Neurocritical Care of Patients with Central Nervous System Infections

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Current Infectious Disease Reports 2007, **9:**308–314
Current Medicine Group LLC ISSN 1523-3847

Bacterial meningitis and viral encephalitis are life-threatening infections with high mortality rates. Patients who survive these infections often remain permanently disabled. Potential neurologic complications requiring careful attention include impaired consciousness, elevated intracranial pressure, hydrocephalus, stroke, and seizures. Systemic complications are also common and are frequently the immediate cause of death. Critical care of these patients should focus not only on treatment of the underlying infection and its immediate complications but also on minimizing secondary brain injury. Given the increasing complexity of the diagnostic and therapeutic modalities available in managing central nervous system infections, the involvement of neurocritical care units and neurointensivists may be particularly helpful in improving outcomes.

Introduction

Bacterial meningitis and viral encephalitis are life-threatening infections of the central nervous system (CNS). Community-acquired bacterial meningitis in adults has a mortality rate of about 20% to 25%, and survivors may be left with a variety of lasting neurologic complications such as hearing loss, hemiparesis, aphasia, and epilepsy [1••,2]. Even patients who do not manifest obvious disability at the time of hospital discharge can subsequently be demonstrated to have more subtle cognitive abnormalities on neuropsychologic testing [3]. Death and permanent neurologic sequelae are more common when the pathogen is *Streptococcus pneumoniae* rather than *Neisseria meningitidis*.

Similarly, patient outcomes with viral encephalitis depend in large part upon the virulence of the particular pathogen involved. In the absence of an epidemic, the most commonly diagnosed cause of encephalitis in the United States is herpes simplex virus (HSV). Untreated, HSV encephalitis is fatal in about 70% of cases. The use of intravenous acyclovir has helped reduce this figure to less than 25%, although more than 20% of survivors are still left with severe disability [4,5]. Encephalitis due to West Nile virus (WNV) has been common in North America over the past few years, and is associated with a mortality rate of 10% to 20%; only a minority of patients can be discharged home without requiring assistance [6].

Because of the substantial morbidity and mortality associated with these conditions, many patients are admitted to intensive care units (ICUs). The availability of specialist neurocritical care units has proven to be beneficial in the care of patients with a variety of cerebral insults, most notably traumatic brain injury (TBI) and intracranial hemorrhage, although their impact specifically on the outcome of CNS infections has not yet been assessed [7]. The goal of neurocritical care units is not only to optimize therapy for the primary condition threatening the brain but also to minimize secondary cerebral insults that result from factors such as elevated intracranial pressure (ICP), seizures, and ischemia. The importance of meticulous multidisciplinary critical care is emphasized by the fact that a substantial proportion of these patients, particularly the elderly, die of systemic rather than neurologic complications [2].

Neurologic Complications

Altered level of consciousness

Most patients with CNS infections have altered mental status. If the level of consciousness is impaired to the point of failure by the patient to clear secretions and maintain a patent airway, endotracheal intubation is required. In patients with bacterial meningitis, the average Glasgow Coma Scale (GCS) at hospital admission is approximately 10 to 11, and 10% to 20% of patients are comatose (respond only reflexively to noxious stimuli) [1••,8]. These figures are similar when the condition is HSV encephalitis [5,9]. In one large series of patients with WNV encephalitis, 38% presented with delirium, 27% with stupor, and 22% with coma [6]. The level of consciousness at the time of ICU admission is a major predictor of outcome [4,8,10]. In one study of ICU patients with meningitis, mortality was 33% in those patients with a GCS score of three to eight, 10% with a score of nine to 12, and 0%

with a score of 13 to 15 [8]. Nevertheless, recovery after prolonged, deep coma due to CNS infections has been reported. Death by neurologic criteria can occasionally occur, and organs from donors who died from bacterial meningitis have been successfully transplanted.

Raised intracranial pressure

Many patients with CNS infections, particularly those with stupor and coma, have raised ICP. In patients with bacterial meningitis, the presence of cell-wall components induces inflammation and increases concentrations of various cytokines within the subarachnoid space. The inflammatory milieu and release of factors such as oxygen-derived free radicals, excitatory amino acids, and matrix metalloproteinases combine to induce direct cellular toxicity (resulting in cytotoxic edema) and disruption of the blood-brain barrier (resulting in vasogenic edema). The normal absorption of cerebrospinal fluid (CSF) in the arachnoid villi is slowed, leading to the development of communicating hydrocephalus and interstitial edema [11]. In patients with viral encephalitis, there is induction of perivascular lymphocytic inflammation, primarily in the gray matter and at the gray-white matter junction [12].

