# Chapter 13
# Neurological Infections

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## 13.1 Introduction

Meningitis and encephalitis are life-threatening central nervous system (CNS) infections or inflammatory states that most advanced practice clinicians (APC) will encounter at some point in their careers, much more so if they practice in the neurocritical care realm. These conditions differ from other infectious processes, such as pneumonia or urinary tract infections, because of the high morbidity and mortality associated not only with the conditions themselves, but also with a delay in the initiation of appropriate empiric therapy. In this chapter we will discuss the diagnosis and management of this constellation of diseases from initial presentation to initial management goals and ongoing tailoring of therapies as more data becomes available. We will also

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dive deeper into the epidemiology of the most common etiologies with specific considerations if a specific pathogen or etiology is suspected.

Meningitis is defined as the inflammation of one, two, or all three meningeal layers: the dura, arachnoid, and pial membranes. Encephalitis is an inflammation of the brain parenchyma. An inflammation that includes both the brain and the spinal cord is called encephalomyelitis. The etiologies of these CNS inflammatory states can be divided into infectious and noninfectious. Infectious etiologies underlying CNS inflammation include bacterial, viral, and, more rarely, fungal and parasitic. Presentations vary widely and depend on the etiology and progression of the disease. A timely assessment for the possibility of CNS infection is of the utmost importance, as initiation of treatment is emergent, and a delay can significantly affect morbidity and mortality.

## 13.2 Case Presentation

A 28-year-old woman is brought to your emergency department by her roommate because of fever, severe headache, and stiff neck. On initial exam, she is sleepy but arousable and generally ill appearing. Her vital signs are temperature, 38.7 °C; heart rate, 122; blood pressure, 116/60; and respiratory rate, 12. Her neck and back are very stiff and rigid, particularly to flexion and extension. Inspection of her eyes and retina with the ophthalmoscope demonstrates optic nerve head swelling (papilledema). She has no other pertinent findings. Given the high clinical suspicion, emergent empiric antibiotic therapy with vancomycin, ceftriaxone, and dexamethasone is started immediately after the clinical exam and before any other diagnostic method is pursued. A head CT is performed and is read by both you and the radiologist as normal. Her pertinent laboratory values

include a blood white blood cell count of 18,000 with 89% neutrophils. Her serum glucose is 110 mg/dl. A lumbar puncture (LP) is performed, demonstrating a glucose of 33 mg/dl [normal value: 50–100], protein of 123 mg/dl [50–90], a CSF white blood count of 8,000 (90% neutrophils) [0–5], and 6 RBC [0–5]. On gram stain, there are gram (+) diplococci seen. You admit her to the general medicine floor with neurology consult. Her LP culture eventually grows out *S. pneumoniae*. You discontinue the dexamethasone on hospital day 5, and once you get back the sensitivity profile from the LP culture, you narrow to just ceftriaxone. The patient is discharged on hospital day 9 with neurology and primary care provider (PCP) follow-up. Her deficits at the time of discharge were persistent headache and transient short-term memory deficits.

## 13.3 Initial Evaluation

### *13.3.1 Presentation*

Meningitis presents with fever, severe headache, nausea, vomiting, photophobia, meningeal signs, and, in some cases, decreased level of arousal and papilledema. Encephalitis presents with meningitic signs and symptoms plus focal signs. Myelitis presents with meningitic symptoms plus complete or incomplete cord syndromes. The key difference between patients with a CNS infection and those patients with stroke-like symptoms alone, and from whom you cannot get the stiff neck or headache story from, will often be the patient's temperature. In a recent study of 696 patients with community-acquired bacterial meningitis, the mean initial temperature was 38.8 °C, and fully 77% were febrile at initial presentation. In a large pooled study of patients with meningitis, 95% had two of the three symptoms of the classic triad of symptoms of

meningitis: fever, stiff neck, and change in mental status [27]. Bacterial meningitis will have a rapid and severe progression, usually a matter of hours. Manifestations of viral meningitis or encephalitis are more subtle, with possibly days of worsening symptoms before presentation to the emergency department.

### *13.3.2 Stabilization*

The initial management of a patient admitted to the emergency room with suspected CNS infection begins the same as with any other infectious patient. ABCs should be assessed and measures taken to support airway, breathing, and circulation. Vital signs should be measured in triage including core temperature whenever possible. Assessment of neurological status should also be obtained immediately, paying particular attention to the presence of focal neurologic deficits. Two large bore IVs should be placed and an initial liter bolus of normal saline started. Many patients with bacterial meningitis will present with sepsis and septic shock. Therefore, the initial resuscitation of these patients will proceed as any other patient in septic shock. This chapter won't dive into the debate of sepsis care, but fluid resuscitation and if necessary vasopressor initiation (norepinephrine) should be started without delay. In most cases of CNS infection, but particularly in bacterial meningitis, the patient's intracranial pressure (ICP) is usually elevated. Therefore, ensuring an appropriate mean arterial pressure and cerebral perfusion pressure is paramount. Initial laboratory studies of peripheral blood should include cultures, CBC with differential, chemistries, serum lactate, and coagulation studies. If the patient is capable of giving a history, particular care should be taken to elicit the timing of the illness. Refer to Fig. 13.1 for suggested diagnostic and therapeutic approach for suspected CNS infection.

