Bacterial infections of the nervous system

Etiologic and therapeutic aspects

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In few areas of medicine is a presumptive etiologic diagnosis more likely to be accurate than in bacterial infections of the nervous system. Given the location of the infection; the patient's age; the presence or absence of underlying disease, particularly malignant or pleuropulmonary; sinus or middle ear infection; and the presence or absence of trauma, accidental or surgical; "bacteriologic statistics" permit one to focus on a relatively small number of possible pathogens in any given patient.

Most physicians recognize the well-known predominance of *Hemophilus influenzae,* the pneumococcus, and the meningococcus as the major causes of nonhospital acquired bacterial meningitis following the neonatal period, but they are not equally aware of the predictability of organisms involved in other bacterial infections of the nervous system. For example, in brain abscess the recovery of anaerobic pathogens is the rule. Failure to examine a Gram stain and transport the specimen promptly for proper anaerobic culture may completely misdirect the physician. When trauma results in a simple dural leak, the pneumococcus is most commonly responsible for meningitis. However, trauma which penetrates the dura permits contaminating organisms, such as the staphylococcus and gram-negative enteric bacilli to enter the picture.

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This paper will approach the topic of antimicrobial selection by emphasizing the bacteriology of meningitis, brain abscess, and subdural empyema. Circumstances in which unusual organisms are found will be stressed. Advantages and limitations of the newer antimicrobial agents will be discussed.

Bacterial meningitis

Neonates and children. The pediatrician is constantly challenged by the shifting pattern of neonatal sepsis. In the late 1940s coliform bacilli replaced the beta-hemolytic streptococcus as the major etiologic agents of neonatal septicemia and meningitis. Staphylococcal nursery epidemics in the late 1950s temporarily altered this pattern. As the staphylococcal problem subsided in the 1960s, coliform bacilli again emerged as the most frequent cause of neonatal meningitis. Recent experiences in Houston typify current etiologic considerations in infants and children with bacterial meningitis.[1] From birth through 30 days of age, 30% of the Houston cases were caused by enteric bacilli (*Escherichia coli, Proteus, Klebsiella-Enterobacter*), 25% to 35% by group B beta-hemolytic streptococci and 10% by listeria. The pneumococcus and the staphylococcus each accounted for approximately 5% of cases, with single cases due to *Hemophilus influenzae,* pseudomonas and group A beta-hemolytic streptococcus. In infants 31 to 60 days of age, 40% of the cases were due to group B beta-hemolytic streptococci, but only 5% were due to enteric bacilli; approximately 15% each were caused by the meningococcus and *H. influenzae,* with single cases due to pneumococcus, staphylococcus, group D streptococcus, and *Bacillus anitratum*. In children from 2 months to 14 years, 94% of the cases were caused by the three traditional major pathogens. *H. influenzae* accounted for 52% of the cases, the meningococcus for 25%, and the pneumococcus for 19%. After 3 years of age, meningitis due to *H. influenzae* decreased abruptly, and in this series of 219 patients there were no cases after 10 years of age. If *H. influenzae* meningitis occurs in an individual older than 10 years, one should suspect an immunoglobulin deficiency, a dural defect, or a parameningeal focus of infection.

Thus, while gram-negative enteric infections remain prevalent in the newborn, group B streptococci have emerged as a major pathogen. In the second month of life, the infant occupies a "grey zone" with respect to meningeal invasion. Still at some risk from the same organisms, particularly the group B streptococcus, other pathogens including *H. influenzae,* the meningococcus and the pneumococcus begin to pose a threat and take over almost completely after that, with *H. influenzae* dropping out almost entirely after 4 years of age.

***Streptococcus agalactiae* (group B beta-hemolytic streptococcus).** The group B streptococcus, *Streptococcus agalactiae* is now a major cause of perinatal infection. This organism and the more familiar *Listeria monocytogenes,* also of increasing importance, share many epidemiologic, pathogenetic, and clinical features.[2] Both gram-positive bacteria have a proclivity for the cervix and vagina of asymptomatic pregnant women, possibly via venereal transmission from asymptomatic men. Infection of the gravid woman by either organism may result in abortion, a normal birth, or de-

livery of an infant with septicemia presenting in one of two patterns: an early septicemia or a delayed meningitic form. Early disease is acquired in utero or during delivery; symptoms of respiratory distress and shock appear at birth or within the first 24 hours of life. The lungs are primarily involved, presumably from aspiration of infected amniotic fluid, and the pathogen is recovered from multiple sites including the blood, nasopharynx, skin, and meconium. Most of the affected infants die within 24 to 48 hours. The delayed form of septicemia usually begins after the first week of life, as late as 12 weeks, with a more insidious onset invariably involving the meninges; the prognosis is considerably better and most patients survive, although neurologic and mental abnormalities may result.

