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Diagnosis and Treatment of Central Nervous System Infections in the Emergency Department

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Abstract

Central nervous system (CNS) infections, including meningitis, encephalitis, and brain abscess, are rare but time-sensitive emergency department (ED) diagnoses. Patients with CNS infection can present to the ED with a host of non-specific signs and symptoms, including headache, fever, altered mental status, and behavioral changes. In meningitis, the classic triad of fever, neck stiffness, and altered mental status occurs in only a minority of patients. Classic physical examination maneuvers, such Kernig's and Brudzinski's signs, are relatively insensitive although specific for predicting cerebrospinal fluid (CSF) pleocytosis. Patients with parenchymal involvement, as occurs with encephalitis and brain abscess, may also have focal neurologic deficits or seizures. Neuroimaging and CSF fluid analysis can appear benign early in the course of meningitis and encephalitis, and clinicians should not be falsely reassured. Delaying antibiotic and antiviral therapies negatively impacts outcomes, particularly with bacterial meningitis and herpes simplex virus encephalitis. As with other rare, life-threatening diagnoses encountered in emergency medicine, the diagnosis and treatment of CNS infections requires vigilance and a high index of suspicion based on the history and physical examination which must be confirmed with appropriate imaging and laboratory evaluation.

Keywords

meningitis; encephalitis; brain abscess; emergency department; diagnosis; treatment

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INTRODUCTION

A key clinical responsibility of the emergency physician is to consider the “worst case scenario” for a given chief complaint. When it comes to infections of the central nervous system (CNS), the greatest challenge is identifying patients that have a rare life-threatening diagnosis amidst the multitude of patients presenting with non-specific symptoms. Alone or in combination, fever, headache, altered mental status, and behavior changes encompass a broad differential diagnosis. A diagnosis not considered is a diagnosis never made. In this vein, this review will discuss the clinical signs and symptoms that should lead emergency physicians to consider CNS infection, paying particular attention to the sensitivity and specificity of different clinical findings at the bedside. Subsequently, the diagnostic workup and management of patients for whom there is high clinical suspicion for CNS infection is discussed.

MENINGITIS

The term “meningitis” applies broadly to inflammation of the meninges. While meningitis can arise from a wide variety of pathologies, infectious and noninfectious, for the purpose of this review we specifically refer to acute infections of the meninges of bacterial, viral, or fungal origin. Bacterial meningitis occurs when organisms gain access to the subarachnoid space either through bacteremia (usually from an upper airway source), contiguous spread from dental or sinus infections, traumatic or congenital communications with the exterior, or a neurosurgical procedure.[1] The severe inflammation associated with bacterial meningitis results in edema of the brain and meninges, and eventually increased intracranial pressure once the compensatory mechanisms for cerebrospinal fluid (CSF) displacement have been overwhelmed.[1] Bacterial meningitis is associated with significant morbidity with mortality rates ranging from 13 to 27%.[2]

In contrast to bacterial infection, meningitis caused by viral infection is usually less severe. The most common causes are enteroviruses (*e.g.*, Coxsackie A & B, echovirus). Herpes simplex virus (HSV, types 1 and 2), cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella zoster virus (VZV), mumps virus, and HIV may also cause viral meningitis.[3] Fungal meningitis is usually secondary to systemic mycoses (*e.g., Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum*) originating elsewhere in the body, usually from a pulmonary focus of infection in an immunocompromised patient.[4] Rare fungal infections have also been associated with contaminated glucocorticoid injections to treat chronic pain.[5]

Meningitis is a poster child for the success of childhood vaccination in reducing the incidence of many life- threatening infectious diseases. Prior to the introduction of an effective vaccine in 1988, *Haemophilus influenzae type B* (Hib) was the leading cause of bacterial meningitis in the United States. After the recommendation that all infants receive the Hib vaccination starting at age 2 months, the incidence of Hib meningitis among children < 5 years of age declined by > 99%.[6] Similarly, the advent of the pneumococcal seven-valent conjugate vaccine (PCV7) and the meningococcal conjugate vaccine (MCV4) significantly decreased the incidence and mortality of pneumococcal and meningococcal

meningitis in the U.S.[7] Meningitis due to nosocomial pathogens including Gram-negative bacteria and *Staphylococcus* have now surpassed *N. meningitidis* and *H. influenzae* in incidence.[7] With changing pathogen demographics, the average age of a patient with meningitis has increased from 15 months of age in 1986 to 35 years in the present day.[8]

Meningitis is a relatively rare diagnosis in U.S. emergency departments (ED). Between 1993 and 2008, approximately 66,000 U.S. ED patients were diagnosed with meningitis annually, with an incidence of 62 per 100,000 visits.[9] With regards to the etiology of meningitis, ED diagnoses include unspecified (60%), viral (31%), bacterial (8%), and fungal (1%) causes. Bacterial meningitis is much more prevalent in developing countries, where the average incidence approaches 50 cases per 100,000 and 1 in 250 children are affected within the first year of life.[8]

Clinical Presentation

The number of patients presenting to the ED with symptoms suggestive of meningitis far exceeds the number of patients who actually have the disease. The classic symptom triad of fever, neck stiffness, and altered mental status is present in only a minority of patients.[10] Other associated symptoms may include nausea and vomiting, cranial nerve abnormalities, rash, and seizure. Infants can also present with non-specific symptoms such as lethargy and irritability. With regards to the accuracy of the clinical history and physical examination in diagnosing meningitis in adults, low sensitivity plagues common complaints and findings including headache (27–81%), nausea and vomiting (29–32%), and neck pain (28%).[11] Sensitivity varies for individual components of the “classic triad” of fever (42–97%), neck stiffness (15–92%), and altered mental status (32–89%). In some cases, 99–100% of patients found to have meningitis had at least one component of the classic triad. Therefore, if the patient presenting with acute headache does not have neck stiffness or fever and is mentating normally, it is extremely unlikely that they have meningitis.[12,13] A prospective study of children ages 2 months to 16 years from Israel also demonstrated the non-discriminatory value of symptoms in diagnosing meningitis.[14]

Classic physical examination maneuvers for the evaluation of meningitis have been taught to generations of physicians. Kernig’s sign, first described in 1882, consists of flexing the patient’s neck and then extending the patient’s knees. It is considered positive when the maneuver elicits pain at an angle of less than 135°.[15] First reported in 1909, Brudzinski’s sign, where the neck is passively flexed with the patient in supine position, is considered positive if it results in flexion of the hips and knees. The sensitivities of Kernig’s and Brudzinski’s signs reported in Brudzinski’s original paper were 42% and 97% respectively. However, most of Kernig’s and Brudzinski’s patients were children with meningitis due to *M. tuberculosis* and *S. pneumoniae*, both of which are associated with severe meningeal inflammation.[15] Several recent studies have examined the usefulness of these classic signs in contemporary patient populations. These studies collectively demonstrate that these signs have low sensitivity in predicting cerebrospinal fluid (CSF) pleocytosis (Table 1).[10,16,17] The absence of these clinical signs, therefore, cannot adequately rule out of the presence of meningitis or obviate the need for a lumbar puncture (LP). However, Kernig’s and

Brudzinski's signs are quite specific (92 – 98%) for predicting CSF pleocytosis and therefore, their presence should increase clinical suspicion for meningitis.