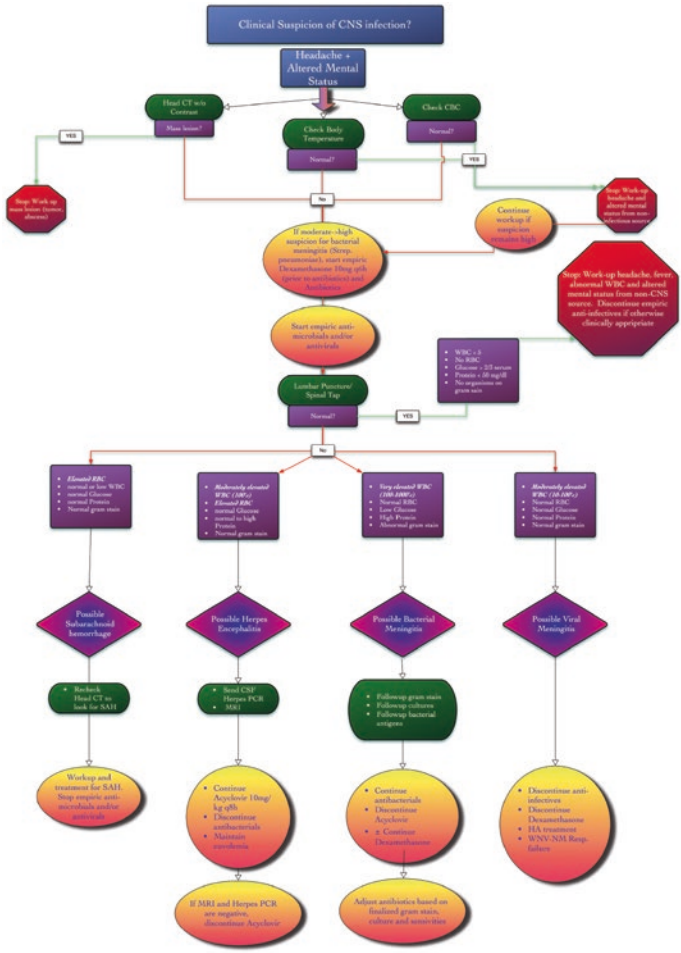


**Fig. 13.1** Neurological infection workup and management algorithm

### *13.3.3 Empirical Antimicrobial Therapy*

The next step in the management of CNS infections is to start antibiotic treatment. Antibiotics should be started immediately after completing the physical exam, even before obtaining a CT scan and performing an LP. Importantly, timely administration of appropriate antimicrobial therapy improves both morbidity and mortality. A retrospective case record study of 119 patients diagnosed with adult acute bacterial meningitis aged greater than or equal to 16 years assessed the association between meningitis mortality and door-to-antibiotic time. If appropriate antibiotic therapy was delayed 6–8 h mortality rose to 45% and if delayed to the 8–10 h range the mortality increased to 75% [20]. In ICU patients with community acquired pneumococcal meningitis, in-hospital antibiotic delay exceeding 3 h was the strongest indicator of mortality, with a 14-fold increase in the mortality risk over the group receiving antibiotics in less than 3 h of admission [3]. Another study found that in the first 12 h from admission, the odds for an unfavorable outcome increased 30% with every hour that antibiotics were delayed [17].

The significant predictors for delay in initiation of antibiotics were found to be no antibiotic prior to transfer from another hospital; the diagnostic–treatment sequence of CT of the head followed by lumbar puncture followed by antibiotics; partial meningitis treatment; and absence of the meningitis triad at presentation/atypical presentation, lack of fever, and patients with concomitant pneumonia [3, 20].

Choice of initial antimicrobial therapy will differ between institutions based on formulary availability; generally speaking, for adult patients with normal renal function, the empiric regimen of choice includes:

- Vancomycin 15–20 mg/kg IV every 12 h
- Ceftriaxone 2 G IV every 12 h (or alternative third-generation cephalosporin at CNS dosing)

- +/− Acyclovir 10–15 mg/kg IV every 8 h for suspected (when encephalitic signs are present). In patients with a prior history of severe penicillin allergy, vancomycin and trimethoprim–sulfamethoxazole is a reasonable first-line regimen, with acyclovir for those with suspected viral encephalitis. Many institutions have fairly rapid polymerase chain reaction (PCR) testing for the most common viral causes of meningitis, so you should feel comfortable starting acyclovir empirically, knowing that you will likely have a confirmatory or rule out result soon. Older and immunocompromised adults are at higher risk of *Listeria monocytogenes* and should be prescribed ampicillin in addition to the agents listed above.