Listeria meningitis. Listeriosis has been reported with increasing frequency in the past decade. Animals were once considered the principal source for human infections, but most recent cases have been in urban residents without animal contacts. Since many human isolates were from neonates and products of conception, listeriosis was once considered primarily an obstetric/pediatric problem. An association with lymphoproliferative disease was noted in the late 1960s.[3-5] Influenced by these reports, human listeriosis came to be regarded primarily as a complication of underlying diseases (malignancy, cirrhosis, immune deficiency states) or the neonatal period; but healthy persons of any age, without a rural background or animal contact, can be infected.[6]

L. monocytogenes is a small, ubiquitous, gram-positive, nonsporeforming, motile bacterium, which grows readily on artificial media, but is often discarded as a "diphtheroid contaminant." Any gram-positive, uniformly staining, diphtheroid-like rod which is motile at room temperature on semisolid media, gives beta-hemolysis on blood agar and has been isolated from blood, spinal fluid, or other tissues is almost certainly *L. monocytogenes*. The major clinical syndromes in humans are abortion, conjunctivitis, endocarditis, meningoencephalitis, pneumonitis, pyoderma, septicemia, or urethritis.

Twenty-five patients with listeria meningitis at the Los Angeles County-University of Southern California Medical Center represented 0.8% of the total admissions for bacterial meningitis in a 10-year period.[7] Nine were neonates but 11 were 55 years of age or older; 21 patients (84%) were males, a very high ratio, perhaps explained by the neonatal male excess. No organisms were seen on Gram stain of the admission cerebrospinal fluid (CSF) in 19 patients. The remaining six specimens contained gram-negative or gram-positive organisms, but only two had gram-positive coccobacilli or gram-positive bacilli. There was a significant association between an initial CSF glucose of less than 30 mg/100 ml and a fatal outcome.[3, 7] Listeria meningitis is often insidious in onset with fluctuating signs of mental dysfunction preceding other signs of infection by a week or more, but is not otherwise distinctive. Listeria may incite either a profound mononuclear response in the CSF or, especially in patients with a brief illness, a striking polymorphonuclear response, occasionally with a profound blood lymphocytosis mimicking mononucleosis.[3] Occasionally, listeria accompanies other opportun-

istic organisms, such as *E. coli,* the tubercle bacillus, or a cryptococcus.

Adult and the less common meningitides. Beyond the second month of life, meningitis caused by unusual bacteria occurs in a setting of underlying disease, particularly malignancy, trauma, or anatomic defects, which favor the introduction of "contaminating bacteria," such as gram-negative bacilli or staphylococci. Immunologic defects or endocarditis should be considered as well.

Hand and Sanford[8] outlined the features of posttraumatic meningitis as seen in the antibiotic area. The pneumococcus was responsible for 83% of the episodes. Meningeal infection usually developed within 2 weeks of injury, but in a number of patients the onset was delayed for more than a year. All patients had either a skull fracture or CSF rhinorrhea or both; recurrent meningitis was a feature in a third of these patients. Meningitis in patients with recent cranial or spinal trauma so severe as to warrant immediate hospitalization may have a different pattern.[9] With a nonpenetrating, nondepressed head injury, if meningitis occurs within 3 days of injury, the pneumococcus is still so likely to be the infecting agent that penicillin alone is adequate. With open or penetrating head wounds or delayed onset meningitis (5 days or later), the antibiotic regimen must be broader since staphylococci and various gram-negative bacilli, including *E. coli,* proteus, bacteroides, and pseudomonas appear.

Pneumococcal meningitis is usually associated with acute or chronic otitis media, mastoiditis, sinusitis or pneumonia; one third of patients have no apparent source. Sickle cell disease also predisposes to the development of pneumococcal meningitis. Each patient with pneumococcal meningitis should be evaluated for a dural tear; 11% of patients with pneumococcal meningitis have had more than one episode of meningitis in contrast to 0.5% of patients with meningitis of other etiologies.[10] Recurrent disease is more frequent in younger persons and in males. A history of severe head trauma is more frequent in those with recurrent disease (35%) than in those without (0.4%), but is often overlooked by the patient even in the presence of CSF rhinorrhea, since the trauma usually precedes the initial episode of meningitis by 6 or more months.

After the age of 2 months, meningitis due to an unusual organism, such as a staphylococcus, streptococcus or gram-negative bacillus, especially if recurrent, should direct attention to a possible midline congenital dermal sinus tract from the skin surface into the subarachnoid space. The entire midline skin from the bregma over the vertex and the suboccipital area to the tip of the coccyx should be carefully examined for a sinus tract opening, erythema of the skin, tufts of hair, or abnormal discharge of fluid.[11]

Organisms responsible for central nervous system (CNS) infection in cancer patients differ from those attacking the general population and are mainly fungi and opportunistic bacteria.[12] One third are due to fungi, predominantly *Cryptococcus neoformans.* The pneumococcus is responsible for about 15% of cases of meningitis; listeria (22%); pseudomonas, staphylococci, and *E. coli* account for another 75% of the infections in this group. *H. influenzae,* the meningococ-

cus and *Mycobacterium tuberculosis* are rarely seen.[12]

Most CNS infections develop outside the hospital in patients with lymphoma. Prior immunosuppressive therapy is not a prerequisite, since immune mechanisms are suppressed by the disease itself. Most of these patients have normal white blood cell counts when admitted with meningitis, usually caused by cryptococcus, listeria, or the pneumococcus. Only in lymphoma patients on immunosuppressive therapy with low white blood cell counts do pseudomonas and *E. coli* invade the nervous system. Susceptibility to herpes simplex, varicella-zoster and the agent of progressive multifocal leukoencephalopathy is also a characteristic of lymphoma. *Toxoplasma gondii* shows a predilection for patients with either leukemias or lymphomas.

