugs, which makes the treatment of nervous system infections unique. The choice of appropriate antibiotics is restricted because of this barrier, and the toxicity of antibiotic treatment may be amplified since higher systemic doses may be necessary. Within brain substance, this barrier exists between the blood and cerebrospinal fluid, blood and brain substance, and blood and lesions.

THE BLOOD–CEREBROSPINAL FLUID BARRIER

After intravenous administration a large number of factors affect the amount of antibiotic that becomes available in the cerebrospinal fluid. Some of these factors are outlined in Figure 132–1.[121,124] The amount of free antibiotic available to pass into the cerebrospinal fluid is affected by both the amount of protein binding and the serum pH. Major impacts on the migration of drugs into the cerebrospinal fluid are lipid solubility, membrane integrity, and the possible presence of an active transport mechanism. There are drugs, such as penicillin, that once inside have an active transport mechanism for removing the drugs from the cerebrospinal fluid. Probenecid can block this mechanism in the case of penicillin. The drug may once again bind with accessible proteins after entering the

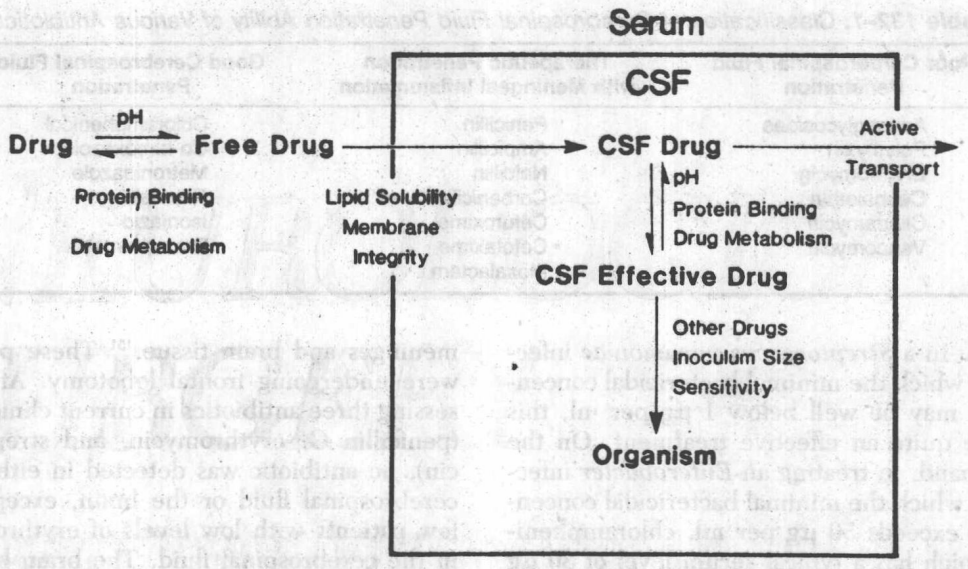

Figure 132–1. Schematic representation of factors influencing antibiotic penetration into the cerebrospinal fluid. (From Haines, S. J.: Antibiotics in neurosurgery. A selective review. *In* Brock, M., and Reerless, S., eds.: Modern Neurosurgery 2. Berlin, Springer-Verlag, in press. Reprinted by permission.)

cerebrospinal fluid, and the pH of the new milieu will again affect the amount of available drug. Metabolism of the drug to inactive forms, the minimal bactericidal concentration of the drug for the specific organism, and the effect of inoculum size, which may independently alter the effective minimal bactericidal concentration, are other factors that may determine the therapeutic efficacy of the drug in the cerebrospinal fluid.

