REVIEW ARTICLE

CURRENT CONCEPTS

Nosocomial Bacterial Meningitis

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Nosocomial bacterial meningitis may result from invasive procedures (e.g., craniotomy, placement of internal or external ventricular catheters, lumbar puncture, intrathecal infusions of medications, or spinal anesthesia), complicated head trauma, or in rare cases, metastatic infection in patients with hospital-acquired bacteremia. These cases of meningitis are caused by a different spectrum of microorganisms than cases acquired in the community setting, and illness is the result of diverse pathogenetic mechanisms (Fig. 1).

Epidemiology and Pathogenesis

The central nervous system is protected against microbial entry from the bloodstream by the blood–brain barrier and by an external barrier that is formed by the skull and leptomeninges. Consequently, pathogens may enter the central nervous system by direct invasion through the external barrier or through the bloodstream in association with a breakdown of the blood–brain barrier. The following sections review the predisposing conditions and risk factors for the development of nosocomial meningitis.

Craniotomy

Bacterial meningitis is a serious complication of craniotomy; it occurs in 0.8 to 1.5% of patients who undergo craniotomy.[1,2] Among cases of meningitis that develop in patients after craniotomy, approximately one third occur in the first week after surgery, one third in the second week, and one third after the second week, with some cases occurring years after the initial surgery.[1] The risk of postoperative meningitis can be minimized by the practice of careful surgical techniques, especially those that decrease the likelihood of cerebrospinal fluid leakage.[1] Other factors that are associated with the development of meningitis after craniotomy are concomitant infection at the site of the incision and a duration of surgery of more than 4 hours. Specific neurosurgical techniques that may minimize the risk of postoperative meningitis are listed in Table 1.

Internal Ventricular Catheters

The case incidence of meningitis associated with internal ventricular catheters (i.e., cerebrospinal fluid shunts), which are commonly used for the treatment of hydrocephalus, ranges from 4 to 17%.[3,4] The most important causal factor is colonization of the catheter at the time of surgery, since the majority of infections are manifested within 1 month after surgery.[3,4] One prospective, observational study identified holes in the surgical gloves, combined with direct handling of the shunt catheter by the surgical team, as a possible risk factor[5]; double gloving led to a reduction in the rates of catheter infections as compared with the rates among historical controls.[6] One study suggested that changing the outer pair of gloves before handling catheter material during surgery may further decrease the rates of infection.[7]

EXTERNAL VENTRICULAR CATHETERS

External ventricular catheters are used for the monitoring of intracranial pressure or the temporary diversion of cerebrospinal fluid from an obstructed ventricular system, or as part of the treatment approach for infected internal catheters. The rate of infection associated with external catheters is approximately 8%.[8] The risk of infection is reported to be increased with an increased duration of drainage, but the extent of increase per unit of time is uncertain. Although one study showed a sharp increase in the risk of infection after 5 days of external drainage,[8] a prospective, randomized trial showed that removing external catheters within 5 days is unnecessary and that catheters can be left in place for longer periods with no obvious increase in the daily risk of infection.[9] Since infection may be acquired by the introduction of bacteria after the insertion of a new catheter, changing uninfected catheters might actually increase the risk of infection. Other risk factors for infection are the routine sampling of cerebrospinal fluid, leakage of cerebrospinal fluid at the site, blockage of the drain, and intraventricular hemorrhage.

EXTERNAL LUMBAR CATHETERS

External lumbar catheters, which are placed mainly to aid in the diagnosis of normal-pressure hydrocephalus, have been associated with meningitis rates of up to 5%.[10] The risk factors associated with these catheters include disconnection of the external drainage system and the presence of other infections. In a recent study involving 233 consecutive patients who underwent placement of an external lumbar catheter, the rate of meningitis was low (0.8%)[10]; the investigators in that study used a strict protocol that called for no surveillance testing of cerebrospinal fluid, drainage of cerebrospinal fluid for a maximum of 5 days, sterile reconnection after disconnection or fracture of the drain, and permanent removal of the catheter after a second disconnection or fracture — protocols that minimized the risk of infection.