Neither physical examination nor CT scanning is sensitive for detecting high ICP. In patients with bacterial meningitis, van de Beek et al. [1••] reported that the mean opening pressure during lumbar puncture was significantly elevated at 37 cm H_2O. The mean opening pressure was more than 40 cm H_2O in 39% of cases, and these patients were more likely to be comatose (24%) than those with lower values (11%). Of 15 patients with a GCS of eight or less who were admitted to a Swedish neurocritical care unit for ICP monitoring, nine (60%) were found to have raised ICP. All but one of the patients developed intracranial hypertension at some point during their ICU stay. In some cases, ICP elevation was dramatic, reaching values of more than 100 mm Hg. Mean ICP at the time of insertion was markedly higher among nonsurvivors (46 mm Hg) than in survivors (20 mm Hg) [13••]. Similarly, intracranial hypertension is common in patients with HSV encephalitis, particularly in those who ultimately die from their infection [9,14]. In a study of 144 patients with Japanese encephalitis, more than 10% of patients had opening pressures in excess of 25 cm H_2O. Mortality was significantly higher in these patients, and herniation syndromes were a common contributor to death [15].

No randomized controlled trials have investigated the utility of ICP monitoring in comatose patients with CNS infections. Probably for this reason and the fact that many patients are cared for in medical rather than neurologic ICUs, ICP monitors are infrequently used. Nevertheless, it is very likely that ICP elevation of the magnitude described above induces secondary brain injury, both by causing brain tissue shifts and by reducing cerebral perfusion pressure (CPP) (equal to mean arterial pressure minus ICP), which in turn leads to ischemia. ICP monitors are widely recommended and used with other CNS disorders (eg, TBI, intracranial hemorrhage, hepatic encephalopathy), even though randomized clinical trials demonstrating their utility have not been performed. It is our opinion that ICP measurement should be strongly considered in selected patients with CNS infections, particularly those who are comatose. Determination of opening pressure during lumbar puncture is a useful surrogate but may not always reflect true ICP, does not measure pressure continuously, and is sometimes contraindicated due to fear of inducing cerebral herniation. Clinicians should have a low threshold to reimage the brain to rule out hydrocephalus, which may develop in as many as 20% of cases of meningitis and mandates either repeated large volume lumbar punctures, placement of a lumbar drain, or ventriculostomy (Fig. 1) [16•].

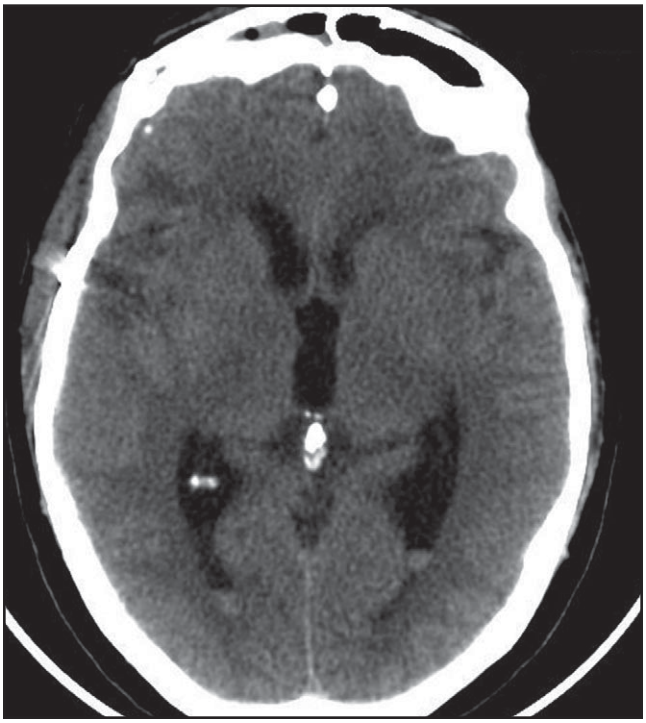

Figure 1. CT scan of a 52-year-old woman with pneumococcal meningitis demonstrating mild hydrocephalus. Hyperdense debris layering in occipital horns of lateral ventricles suggests pyogenic ventriculitis. Initial opening pressure was 48 cm H_2O and leukocyte count was greater than 5000 cells/μL (more than 90% neutrophils).