Many factors influence cerebrospinal fluid levels in various experimental and clinical situations. These factors must be taken into account when attempting to assess the cerebrospinal fluid penetration of various antibiotics. Species differences must be contended with when using animal models. Also, the method of drug assay can confuse the results in both animal and human data. For example, the *Sarcina lutea* bioassay also measures the metabolite desacetylcephalothin, which is active against *Sarcina* but generally not against clinically important microorganisms.[87] Other issues confusing the picture in human studies are differences in age, dosage, dosage timing, the type of lesion being treated, and other therapies being applied. The end result of these numerous interacting variables is that, especially in human data, there is an immense amount of variation. Figures taken from a large review of these data indicate that percentage cerebrospinal fluid penetration (cerebrospinal fluid level divided by simultaneous serum level) for amikacin ranges from 0 to 49 per cent, for cephalothin ranges from 0 to 88.6 per cent, and for penicillin G ranges from 0.39 to 807.9 per cent.[110] Therefore, on the basis of human data alone, it is impossible to classify various antibiotics with regard to their cerebrospinal fluid penetration. It is possible, however, to classify certain common antibiotics by their expected ability to penetrate into the cerebrospinal fluid on the basis of the consensus examination of both animal and human data (Table 132–1).[54,61] These classifications can be used as general guidelines only. For individual cases a particular antibiotic may be rendered more or less effective than one would predict owing to interactions of the variables mentioned above. The lists are not intended to be complete but to be representative.

In estimating the therapeutic efficacy of drugs for the treatment of infection in the cerebrospinal fluid, an important consideration is that in the final analysis the efficacy of treatment against a specific organism is determined by the ratio of the attained cerebrospinal fluid drug level to the minimal bactericidal concentration of that drug. A poorly penetrating drug may be more effective when used against a highly sensitive organism than a drug that penetrates well that is used against a relatively resistant organism. As an example, penicillin G can be given in systemic doses that produce a cerebrospinal fluid level of 5 μg per ml of cerebrospinal fluid since it may, on the average, have about 5 per cent pene-

*Table 132–1. Classification of Cerebrospinal Fluid Penetration Ability of Various Antibiotics**

Poor Cerebrospinal Fluid Penetration	Therapeutic Penetration with Meningeal Inflammation	Good Cerebrospinal Fluid Penetration
Aminoglycosides	Penicillin	Chloramphenicol
Polymyxin	Ampicillin	Co-trimoxazole
Erythromycin	Nafcillin	Metronidazole
Cephalothin	Carbenicillin	Rifampin
Clindamycin	Cefuroxime	Isoniazid
Vancomycin	Cefotaxime	Praziquantel
	Moxalactam	

tration. In a *Streptococcus pneumoniae* infection in which the minimal bactericidal concentration may be well below 1 μg per ml, this will be quite an effective treatment. On the other hand, in treating an *Enterobacter* infection in which the minimal bactericidal concentration exceeds 50 μg per ml, chloramphenicol, which has a typical serum level of 30 μg per ml and 50 per cent cerebrospinal fluid penetration, will be an ineffective treatment.

Careful attention to all these factors as they influence the individual case is essential when selecting appropriate drugs for the treatment of meningitis.

THE BLOOD-BRAIN BARRIER

The factors involved in penetration of antibiotics into brain substance are very similar to those outlined for cerebrospinal fluid penetration. It is well documented that the blood–cerebrospinal fluid barrier and the blood-brain barrier are not identical. Much less information is available about the penetration of antibiotics in the brain substance than about their penetration into the cerebrospinal fluid. Because of the practical and ethical difficulty in obtaining tissue specimens for analysis, human data are far more limited. Two facts seem to stand out with regard to animal data. First, it cannot be necessarily predicted from cerebrospinal fluid penetration what the brain penetration will be. Beam and Allen found both cefamandole and ampicillin to penetrate the brain better than the cerebrospinal fluid in animals with normal meninges.[9] On the other hand, Ruedy found no difference between cerebrospinal fluid level and brain penetration for a number of penicillins.[117] Cerebrospinal fluid penetration far exceeded brain penetration in both studies when the meninges were inflamed. Only one study compares cerebrospinal fluid and brain penetration in humans who were presumed to have normal meninges and brain tissue.[151] These patients were undergoing frontal lobotomy. After assessing three antibiotics in current clinical use (penicillin G, erythromycin, and streptomycin), no antibiotic was detected in either the cerebrospinal fluid or the brain, except in a few patients with low levels of erythromycin in the cerebrospinal fluid. The brain level of antibiotic may have been influenced by preexisting brain lesions in the two remaining human studies. Kramer and associates found percentages of brain penetration ranging from 0.2 for ampicillin to 900 for chloramphenicol.[85] Frame and colleagues noted three- to fivefold increases in antibiotic penetration into "abnormal" brain in or near intracranial lesions as opposed to "normal" brain at some distance from the lesion.[59]