An additional maneuver to elicit meningeal irritation is the "head jolt" test. The patient is asked to move their head back and forth in the horizontal plane at a rate of 2–3 turns/second. It is considered positive if the patient's headache worsens. It was initially tested in a cohort of patients with both fever and headache, and had a reported sensitivity of 97% for CSF pleocytosis.[18] Two subsequent studies in U.S. ED patients and intensive care unit (ICU) patients in India demonstrated much lower sensitivity (6–21%), suggesting that the absence of a positive head jolt does not effectively rule out meningitis.[10,16]

Given the poor performance of clinical signs and the physical examination in ruling out meningitis, overall clinical gestalt remains an important part of making the diagnosis. In a prospective cohort, Nakoa *et al.* found that physician suspicion had a sensitivity of only 44% in predicting pleocytosis.[16] However, in three patients where the CSF culture grew an infective organism (*N. meningitidis, C. neoformans, and Enterovirus*), clinicians suspected bacterial meningitis before performing the LP, suggesting that physician judgment may be our best current diagnostic tool.

Diagnostic workup

In the absence of clear contraindications, patients suspected of having meningitis should undergo LP. If the clinical suspicion for bacterial meningitis is high, *empiric antibiotics should be started immediately when the LP cannot be performed right away.*[19–21] While the sensitivity of the CSF culture decreases with antibiotic administration, cultures can remain positive for up to 4 hours afterwards.[22]

In patients at risk for an intracranial mass or midline shift, it is recommended that computed tomography (CT) of the head be obtained prior to LP given the potential for brain herniation.[23] Current guidelines from the Infectious Disease Society of America (IDSA) recommend obtaining a head CT before LP in patients who are immunocompromised, have a history of CNS disease, have had a new-onset seizure within one week of presentation, or have examination findings consistent with papilledema, abnormal level of consciousness, or focal neurologic deficit.[24] In patients in whom head CT is thought to be necessary, the correct sequence of actions are first, immediate administration of antibiotics, then CT, followed by LP as soon as possible.

In Sweden, it was found that adoption of guidelines recommending head CT prior to LP in patients with altered mental status led to increased CT use even in patients who did not meet criteria. Far worse, adherence to guidelines for early empiric antibiotics in suspected bacterial meningitis was poor.[25] This undesirable practice pattern has been replicated in other environments as well.[22] In 2009, moderate to severe impairment of mental status and new onset seizures were removed from the list of indications for head CT before LP in the Swedish guidelines, leading to significantly earlier treatment of bacterial meningitis and a decrease in overall mortality.[25]

Once the LP has been completed, ideally with an opening-pressure performed, CSF fluid analysis can help predict a bacterial, viral, or fungal etiology for meningitis (Table 2).[1,2] In addition to cell count, glucose, and protein, CSF should be sent for culture. Molecular studies such as polymerase chain reaction (PCR) assays for HSV should be considered in immunocompetent individuals. Special CSF testing for fungal (*e.g.*, cryptococcal antigen, fungal culture) and mycobacterial infection (*e.g.*, acid fast bacteria stain and mycobacterial culture) can be sent in cases where there is higher clinical suspicion for an atypical infection, particularly in immunocompromised patients.

While certain CSF fluid profiles are highly suggestive of viral or bacterial infection, emergency physicians should not be falsely reassured by CSF fluid profiles suggestive that a patient has viral rather than bacterial meningitis. In a prospective study of 696 patients with culture-proven bacterial meningitis, only 88% of patients had one or more CSF findings predictive of bacterial meningitis.[26] A fifth had a negative CSF Gram stain. Two studies have assessed the discriminatory value of CSF laboratory tests in distinguishing viral versus bacterial meningitis in the setting of a negative Gram stain.[27,28] Both studies found low discriminatory value for classic CSF parameters including significantly elevated neutrophil count, high protein, or low glucose in distinguishing bacterial from viral meningitis.[28] For example, 50% of patients with bacterial meningitis had a neutrophil count < 440/mm^3 and > 10% of the patients with viral meningitis had a neutrophil count of > 500/mm^3.

Several studies have assessed the discriminatory value of CSF lactate in distinguishing viral from bacterial meningitis. CSF lactate, produced by bacterial anaerobic metabolism or ischemic brain tissue, is not affected by blood lactate concentration.[29] A meta-analysis assessing the diagnostic accuracy of CSF lactate for differentiating bacterial from viral meningitis found that in both pediatric and adult patients with Gram stain-positive or culture-proven bacterial meningitis, a CSF lactate level of greater than 3.9 mmol/L had a sensitivity of 96 % [95% confidence interval (CI) 93 % – 98%) and specificity of 97% (95% CI 96% – 99%) for differentiating bacterial meningitis.[30] The sensitivity of the test dropped dramatically to 29% (95% CI 23% – 75%) in the subset of patients pre-treated with antibiotics.

Apart from CSF analysis, procalcitonin is a serum marker that has shown promise in distinguishing bacterial from viral meningitis. In general, serum procalcitonin is an inflammatory marker that increases disproportionately in patients with underlying bacterial infection.[31,32] It has been used in a wide-variety of clinical settings to assess likelihood of underlying bacterial infection.[32] In the setting of suspected meningitis but a negative CSF Gram stain, a serum procalcitonin level of greater than 0.98 ng/mL was found to have a sensitivity of 87%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 99% for identifying bacterial meningitis.[27]

Generally, in patients with CSF pleocytosis or with moderate to high clinical suspicion for bacterial meningitis, empiric antibiotics should be continued pending finalization of CSF cultures and other diagnostic tests when indicated. In the pediatric population, the Bacterial Meningitis Score is a validated clinical prediction tool that identifies children with CSF pleocytosis at very low risk for bacterial meningitis. Patients are considered “very low risk”

for bacterial meningitis if they lack all of the following criteria: positive CSF Gram stain, CSF absolute neutrophil count (ANC) of at least 1000 cell/μl, CSF protein of at least 80 mg/dL, peripheral blood ANC of at least 10,000 cells/μl and a history of seizure before or at time of presentation.[33–35] As the Bacterial Meningtitis Score was developed to assist clinicians in deciding which patients warrant admission for parental antibiotics in the presence of CSF pleocytosis, patients warranting admission regardless were excluded from the derivation and validation cohorts. Thus, the score does not apply to patients < 29 days of age or those with critical illness, a ventricular shunt device, recent neurosurgery, immunosuppression or other bacterial infection necessitating inpatient antibiotic therapy. Patients who were pre-treated with antibiotics were also excluded. In a meta-analysis of eight independent validation studies, the Bacterial Meningitis Score was 99.3 % (95% CI 98.7% to 99.7%) sensitive for bacterial meningitis, with a negative predictive value of 99.7% (95% CI 99.3% to 99.9%). Out of 4,896 patients with CSF pleocytosis, the Bacterial Meningitis Score misclassified nine as having aseptic rather than bacterial meningitis. As seven of these children were either less than two months of age or had petechiae or purpura on exam, the authors recommended that the score only be applied to non-ill appearing children older than two months of age who do not have petechiae or purpura on exam and have not been pre-treated with antibiotics.