The approach to treating intracranial hypertension in patients with CNS infections is aided by the experience of neurocritical care units with other common conditions that cause cerebral edema, especially TBI. Effective control of ICP is difficult without a monitor to guide therapy. The head of the bed should generally be elevated to 30°, both to reduce ICP and to decrease the risk of ventilator-associated pneumonia. Raising the head of the bed to even higher levels will often lower ICP further, but adequate CPP must be maintained. Adequate analgesia and sedation help reduce ICP by decreasing cerebral metabolic

rate and in turn cerebral blood flow (CBF) while also decreasing intrathoracic pressure and improving jugular venous outflow. Hyperventilation is an effective method to reduce ICP quickly when it is dangerously elevated, but should only be used as a short-term intervention, because it may induce cerebral ischemia [10]. Patients with CNS infections may spontaneously hyperventilate and develop a respiratory alkalosis. If mechanical ventilation is required, the initial minute ventilation should be set to avoid a rapid increase in PCO_2, as this will cause cerebral vasodilatation and exacerbate intracranial hypertension. If a ventriculostomy is placed for treatment of hydrocephalus, intermittent drainage of CSF is very effective in controlling ICP.

Although it has not been systematically studied in the setting of CNS infections, osmotic therapy with mannitol is first-line therapy for treatment of intracranial hypertension. A bolus of mannitol increases intravascular volume and reduces blood viscosity, leading to increased CBF, which in turn causes cerebral vasoconstriction. This is followed by the osmotic action of mannitol, drawing water out of the brain, an effect that is maximal in conditions that affect the brain diffusely and where the blood-brain barrier remains relatively in tact. With unilateral brain injury, at least theoretically, there can be greater removal of water by mannitol in the unaffected parts of the brain, resulting in increased brain tissue shift [17]. Whether this phenomenon is clinically important or happens specifically with CNS infections is uncertain, but it could conceivably be problematic in patients with HSV encephalitis, where the temporal lobes are often preferentially involved. Smaller doses (0.25–0.5 g/kg) of mannitol have similar efficacy to larger doses (0.5–1.5 g/kg). In order to avoid complications, it is frequently recommended that mannitol no longer be administered when the serum osmolality exceeds 320 mOsm/L; however, this threshold is arbitrary and does not predict an increased risk of renal failure. Determination of the serum osmolar gap in between doses of mannitol is a more rationale way to ensure that it is not accumulating [17].

Hypertonic saline (HTS) has emerged as an alternative osmotic agent to treat intracranial hypertension. HTS is most often administered as a bolus in response to elevated ICP and appears to be at least as effective as mannitol. Alternatively, HTS can be delivered as an infusion, with the goal being to induce hypernatremia to a level of 145–155 mmol/L and prevent repeated surges in ICP [18]. Patients with CNS infections may also develop hyponatremia as a result of the syndrome of inappropriate antidiuretic hormone. Given that low serum osmolarity can worsen cerebral edema, hyponatremia should probably be treated, if necessary even with hypertonic saline, taking the usual precautions to avoid osmotic demyelination.

Fever is a common manifestation of CNS infections. Mounting experimental and clinical evidence exists that elevated body temperature may not only raise ICP, but also worsen secondary brain injury [19•]. Therefore, we believe that fever should be treated and relative normothermia maintained in patients with bacterial meningitis or viral encephalitis. The use of antipyretics and conventional methods of surface cooling have limited efficacy at controlling temperature in febrile critically ill patients. If these measures fail to maintain normothermia, a variety of novel endovascular and surface cooling methods have recently become available for more consistent temperature control. Although induced hypothermia has shown promise in reducing inflammation in animal studies of bacterial meningitis [20], it requires further study before being considered for routine use in patients with CNS infections.

When ICP remains dangerously elevated in spite of the preceding interventions, other options may be considered in neurocritical care units, including barbiturate coma or decompressive craniectomy. Barbiturates are typically administered with the aid of electroencephalogram (EEG) monitoring in order to use the smallest dose that induces a suppression-burst pattern. However, many potential adverse effects exist including hypotension, immunosuppression, hypo- or hyperkalemia, and prolonged coma even after cessation of the infusion. Decompressive craniectomy increasingly has been used to control refractory ICP in patients with TBI, but randomized controlled trials are only now underway to determine whether it improves long-term outcomes. Although uncommon, both barbiturate coma and decompressive craniectomy have been used in selected cases of bacterial meningitis and viral encephalitis to control ICP [21,22].