HEAD TRAUMA

The incidence of meningitis after moderate or severe head trauma is estimated to be 1.4%.[11] Open compound cranial fractures are complications of up to 5% of head injuries and have been associated with rates of meningitis that range from 2 to 11%.[12] In patients with compound fractures in which the skull is depressed deeper than the thickness of the cranium, the wound should be carefully examined and débrided, and preventive antimicrobial therapy should be administered (Table 1). Nonoperative management is an option if there is no clinical or radiographic evidence of the following: dural penetration, large intracranial hematoma, depression that is deeper than 1 cm, involvement of the frontal sinuses, gross cosmetic deformity, wound infection, pneumocephalus, or gross contamination of the wound.[12]

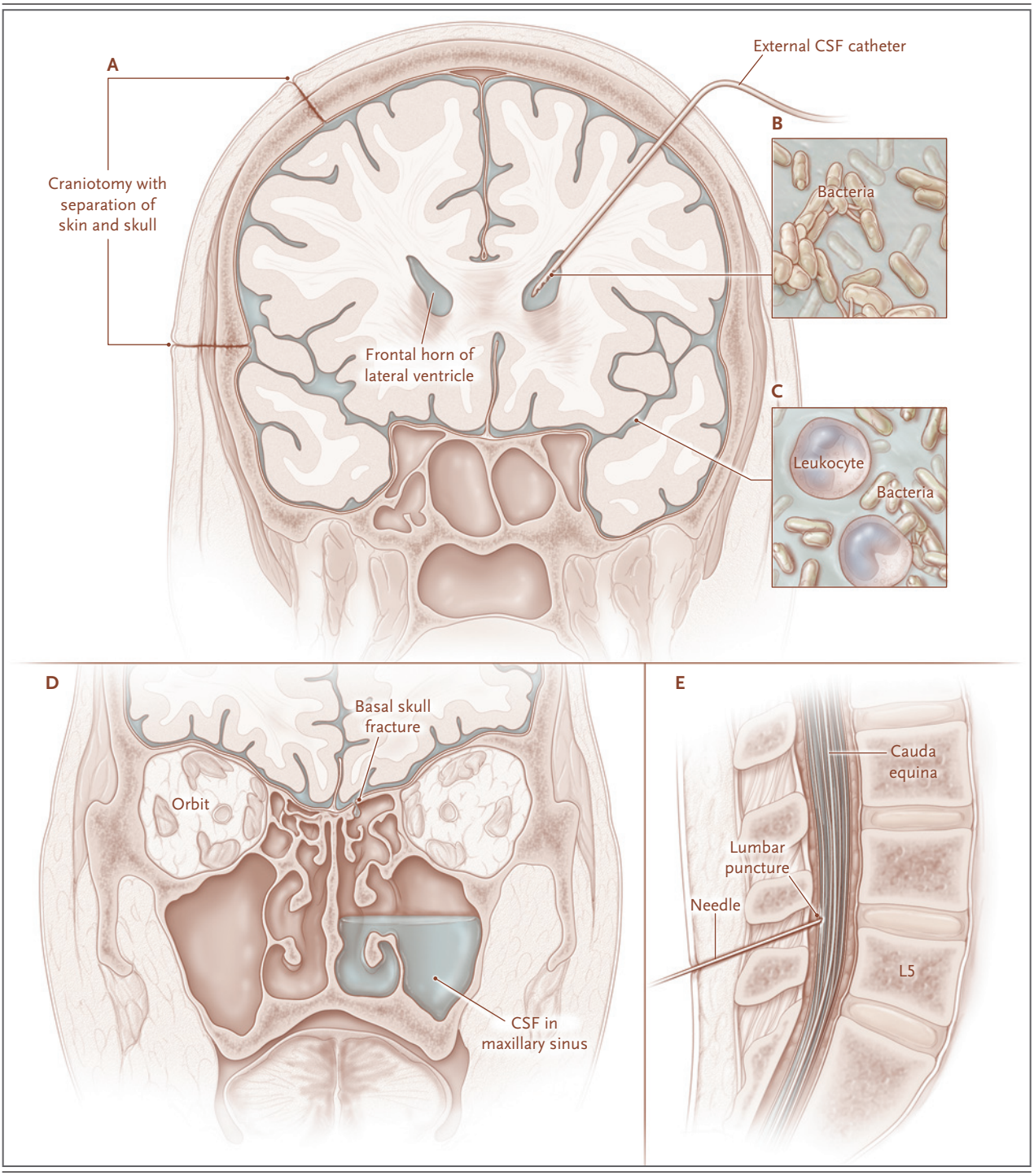
The majority of patients in whom meningitis develops as a complication of closed head trauma have a basilar skull fracture,[11] which causes the subarachnoid space to be connected to the sinus cavity and is associated with an increased risk of infection; rates of infection are reported to be as high as 25%, with a median time between injury and the onset of meningitis of 11 days.[11,13] Leakage of cerebrospinal fluid is the major risk factor for the development of meningitis, although most leaks that occur after trauma are unrecognized.[11,13] Most leaks resolve spontaneously within 7 days, but surgical intervention is indicated if leakage persists. Head trauma is the most common cause of recurrent bacterial meningitis.[14]