Treatment

Bacterial Meningitis—Common pathogens responsible for bacterial meningitis vary with age, degree of immunocompromise, and clinical history (Table 3).[8] For example, in neonates, the most common causative organisms in the first week of life, *Streptococcus galactiae, E. coli*, and *L. monocytogenes*, are replaced by *S. pneumoniae* and *N. meningitidis* by the sixth week. Antibacterial therapy should be geared towards the most likely pathogen (Table 2).[8] With the exception of the very young, patients who have recently undergone a neurosurgical procedure, or those who have suffered penetrating head trauma, *S. pneumoniae* remains the most common bacterial pathogen. This is treated intravenously with a combination of a high-dose third-generation cephalosporin (*e.g.*, ceftriaxone) and vancomycin in light of worldwide emergence of resistant *S. pneumoniae*.[8]

In addition to prompt antibiotic therapy, corticosteroids should be considered as adjunctive therapy in some cases of suspected bacterial meningitis. The use of corticosteroids for the treatment of meningitis was prompted by the finding in animal models that meningitis outcomes were worse with increasing severity of the inflammatory process in the subarachnoid space.[36] There have been conflicting results as to their benefit in bacterial meningitis ever since the first clinical trials examining their use were published in the 1960's. A 2013 Cochrane review analyzed 25 randomized control trials spanning patients of all ages and types of bacterial meningitis to determine the benefit of corticosteroids in reducing overall mortality, deafness, and other neurologic sequelae.[37] Overall, there was a non-significant reduction in mortality [17.7% *vs*. 19.9%; risk ratio (RR) 0.90, 95% confidence interval 0.80–1.01] with corticosteroid use. However, in subgroup analysis, corticosteroids reduced mortality in patients with bacterial meningitis due to *S. pneumoniae* (RR 0.84, 95% CI 0.72 – 0.98) but not *H. influenzae* or *N. meningitidis*. There was a significant reduction in hearing loss (RR 0.74, 95% CI 0.63 – 0.87) and subsequent

neurologic sequelae (RR 0.83, 95% CI 0.69 – 1). There was no benefit found for patients treated with corticosteroids in low income countries. With regards to the timing of corticosteroid administration, it is traditionally thought that they should be administered prior to or at the time of antibiotic infusion. However, the results of the Cochrane review suggest that there is no significant difference in mortality reduction if corticosteroids are administered before, with, or after antibiotics are given. There was a slightly more favorable effect on reducing hearing loss and short-term neurologic sequelae if corticosteroids were administered before or with antibiotics.

Viral Meningitis—There is no specific anti-viral therapy for most viral causes of meningitis and treatment is largely supportive with spontaneous recovery anticipated in most cases. Herpes simplex viruses (HSV-1 and HSV-2) cause different CNS diseases in adults. While HSV-1 is associated with devastating encephalitis, HSV-2 causes a benign viral meningitis with meningeal signs and CSF pleocytosis, usually in the concurrent setting of primary genital infection.[38] If HSV-2 meningitis is suspected or confirmed in an *adult*, treatment with acyclovir can be initiated but is of unclear benefit. In stark contrast, HSV-2 infection in an infant can lead to life-threatening encephalitis.

Fungal Meningitis—Fungal meningitis is almost always a disease of the immunocompromised. If the clinical suspicion for fungal meningitis is high, empiric antifungal therapy with amphotericin B is appropriate pending isolation of a specific fungus to tailor antifungal therapy.

ENCEPHALITIS

Encephalitis is inflammation of the brain parenchyma. It is technically a pathologic diagnosis, but the term is commonly used to describe a clinical syndrome of brain inflammation.[39] The differential diagnosis for encephalitis is broad, with infectious (viral, bacterial, or parasitic), post-infectious, and non-infectious (metabolic, toxic, autoimmune, paraneoplastic) causes possible. Viral infections are associated with two distinct forms of encephalitis. The first is a direct infection of the brain parenchyma due to viremia (*e.g.*, West Nile virus) or viral reactivation in neuronal tissue (*e.g.*, HSV, VZV).[40] The second is a post-infectious encephalomyelitis [also known as acute disseminated encephalomyelitis (ADEM)], likely an autoimmune phenomenon more often seen in children and young adults following a disseminated viral illness or vaccination.[40,41] We will focus on viral encephalitis due to direct infection because it is responsible for the majority of acute encephalitis encountered in emergency care.

In the Western world, encephalitis is an uncommon disorder. The reported incidence of encephalitis from all etiologies ranges from 0.7 – 12.6 per 100,000 adults and 10.5 – 13.8 per 100,000 children.[39] Worldwide, the causes of encephalitis remain unidentified in up to 85% of cases, due in part to limited diagnostic capabilities as well as emerging pathogens.[42] Even in a British study in which 203 patient samples underwent exhaustive testing for infectious and non-infectious causes of encephalitis, 37% of causes were unknown.[42] HSV encephalitis (HSV-1) remains the most common cause of sporadic viral encephalitis in industrialized nations, accounting for 10–15% of cases with an annual incidence of 1 in

250,000 to 500,000, and a bimodal age distribution primarily affecting the very young and the elderly.[43,44] Varicella zoster virus (VZV) comes in at a close second, and is actually more common than HSV in immunocompromised individuals, accounting for 19–29% of encephalitis cases.[42,45,46]