### *13.3.4 Dexamethasone*

There is evidence for the use of dexamethasone in bacterial meningitis, particularly in CNS infections caused by *Streptococcus pneumoniae*. One trial enrolled 301 patients with the treatment group receiving 10 mg of dexamethasone every 6 h for 4 days [8]. Note that the first dose was given prior to, or at the time of, antibiotic administration. The trial demonstrated significant improvement in outcome in those patients receiving dexamethasone. This improvement in outcome and decrease in mortality was almost exclusively in the group of patients that were identified as having pneumococcus. Analysis for different bacteria causing meningitis showed that patients with meningitis due to *Streptococcus pneumoniae* (*S. pneumoniae*) treated with corticosteroids had a lower death rate (29.9% versus 36.0%), while no effect on mortality was seen in patients with *Haemophilus influenzae* (*H. influenzae*) and *Neisseria meningitidis* (*N. meningitidis*) meningitis. Dexamethasone increased the rate of recurrent fever, but was not associated with other adverse events [4].

In situations where it is clearly evident that the suspected organism is not *S. pneumoniae*, dexamethasone may be withheld.

Otherwise, empiric use of dexamethasone until cultures return is reasonable [11]. The Infectious Disease Society of America's practice guidelines state: "some authorities would initiate dexamethasone in all adults with suspected bacterial meningitis because the etiology of meningitis is not always ascertained at initial evaluation" [26]. Patients should be given 10 mg of IV dexamethasone immediately and every 6 h thereafter for a duration of 4 days [8]. Ideally, the steroid should be given prior to or at the start of antibiotic therapy [11, 26]. The rationale for dosing the dexamethasone prior to antibiotic administration is to diminish the inflammatory response triggered by endotoxins from bacterial lysis that occurs following antibiotic administration.

### *13.3.5 Imaging*

Early on in the workup of this type of patient an emergent noncontrast head CT should be ordered. In the management of the patient with a suspected CNS infection, certain findings on head CT such as subarachnoid or intraparenchymal hemorrhage or mass lesion which adequately explain the patient's neurologic deficits will abort the workup for CNS infection and the provider should proceed with management of the alternate diagnosis found on the CT. The initial antimicrobial orders can then be canceled as they will not significantly affect the ongoing management of a bleed or lesion.

If the patient's head CT is grossly normal, the provider should proceed with lumbar puncture as soon as possible. Various studies have been done on CSF analysis after antibiotic administration and show that even the most antibiotic-sensitive pathogens will still be present and culturable in CSF for the first 4 h after antibiotic administration. Collection of CSF for culture and immunohistochemical testing for viral and other rarer pathogens will be the single greatest driver of antimicrobial therapy adjustment going forward, as it is always best to narrow your antimicrobial regimen as early as possible to avoid very real medication side effects.

### 13.3.6 Lumbar Puncture

Ideally a lumbar puncture (LP) would be performed prior to antibiotic administration. Administration of antibiotics prior to performing an LP raises the issue of the diagnostic value of the CSF examination. Gram stain has 92% sensitivity and greater than 99% specificity in diagnosing bacterial or fungal meningitis in those who have received no treatment [9]. Michael et al. show that CSF culture is still likely to be positive in adults with bacterial meningitis if the LP is performed within a few hours of starting the antibiotics. Beyond 4 h, the chance of positive cultures drops significantly, and beyond 8 h, no culture was positive [18]. Another study also found that beyond 4 h after antibiotic administration, chances of a positive CSF culture are low [14].

Performing a lumbar puncture before obtaining a head computed tomography (CT) is a source of controversy due to the risk of brain herniation which may occur in patients with elevated intracranial pressure and or mass-occupying lesions. A CT scan of the brain is typically not required or needed to diagnose bacterial meningitis, but it is useful in excluding other diagnoses. CT is also useful for excluding mass-occupying lesions that might complicate the lumbar puncture done for diagnosis. There is minimal evidence supporting the need for a CT scan of the brain prior to LP. Somewhere between 3% and 5% of patients with meningitis develop fatal herniation syndromes within the first 7 days of hospitalization, around 60% of those within the first hours post LP [10]. There are also studies demonstrating that normal CT scans do not eliminate the risk for herniation nor do abnormal CT scans predict herniation after LP [12].

Head CT should be expedited prior to lumbar puncture in patients with any of the following: altered mental status, focal neurologic deficits, papilledema or loss of venous pulsations on fundoscopic examination, new onset seizures or a history of CNS disease such as stroke or intracranial mass lesions, and known or

suspected immunosuppression [26]. Unfortunately, from a diagnostic standpoint, most patients who present with symptoms consistent with acute bacterial meningitis will likely meet criteria for a head CT prior to LP.