It is difficult to draw firm conclusions from this information. It appears from animal data that although cerebrospinal fluid and brain penetration may follow roughly similar trends, one is not necessarily predictable from the other. Also, it seems that meningeal inflammation leads to a much greater increase in cerebrospinal fluid penetration of antibiotic than in brain penetration of antibiotic. Finally, it is also suggested from the chloramphenicol data of Kramer and associates that it is possible that some antibiotics may actually accumulate in the brain tissue and achieve levels substantially above those found in the blood.

THE BLOOD-LESION BARRIER

The information available regarding penetration of brain lesions by antibiotics is even more limited than for brain penetration. The presence of brain lesions adds an additional source of variation. The size of the lesion; its type, location, and vascularity; and the vascular integrity within the lesion may affect the delivery of the antibiotic. The lesion may also alter both the blood-brain and blood–cerebro-

spinal fluid barriers. Two studies of antibiotic penetration into the pus removed from cerebral abscesses show a marked degree of variation in levels attained (Table 132–2).[17,46] In both studies, there was variation in the timing of antibiotic administration and specimen acquisition, as also in the duration of preinvestigation antibiotic therapy. It can be simply concluded from these studies that it is possible to achieve therapeutic concentrations of various antibiotics in the center of brain abscesses. Careful monitoring of the clinical course may dictate a need to change antibiotics if adequate response is not demonstrated, as the levels obtained do not seem to be predictable. It may be that measurements of antibiotic levels in lesions that do not appear to be responding could be of help in guiding such decisions.

Osteomyelitis of the Skull

The skull is relatively resistant to infection, which is indicated by the fact that hematogenous osteomyelitis of the skull is quite uncommon. Osteomyelitis of the skull has become even more uncommon since antibiotic therapy has brought infection of the sinuses and mastoid air cells under better control. It is, however, important to diagnose and treat osteomyelitis of the skull early in its course because of the propensity to the formation of epidural abscesses and the possibility of development of brain abscesses.

Etiology

No cases of hematogenous osteomyelitis are shown in several relatively large series reported by otolaryngologists and neurosurgeons, although there are scattered case reports of a hematogenous origin of osteomyelitis of the skull. Most osteomyelitis of the skull is related to infection in adjacent sites or to trauma.

An untreated subgaleal or subperiosteal abscess may progress to involve the underlying skull, but most contiguous spread is from an infected sinus. By far the most common form of osteomyelitis of the skull is osteomyelitis of the frontal bones secondary to frontal sinus infection. Contiguous spread from infected mastoid air cells has been reported.

Osteomyelitis may follow injury or craniotomy wound infection. Indeed, compound skull fractures are quite susceptible to osteomyelitis. In Braakman's series of 165 compound depressed skull fractures, five of 11 infected cases (45 per cent) developed osteomyelitis.[24] Only eight (15 per cent) of 54 postoperative craniotomy infections reported by Balch were complicated by osteomyelitis.[5]

The relative frequency of osteomyelitis secondary to trauma and osteomyelitis secondary to contiguous infections cannot be determined from existing reports. Contiguous infection predominates in otolaryngologic series, while postoperative infection dominates in neurosurgical series.

Clinical Features

Patients with osteomyelitis present on a continuum ranging from being nearly asymptomatic to having a fulminating, life-threatening infection, usually associated with epidural or subdural empyema. For purposes of discussion, the presentation may be considered either acute or chronic.

Nearly all cases of acute osteomyelitis of the skull are limited to the frontal bone as a complication of sinus infection. The patient is

Table 132–2. Antibiotic Penetration of Cerebral Abscess

Drug	Percentage Penetration*	Mean	(N)†
Penicillin	0–infinite	105	(11)
Ampicillin	5–100	38	(4)
Cloxacillin	5–18	10	(3)
Methicillin	5–67		(2)
Cephaloridine	47–infinite	73	(2)
Gentamicin	0–100	67	(2)
Chloramphenicol	0–100	45	(3)
Lincomycin	50		(1)

*Percentage penetration equals abscess concentration/serum concentration × 100. See references 17 and 47.
†Mean based on N measurements excluding levels of 0 and infinite levels.

systemically toxic and febrile, and there is pain, tenderness, and swelling over the involved bone. This swelling of the scalp has been called "Potts' puffy tumor." There is a propensity to formation of an epidural abscess, which may produce focal neurological signs or increased intracranial pressure.