Corticosteroids may ameliorate the subarachnoid space inflammatory response in patients with bacterial meningitis, thereby reducing neuronal injury and cerebral edema. The effects of corticosteroids on ICP in patients with established intracranial hypertension have not been specifically studied. In a large, randomized, controlled trial consisting largely of patients with pneumococcal meningitis, de Gans and van de Beek [23] showed that dexamethasone administered prior to the first dose of antibiotics unequivocally improved mortality and neurologic outcome. Whether the results of this trial should be extrapolated to pathogens other than *S. pneumoniae*, however, is a controversial issue. It is not uncommon for patients with bacterial meningitis to arrive in the ICU having already received antibiotics but not corticosteroids. Much of the inflammation with meningitis occurs in response to the destruction of bacteria by antibiotics, such that introducing corticosteroids at a later time is less likely to be beneficial. Furthermore, corticosteroids may decrease the penetration of vancomycin into the CSF; and although the clinical relevance of this observation is uncertain, it may become more important as resistance to third generation cephalosporins in pneumococci continues to increase. On balance, the early use of dexamethasone in conjunction with antibiotics, even when the initial suspicion of meningitis is only low or moderate, should be

encouraged presently. Still, clinicians will sometimes be faced with the difficult decision of whether or not to start adjunctive dexamethasone at a later time.

Though not as well studied as in bacterial meningitis, the use corticosteroids in patients with viral encephalitis is common, particularly if the pathogen is HSV [4]. A recent retrospective study suggested that their use is associated with improved outcome [24•]. An animal study demonstrated that steroids may reduce the degree of radiographic abnormalities seen on MRI several months after infection [25]. Despite their immunosuppressive effects, corticosteroids do not appear to enhance viral replication [26].

Because of the possibility of raised ICP in patients with CNS infections, physicians are often concerned about the safety of performing a lumbar puncture. Numerous case reports describe declining mental status and cerebral herniation following lumbar puncture, although it is not always clear whether the deterioration was in fact due to the procedure or simply resulted from worsening cerebral edema. The reduction in pressure induced by withdrawal of CSF from the lumbar cistern may increase the gradient for downward brain tissue shifts. Still, intracranial hypertension alone should not be regarded as a barrier to the safe performance of lumbar puncture. Instead, the presence of a space-occupying lesion with significant mass effect, which may occur regardless of the ICP, is a contraindication [27]. If a decision is made to perform a lumbar puncture in a relatively high-risk patient, precautions that may help reduce the chance of herniation include use of a smaller spinal needle (eg, 22- or 25-gauge), removal of as little fluid as possible, and maneuvers to lower ICP prior to the procedure (eg, administration of mannitol or temporary hyperventilation).

Cerebral blood flow disturbances

Patients with bacterial meningitis commonly have abnormal CBF autoregulation [28]. Rather than responding appropriately with vasoconstriction or vasodilatation in response to changes in arterial blood pressure in order to maintain constant CBF, the cerebral circulation becomes directly dependent upon the blood pressure. Furthermore, angiographic studies have documented that patients with meningitis often develop a vasculopathy, putting them at significant risk of ischemic stroke [29]. Meningitis may also be complicated by cerebral venous thrombosis, which in turn may cause venous infarcts, intracerebral hemorrhage, and further elevation in ICP. Despite the risk of hemorrhage, careful anticoagulation appears to be safe in patients with cerebral venous thrombosis and is often recommended, although this has not been studied specifically when the etiology is a CNS infection [30]. Either arterial or venous cerebrovascular complications have been reported in as many as 20% to 30% of patients [2,31]. Consequently, if the neurologic status of patients with CNS infections deteriorates or fails to improve with appropriate antimicrobial therapy, CT or magnetic resonance angiography and venography should be strongly considered to rule out a vascular complication.

In light of these CBF derangements, extremes of blood pressure are poorly tolerated. The presence of hypotension, particularly in the face of an elevated ICP and vasculopathy, can produce cerebral ischemia. The lower limit of safe CPP in this setting is unknown, and probably varies from patient to patient. However, even when autoregulation is intact and there is no vasculopathy, CBF begins to fall at CPP values of less than 50 mm Hg. Thus, CPP should probably be kept above 60 to 70 mm Hg, and perhaps significantly higher in patients with an "ischemic penumbra." Recent advances in neuroimaging and monitoring capabilities in neurocritical care units with modalities such as perfusion CT, parenchymal brain tissue oxygen probes, and microdialysis catheters are enabling more sophisticated assessment of CBF and cerebral energy metabolism and will likely be increasingly used in the future management of patients with CNS infections.