#### 13.3.6.1 Opening Pressure

The opening pressure is usually elevated in cases of bacterial meningitis. Over 80% of patients have an opening pressure greater than 20 cm water, and 20–40% of patients have an opening pressure greater than 40 cm water [10, 27]. Some recommend that if the spinal fluid pressure is found to be greatly elevated (i.e., greater than 40 cm water), the needle stylet should be left in place and mannitol administered. The risk is that with such an elevated pressure, the CSF will continue to leak from the LP site and increase the risk of herniation. It may be prudent to recheck the pressure after a few minutes to determine that it has declined, before removing the needle [11].

#### 13.3.6.2 CSF Analysis

A 12-year study of 100 patients aged 16 years or older found that the vast majority exhibited some degree of CSF leukocytosis; approximately 10% of quantified samples had CSF leucocyte counts of <100 white blood cells/millimeter$^3$ (WBC/mm$^3$), 90% had counts >100 WBC/mm$^3$, and 56% had greater than or equal to 1,000 WBC/mm$^3$, with about 14% of all samples exceeding 10,000 WBC/mm$^3$. Ninety percent of differentiated samples displayed neutrophil predominance. Seventy-eight percent of all CSF samples were cloudy [13].

Gram staining of CSF revealed no bacteria in 53% cases; of those, 47% subsequently became culture positive for a total of 64% culture-positive CSF. Around 78% of the patients were either CSF and/or blood culture positive [13]. Almost all patients will have CSF protein levels above 45 mg/dL, with 66%

above 200 mg/dL [10, 13]. Ten percent of positive cerebrospinal fluid smears were misinterpreted. The most frequent error (occurring in 7 of 17 cases) was misidentification of listeria as *Strep pneumoniae* [10].

One study found that half of all patients had hypoglycorrhachia (defined as CSF glucose <40 mg/dL). In another study 70% of patients had hypoglycorrhachia, defined as glucose less than or equal to 50 mg/dL; of the cases with CSF glucose >50 mg/dL, 55% had levels less than or equal to 50% of serum values at the time of collection [10, 13].

See Tables 13.1 and 13.2 for summary of initial CSF evaluation and results.

**Table 13.1** Initial CSF studies

| | |
|---|---|
| Tube 1 | Cell count and differential |
| | Gram stain and cultures |
| Tube 2 | Glucose |
| | Protein |
| | Lactate |
| Tube 3 | HSV PCR |
| | VZV PCR |
| Tube 4 | Cell count and differential |

**Table 13.2** CSF values for most common diagnoses

| | Glucose | Protein | WBC's | Lymphocytes | Neutrophils | RBC's |
|---|---|---|---|---|---|---|
| Normal CSF | 50 | 50 | <5 | <5 | <5 | 0[a] |
| Bacterial meningitis | − − | + | (+ +) 1 k–10 k+ | + | +++ | 0 |
| Viral encephalitis (HSV, EVB, VZV, WNV, etc. | 50 or (−) | + | (+) 100–1 k | + + | + | 0 or (+ in HSE) |
| Aseptic meningitis *aka* viral meningitis | 50 or (−) | + | (+) 100–1 k | + + | + | 0 |
| Subarachnoid hemorrhage | (−) | + | (+) | + | + | (+++) 1 k to >1 m |

[a]In traumatic tap will be high in tube 1 and low to 0 in tube 4

### *13.3.7 Differential Diagnosis*

There are many differential diagnoses for patients with suspected CNS infection (Table 13.3). Bacterial meningitis is at the top, followed by non-bacterial meningitis, usually referred to as aseptic meningitis (a vast majority of which are viral). Patients with aseptic meningitis have clinical and laboratory evidence for meningeal inflammation inconsistent with bacterial infection and bacterial cultures of CSF that are negative. Encephalitis and intracranial abscess or empyema can have similar presentations. Additional etiologies include other non-bacterial infections (mycobacteria, e.g., tuberculosis and other mycobacterium (very rare), fungi, protozoa, e.g., amoeba, trypanosomes, malaria, toxoplasma, and helminths (parasitic worms), e.g., trichinosis, cysticercosis), but these

**Table 13.3** Differential diagnoses for CNS infection

| Diagnosis | Clinical features |
|---|---|
| Bacterial meningitis | Toxic appearing, very low CSF glucose |
| Aseptic meningitis | Slower onset than bacterial, days not hours |
| Viral encephalitis | History of HSV, isolated mental status changes, seizures |
| Chemical meningitis | Difficult to diagnose, many times is misdiagnosed as psychosis and patients often get admitted to psychiatric units, can be due to NSAIDs, anti-tNFa drugs, seizure medications (lamotrigine or carbamazepine) |
| Brain abscess/ subdural empyema | Usually has history of distinct vector: neurosurgery, dental procedure, sinusitis, recurrent otitis media, and endocarditis but can also be hematogenous in the immunocompromised patient |
| Subarachnoid hemorrhage | Thunderclap headache, severe instantaneous decline in mental status, “worst headache of my life” |
| Migraine/atypical migraine | Usually unilateral with associated photophobia / phonophobia |

are quite rare. There are also noninfectious causes of meningeal symptoms which include subarachnoid hemorrhage, postictal state, complex migraine headache, brain tumors, carcinomatosis, cysts, illicit drug, or alcohol intoxication. Although rare, there are also prescription drug-related cases of aseptic meningitis, also known as chemical meningitis, including from antibiotics, particularly trimethoprim-sulfamethoxazole, trimethoprim alone, and amoxicillin; NSAIDs, especially ibuprofen; immunosuppressive immunomodulatory drugs including monoclonal antibodies, (mainly tumor necrosis factor inhibitors) and intravenous immunoglobulins; and the antiepileptics lamotrigine and carbamazepine [19].