Clinical Presentation

The first step in approaching a patient with suspected CNS infection is to determine if bacterial meningitis is present necessitating emergent empiric antibiotic therapy. However, when there is also evidence of brain parenchymal involvement in the form of focal neurologic findings or seizures, one must consider encephalitis as well. The clinical presentation of encephalitis correlates with the underlying function of the brain parenchyma involved (Table 4). For example, because HSV encephalitis is classically associated with the temporal lobes, it can present with personality changes, psychosis, olfactory or gustatory hallucinations, or acute episodes of terror that may initially be misdiagnosed as a psychiatric disorder.[40,47] Inferior frontal and temporal lobe involvement may also present with upper-quadrant visual field deficits, difficulty storing or recalling new information, hemiparesis with greater involvement of the face and arm, or aphasia when the dominant hemisphere is involved.[40] Certain viruses, such as West Nile virus and Eastern equine encephalitis virus, have a predilection for basal ganglia and thalamus and are associated with tremors or other movement disorders.[48,49,50] A number of bacterial and viral causes, including *Bartonella henselae, Mycobacterium tuberculosis*, Enterovirus-71, flaviviruses (*e.g.*, West Nile virus, Japanese encephalitis virus), and alphaviruses (*e.g.*, Eastern equine encephalitis virus) can cause brainstem encephalitis manifesting as autonomic dysfunction, lower cranial nerve involvement, and respiratory drive disturbance.[39,42] Despite these classic associations, no presenting sign, symptom, or CSF finding alone or in combination with another can accurately distinguish one cause of encephalitis from another.[42]

Diagnosis

Since antibiotic therapy should be initiated rapidly in a patient with suspected CNS infection, the most urgent question to ask when you suspect encephalitis is whether a patient requires antiviral coverage in addition to standard antibiotics. The initial approach to diagnosis parallels that of meningitis (Figure 1). All patients should have a LP, unless there is a clear clinical contraindication such as a coagulation abnormality, local infection at the lumbar puncture site, or evidence of significant mass effect on imaging studies. Head CT should be performed prior to LP if the patient has moderate to severe impairment of consciousness, focal neurologic deficit, posturing, papilledema, seizures, relative bradycardia with hypertension, or immunocompromise.[39] In addition to a standard laboratory evaluation, all patients with suspected encephalitis should be tested for HIV infection as this may change the scope of subsequent diagnostic testing and empiric treatment. CSF findings in HSV encephalitis vary along a spectrum from normal to lymphocytic pleocytosis to hemorrhagic. However, no general CSF findings can reliably distinguish HSV from other causes of viral encephalitis.[43,47] As a consequence, molecular (*e.g.*, PCR) and serologic testing are important for establishing a specific diagnosis (Table 4). During early infection, initial diagnostic tests may be negative. Approximately 5–10% of adults with HSV encephalitis will initially have a normal CSF profile and a negative HSV

PCR. In patients in whom the diagnosis is strongly suspected, a repeat LP at 24–48 hours is recommended.[39] From the perspective of emergency medicine, treatable causes of viral encephalitis are limited predominantly to HSV and VZV and it is unlikely that sending a diverse battery of expensive diagnostic molecular tests will influence immediate care. However, it can be helpful to have the microbiology laboratory save CSF so that other clinicians can expand the initial diagnostic workup as needed without repeating the LP.

Magnetic resonance imaging (MRI) is significantly more sensitive than CT in detecting early cerebral changes in viral encephalitis. In HSV encephalitis, CT is abnormal in approximately a quarter of patients. MRI is abnormal in approximately 90% of patients, with the most characteristic findings being edematous changes in the orbital surfaces of the frontal lobes and medial temporal lobe.[39] MRI also offers the advantage of identifying alternative causes of encephalitis, and thus should be performed on all patients with suspected encephalitis in whom the diagnosis remains uncertain.[39,51]

An electroencephalogram (EEG) does not need to be performed routinely in all patients with suspected encephalitis. However, it is a potentially useful adjunct in several situations. First, in patients who are comatose or poorly responsive, EEG may reveal non-convulsive status epilepticus requiring anti-epileptic management. In a subset of patients presenting with psychiatric symptoms, an abnormal EEG can point to an organic cause. For instance, HSV encephalitis is associated with characteristic non-specific diffuse high amplitude slow waves, sometimes with temporal lobe spike-and-wave activity and periodic lateralized epileptiform discharges.[39]

Treatment

The management of encephalitis should be directed towards the underlying etiology. As no clinical sign, symptom, or CSF finding can reliably differentiate HSV from other viral etiologies of encephalitis, the initiation of empiric treatment with intravenous acyclovir is indicated in any patient suspected to have viral encephalitis until a definitive diagnosis can be achieved. The most significant factor determining outcome in HSV encephalitis is starting antiviral treatment as early as possible, ideally within 6 hours of presentation.[52,53] A multicenter observational study of 93 patients found that the only two factors significantly associated with poor outcome were how sick the patient was at presentation (Simplified Acute Physiology score > 27) and the initiation of acyclovir more than two days after initial presentation.[54]

In the study mentioned above, 41% of patients did not have acyclovir initiated until after two days of presentation.[54] This proportion of patient was similar to a second retrospective study of 184 patients in which acyclovir was initiated more than 1 day after hospital admission in 37% of patients eventually diagnosed with HSV encephalitis.[55] This data suggests that HSV encephalitis can be difficult to diagnose and requires a high degree of initial clinical suspicion. In a retrospective study, several patient characteristics were significantly associated with delay of acyclovir initiation including severe underlying disease (OR 4.1; 95% CI 1.5 – 11.7), alcohol abuse (OR 3.4; 95% CI 1.3 – 8.9), delay of > 1 day from admission to first brain imaging (OR 8.4; 95% CI 3.9 – 18.0), and a finding of < 10 leukocytes/mm^3 in CSF at admission (OR 2.5; 95% CI 0.7 – 5.8).

Acyclovir is dosed according to weight and age. The ideal body weight should be used to calculate the acyclovir dose [Males: IBW (kg) = 50 kg + 2.3 kg for each inch over 5 feet; Females: IBW (kg) = 45.5 kg + 2.3 kg for each inch over 5 feet].[56] The dose should be reduced in patients with pre-existing renal impairment as acyclovir is renally-excreted. In order to help prevent acyclovir-induced crystalluria and nephrotoxicity, patients should be well-hydrated to maintain adequate urine output. Concurrent administration of nephrotoxic drugs should be minimized.

BRAIN ABSCESS

A brain abscess is a collection of purulent material resulting from infection within the brain parenchyma. Focal inflammation and edema (early cerebritis) expand and progress over days to a wider inflammatory response in the white matter, surrounding an increasingly necrotic core (late cerebritis). In the course of a few weeks, a collagenous capsule surrounds and walls off the core, although surrounding inflammation and edema may persist. A predisposing contiguous foci of infection is present in more than half of all cases of bacterial (pyogenic) abscess, with otitis, mastoiditis, sinusitis, meningitis, and odontogenic infections being the most common.[57] Metastatic or hematogenous seeding of the brain parenchyma from a distant source of infection (*e.g.*, bacterial endocarditis, congenital heart disease with right-to-left shunt, pulmonary infection) accounts for up to a third of cases. Traumatic inoculation through gunshot wounds and other penetrating injuries can likewise predispose to brain abscess formation, as can open neurosurgical procedures.