Seizures

Overt seizures occur in 15% to 25% of cases of bacterial meningitis [1••,32] and are associated with a worse outcome [32]. The incidence of seizures with viral encephalitis varies from relatively infrequent in patients with WNV encephalitis [6], to more than one third when the pathogen is HSV, and to 85% in children with Japanese encephalitis [5,9,33]. Sustained or recurrent seizures lasting for more than 5 to 10 minutes without the patient regaining consciousness is defined as status epilepticus (SE).

Treatment of SE is a medical emergency for a number of reasons. First, dangerous systemic complications, such as aspiration, hypoxemia, hypotension, rhabdomyolysis, lactic acidosis, and hyperthermia may occur. Second, ongoing seizure activity may induce permanent neurologic damage. Third, delays in therapy may cause SE to become more difficult to abort. First-line therapy for SE consists of 2 mg increments of lorazepam with a maximum dose of 0.1 mg/kg. If the patient fails to respond, it is relatively unlikely that another conventional agent like phenytoin, diazepam, or phenobarbital will be effective [34]. At this point, the patient has refractory SE and should be intubated, such that deep sedation, usually with midazolam or propofol, can be used to control seizures. High doses of barbiturates can also be used, but these are longer acting and associated with more adverse effects. SE due to viral encephalitis is more likely to be refractory to conventional therapy than are other etiologies [35•].

If the level of consciousness remains depressed even after overt convulsions have stopped, the patient may be having nonconvulsive seizures (NCS), and an EEG should be performed as soon as possible. Sedatives should be titrated upward with the goal of abolishing seizures. The diagnosis of NCS or even nonconvulsive SE (NCSE) should be considered in any patient with a CNS infection associated with stupor or coma. NCSE is generally defined

as abnormal mental status with continuous or near-continuous seizures observed electrographically for at least 30 minutes. NCSE is remarkably common with CNS infections, occurring in more than 25% of cases admitted to neurocritical care units [36•]. This can only be discovered if an EEG is performed, with the yield improved significantly by monitoring patients continuously for 24 to 48 hours. How aggressively NCSE should be treated is controversial, but the presence of NCSE is associated with a high mortality.

Systemic Complications

Airway management

Indications for endotracheal intubation in patients with CNS infections include inability to protect the airway, ICP management, severe hypoxemia, impaired ventilation, increased work of breathing, or the need to safely complete an important diagnostic test. Once the decision is made to intubate a patient, every effort should be made to minimize further increases in ICP, hypotension, and hypoxemia. These derangements commonly occur with laryngoscopy and intubation, and they may contribute to secondary brain injury. Careful use of appropriate drugs to facilitate airway management can help attenuate hemodynamic instability and raised ICP. Etomidate is a widely used induction agent with the advantage of producing less hypotension than other common sedatives. Because it causes transient adrenal insufficiency, which in turn is known to be particularly deleterious in septic shock, the use of etomidate in the setting of sepsis has recently been discouraged. Given that many patients with bacterial meningitis now routinely receive intravenous dexamethasone for 96 hours, the significance of temporary adrenal insufficiency is unclear. Intravenous lidocaine blunts the rise in ICP associated with intubation, although the efficacy of its use has been debated [37].

Mechanical ventilation

Patients with CNS infections may develop acute lung injury or acute respiratory distress syndrome due to sepsis, aspiration, concomitant pneumonia, or in association with neurogenic pulmonary edema. Because most patients have an altered level of consciousness, noninvasive ventilation is used infrequently. If mechanical ventilation is necessary, it is important to limit tidal volumes (to ~ 6 mL/kg predicted body weight) and plateau pressures [38]. However, permissive hypercapnia and respiratory acidosis should be avoided, as this may increase ICP. Indeed, patients with intracranial hypertension were largely excluded from trials investigating lung protective ventilation. Fortunately, even when tidal volumes are reduced, relatively normal PCO_2 levels can usually be maintained simply by increasing the respiratory rate to maintain similar minute ventilation.