The situation differs in acute leukemia, since most infections are acquired in the hospital by patients with low white blood cell counts receiving chemotherapy.[12] The offending agents are usually gram-negative rods. In acute leukemia, intracranial infection is essentially nonexistent unless the white blood cell count is depressed. Staphylococcal infections are rare in this group.

In patients with head and spine tumors, organisms gain entry either by surgical defects or by the tumor itself creating an artificial communication between the external environment and the intracranial spaces. These patients usually have an intact immune system in the absence of chemotherapy. Infection is generally acquired postoperatively. A variety of gram-positive and gram-negative organisms is responsible, most commonly *Staphylococcus aureus* and gram-negative rods. Fungal meningitis is rare, but anaerobic brain abscesses are seen.

Streptococcal meningitis beyond 2 months of age is uncommon. Aseptic meningeal reactions are more typical in subacute bacterial endocarditis, but purulent meningitis does occur and, classic teaching notwithstanding, the organism can sometimes be grown from the CSF. In my recent experience, trauma, dural defects, alcoholic cirrhosis, vertebral infection secondary to surgery, malignancy, and peritonitis secondary to chronic peritoneal dialysis were the antecedent factors in the evolution of streptococcal meningitis in adults, in addition to several cases associated with subacute bacterial endocarditis. Since streptococci are commonly found in sinus infections, it is surprising that they are not involved more frequently in meningeal infections.

Staphylococcal meningitis is uncommon. Even during the peak of the staphylococcal epidemic in the 1950s, it never accounted for more than 7% to 8% of the total cases in large series. In most instances, underlying disease or injury is present, usually lesions of the CNS or injuries to the skull. Currently, staphylococcal infection of the meninges occurs most often following neurosurgical procedures or in the course of staphylococcal bacteremia with or without endocarditis. Spinal epidural abscess and spinal subdural empyema are most frequently caused by coagulase-positive staphylococci.[13]

Meningitis complicating spinal anesthesia may be aseptic or septic. Either a polymorphonuclear or a mononuclear cell response may be provoked in the spinal fluid under normal circumstances by the sterile anesthetic

agent. Pseudomonas is the most common culprit, but the genus Bacillus has also been implicated.[14] Purulent meningitis following a diagnostic lumbar puncture is rare. Gram-negative enteric bacilli and *S. aureus,* commonly found on skin surfaces, rarely may be carried into the CSF by the exploring needle. Both streptococcal and pneumococcal meningitis have been reported following pneumoencephalography.[15]

Organisms usually considered nonpathogens (bacillus, diphtheroids, coagulase-negative staphylococci) are most frequently responsible for infection of ventriculoatrial shunts. Signs of infection are often minimal or mimic subacute bacterial endocarditis, including proliferative and membranous glomerulonephritis. Similar organisms have been recovered from the fluid of infected Ommaya subcutaneous reservoirs in asymptomatic patients with simultaneous negative cultures of lumbar CSF.

Brain abscess and subdural empyema

Heineman and Braude[16] suspected that "sterile" brain abscesses, reported in 9% to 63% of the cases in various series, actually contained anaerobic organisms, since gram-positive cocci were often seen on smear. In 18 patients with brain abscess at the University of Pittsburgh (1957–1963), excluding patients with congenital heart disease, septicemia, or penetrating head trauma, cultures were sterile in only two cases, although bacteria were seen on smear in one. Anaerobes grew from the remaining 16 abscesses; only six yielded aerobic bacteria. The pus was putrid, and in some cases associated with large quantities of gas.

Most commonly isolated was the anaerobic streptococcus (peptostreptococcus); Bacteroides, Actinomyces, Veillonella, and anaerobic corynebacteria were found less commonly. The aerobic organisms were mainly gram-negative bacilli such as "paracolon" and proteus. In 12 of the 16 cases, anaerobes were recovered in mixed culture, together with other anaerobes or aerobes or both. Most of these patients had chronic otitis media, sinusitis or chronic pulmonary infections, such as empyema or lung abscesses, so the prominence of anaerobes was not unexpected. Limited data suggest that anaerobes are also frequently involved when brain abscess is associated with cyanotic congenital heart disease. Since the majority of brain abscesses arise in either of these settings, anaerobes are probably the chief pathogens in all brain abscesses except those associated with septicemia or head trauma, even though aerobic pathogens may also be present. The spectrum of etiologic agents in brain abscess differs in patients with underlying malignant disease; few brain abscesses yield anaerobes or no growth, while *E. coli, pseudomonas,* Proteus species, all rare in the general population, are most common.[12] Fungi are present in 33% (aspergillus and phycomycetes), and *Toxoplasma gondii* may also cause brain abscess in these circumstances.