LUMBAR PUNCTURE

Meningitis develops after lumbar puncture in approximately 1 in 50,000 cases, with about 80 cases reported annually in the United States.[15] The majority of cases occur after spinal anesthesia or myelography. The risk of meningitis after lumbar puncture may be substantially decreased if aseptic conditions are met (i.e., hand disinfection and the use of sterile gloves) and if operators wear face masks and operating caps when performing spinal anesthesia or myelography.

PATHOGENS

The specific bacteria that cause nosocomial meningitis vary according to the pathogenesis and timing of the infection after the predisposing event.[1,2,11,13,15-17] Meningitis that develops after neurosurgery or in patients who are hospitalized for a prolonged period after penetrating trauma or basilar skull fracture can be caused by staphylococci or by facultative or aerobic gram-negative bacilli. In patients in whom foreign bodies (e.g., internal ventricular drains) have been placed, meningitis is often caused by cutaneous organisms such as coagulase-negative staphylococci or *Propionibacterium acnes*. The majority of meningitis cases



that occur after basilar skull fracture or early after otorhinologic surgery are caused by microorganisms that colonize the nasopharynx (especially *Streptococcus pneumoniae*). These infecting microorganisms are important to consider in the approach to empirical antimicrobial therapy (see below).

CLINICAL FINDINGS AND DIAGNOSIS

A clinical suspicion of nosocomial bacterial meningitis should prompt a diagnostic workup and antimicrobial therapy. Fever and a decreased level of consciousness are the most consistent clinical

Figure 1 (facing page). Pathogenetic Mechanisms at the Most Common Sites of Nosocomial Bacterial Meningitis.

Bacteria may enter the meninges and subarachnoid space from contiguous sites of colonization or foci of suppuration after craniotomy (Panel A). Cerebrospinal fluid (CSF) catheters (Panel B) have a proximal portion that enters the cerebrospinal fluid space and a distal portion that may also be internal, terminating in the peritoneal, pleural, or vascular space, or that may be external, when the need for the catheter is temporary. Cerebrospinal fluid catheters may become infected by retrograde infection from the distal end of the shunt, wound or skin breakdown overlying the catheter, metastatic infection in patients with bacteremia, or colonization of the catheter at the time of surgery. Concentrations of leukocytes, antibodies, and complement components in the subarachnoid space are low, facilitating multiplication of bacteria (Panel C). After head trauma, microorganisms may enter the subarachnoid space through direct invasion as a result of the trauma or, in the case of a basilar skull fracture, through a dural tear, which may provide an avenue for invasion of the central nervous system by bacteria located in the auditory canal, nose, or nasopharynx (Panel D). Bacteria may also be introduced by lumbar puncture (Panel E).