### *13.3.8 Disposition*

Most of these patients will require ICU care and monitoring, even if mechanical ventilation or hemodynamic support with vasopressors is not needed.

## 13.4 Interventions and Management

### *13.4.1 Community-Acquired Bacterial Meningitis (CABM)*

#### 13.4.1.1 Epidemiology

In adults, the annual incidence of CABM in the United States is between two and six cases per 100,000 persons [24, 27]. Mortality from bacterial meningitis can be as high as 34% [28] and is highest with *Streptococcus pneumonia*e and *Listeria monocytogenes*.

Long-term neurologic deficits occur in about half of all patients [8, 22, 33]. Bacteria reach the subarachnoid space via the bloodstream and less often from a contiguous infection such as from the ears or sinuses. The predominant causative organisms are *Streptococcus pneumonia*e (pneumococcus) and *Neisseria meningitidis* (meningococcus), which are responsible for about 80% of all cases [1, 23, 28].

#### 13.4.1.2 Presentation

Symptoms of acute CABM develop over several hours to 1–2 days with non-bacterial forms of meningitis *generally* being less acute. Because meningitis by definition affects the meninges, there is less likelihood of focal deficits compared to encephalitis or brain abscess. However, as the disease progresses, the brain parenchyma frequently becomes involved in the inflammatory response leading to *meningoencephalitis*. As a result, focal neurologic deficits are seen in about 20–33% of patients on presentation and many more during the course of their illness [3, 13, 27].

Obtain the patient's history, including identifying sources of possible exposure and previous and recent infections. Examine for general symptoms of infection (fever, chills, myalgias, fatigue) as well as for signs suggesting central nervous system infection (photophobia, headache, stiff neck, nausea, vomiting, focal neurologic symptoms, and changes in mental status).

Classic signs of meningeal irritation include nuchal rigidity and Kernig's and Brudzinski's signs. *Nuchal rigidity* is present when the neck resists passive flexion. *Kernig's sign* is elicited with the patient in the supine position. The thighs and knees are flexed; attempts to passively extend the knee elicit pain when meningeal irritation is present. *Brudzinski's sign* is elicited with the patient in the supine position and is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees. The presence of Kernig's sign, Brudzinski's sign, or

nuchal rigidity has good positive, but no negative predictive value. One study of 297 patients found that Kernig's and Brudzinski's signs had poor sensitivity (5%) but high specificity (95%), while nuchal rigidity had a sensitivity and specificity of 30% and 68%, respectively [25].

The absence of all three signs of the classic triad of fever, neck stiffness (nuchal rigidity), and an altered mental status virtually eliminates a diagnosis of meningitis [2]. In a nationwide prospective study of 696 adults with CABM [27], the classic triad of fever, nuchal rigidity, and a change in mental status was present in only 44% of patients. However 95% of patients with CABM had at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status. There was headache in 87% of cases, nuchal rigidity in 83%, fever (>38 °C) in 77%, and impairment of consciousness (<14 on the Glasgow Coma Scale) in 69% of cases. Hypothermia can also be consistent with CNS infection.

#### 13.4.1.3 Treatment Monitoring

If there is no clinical improvement after 48 h of antimicrobial therapy, repeat CSF analysis should be performed [26]. Resolution of hypoglycorrhachia and reduction of the cerebrospinal fluid lactate level are the earliest indicators of improvement [7]. Rule out persistence of source of primary infection, e.g., pneumonia, bacterial endocarditis, mastoiditis, or otitis, and consider secondary infection [6]. Another mainstay of therapy is narrowing of antimicrobial spectra based on PCR, culture, and repeat culture data. All antibiotics and antimicrobials have side effects, and the patient with suspected CNS infection will be getting big doses of multiple agents until further data can drive the narrowing of therapy. Whenever possible, narrow therapy. This will help prevent secondary infections, antibiotic resistance, and even antibiotic-induced delirium.

#### 13.4.1.4 Seizures

Seizures occur in 15–23% of patients with bacterial meningitis [13, 27]. Electroencephalographic (EEG) monitoring, especially in patients with history of seizure or fluctuating mental status, should be considered [28]. Although the need for an anticonvulsant as seizure prophylaxis for all patients with bacterial meningitis is not clear, the use of anticonvulsants is warranted once clinical or electrographic evidence of seizure is noted.