Anaerobes remain elusive when specific attention is not directed to their recovery. As Samson and Clark[17] noted, "when surgery was performed at irregular hours, cultures were not plated with great dispatch." The low yield of anaerobic organisms in their series emphasizes that immediate culture, or storage and transport of the specimen in an anaerobic environment, is most important, since the

aerobic culture alone may be misleading.

Subdural empyema is most often associated with otorhinologic infection but also occurs after trauma, intracranial surgery, and hematogenous seeding of the subdural space. Streptococci, many of them anaerobic, usually in combination with other organisms, such as *S. aureus* or gram-negative bacilli have been reported in recent studies of subdural empyema.[18] Further attention to the anaerobic aspects of this intracranial infection will undoubtedly uncover a spectrum of pathogens similar to that found in brain abscess. Patients with chronic sinusitis yield anaerobes in a third of all cases.[19]

Current therapeutic considerations in bacterial meningitis

Neonatal meningitis. Until recently, therapy for the dreaded occurrence of neonatal meningitis consisted of ampicillin and kanamycin, based on the prevalence of gram-negative bacilli, and gram-positive pathogens such as listeria and group B beta-hemolytic streptococci. Except for a rare pseudomonas, the gram-negative bacilli involved were susceptible to 5.0 μg/ml of kanamycin. Eichenwald[20] had demonstrated mean peak CSF kanamycin concentrations of 9 μg/ml after 7.5 mg/kg intramuscular injections of kanamycin in eight infants with bacterial meningitis, more than twice the level in infants with normal meninges.[20]

Unable to eradicate susceptible *E. coli* strains from the CSF in certain cases, later investigators studied two doses of kanamycin; 7.5 or 12.5 mg/kg. CSF levels did not reach a therapeutic range of kanamycin with either dose (range, 1 to 3 μg/ml; occasional value to 6 μg/ml) even in patients with a brisk inflammatory CSF response.[21]

Gentamicin, an aminoglycoside related to kanamycin, is also active against pseudomonas. Due to an increasing incidence of kanamycin-resistant *E. coli* in nurseries (up to 30%), gentamicin is now recommended in neonatal meningitis; 2.5 mg/kg given parenterally every 8 hours (7.5 mg/kg/day) yields CSF levels of 1 to 2 μg/ml, never higher than 2.5 μg/ml, but CSF concentrations of 3 to 6 μg/ml routinely follow daily intrathecal injections of 1 mg of gentamicin.[22]

McCracken[23] analyzed the bacteriologic response to antimicrobial therapy in 38 cases of neonatal meningitis. CSF cultures from 15 of 16 infants with gram-positive meningitis were promptly sterilized, but 13 of 22 infants with gram-negative meningitis had positive CSF cultures for 2 to 11 days (mean, 6 days) after the start of therapy. Antibiotic levels in CSF varied greatly and even in vitro bactericidal titers did not ensure CSF sterility. A bactericidal titer of 1:4 or more was observed in half the CSF specimens which grew pathogens. One CSF grew *Salmonella infantis* [minimal inhibitory concentration (MIC), 1.25 μg/ml] despite an ampicillin level of 59 μg/ml and a bactericidal titer of 1:32; enterobacter grew from a ventricular sample (MIC, 1.25 μg/ml) despite bactericidal titers of 1:4–1:128 and gentamicin levels of 9–102 μg/ml in the same fluid.

Peak CSF concentrations of kanamycin and gentamicin only approximate the MICs of enteric species. Ampicillin alone or with an aminoglycoside may yield higher CSF bactericidal titers, possibly because CSF concentrations are often 5 to 10 times

the MIC of many *E. coli,* and the combination is synergistic for 30% of *E. coli.* McCracken[23] suggests ampicillin (100 mg/kg/day in infants less than 1 week old and 200 mg/kg/day in infants 1 to 4 weeks of age), and gentamicin (5 mg/kg/day in infants less than 1 week and 7.5 mg/kg/day in infants 1 to 4 weeks of age) as initial therapy. If the culture remains positive after 24 hours, daily intrathecal injections of gentamicin (1 mg) are given until the culture becomes negative.

The primary flow of CSF is from the ventricles to the cisterna magna, then to the basal cisterns, around the brainstem in the ambient cisterns into the corpus callosal cisterns before finally entering the cerebral subarachnoid spaces. Small amounts of drug injected into the lumbar theca are unlikely to yield significant drug concentrations more cephalad, particularly in the ventricular fluid.[24] When injected in a volume that approximates 10% of the estimated total CSF volume, significant drug concentrations are achieved in the basal cisterns. When a volume approximately 25% of estimated CSF is injected, drug is distributed throughout the CSF, subarachnoid, and ventricular systems.