Streptococcus and *Staphylococcus* species are implicated in the vast majority of bacterial brain abscesses, although Gram-negative bacteria (*Proteus* spp, *Klebsiella* spp, *Escherichia coli*, and *Enterobacteriae*) have been found in up to 15% of cases, particularly in Europe, Asia, and Africa.[57] Nearly a quarter of all brain abscesses are polymicrobial in nature. *Nocardia*, fungal (*e.g., Aspergillus* spp, *Candida* spp, *C. neoformans*), and parasitic (*e.g., Toxoplasma gondii*) brain abscesses are most likely to be encountered in the setting of severe immunocompromise (*e.g.*, HIV infection, transplantation).

The reported incidence of brain abscess ranges from 0.4 – 0.9 cases per 100,000 persons, with higher incidence reported in immunocompromised populations.[58,59] Most patients present in the third or fourth decade of life, and brain abscess is more commonly diagnosed in men.[57,59] Mortality from brain abscess has historically run as high as 40%, but has decreased to 10% since 2000, owing much to advances in diagnostic imaging and management strategies.[57]

Clinical presentation

The classic triad of headache, fever, and focal neurologic deficits associated with brain abscess is present in only 20% of patients.[57] Fever is only present in half of cases.[57] Onset of neurologic symptoms can be subtle and indolent, spanning days to weeks, manifesting as hemiparesis, cranial nerve palsy, gait disorders, or signs and symptoms of increased intracranial pressure (*e.g.*, nausea, vomiting, papilledema, altered mental status).[60] Up to a quarter of cases may be accompanied by focal or generalized seizures.[57] Frontal lobe abscess may present as headache and behavioral changes. An occipital lobe abscess,

cerebellar abscess, or abscess with concomitant meningitis or intraventricular rupture can present with neck stiffness. In many cases, headache alone may be the only initial symptom of a brain abscess, particularly in its earliest stages. In the absence of associated neurological findings, a heightened clinical suspicion for brain abscess, particularly in immunocompromised patients, is necessary to carry the evaluation forward.

Diagnosis

Imaging is paramount to diagnosing brain abscess. Emergent CT with contrast can reveal ring-enhancing lesions characteristic of abscess in the late stages of cerebritis and as the lesion encapsulates.[61] MRI with gadolinium remains the most sensitive modality to look for and characterize the extent of brain abscess, particularly in early cerebritis as well as in the posterior fossa (*e.g.*, brainstem) where visualization by CT may be limited. Given the hematogenous nature of many brain abscesses, blood cultures can aid with identifying a causative organism in a quarter of cases.[57] In most cases, the CSF is sterile; however if there is suspicion for concomitant meningitis or abscess rupture into a ventricle, LP may be useful in obtaining CSF for culture. In this situation, contraindications to LP, including the risk for brain herniation due to mass effect, must be carefully weighed against any potential benefit, particularly if neurosurgical aspiration, drainage, or excision of the abscess is already anticipated.

Treatment

A multidisciplinary approach combining surgical and medical therapy to treat brain abscess optimizes clinical outcomes. Neurosurgical consultation should be sought to determine whether an invasive procedure is necessary to obtain a culture from the abscess to guide antibiotic therapy and definitively drain its contents. Stereotactic needle abscess aspiration under CT or other imaging guidance is preferred in most situations, although surgical excision may be needed in others (*e.g.*, patients at high risk for brain herniation due to mass effect or with multi-loculated abscess).

If surgical intervention is planned within hours and the patient is clinically stable, empiric antibiotic therapy may be withheld to optimize the yield of bacterial cultures obtained from the abscess, but this decision is best made in conjunction with the neurosurgeon. Empiric broad-spectrum antibiotic *therapy targeted against Staphylococcus*, Streptococcus, Gram-negative organisms, and anaerobes can be achieved through a combination of intravenous vancomycin, a third or fourth-generation cephalosporin (*e.g.*, ceftriaxone, cefepime), and metronidazole. Long-term intravenous antibiotic therapy, tailored to causative organisms identified on culture, is favored and traditionally averages 6 to 8 weeks.[57]

SPECIAL SITUATIONS

The Febrile Neonate

In infants < 48 hours old, CNS infection can present as temperature instability, spells of apnea and bradycardia, feeding difficulty, and irritability alternating with lethargy. At > 48 hours of age, infants with CNS infection are more likely to present with neurologic symptoms, including seizures, a bulging anterior fontanel, extensor posturing, focal cerebral

signs, or cranial nerve palsies. While the workup and management of an ill-appearing infant is relatively clear-cut (blood, urine, and CSF cultures accompanied by timely initiation of empiric antibiotics), the more common clinical conundrum encountered is the diagnostic workup and management of the well-appearing febrile infant younger than 90 days. Many febrile infants in this age group will have no focus of infection on physical examination, but ~10% will have an underlying serious bacterial infection (SBI).[62] The majority of these are urinary tract infections (7–9 % overall) whereas meningitis represents < 0.5%. This opens the door to a wide variety of practice patterns when it comes to deciding when it is appropriate to perform a LP.[62–64] As infants < 28 days are at greater risk for SBI (overall prevalence of 11–25%), the general consensus favors performing a LP in all cases and admitting to the hospital pending culture results.[62] Well-appearing febrile infants 28–90 days old present more of a management dilemma. A number of criteria (Rochester, Boston, Philadelphia, and subsequent derivations) have been developed to determine both which patients should undergo LP in the first place and who should be admitted for empiric antibiotics pending culture results.[65–67] Only the Rochester criteria do not include a mandatory CSF analysis (Table 5). In the original study, 1% of the low risk infants had an SBI, which included UTIs and one case of *N. meningitidis* bacteremia.[67] Procalcitonin is a promising marker of SBI (including meningitis) in the pediatric population, but may not be widely available as a rapid diagnostic test.[68] In general, in low-risk infants < 90 days of age, empiric antibiotics should not be administered without performing a LP.

In addition to SBI, neonates, especially between days 9–17 days of life, are at significant risk for HSV-2 infection. Apart from the typical features of infection in neonates, HSV should be suspected if a neonate presents with seizures, hepatic failure, characteristic skin lesions (present in 35% of neonates with HSV), or if there is a maternal history of HSV-2 genital infection.[69] Empiric antibiotic coverage for the neonate (Table 3) generally consists of a third-generation cephalosporin in combination with ampicillin. Acyclovir should be added if there is sufficient suspicion for HSV infection.