features,[3,4,11,14-16] although they are nonspecific and difficult to recognize in patients who are sedated, who have just undergone neurosurgery, or who have an underlying disease that may mask the symptoms.[18] Infections associated with cerebrospinal fluid shunts may cause nonspecific symptoms such as low-grade fever or general malaise[3]; signs of meningeal irritation are seen in less than 50% of patients. Symptoms and signs of infection may also be associated with the distal portion of the shunt (i.e., peritonitis or bacteremia).

The diagnostic workup consists of neuroimaging, cerebrospinal fluid analysis (cell counts, Gram's staining, biochemical tests for glucose and protein, and cultures), and cultures of blood. Neuroimaging is indicated in most patients with suspected nosocomial bacterial meningitis, since it allows for an evaluation of ventricular size and provides information on whether there is a malfunction of the shunt or whether potentially contaminated catheters retained from previous surgical procedures are present. Multislice computed tomographic (CT) scanners with multiplanar reformatting capabilities may be helpful in localizing leaks of cerebrospinal fluid (Fig. 2). Neuroimaging may also show expanding masses (i.e., hemorrhage, subdural empyema, or hydrocephalus) and brain shift, which should be identified before lumbar puncture is performed. Cerebrospinal fluid can be obtained through the catheter in patients with internal or external ventricular catheters; otherwise, a lumbar puncture is necessary. However, in patients with obstructive hydrocephalus, lumbar cerebrospinal fluid may not be reflective of ventricular infection because of the lack of communication between ventricular and lumbar cerebrospinal fluid.

The diagnosis of nosocomial bacterial meningitis is made on the basis of the results of a cerebrospinal fluid culture; aerobic and anaerobic culturing techniques are obligatory. However, cultures require prolonged incubation before being confirmed as negative, and results may be negative in patients who have received previous antimicrobial therapy. Cerebrospinal fluid should be analyzed to determine cell counts, including differential counts, and biochemical tests for glucose and protein, as well as Gram's staining, should be performed. One study that compared Gram's staining with cerebrospinal fluid cultures for the diagnosis of bacterial meningitis showed that Gram's staining had a high specificity but a low sensitivity.[19]

Cell counts in cerebrospinal fluid may be helpful but have low sensitivity and specificity in clinical subgroups of patients.[17,19] In a prospective study involving 172 patients with external ventricular catheters, cell counts in cerebrospinal fluid were normal in 4 of 18 patients in whom meningitis was confirmed by culture (22%)[17]; a similar proportion of patients without positive cultures had pleocytosis. The interpretation of the numbers of white cells in cerebrospinal fluid is especially problematic in patients who have meningitis that develops after intraventricular hemorrhage; although a formula has been proposed for interpretation,[20] the diagnostic accuracy is unknown.[21] Among patients assessed for postoperative meningitis, aseptic meningitis as a result of the local inflammatory reaction to blood breakdown products may account for up to 70% of cases.[22]

Additional tests to establish the diagnosis of bacterial meningitis have been evaluated. In patients who had undergone neurosurgery, a lactate concentration of 4 mmol per liter or more in the cerebrospinal fluid was shown to have a sensitivity of 88%, a specificity of 98%, a positive predictive value of 96%, and a negative predictive value of 94% for the diagnosis of bacterial meningitis.[23] However, a retrospective review of cases of bac-

Table 1. Neurosurgical Techniques to Minimize the Risk of Postoperative Meningitis.