Ventriculitis should be treated as a brain abscess with direct instillation of antibiotics.[25] Intraventricular gentamicin has been employed with some success.[26] Periodic irrigation and drainage may be necessary to produce therapeutic ventricular fluid antibiotic levels. Flow between the two lateral ventricles may not be intact, so both ventricles should be studied. Ventricular fluid gentamicin levels of 4.3 to >60 μg/ml (mean, 15.8 μg/ml) have been recorded 24 hours after instillation of 0.5 to 1.0 mg of gentamicin.[22]

Penicillin(s), bactericidal for most gram-positive organisms, are usually only bacteriostatic against listeria, a potential disadvantage since they behave as facultative intracellular parasites in the host.[4] Although good clinical results have been reported with penicillin, ampicillin, tetracycline, chloramphenicol, erythromycin, streptomycin, and sulfonamides, failures have been noted with each. The minimal bactericidal concentration (MBC) of 20 strains of listeria for both ampicillin and penicillin is much higher than the MIC.[27] A combination of penicillin or ampicillin plus an aminoglycoside, such as gentamicin or streptomycin enhances killing of all strains suggesting the combined use of penicillin or ampicillin plus streptomycin or gentamicin when listeria infections occur in patients with impaired host defenses or who have relapsed after treatment with penicillin or ampicillin alone.

Hemophilus, pneumococcal, and meningococcal infections. Conventional therapy for *H. influenzae* meningitis and for meningitis of uncertain etiology in children formerly included chloramphenicol alone or in combination with one or more additional drugs. Ampicillin is comparable to penicillin G in its activity against the meningococcus and pneumococcus, but is more active against *H. influenzae,* and single drug treatment proved feasible after it was introduced in the early 1960s.

The success of ampicillin as a substitute for "triple therapy" generated renewed interest in defining the factors which influence a favorable out-

come in patients with meningitis. CSF ampicillin levels are variable, much more so than expected (from <0.03 to 38 μg/ml) with higher levels during the first 3 days than during days 4 to 9 or later.[28, 29] As CSF values return to normal, less ampicillin penetrates. Clinical outcome bears no relationship to ampicillin levels achieved in the CSF, and certain patients recover uneventfully despite the absence of detectable CSF antibiotic during the acute stage of their illness.[28]

Chloramphenicol was added to ampicillin, hoping to improve the still significant incidence of morbidity and mortality despite theoretical objections to the combination.[30] Lepper and Dowling[31] observed a much higher case fatality rate (80%) in patients with pneumococcal meningitis receiving penicillin plus chlortetracycline than in a similar group treated with penicillin alone (30%). During a 1-year period, Mathies et al[30] assigned 264 patients with meningitis 2 months of age or older to a single drug (ampicillin, 150 mg/kg/day), or a combination of drugs (ampicillin, 150 mg/kg/day; chloramphenicol, 100 mg/kg/day to a maximum of 4 g/day; and streptomycin 40 mg/kg to a maximum of 2 g/day, 48 hours only). The groups were comparable with respect to age, severity of disease, and etiology. Six of 140 patients (4.3%) in the single drug group died; there were 13 deaths among 124 patients (10.5%) receiving multiple therapy. The latter group also had an increased rate of neurologic residua. These differences were observed mainly in patients severely ill on admission, but were not restricted to any age group or etiologic category.

Reports of "ampicillin failure" in *H. influenzae* meningitis have provoked a reexamination of the role of ampicillin in this disease. Virtually all strains of *H. influenzae* tested had been uniformly sensitive to ampicillin until the spring of 1974.[32, 33] *H. influenzae* strains that appeared resistant by antibiotic disk tests prior to early 1974 were usually sensitive by tube dilution or agar diffusion techniques. Inadequate doses of ampicillin, residual focal sequestration, and the duration of infection prior to initiation of appropriate therapy are conspicuous features of certain cases which relapsed; the use of intramuscular ampicillin may account for some treatment failures. Approximately six cases of ampicillin-resistant *H. influenzae* meningitis have now been documented.[33] Relapse of *H. influenzae* meningitis following chloramphenicol treatment has been reported, but in all but three cases, failure occurred in patients who received a portion of their treatment intramuscularly, an unreliable and no longer sanctioned route.[34] Chloramphenicol may have an advantage in advanced cases where cerebritis is likely. Ampicillin penetrates the noninflamed human brain with average concentrations of only 0.4 μg/g tissue, occasionally as high as 2 μg/g tissue; chloramphenicol concentrations in noninflamed human brains range from 10 to 63 μg/g (mean, 36 μg/g) tissue, nine times greater than in the blood.[35] Intravenous tetracycline is also an effective alternative when needed in *H. influenzae* meningitis.[36]

Therapy for pneumococcal meningitis consists of 2 million units of penicillin G intravenously every 2 hours.

Ampicillin is equally effective, but cost and the greater risk of cutaneous reactions favor the use of penicillin. Intrathecal penicillin is seldom recommended currently in the management of pneumococcal meningitis. Alternative therapeutic agents for the penicillin-allergic patient include chloramphenicol, erythromycin, and tetracycline, although it should be noted that 5% of pneumococci are tetracycline-resistant.