#### 13.4.1.5 Hydrocephalus

Acute hydrocephalus occurs in 3–8% of cases of bacterial meningitis [28]. Hydrocephalus can develop because the flow of cerebrospinal fluid may be blocked at the third or fourth ventricles due to tissue swelling from inflammation (obstructive hydrocephalus) and/or due to exudate from the infection interfering with CSF reabsorption at the arachnoid villi (communicating hydrocephalus). Elevated opening pressure may suggest the presence of hydrocephalus, and the diagnosis is confirmed by cranial imaging. A repeat lumbar puncture, ventriculostomy, or ventricular shunt placement should be considered to treat acute hydrocephalus or elevated intracranial pressure [21, 26, 28].

There have been no randomized clinical trials published in regard to treatment of increased intracranial pressure without hydrocephalus. Any literature available is inconclusive. It is unclear whether treating intracranial hypertension with hypertonic agents such as mannitol or hypertonic saline is useful, as the impaired blood–brain barrier associated with meningitis which may reduce their utility. Therapeutic hypothermia has been tested for ICP control. Although hypothermia does lower ICP, the outcomes generally were not better and possibly even worse. The methodology was also questionable. However, given what we know about fever and the increased metabolic demands

of the brain and the associated increased ICPs, maintaining euthermia may be a safe and helpful strategy.

#### 13.4.1.6 Dysnatremia

Approximately 25–28% of patients with bacterial meningitis develop hyponatremia [28]. Etiologies of hyponatremia can be multifactorial, such as salt wasting, SIADH, or adrenal insufficiency. Transient diabetes insipidus has been known to occur with bacterial meningitis, but it is uncommon. Most causes of hypernatremia are related to fluid resuscitation, insensible losses, etc.

Frequent electrolyte monitoring and correction are recommended. See Chap. 23 *Common Complications in the Neuro ICU* for more information on evaluation and treatment of dysnatremias.

#### 13.4.1.7 Others

Raised intracranial pressure from cerebral edema or obstructive hydrocephalus is a rare, but serious and life-threatening complication of meningitis. If one of these pathologies is suspected based on clinical exam (acute decline in mental status, papilledema on fundoscopic exam, or Cushing's response), expeditious neuroimaging should be obtained and measures taken to treat increased intracranial pressure. Please refer to the Chap. 11 for further details. Vascular complications (arteritis or venous sinus thrombosis) leading to cerebral ischemia again are rare but very serious complications. These are very difficult to diagnose clinically and require CT angiogram or venogram vs. digital subtraction angiography or MRI/MRA/MRV to diagnose. In such cases close consultation with vascular neurology or vascular neurosurgery will be crucial. Failure of appropriate response to appropriate antimicrobial therapy

should also raise your suspicion for epileptic seizures (specifically: non-convulsive status epilepticus (NCSE)) and would warrant routine or continuous electroencephalography (EEG.) In patients in closely monitored units who you are suspicious of NCSE, a trial dose of benzodiazepine would be reasonable (lorazepam or midazolam.) And finally, always consider persistence of source of primary infection (e.g., pneumonia, bacterial endocarditis, mastoiditis, or otitis) [6].

#### 13.4.1.8 Prognosis

Indicators of poor outcome include the presence of symptoms for less than 24 h before admission, seizures, pneumonia, an immunocompromised state, a heart rate below 60 bpm or greater than 120 bpm, and hypotension (defined as a diastolic blood pressure of less than 60 mm Hg). The causative organism has been shown to have an independent effect on outcome with an unfavorable outcome being six times that among patients infected with *S. pneumoniae* compared with patients infected with *N. meningitidis*, even after adjustment for other clinical predictors [27]. The average mortality rate in this study was 21% and varied depending on the causative organism; it was 30% for pneumococcal meningitis, compared with 7% for meningococcal meningitis and 20% for meningitis due to other pathogens. The most common neurologic deficits identified were hearing loss and hemiparesis [27]. However cognitive dysfunction, behavioral changes, seizures, and motor impairment are additional common complications of meningitis.

#### 13.4.1.9 Immunizations

There are at least 12 serogroups of *Neisseria meningitidis*. Serogroups A, B, C, W, and Y cause most meningococcal dis-

ease, and there are vaccines for all five. Recently approved by the FDA in Oct 2014 and Jan 2015 are two new *Neisseria meningitidis* serogroup B vaccines known as Meningococcal B or MenB. Previously established vaccines for causative agents include Meningococcal ACWY (MenACWY), Pneumococcal conjugate vaccine 13-valent (PCV13), Pneumococcal polysaccharide vaccine 23-valent (PPSV23), and *Haemophilus influenzae* type B vaccine (Hib). All of these vaccines are included in the CDC's Advisory Committee on Immunization Practices (ACIP), recommended immunization schedules. *Haemophilus influenzae* type B was historically most common cause of CABM, mostly affecting young children. However, since the introduction of the Hib vaccine in 1985, the number of cases of invasive Hib disease (not specifically meningitis) has decreased by more than 99% in children under the age 5 according to the CDC. Many more cases of community-acquired bacterial meningitis can be prevented with proper vaccination [5, 15].