The Elderly Patient

At the opposite end of life's continuum, clinical signs and symptoms of CNS infection vary and atypical presentations abound. Fever, headache, and neck stiffness are less common features in older patients with bacterial meningitis than non-specific symptoms such as altered mental status, stupor, or coma.[70–73] Kernig's and Brudzinski's signs are also less likely to be present or reliable. In light of this, performing a LP as part of the evaluation of mental status change, even in the absence of fever, should be strongly considered in this population. In contrast to younger adults where bacterial meningitis due to *N. meningitidis* is common, patients 65 years and older are more likely to develop meningitis due to *S. pneumoniae, Listeria monocytogenes*, Gram-negative bacteria, or of an unknown origin.[70,71] Empiric antibiotic therapy in the elderly patient should therefore include expanded coverage for *L. monocytogenes* with intravenous ampicillin in addition to vancomycin and a third-generation cephalosporin.

While the differential diagnoses for mental status change and behavioral changes in the elderly patient can be wide-ranging, HSV encephalitis should always be considered. In a

Swedish national retrospective study, HSV encephalitis was more commonly seen in those over the age of 60 years and was associated with significantly greater mortality in those over 70 years.[74] If the clinical suspicion for HSV encephalitis is high, a LP should be performed and empiric acyclovir started pending molecular testing of the CSF for HSV.

Patients with exposure to arthropod vectors

Arthropod vectors, including ticks and mosquitoes, can transmit a range of pathogens capable of causing CNS infection. Lyme disease, a tick-borne infection associated predominantly with the *spirochete Borrelia* burgdorferi and the most common vector-borne illness in the U.S., can lead to neurological disease in up to 12% of untreated patients.[75] Lymphocytic meningitis and encephalitis associated with Lyme disease are acute in onset and can be hard to distinguish from viral CNS infections. Lyme meningitis is often associated with cranial neuropathies, particularly involving the seventh cranial nerve (facial nerve palsy), as well as radiculoneuritis leading to pain in peripheral nerve distributions. In patients with suspected CNS infection due to *B. burgdorferi*, CSF should be sent to assess for presence of antibodies to this pathogen. Antibiotic therapy should consist of intravenous ceftriaxone, cefotaxime, or penicillin G. Rocky Mountain Spotted Fever (RMSF), an infection caused by *Rickettsia rickettsii*, is classically associated with a constellation of fever, headache, and a diffuse macular and/or petechial rash that is inclusive of the palms and soles. In some cases, a lymphocytic meningitis and encephalitis can also be seen with RMSF. Doxycycline is the preferred antibiotic for treating RMSF. Human monocytic ehrlichiosis (HME) due to *Ehrlichia chaffeensis* and human granulocytic anaplasmosis (HGA) due to *Anaplasma phagocytophilum* are likewise tick-borne and can manifest with CSF lymphocytic pleocytosis; both are also treated with doxycycline. Apart from ticks, mosquito vectors can carry arboviruses (*e.g.*, West Nile virus, St. Louis encephalitis virus, Eastern and Western equine encephalitis virus) responsible for causing meningitis and/or encephalitis as already discussed before.

Arthropod-borne infections follow seasonal and geographic patterns centered on the life cycle and distribution of the vectors. Infections generally peak in the warm, summer months (June, July, and August) when vectors are active and patients are most likely to come into contact with them. Vectors such as the *Ixodes* tick that transmits Lyme disease are found primarily in the eastern U.S. whereas the *Dermacentor* tick responsible for RMSF has a wider distribution across southeastern and south central states. Infections associated with these ticks tend to fall along similar geographic lines. The same can be said of HME and HGA. Therefore, knowledge of the geographic distribution of potential arthropod vectors and careful assessment of other epidemiological risk factors in combination with a recent history of arthropod exposure and/or bite are important considerations when considering the diagnosis of an arthropod-borne CNS infection.

HIV and other Immunocompromised States

Human immunodeficiency virus (HIV) infection preferentially impairs cell-mediated immunity, predisposing patients to viral, fungal, and parasitic diseases. In addition to the common CNS infections seen in the general population, HIV-related CNS infections are frequently opportunistic, stemming from the reactivation of latent pathogens such as JC

virus, Epstein-Barr virus, cytomegalovirus, and *T. gondii*.[76,77] Disseminated histoplasmosis with CNS involvement can result from either acute infection or reactivation. Susceptibility to such infections occurs when the $CD4^+$ count falls below 200 cells per μl and many are considered acquired immunodeficiency syndrome (AIDS)-defining illnesses.

Opportunistic CNS infection should always be considered in patients with advanced HIV who present with signs or symptoms of CNS infection including altered mental status, fever, headache, seizures, or focal neurologic signs. The underlying etiology hinges upon the overall clinical presentation, time course of disease, CSF analysis, and radiographic features (Table 6). Chronic headache with indolent symptoms (*e.g.*, low-grade fever) can be characteristic of CNS tuberculosis as well as fungal meningitis due to *C. neoformans, C. immitis*, or *H. capsulatum.* Multiple brain abscesses on imaging and a history of a positive *T. gondii* serum immunoglobulin G (IgG) should trigger concern for toxoplasmosis. Co-infections may be present in up to 15% of patients.[76] The initial diagnostic workup for patients with HIV infection and presumed CNS opportunistic infection is outlined in Figure 2. Treatment depends on the most likely cause and should be initially broad pending the results of this workup. In addition to empiric antibiotic therapy, treatment may consist of initiating or continuing antiretroviral therapy (ART). Paradoxical worsening of the infection following initiation of ART therapy can occur as a result of immune reconstitution inflammatory syndrome (IRIS), a consequence of exaggerated activation of the recovering immune system classically encountered in patients with tuberculosis, cryptococcal meningitis, or progressive multifocal leukoencephalopathy (PML).[78]

While syphilis can cause CNS infections in immunocompetent patients, neurosyphilis has become closely associated with co-existing HIV infection in the post-penicillin era.[79–81] In general, the neurologic manifestations of syphilis are classified as either early or late neurosyphilis. Early symptomatic neurosyphilis (also known as acute syphilitic meningitis) usually occurs within the first 12 months of infection and involves diffuse inflammation of the meninges, resulting in headache, photophobia, nausea, vomiting and cranial nerve palsies.[79] Ocular findings, most commonly uveitis, can also be observed.[81] Acute syphilitic meningitis, with and without ocular manifestations, has become the most common neurologic infection in HIV patients and can occur even after the patient received initial treatment for primary or secondary syphilis.[81] Late neurosyphilis can take upwards of 15–20 years to develop and includes manifestations such as meningovascular syphilis, tabes dorsalis and CNS gummas. A low CD4 count (< 350 cells/ml) is an independent risk factor for developing neurosyphilis.[80] For patients suspected of having neurosyphilis, a serum non-treponemal test, usually a rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL), should be sent but may be non-reactive in late disease. In such cases, a serum treponemal test, such as fluorescent treponemal antibody absorption (FTA-ABS), should also be sent as these tests remain reactive lifelong after infection with syphilis. The diagnosis of neurosyphilis is usually established by the presence of a reactive CSF-VDRL but cannot be excluded if the test is non-reactive.[81] Treatment with penicillin G is the standard for neurosyphilis.