Cephalothin is a semisynthetic cephalosporin compound structurally similar to penicillin and widely employed in penicillin-allergic patients. The drug diffuses poorly into CSF in patients without meningitis, but in the presence of meningitis adequate concentrations have been found. Four of 12 patients with meningococcal meningitis treated with cephalothin (100 to 250 mg/kg/day), because of penicillin allergy, failed to respond; all four recovered when therapy was changed to tetracycline.[37] Failure of treatment did not correlate with in vitro resistance to the drug and, furthermore, CSF cephalothin concentrations were as high as 46.5 μg/ml, although several samples had no detectable drug. Meningococci grew in the CSF specimen which contained 46.5 μg/ml of cephalothin. They concluded that cephalothin is not a satisfactory substitute for penicillin in meningococcal meningitis. Hodgkin's disease, multiple myeloma, and alcoholism with diabetes mellitus were underlying conditions in four of five patients who developed meningitis while receiving cephalothin; pneumococci, a meningococcus, *L. monocytogenes* and Klebsiella were isolated from these cases.[38] At least 30% of cephalothin is metabolized to desacetylcephalothin, a metabolite with one fourth the antimicrobial activity of cephalothin, which may be particularly important in the case of the meningococcus which is 10 times more resistant to desacetylcephalothin than to cephalothin. These latter two reports have discouraged any enthusiasm for exploring the role of cephalothin in pneumococcal meningitis.

Cephaloridine is more active in vitro than cephalothin. It is well tolerated when injected parenterally, but is nephrotoxic in doses in excess of 4 g/day in an adult. A combination of parenteral and intrathecal cephaloridine has been used successfully in pneumococcal meningitis, although following parenteral injection alone, cephaloridine passes readily through inflamed meninges into the CSF.[39, 40] Nephrotoxicity, particularly in the hands of the inexperienced, precludes an enthusiastic recommendation for cephaloridine as a penicillin substitute in pneumococcal meningitis. Cefazolin, a newer parenteral cephalosporin now available, enters CSF poorly, even in the presence of inflamed meninges. Lincomycin should be an adequate substitute for penicillin in pneumococcal meningitis, as it also penetrates the CSF well in the presence of meningeal inflammation, but accumulated experiences to date are few. Clindamycin penetrates the CSF poorly, even in the presence of meningeal inflammation and should be avoided in all types of meningitis, pending further studies.

The modern treatment of meningococcal meningitis is dictated by the prevalence of sulfonamide-resistant groups B and C, and most recently group A meningococci. Currently, 70% of the reported cases of meningo-

coccal bacteremia and meningitis are caused by sulfonamide-resistant meningococci. The organisms remain susceptible to penicillin G, and treatment with this drug is entirely satisfactory. In patients allergic to penicillin, chloramphenicol is an alternative drug of choice, although erythromycin and tetracycline are also effective.

Gram-negative meningitis in adults. Rahal[41] reviewed the status of therapy for gram-negative bacillary meningitis in adults. Optimal therapy should provide the widest possible coverage as well as effective CSF concentrations, so chloramphenicol, polymyxin B, kanamycin, carbenicillin, and gentamicin are the most useful agents. The overall success with any of these drugs is difficult to assess because of a limited number of reports and the tendency to report only those cases treated successfully. High level resistance of most gram-negative bacilli to sulfonamides, the tetracyclines, and streptomycin precludes their playing an important role in this area.

Although ampicillin, cephalothin and cephaloridine are active in vitro against *E. coli* and *Proteus mirabilis* there is considerable resistance among the Klebsiella-Enterobacter-Serratia group. Large parenteral doses of ampicillin are needed to treat even the very sensitive gram-negative *H. influenzae*. Few other gram-negative bacilli fall into this highly sensitive category; *P. mirabilis* meningitis has been cured by the intravenous administration of ampicillin, but success in *E. coli* meningitis has been variable with treatment failures in the face of organisms susceptible to as little as 6.3 μg/ml. Cephalosporins probably have no role in this type of meningitis.

Chloramphenicol is uniquely important in the treatment of gram-negative meningitis in adults. CSF levels are one third to one half of those found in the blood in individuals with normal meninges. Whether still greater diffusion occurs during active meningitis has yet to be documented. Chloramphenicol also penetrates the human brain in concentrations several fold greater than those of penicillin, ampicillin, and the cephalosporins.[35] Rahal[41] recommends the use of 6 to 8 g/day of chloramphenicol to achieve optimal CSF levels for meningitis caused by gram-negative bacilli other than *H. influenzae*.

Since most gram-negative bacilli are suppressed by 1 to 5 μg/ml of gentamicin, it is unlikely that currently recommended doses of parenteral gentamicin will routinely result in adequate CSF levels. Accumulated experiences suggest that the proper dose of gentamicin for intrathecal use in children has yet to be determined, but in adults, 4 mg given by the intrathecal route every 18 hours maintains therapeutic concentrations in lumbar CSF, without apparent ill effects.[42] The accidental administration of 80 mg intrathecally without adverse effects suggests that the upper limit is not known.

Intrathecal polymyxin B has been employed for many years, particularly for pseudomonas infections, but convincing data as to efficacy and specific dosage programs remain obscure. The intrathecal dose of 5 mg frequently given to adults may produce meningeal or nerve root irritation, although many patients tolerate this dose without reaction. Parenteral polymyxin B does not cross the blood-brain barrier, even in the presence of inflamed meninges.