It may take up to 2 weeks before sufficient bone destruction is present to be evident on x-ray films, and therefore roentgenographic changes may be absent in the acute phase.

Acute osteomyelitis is more likely to be complicated by central nervous system involvement than chronic osteomyelitis, according to Schenck.[127] In four of 43 cases (9 per cent) of chronic osteomyelitis and in eight of 13 cases (62 per cent) of acute osteomyelitis, epidural and subdural abscesses, meningitis, or cerebral abscess were seen.

Chronic osteomyelitis of the skull often presents with no signs of toxicity. The scalp may be tender and swollen with chronically draining sinus tracts, or there may be only painless swelling of the scalp. Any portion of the skull may be involved. There are several case reports of osteomyelitis of the base of the skull that simulates a tumor. Changes of mottled, irregular bone destruction are usually well established in radiographic studies, which make them quite helpful in the diagnosis of chronic osteomyelitis. Because of the irregularities of the normal skull base, these changes may be difficult to demonstrate. A large experience with computed tomography has not yet been reported; however, it may identify these lesions at an early stage.

Bacteriology

The single most common pathogen in osteomyelitis of the skull is *Staphylococcus*. In a report by Bullitt and Lehman, *Staphylococcus aureus* accounted for 43 per cent of infections, *Staphylococcus epidermidis* for 18 per cent, and *Staphylococcus* associated with mixed flora for 14 per cent; thus, 75 per cent of the infections involved *Staphylococcus*.[32] The total incidence of staphylococcal infection was 82 per cent and *Staphylococcus aureus* accounted for 41 per cent of the infections in the series of Bordley and Bischofberger.[21] More recently, other organisms have been reported with increasing frequency, including *Escherichia coli*, *Proteus*, *Pseudomonas*, various anaerobes, and *Mycobacterium tuberculosis*.

The low incidence of hematogenous osteomyelitis of the skull suggests that blood culture is not likely to be a useful diagnostic test in this condition, although blood cultures may show growth in up to 50 per cent of the cases of acute untreated hematogenous osteomyelitis.[147] The best diagnostic procedures are likely to be direct bone biopsy and aspiration of purulent collections. Sinus tract cultures may be misleading.[92] Anaerobic cultures should be obtained by aspiration or when the wound is first entered, although they may be difficult to interpret when obtained from a chronically open wound.

Treatment

There has been a decreased incidence of acute osteomyelitis of the skull, because antibiotics have had a major impact in providing adequate treatment of sinus infections. Antibiotics administered before culture results are available are chosen on the basis of several factors. Until its presence is ruled out, coverage of *Staphylococcus* must be provided. The use of other possible organisms depends on the clinical setting. Concurrent infections are the likely source of the organism causing osteomyelitis. There may be unusual organisms present in the immunosuppressed patient. Common infective organisms are *Salmonella* in patients with hemoglobinopathies, *Pseudomonas* in drug addicts, and *Escherichia coli* in neonates. When culture results become available, antibiotic regimens must be adjusted.

The duration of antibiotic therapy and its route of administration remain controversial. Some studies of orthopedic osteomyelitis using relatively short courses of intravenous therapy followed by a long course of oral therapy have reported these to be successful. The only comparison of therapeutic regimens in osteomyelitis of the skull is retrospective. The best results found by Bullitt and Lehman were in patients who had at least 8 weeks of oral or intravenous postoperative antibiotic therapy.[32] It therefore seems reasonable to recommend 1 to 2 weeks of intravenous therapy followed by 6 to 12 weeks of oral therapy. During the period of oral therapy, adequate antibiotic levels should be verified.

Antibiotics have not eliminated the need for operation in the treatment of osteomyelitis of the skull. The only series comparing medical and operative therapy is that of Bullitt and Lehman.[32] Their patients were treated in the