Before surgery
Wash scalp hair, remove dirt or debris, and cover open wounds with a clean dressing
Clip, but do not shave, hair
Use chlorhexidine or an iodine-based skin preparation
Drape the surgical site with adhesive drapes and transparent adhesive film to prevent implantable hardware from coming in contact with exposed skin
Maintain sterile field with careful aseptic techniques
Administer prophylactic antibiotics to achieve adequate tissue concentrations before incision
During surgery
Minimize blood loss and tissue trauma; avoid hypothermia unless it is deliberately induced
Remove devitalized and grossly contaminated tissue and small bone fragments
Use a double layer of gloves when handling implantable devices
Irrigate the operative field with warmed sterile physiologic solution
Perform careful hemostasis to avoid postoperative wound hematomas
Position the cerebrospinal fluid drainage devices carefully to maintain a continuous flow of cerebrospinal fluid; ensure that the exit site is fashioned so that there is no leakage around the cerebrospinal fluid drain; ensure that the catheter is tunneled from the insertion site and secured to the skin so that it cannot be dislodged and that it is connected securely to a sterile drainage system; sample the cerebrospinal fluid under sterile conditions
Close the skin carefully, with wound edges secured to prevent leakage of cerebrospinal fluid but with good skin perfusion; avoid passing hardware directly beneath the incision
After surgery
Use percutaneous drains to collect postoperative hemorrhage; ensure that the drains are tunneled so that they will not leak and secured so that they cannot be dislodged
Apply a barrier dressing where necessary, particularly to prevent the patient from inadvertently opening the wound
Avoid putting pressure on the wound in the postoperative period; take measures to prevent pressure sores in other areas

terial meningitis associated with a cerebrospinal fluid shunt showed that with the use of that cutoff value for lactate, almost half of the infections would have been missed.[3] Concentrations of C-reactive protein in serum or cerebrospinal fluid, and serum concentrations of procalcitonin, have been evaluated for their usefulness in determining the diagnosis[24]; although elevated concentrations are suggestive of bacterial infection, they do not establish the diagnosis, and further studies are needed to determine the usefulness of these markers in the diagnosis of nosocomial bacterial meningitis.

Nucleic acid–amplification tests, such as polymerase-chain-reaction (PCR) assays, have been evaluated for their effectiveness in detecting the presence of bacterial DNA in cerebrospinal fluid from patients with ventricular catheters. In one study that used PCR to detect gram-positive bacteria in 86 specimens, 42 were negative as assessed by culture but positive as assessed by PCR; there were no positive culture results in patients with negative PCR results, suggesting that a negative PCR result is predictive of the absence of infection.[25] More studies are needed, however, before routine use of PCR assays is recommended for the diagnosis of bacterial meningitis, especially because contaminating bacteria may lead to false positive results.

ANTIMICROBIAL THERAPY

The choice of empirical antimicrobial therapy for nosocomial bacterial meningitis depends on the pathogenesis of the infection (Table 2). The therapy for patients in whom meningitis develops after neurosurgery or for patients who are hospitalized for a prolonged period after penetrating head trauma or basilar skull fracture should consist of vancomycin in combination with cefepime, ceftazidime, or meropenem[26]; the choice of the second agent should be based on the antimicrobial-susceptibility profiles of the local gram-negative bacilli. Meropenem is the agent of choice if one of the carbapenems is used, given the lower risk of seizure with meropenem than with imipenem, and given the clinical studies that have shown its usefulness in the treatment of bacterial meningitis.[26] Empirical therapy after basilar skull fracture or early after otorhinologic surgery should consist of vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone).[11,13,14] Once a specific pathogen has been isolated, antimicrobial therapy can be modified for optimal management.