Intravenous carbenicillin with or without intrathecal administration has been reported to cure cases of meningitis caused by proteus, pseudomonas and "paracolon" species. In the absence of meningeal inflammation, CSF levels are 15% of those in the blood, and in meningitis greater diffusion probably occurs; however, since 50–200 μg/ml are required to inhibit most pseudomonas strains, intrathecal administration will probably be necessary in most situations where this drug is employed. Indole-positive proteus (*P. morganii, P. vulgaris,* etc.) are considerably more susceptible in vitro, to as little as 2 to 10 μg/ml.

Presumptive therapy for gram-negative meningitis in adults should include gentamicin parenterally (either intravenously or intramuscularly in a dose of 5 mg/kg/day) with an intrathecal injection of 4 mg repeated every 12 to 18 hours to maintain adequate CSF levels. Chloramphenicol, 6 to 8 g, or carbenicillin 30 to 40 g daily are also recommended. Neuromuscular irritability and seizures have followed the administration of carbenicillin to patients with renal failure. A "safe" dose of carbenicillin in these circumstances has not been determined; as little as 4 g/day has been associated with this reaction. All penicillins should be employed with caution in the presence of impaired renal function.[43]

Therapy of staphylococcal infections. The infrequency of staphylococcal meningitis and the declining incidence of staphylococcal infections in general, except following accidental or surgical trauma, probably account for the relative paucity of data concerning the CSF penetration of the semisynthetic penicillinase-resistant penicillins, such as methicillin, oxacillin, and nafcillin. In general, these drugs follow the pattern of penicillin G with little or no penetration in the absence of meningeal inflammation, while therapeutic concentrations do enter in the presence of meningeal inflammation.

Methicillin-resistant staphylococci have been responsible for widespread hospital outbreaks in Europe and England; major problems have not yet been seen in this country. There is cross-resistance among all the semisynthetic penicillins and to the cephalosporins as well. Therapy for CNS infections with methicillin-resistant staphylococci would pose a number of problems. Although CSF penetration of vancomycin has not been well documented, several cases of meningitis have been treated successfully.[44]

No strains of coagulase-positive staphylococci are known to be resistant to vancomycin, so this drug may be useful and necessary despite its nephrotoxic potential. Erythromycin, lincomycin, clindamycin and gentamicin or kanamycin may also play a role. Bacitracin, intrathecal and intramuscular, and occasionally intraventricular, was used to treat successfully a small number of patients with staphylococcal meningitis.[45] Since there are no known bacitracin-resistant staphylococci, judicious use of this antibiotic may again have to be considered.

Treatment of brain abscess and subdural empyema

The consistent recovery of anaerobic bacteria led to the combined use of penicillin and tetracycline or chloramphenicol for brain abscess.[16] Despite the occasional presence of enteric orga-

nisms, such as proteus, mixed with the anaerobes, other drugs, such as aminoglycosides were thought unnecessary. If brain abscess is a true example of a synergistic infection, then therapy directed at the major pathogen(s) is the primary goal. Intravenous penicillin G (20 million units/day) and tetracycline (1.5–2.0 g/day) or chloramphenicol (2.0 to 4.0 g/day) are the drugs of choice. Approximately 30% to 40% of *Bacteroides fragilis* are resistant to tetracycline as are many anaerobic and microaerophilic streptococci. Although *B. fragilis* strains are less commonly found in brain abscess, this organism favors the choice of chloramphenicol over tetracycline. Heineman et al[46] described six cases of focal intracranial infection in which they believed that abscess development was either aborted or reversed before irreversible damage had occurred. They admit their inability to differentiate among brain abscess, subdural empyema or septic corticothrombophlebitis in the absence of surgical intervention. When an obvious portal of entry suggests that the infection arose other than in the ear, sinus, or thorax, the choice of drug may be individualized. Involvement of the CNS during septicemia or endocarditis must be assumed to be due to the organism identified in the blood. The bacteriology of acute sinusitis most often points toward the pneumococcus or the staphylococcus in adults, but anaerobes are present in 33% of patients with chronic sinusitis.[19] Therefore, in the absence of a purulent subdural collection secondary to meningitis, as with *H. influenzae* or in the rare instance of bacteremic seeding of a subdural hematoma, the same antimicrobial considerations for brain abscess apply to subdural empyema and intracranial epidural abscess as well.

Clindamycin, a halogenated analogue of lincomycin, rivals chloramphenicol in its broad activity against anaerobes, including *B. fragilis;* preliminary data indicate poor penetration into CSF even in the presence of meningeal inflammation; there are no studies on penetration into brain tissue. Kramer et al[35] studied the concentration of chloramphenicol, cephalothin, ampicillin, penicillin G, and cephaloridine in the brains of patients with noninflamed meninges each given 2 g of an antibiotic as a single dose before elective surgery for brain tumor or trauma. Ampicillin, penicillin, and cephaloridine achieved blood to brain ratios ranging from 20:1 to 50:1. Average brain levels in μg/g of tissue were 1.6 for cephalothin in conjunction with a blood level of 11.7 μg/ml for a ratio of 7:1. Chloramphenicol concentrations in the brain were impressive, ranging from 20 to 180 μg/ml of brain tissue in the presence of serum levels of only 3.5 to 6.0 μg/ml, for a blood to brain level ratio of 1:9. All five antibiotics achieved tissue levels adequate to inhibit sensitive gram-positive cocci, except for penicillin-resistant staphylococci. Chloramphenicol had the widest spectrum of activity since brain tissue concentrations were capable of inhibiting any gram-negative organism, except for pseudomonas.