It may be necessary to use lower than usual levels of positive end-expiratory pressure in patients with acute respiratory distress syndrome, although the impact of raising positive end-expiratory pressure on ICP remains controversial and has traditionally been overestimated. Liberation from mechanical ventilation may be delayed by a persistently altered level of consciousness once respiratory status has improved. Coplin et al. [39] found that most comatose patients could be successfully extubated if a strong spontaneous cough and minimal secretions were present. In fact, delays in extubation because of concerns about impaired mental status were associated with worse outcome. Alternatively, several other studies have found high rates of extubation failure in patients with a depressed level of consciousness [40]. Better predictors of extubation outcome in neurocritical care patients are required. In those patients with a high likelihood of requiring prolonged mechanical ventilation, early tracheostomy within the first week may be advantageous, although it is our practice to wait until concerns about intracranial hypertension have resolved.

Hemodynamic support and severe sepsis

In patients with severe sepsis and septic shock, early goal-directed therapy, which includes aggressive fluid resuscitation, reduces mortality [41]. Particularly in children, concern has been expressed that excessive volume administration might exacerbate cerebral edema, although a recent systematic review did not support this assertion [42]. Furthermore, an animal model of bacterial meningitis has demonstrated that restricting fluids can reduce CBF and contribute to ischemia [43]. Because of the frequency of elevated ICP and CBF derangements, we believe that hypovolemia and hypotension should be carefully avoided. Traditional static measures of preload, including central venous pressure and pulmonary artery occlusion pressure, have limited capability to effectively guide fluid management. In addition, use of pulmonary artery catheters does not appear to improve outcomes in patients with sepsis [44]. Nevertheless, thermodilution with a pulmonary artery catheter remains a well-validated method for measurement of cardiac output, such that assessment before and after fluid challenges can be used to optimize intravascular volume. A variety of other invasive and noninvasive modalities, including transpulmonary thermodilution, pulse contour analysis, esophageal Doppler probes, and assessment of arterial blood pressure variation, have recently become available to help direct hemodynamic support.

Norepinephrine and dopamine have been recommended as first-line vasopressors in patients with septic shock; the addition of dobutamine may help improve oxygen delivery [45]. Low-dose infusions of vasopressin are sometimes also used; however, given that vasopressin is a cerebral vasodilator and may increase ICP, its safety in the setting of CNS infections and brain injury in general

has not yet been established. Blood pressure and CPP augmentation with norepinephrine appears to improve CBF more effectively than dopamine [46].

Although considerable debate continues about how to define "relative adrenal insufficiency," this phenomenon is present in a significant proportion of patients with septic shock. Patients with "inappropriately" low serum cortisol concentrations (eg, less than 20 to 25 μg/dL in the setting of shock) or in whom there is a blunted response to adrenocorticotropic hormone (eg, less than 9 μg/dL increase), have lower vasopressor requirements, and may have better outcomes, when given low to moderate doses of corticosteroids (200–300 mg hydrocortisone per day) for 7 days [47]. In contrast, high doses of corticosteroids early in the course of septic shock may actually be harmful [48]. Interestingly, despite the relatively high dose used (40 mg/day), much of the mortality benefit of dexamethasone in meningitis demonstrated by van de Beek and de Gans [49] may have been due to a reduction in systemic (rather than neurologic) complications. Putting this information together, some experts have recommended using lower doses of hydrocortisone rather than high-dose dexamethasone in patients with concomitant bacterial meningitis and septic shock; however, this approach has not been validated [50•], and the results of a large European trial of corticosteroids in septic shock will soon be available [51].

Patients with severe sepsis or septic shock and a high risk of death (Acute Physiology and Chronic Health Evaluation [APACHE] II score > 25) may benefit from the administration of recombinant human activated protein C (drotrecogin alfa) [52]. Vincent et al. [53•] combined data from four clinical trials of drotrecogin alfa and found that the median APACHE II score of enrolled patients with meningitis was 22, suggesting that the majority of these patients should not be treated with this agent. Of concern was the observation that 5.7% of patients with bacterial meningitis treated with drotrecogin alfa experienced intracranial hemorrhage, compared with only 1% of control patients [53•]. Thus, the efficacy and safety of drotrecogin alfa specifically in patients with severe sepsis or septic shock due to bacterial meningitis is questionable.

Conclusions

CNS infections are associated with high rates of morbidity and mortality. The importance of emergent administration of appropriate antimicrobial therapy cannot be overstated. The complexity of these conditions is greatly increased by the development of various neurologic and systemic complications, which often mandate admission to an ICU. Critical care of patients with meningitis and encephalitis should focus not only on treatment of the underlying infection and its immediate complications, but also on minimizing secondary brain injury.

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