Concerns have been raised regarding the adequacy of the penetration of vancomycin into the cerebrospinal fluid in patients with nosocomial meningitis, as well as the potential for side effects when the elimination of vancomycin is hampered in patients with multiorgan system dysfunction.[27] Linezolid and daptomycin have been shown to have efficacy in some cases of staphylococcal meningitis[28,29]; linezolid has also been shown to have favorable pharmacokinetic characteristics (i.e., cerebrospinal fluid penetration of approximately

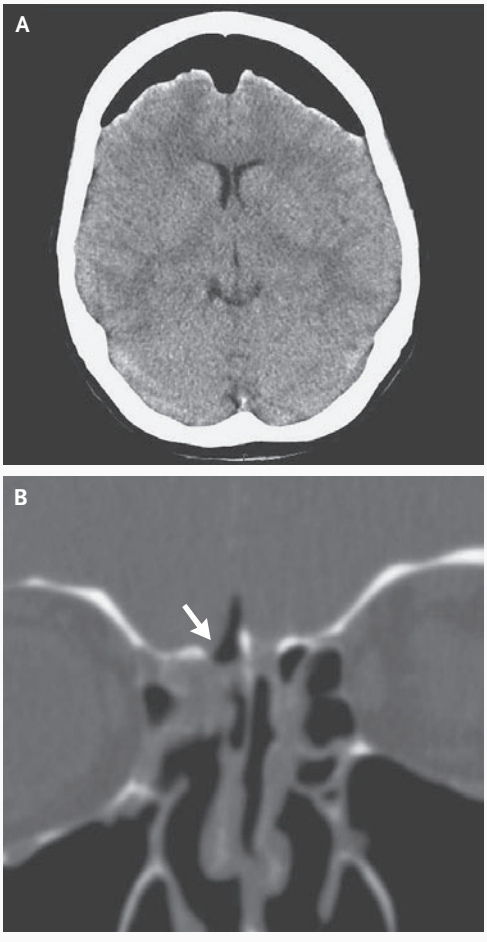


Figure 2. Cranial CT Scans in a 51-Year-Old Woman with Pneumococcal Meningitis 1 Week after Nasal Septum Surgery.

The scan in Panel A shows bilateral subdural air collections, a finding referred to as "Mount Fuji sign." The scan in Panel B shows a bony defect of the lamina cribrosa on the right (arrow). The patient underwent neurosurgical closure of the defect.

80% at steady state) in neurosurgical patients in critical care units.[30] However, vancomycin is recommended as the first-line therapy and is administered at dosages aimed at achieving a serum trough concentration of 15 to 20 μg per milliliter.[26] Alternative agents may be used in patients in whom an adequate response is not seen.

The British Society for Antimicrobial Chemotherapy recommends empirical therapy for all patients who have signs of postoperative meningitis; treatment should be withdrawn after 72 hours if the results of cerebrospinal fluid cultures are negative.[31] When this recommendation was evaluated in a prospective study, complications were shown to be rare after treatment was withdrawn, if Gram's staining of cerebrospinal fluid and cerebrospinal fluid cultures were negative for bacterial meningitis after 72 hours.[22] However, the therapeutic approach to nosocomial bacterial meningitis must be individualized, and some patients, especially those who have received previous or concurrent antimicrobial therapy, may require treatment with an appropriate antimicrobial agent despite negative culture results.

Direct infusion of antimicrobial agents into the ventricles through a catheter is occasionally necessary, when infections that develop after neurosurgical procedures or in association with cerebrospinal fluid catheters are difficult to eradicate with parenteral antimicrobial therapy alone.[26,27,32-34] However, no antimicrobial agent has been approved by the Food and Drug Administration for intraventricular use, and the indications for this mode of administration are not well defined. Vancomycin and gentamicin are the antimicrobial agents that have been used most often.[27,31-34] Dosages have been determined empirically (Table 3), with adjustments made on the basis of the concentration of the agent in the cerebrospinal fluid. The drain is usually closed for 1 hour after the administration of the first intraventricular dose. Subsequent doses can be determined by measuring the trough concentration in a sample of cerebrospinal fluid obtained immediately before the infusion of the next dose. The trough concentration divided by the minimal inhibitory concentration of the agent for the isolated bacterial pathogen should generally exceed 10 to 20 for consistent sterilization of the cerebrospinal fluid. Although this procedure is not standardized, it is a reasonable approach to adopt when agents whose concentrations can be routinely measured are used. At some centers, peak and trough antimicrobial concentrations in cerebrospinal fluid are monitored by the placement of a separate ventricular access device,[36] although it is unclear whether the peak level that is reached above the minimal inhibitory concentration or the length of time that the level remains above the minimal inhibitory concentration is a better predictor of the outcome.[33]