Apart from HIV, other immunocompromised patients, particularly those receiving immunosuppressive therapy for solid organ or hematopoietic stem cell transplantation or

those with hematologic malignancy, are not only at increased risk for bacterial CNS infection but opportunistic infections as well.[82–84] Solid organ transplant recipients are at heightened susceptibility for developing brain abscess due to *Nocardia* as well as fungi (*e.g., Aspergillus* spp, *Candida* spp). In addition to empiric antibiotic therapy directed against usual bacteria, appropriate therapy targeted towards these organisms may be warranted. Consultation with an infectious disease specialist can be beneficial in optimizing empiric therapy in these complex patient populations.

CSF Shunt Infections

CSF shunt infection can be a cause for shunt failure and manifests with signs of increased intracranial pressure and hydrocephalus (*e.g.*, depressed level of consciousness, nausea, vomiting, headache, irritability in young children). It is the most common complication of CSF shunt surgery (> 11% in one multicenter prospective study) and most often seen within 6 months of shunt placement due to intraoperative contamination with skin flora.[85,86] As far as clinical presentation, there are several factors that increase the likelihood that shunt infection is the underlying etiology of shunt malfunction. These include a history of recent shunt revision [adjusted odds ratio (aOR) 2.4; 95% CI 1.3 – 4.4), presence of fever (aOR 8.4; 95% CI 4.3 – 16.3), and WBC > 15,000/μl (aOR 3.2; 95% CI 1.5 – 6.6).[87,88] For patients with ventriculoperitoneal shunts, abdominal pain and peritonitis are less commonly seen, but are highly predictive of shunt infection.[89] Evaluation of patients with suspected CSF shunt infection includes imaging to evaluate for shunt malfunction with either a head CT (sensitivity of 53–92%) or rapid cranial MRI (sensitivity of 51–59%), shunt series radiographs, and sampling of CSF through LP or shunt aspiration, and should involve neurosurgical consultation.[90] Empiric antibiotic therapy should be directed primarily against skin flora and nosocomial pathogens, including *S. aureus* and *Pseudomonas aeruginosa*.

CONCLUSION

Despite the broad range of causative organisms and clinical presentations possible in CNS infection, the initial ED evaluation is fundamentally the same. First, a high index of clinical suspicion is necessary. The diagnosis should be considered in patients presenting with headache, fever, altered mental status, or behavior change, especially in the young, the elderly, or the immunocompromised. Second, the clinical history and physical examination must be viewed as a whole when deciding whether further evaluation for CNS infection is warranted. If a patient has focal neurologic deficits, signs of increased intracranial pressure, a history of neurosurgical procedure or immunocompromise, or is obtunded, neuroimaging should be performed to rule out asymmetric mass effect prior to lumbar puncture. As time is of the essence, empiric antibiotic coverage tailored to the patient's age and clinical risk factors should be initiated as soon as possible if bacterial meningitis or HSV encephalitis is suspected. Finally, benign imaging and CSF analysis can be falsely reassuring early on in disease, and an aggressive course of action is always prudent in cases where a strong clinical suspicion for serious CNS infection exists.

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KEY POINTS

- The classic triad of fever, neck stiffness, and altered mental status is present in only a minority of patients with meningitis.
- Kernig and Brudzinski's signs are poorly sensitive but relatively specific physical examination maneuvers for identifying meningitis.
- Imaging tests and lumbar puncture should not delay initiation of empiric antibiotic therapy in patients suspected to have bacterial meningitis.
- While certain cerebrospinal fluid (CSF) profiles are highly suggestive of viral or bacterial meningitis infection, emergency physicians should not be not falsely reassured by a benign CSF fluid profile supporting a viral etiology.
- Encephalitis should be considered in any patient presenting with new-onset seizure or focal neurologic deficit accompanied by fever, headache, altered mental status, or behavioral changes.