### *13.4.2 Nosocomial Bacterial Meningitis*

Nosocomial bacterial meningitis is usually the result of an invasive procedure, e.g., intracranial surgery, internal or external ventricular catheter placement, lumbar puncture, and intrathecal infusions – including spinal anesthesia, complicated head trauma (complicated requires intracranial neuroimaging abnormalities), or rarely as a complication of hospital-acquired bacteremia [4, 30].

There is a broad spectrum of causative organisms in the hospital setting. Meningitis from an invasive procedure is most often caused by one or more the following: *Pseudomonas aeruginosa, Staphylococcus aureus*, *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *group A beta-hemolytic Streptococci*, *Enterococci spp.*, and *Acinetobacter spp.* [16, 29]. The key point being that broad-spectrum antibiotic coverage should be started urgently to include

coverage of gram-negative and atypical organisms in addition to typical organisms. If there is access to CSF via an existing invasive device, a sample should be collected prior to initiation of the antibiotics. Or alternatively, an LP can be safely performed without delay to aid in diagnosing the infectious species.

### *13.4.3 Acute Encephalitis*

A variety of different organisms, such as herpes simplex virus, arbovirus, rabies, and listeria can cause encephalitis. The most common cause of sporadic fatal encephalitis in the United States is herpes virus (HSV). HSV encephalitis occurs in patients previously infected with either HSV 1 or 2 and is a reactivation of the dormant virus. Cases of HSV encephalitis tend to have higher incidence of seizure versus bacterial meningitis, and such a finding can be a helpful clue in differentiating the HSV encephalitis patient. HSV encephalitis also has characteristic MRI findings which will further confirm or heighten your suspicion for the disease. MRI findings in HSV encephalitis may include parenchymal T1 enhancement after gadolinium and/or T2 hyperintensity in limbic structures including the insula, temporal lobe, cingulate gyrus, and orbitofrontal regions including the gyrus rectus [32]. As encephalitis can present similarly to meningitis, the initial approach to diagnosis and empiric treatment should be initiated as discussed in above Sect. 13.3.

#### 13.4.3.1 Neuroimaging

The CT scan of a patient with herpes simplex virus (HSV) may rarely show mass effect and low density in the temporal lobes. There may also be increased density consistent with a hemorrhagic lesion. The classic MRI abnormality in HSV-1 encephalitis is high signal on T2-weighted images of the medial and inferior

temporal lobe often extending into the insula. HSV also has a predilection for the inferior frontal lobes. Gadolinium enhancement around the periphery of the infection may also be seen.

#### 13.4.3.2 CSF Examination

In the CSF of those patients with HSV encephalitis, the opening pressure may be elevated. The cell predominance is typically lymphocytes rather than the neutrophil predominance of bacterial meningitis. Note should be made, however, that early in the course of the infection, the cell counts can have as many as 40% neutrophils. Red blood cells and/or xanthochromia may be present. The protein content is typically elevated beyond 50 mg/dL but may be normal in up to 25% of patients. The culture and gram stains are negative. Herpes PCR has a sensitivity of 95% with a specificity approaching 100% [9]. One study of 43 patients with herpes encephalitis diagnosed by brain biopsy or necropsy showed positive PCRs for fully 5 days after initiation of acyclovir [9].

Treatment of HSV encephalitis includes acyclovir, standard dosing 15 mg/kg q8 hours. High-dose acyclovir has been known to cause acute renal dysfunction, so it is important to ensure adequate hydration and closely monitor renal function though the duration of prescribed therapy.

Other forms of viral encephalitis, such as those caused by the arboviruses, may also have a subacute presentation. There are no pharmacotherapeutic interventions for these encephalitides, but until exclusion of HSV can be verified, empiric acyclovir is reasonable. For suspected CNS infections that evolve over days in an immunosuppressed patient, fungal meningitis should be considered. Prior history of the CNS disease or systemic fungal infections and rapid disease progression should raise the index of suspicion for fungal meningitis. Empiric amphotericin B should be administered in these cases during diagnostic testing.

### *13.4.4 CNS Space-Occupying Infective Lesions*

Examples of space-occupying lesions of the central nervous system include parenchyma abscesses, epidural abscesses, and empyemas. Because the treatment of subdural empyema is emergent neurosurgery, it is important for the clinician to recognize not only the classical triad (sinusitis, fever, and neurologic deficit) but the signs of cortical inflammation such as focal deficits (75%), seizures (50%), and raised intracranial pressures such as headache, vomiting, and papilledema (50%) [31].