Black et al[47] assayed antibiotic activity in pus aspirated from brain abscesses. Organisms persisted in all six abscesses despite concentrations of chloramphenicol, penicillin, or methicillin equal to or greater than the MIC of the patient's organism. Ex-

pressed as multiples of MIC, the antibiotic levels in the abscess cavity were as high as 32 to 380 for penicillin, 12 to 24 for chloramphenicol and 4 to 5 for methicillin, suggesting adequate antibiotic penetration but poor antibacterial activity within the abscess. Whether local instillation of antibiotic into an abscess cavity is necessary or helpful has never been properly investigated; this study would suggest otherwise.

Chemoprophylaxis of CNS infections

Used in a closed population, small doses of sulfonamide interrupt the transmission of meningococci by eliminating the organism from the nasopharynx of asymptomatic carriers, the source of most meningococcal illness. At present, sulfonamide chemoprophylaxis will be effective only when persons harbor or are exposed to sulfonamide-susceptible meningococci. However, the principle of successful chemoprophylaxis remains intact, i.e., preventing infection by one organism with relatively small doses of a drug to which it is susceptible.

In circumstances where a number of organisms may take advantage of a patient, chemoprophylaxis with so-called "broad-spectrum" coverage is less likely to succeed and more likely to be hazardous. The neurosurgeon is confronted with precisely this situation, namely infections due to gram-negative enteric bacilli and staphylococci in the postoperative period. It remains common practice on many neurosurgical services to employ one of the semisynthetic penicillins or cephalothin as a routine chemoprophylactic in the postoperative period. Price and Sleigh[48] reported an experience that should give pause to all concerned. In 1966, because of an increase in postoperative wound infections due to coagulase-positive staphylococci and antibiotic-sensitive coliforms, prophylactic chemotherapy with ampicillin and cloxacillin was initiated in their unit for all patients at special risk. In addition, ampicillin was used therapeutically for most unconscious patients producing purulent sputum. By the following year, *Klebsiella aerogenes* was routinely present in the sputum of 25% of the patients on the ward. Shortly thereafter, an epidemic of Klebsiella infections swept the neurosurgical intensive care ward and eight patients died with meningitis. Despite isolation of infected cases and treatment with massive doses of appropriate antibiotics, the outbreak could not be controlled. Closing and completely renovating the ward did not interrupt the epidemic.

Faced with 11 deaths from either meningeal or pulmonary Klebsiella infection, the staff accepted the extreme measure of completely discontinuing both prophylactic and therapeutic antibiotics on the premise that suppression of normal flora was detrimental to the patients' ultimate outcome. Within 4 weeks there were no longer any urinary tract infections with this organism and the pulmonary infection rate fell to 2%. Several unconscious patients with pneumonic consolidations responded well to tracheobronchial toilet care only. No further cases of Klebsiella meningitis occurred and fears that infections due to antibiotic-sensitive organisms might increase proved groundless. By withdrawing all antibiotics, Price and Sleigh[48] suggest that antibiotic sensitive and perhaps less virulent bacteria were allowed to regain their normal roles. Proper atten-

tion to tracheobronchial toilet cannot be overemphasized.

Chemoprophylaxis for the interruption of epidemic meningococcal disease has been complicated by the emergence of sulfonamide-resistant organisms. Despite its therapeutic efficacy, penicillin G given orally or parenterally does not consistently eliminate meningococci from asymptomatic nasopharyngeal carriers. Indeed, meningitis has even developed in patients receiving penicillin "prophylaxis." Ampicillin, erythromycin, tetracycline, chloramphenicol, and cephalexin have also failed. Rifampin, 600 mg/day for 4 days, eliminates the carrier state in 90% of individuals, but mass use appears to be limited by a pronounced tendency for meningococci to develop resistance to rifampin. In open populations, unidentified or untreated meningococcal carriers may reinfect susceptible hosts even after they have received appropriate prophylactic antibiotics.[49] Results of various studies indicate that minocycline, a tetracycline analogue, reduces the carrier rate from 60% to 95%.

However, results of a recent study reveal that minocycline was more effective for treatment of the meningococcal carrier state when used conjointly with rifampin.[50] The ultimate role of either of these two agents in the chemoprophylaxis of meningococcal disease remains to be determined, but Hoeprich[51] pointed out that effective chemoprophylaxis requires a drug that will be predictably active at low concentrations against all meningococcal serogroups and readily achieve adequate nasopharyngeal concentrations in healthy carriers lacking a detectable, local inflammatory process to enhance passage of a drug from the blood. Lacrimal secretions contribute to the liquid bathing the nasopharynx, so the presence of drug in tears may be a useful method of screening for effective agents.

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