Table 2. Recommended Empirical Antimicrobial Therapy for Nosocomial Bacterial Meningitis, According to the Pathogenesis of the Infection.

Pathogenesis	Common Bacterial Pathogens	Antimicrobial Therapy*
Postneurosurgical infection	Facultative and aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*), *Staphylococcus aureus*, and coagulase-negative staphylococci (especially *S. epidermidis*)	Vancomycin plus cefepime, ceftazidime, or meropenem†
Ventricular or lumbar catheter	Coagulase-negative staphylococci (especially *S. epidermidis*), *S. aureus*, facultative and aerobic gram-negative bacilli (including *P. aeruginosa*), *Propionibacterium acnes*	Vancomycin plus cefepime, ceftazidime, or meropenem†
Penetrating trauma	*S. aureus*, coagulase-negative staphylococci (especially *S. epidermidis*), facultative and aerobic gram-negative bacilli (including *P. aeruginosa*)	Vancomycin plus cefepime, ceftazidime, or meropenem†
Basilar skull fracture	*Streptococcus pneumoniae*, *Haemophilus influenzae*, group A β-hemolytic streptococci	Vancomycin plus a third-generation cephalosporin (i.e., ceftriaxone or cefotaxime)

* The preferred daily dosages of antimicrobial agents in adults with normal renal and hepatic function are as follows: vancomycin, 15 mg per kilogram of body weight every 8 to 12 hours to maintain a serum vancomycin trough concentration of 15 to 20 μg per milliliter; cefepime, 2 g every 8 hours; ceftazidime, 2 g every 8 hours; meropenem, 2 g every 8 hours; ceftriaxone, 2 g every 12 hours; and cefotaxime, 2 g every 4 to 6 hours. For patients with severe allergy to penicillin or cephalosporins, aztreonam, 2 g every 6 to 8 hours, or ciprofloxacin, 400 mg every 8 to 12 hours, can be used for treatment of infection caused by gram-negative bacilli.

† The choice of the specific agent should be based on local antimicrobial susceptibility of aerobic gram-negative bacilli.

MULTIDRUG-RESISTANT GRAM-NEGATIVE BACILLI

Given the emergence of multidrug-resistant gram-negative bacilli, the approach to antimicrobial therapy in patients with nosocomial meningitis that is caused by these pathogens has become problematic.[37] In particular, acinetobacter species have become more common in patients with nosocomial meningitis,[34] and these bacteria are frequently resistant to third-generation and fourth-generation cephalosporins; resistance to carbapenems has also been reported. Therefore, adequate concentrations of these agents in the cerebrospinal fluid may not be achieved after parenteral administration. For empirical treatment of acinetobacter meningitis, intravenous meropenem, with or without an aminoglycoside administered by the intraventricular or intrathecal route, has been recommended[34]; if the organism is subsequently found to be resistant to carbapenems, colistin (usually formulated as colistimethate sodium) or polymyxin B should be substituted for meropenem and may also need to be administered by the intraventricular or intrathecal route.[37] In a review of 14 patients with multidrug-resistant *Acinetobacter baumannii* meningitis or ventriculitis who were treated with colistin administered either intravenously or by the intraventricular or intrathecal route, cerebrospinal fluid sterilization was achieved in all cases, and 13 patients were cured.[38] In a retrospective review of 51 cases of acinetobacter meningitis, all 8 patients who were treated with intravenous and intrathecal colistin survived.[35]