#### 13.4.4.1 Brain Abscess

Treatment of brain abscess is both surgical and medical. Abscesses greater than 2.5 cm in diameter or those associated with mass effect require CT-guided aspiration or excision. Brain imaging should be followed with repeat scans every 1–2 weeks. In patients not considered surgical candidates, such as those with associated ependymitis or meningitis, hydrocephalus requiring shunting, or those with inaccessible abscesses, medical treatment alone can be attempted. Broad-spectrum antibiotics are used with, initially, weekly brain imaging. This can be spaced out to every 2 weeks during the remainder of the 6–8 week antibiotic course, with follow-up scans every 2–4 months for the following year to assess for recurrences. Empiric drug regimens for immunocompetent patients should include vancomycin, metronidazole, and cefotaxime, typically for 6–8 weeks.

In immunosuppressed patients, treatment should be more individualized depending on relative suspicion for specific entities. In patients who have not been receiving prophylactic therapy who have positive toxoplasmosis serology, empiric treatment with pyrimethamine and sulfadiazine (or clindamycin in those

with sulfa allergies) is reasonable with repeat brain imaging to assess response.

Diagnostic testing may be helpful in differentiating infection from neoplasm. For instance, there will be increased uptake of thallium-201 on SPECT scan in lymphoma, but not in toxoplasmosis. Cerebrospinal fluid polymerase chain reaction (CSF PCR) for the John Cunningham virus (JC virus) formerly known as the *papovavirus* can be helpful in differentiating progressive multifocal leukoencephalopathy (PML) from other lesions in AIDS patients. As the presence of Epstein–Barr virus by PCR in CSF highly correlates to lymphoma, this may add diagnostic value to the evaluation of focal brain lesions in AIDS patients. In other immunosuppressed patients, such as those with neutropenia or those who are post-transplantation, amphotericin B should be empirically used given the high rates of fungal infections, specifically aspergillosis, in this population [8]. Lumbar puncture should not be performed in those with brain abscesses given the risk of herniation.

#### 13.4.4.2 Subdural Empyema

The treatment of subdural empyema is neurosurgical. Treatment within 72 h of symptom onset resulted in less than 10% disability among patients, whereas 70% of patients died or were disabled if the treatment was prolonged beyond 72 h [23].

### *13.4.5 Postoperative Neurosurgical Infections*

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 [16]. Treatment depends largely on source control and whether further

neurosurgical intervention is required. If surgery is not required, these infections are treated like any other meningitis.

### *13.4.6 Ventriculostomy Infections*

Many conditions treated in the neurocritical care setting eventually require placement of an external ventricular drain (EVD) for measurement and control of ICP. Of note, 0–30% (with an average of about 12%) of these catheters result in ventriculitis. Several risk factors have been identified in the development of CNS infections after implantation of an EVD. Factors leading to an increased risk for infection include:

- Intraparenchymal hemorrhage, especially with intraventricular extension
- Repeated sampling or irrigation of the system
- The number of attempts needed to pass the catheter into the ventricular system
- Systemic infection

Although it is clear that the longer a catheter remains in place the higher chance there is of an infection, it is also evident that prophylactic changing of the catheter is of no benefit [31]. Care bundles have been shown to be effective in reducing EVD infection rates and include measures such as maintaining a closed drainage system whenever possible, use of antibiotic-coated catheters, and strict adherence to sterile technique during insertion regardless of setting. See Chap. 23, for example, of EVD care bundle.

Once EVD-associated meningitis/ventriculitis is confirmed, treatment of the infection is similar to that of standard meningitis with three main caveats. First, the offending EVD should be removed at the earliest possible instance. If the patient requires extraventricular drainage of CSF, a new catheter should be placed in another site if possible. Second, since this infection is nosoco-

mial, coverage for *Pseudomonas* should be considered with agents such as cefepime or meropenem. And third, given the higher bacterial burden in the CSF of EVD-associated infections, there may be a role for intrathecal antibiotics, usually vancomycin and or gentamicin depending on the offending organism. This extreme measure should be done in close consultation with the entire care team from pharmacy, to neurosurgery, and infectious diseases.

**Summary Points**

- CNS infections are life-threatening conditions that require prompt recognition and early treatment to minimize morbidity and mortality.
- Initiation of treatment should not be delayed for diagnostic evaluation and should include broad-spectrum antibiotics, and antivirals until the causative organism is identified with the addition of dexamethasone if infection with *S. pneumonia* is suspected.
- Lumbar puncture for CSF analysis is the most useful diagnostic tool in evaluating for CNS infection and guiding treatment from broad empiric therapy to targeted management. Studies should include differential cell count, culture, protein, and glucose evaluation as well as viral PCR studies for VZV and HSV.
- Space-occupying infectious CNS lesions require emergent neurosurgical intervention until proven otherwise as well as prolonged antibiotic therapy for curative treatment.
- CNS infections often cause serious and even life-threatening complications ranging from increased ICP to seizures. Close monitoring and early aggressive treatment for such complications is a mainstay of CNS infection management.

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