REMOVAL OF CATHETERS

If bacterial meningitis develops in a patient who has an external ventricular catheter, the catheter should be removed to increase the likelihood that the infection can be cured. In the case of internal ventricular catheters, antimicrobial therapy, removal of all components of the infected catheter, and placement of an external drain appear to be the most effective treatment, with success in more than 85% of patients; external drainage leads to more rapid resolution of the ventriculitis, allows monitoring of cerebrospinal fluid findings and cultures, and allows continued treatment of the underlying hydrocephalus. The optimal timing for reimplantation of the shunt is not clearly defined, although general guidelines can be suggested. In patients with shunt infections that are caused by a coagulase-negative staphylococcus or *P. acnes* in association with abnormalities of the cerebrospinal fluid (e.g., pleocytosis), antimicrobial therapy

for 7 days is commonly recommended before placement of a new shunt; if repeat cultures are positive, antimicrobial therapy should generally be continued until cerebrospinal fluid cultures have been negative for 10 consecutive days before a new shunt is placed. In the case of shunt infections caused by *Staphylococcus aureus* or gram-negative bacilli, 10 days of antimicrobial therapy after repeated negative cultures are recommended before placement of a new shunt, although some authorities recommend an even longer duration of therapy when gram-negative bacilli are isolated. Some experts have recommended a 3-day observation period after the completion of antimicrobial therapy before a new shunt is placed to confirm that the infection has been cleared, although this is not uniformly recommended.

Removal of the catheter hardware, followed by immediate replacement and intravenous antimicrobial therapy, cures approximately 65% of patients with catheter-related infections.[39] Conservative management (i.e., leaving the internal catheter in place and administering intravenous or intraventricular antimicrobial therapy) has generally been associated with a low success rate (approximately 35%)[39,40] but has been successfully used in selected patients with infections from cerebrospinal fluid catheters that were caused by less virulent microorganisms such as coagulase-negative staphylococci. In an observational study of 43 patients, 84% were cured with systemic and intraventricular antimicrobial agents (infused through a separate ventricular access device), with a 92% success rate in the case of infections caused by bacteria other than *S. aureus*.[35] Regardless of the manner of treatment, infections from cerebrospinal fluid shunts can recur. In one study, the recurrence rate was 26%, with two thirds of the cases caused by the same microorganism.[41]

Table 3. Recommended Doses of Selected Antimicrobial Agents Administered by the Intraventricular Route.*

Antimicrobial Agent	Daily Intraventricular Dose
Vancomycin	5–20 mg†
Gentamicin	1–2 mg in infants and children; 4–8 mg in adults
Amikacin	5–50 mg‡
Polymyxin B	2 mg in infants and children; 5 mg in adults
Colistin, usually formulated as colistimethate sodium	10 mg once daily or 5 mg every 12 hr§

* There are no data that define the exact dose of an antimicrobial agent that may be administered by the intraventricular route, but the dose can be estimated through the measurement of the cerebrospinal fluid trough concentration, in the case of agents for which these measurements can be obtained. Medications administered by the intraventricular route should be preservative-free.
† Most studies have used a 10-mg or 20-mg dose.
‡ The usual daily dose is 30 mg.
§ In one study, patients received 10 mg every 12 hours without an increase in side effects.[35]

FUTURE DIRECTIONS

The prevention and management of nosocomial bacterial meningitis pose a substantial challenge, especially with the emergence of disease caused by multidrug-resistant pathogens. Protocols must be developed to standardize surgical techniques in order to minimize the risk of infection. Clinical trials of simple interventions, such as changing the outer pairs of gloves before handling the catheter material during surgery, should be initiated. Early recognition and aggressive treatment may improve the outcome for patients with nosocomial bacterial meningitis.

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