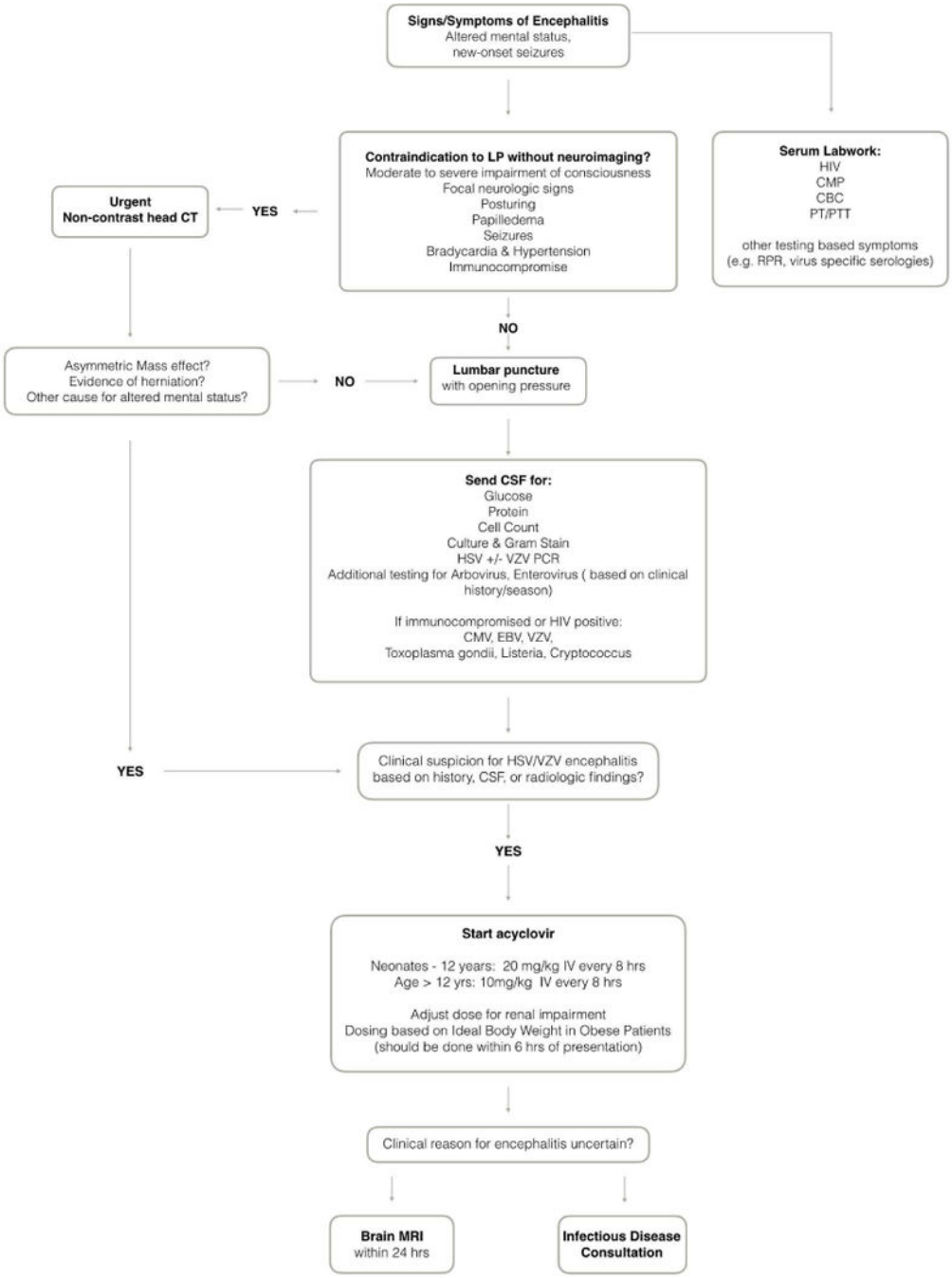

Figure 1. Algorithm for Diagnostic Workup of Encephalitis in the Emergency Department Setting

CBC = Complete Blood Count; CMP = Complete Metabolic Panel; PT/PTT= Prothrombin Time/Partial Thromboplastin Time; HSV = Herpes Simplex Virus; VZV = Varicella Zoster Virus; CMVCytomegalovirus; PCR = Polymerase Chain Reaction

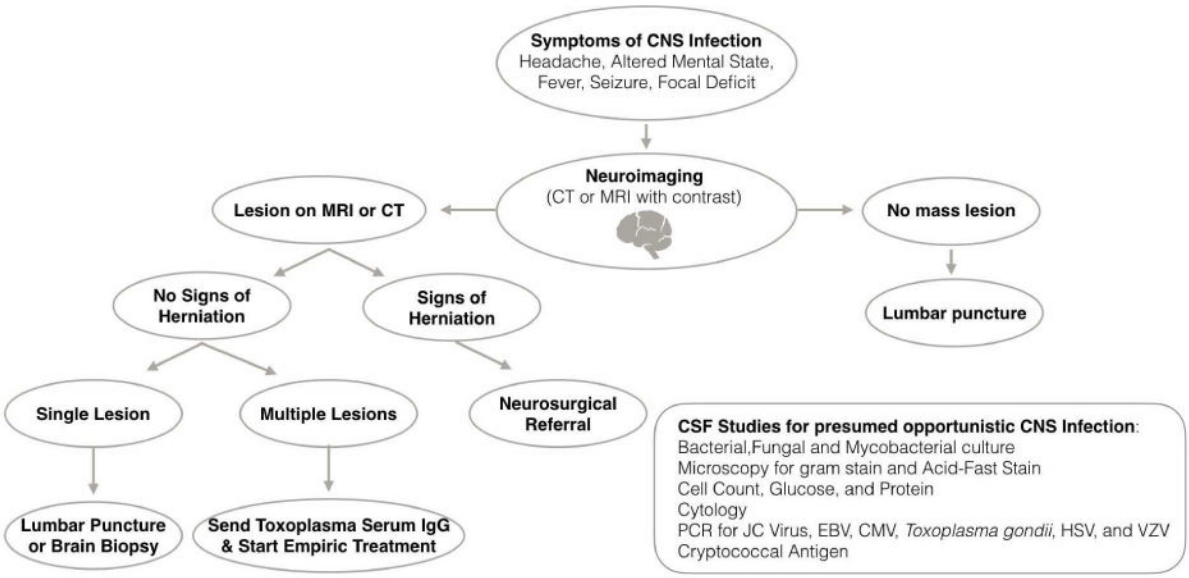

Figure 2. Work-up for presumed CNS infection in a patient with advanced HIV disease

Modified from {Lin Tan 2012}. EBV = Epstein Barr Virus; CMV = Cytomegalovirus; HSV = Herpes Simplex Virus; VZV = Varicella Zoster virus; IgG = immunoglobulin G.

Table 1

Sensitivities, specificities, and likelihood ratios for classic meningeal signs in predicting CSF pleocytosis

	Sensitivity (95% CI)	Sensitivity (95% CI)	LR+	LR−	Reference
Nuchal rigidity	30	68	0.94	1.02	17
	39.4 (29.7, 49.7)	70.3 (59.8, 79.5)	1.33 (0.89,1.98)	0.86 (0.7 – 1.06)	10
	13 (8,17)	80 (74,85)	0.6	1.1	16
Kernig's sign	5	95	0.97	1.0	17
	14.1 (7.95, 22.6)	92.3 (84.8, 96.9)	1.84 (0.77, 4.35)	1.0	10
	2 (0,4)	97 (95,99)	0.8	0.93 (0.84, 1.03)	16
Brudzinski's sign	5	95	0.97	1.0	17
	11.1 (5.68,19)	93.4 (86.2, 97.5)	1.69 (0.65, 4.35)	1.0	10
	2 (0,4)	98 (96,100)	1.0	0.95 (0.87, 1.04)	16
Head jolt	6.06 (2.26, 12.7)	98.9 (94,100)	5.52 (0.67, 44.9)	0.95 (0.89,1.0)	10
	21 (15, 27)	82(76,87)	1.2	1.0	16

CI = confidence interval; LR = likelihood ratio

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Table 2

Typical CSF fluid profiles for bacterial, viral, and fungal meningitis

Parameter	Normal	Bacterial	Viral*	Fungal*
CSF opening pressure	< 170 mm	Elevated	Normal	Normal or Elevated
Cell count	< 5 cells/mm^3	> 1000/mm^3	<1000 mm^3	< 500/mm^3
Cell predominance	–	Neutrophils	Lymphocytes	Lymphocytes
CSF glucose	> 0.66 × serum	Low	Normal	Low
CSF protein	< 45 mg/dL	Elevated	Normal	Elevated

Data from Fitch MT., Abrahamian FM., Moran GJ., et al. Emergency Department Management of Meningitis and Encephalitis. Infect Dis Clin North Am 2008;22(1):33–52 and Tintinalli JE., Stapczynski JS. Tintinalli's emergency medicine: a comprehensive study guide. 7th ed. New York: McGraw-Hill; 2011)

*Findings may not be adequate to rule out bacterial disease in an individual patient.

CSF = cerebrospinal fluid

Table 3

Etiologic & recommended antimicrobial therapy by age and clinical context

Patient subgroup	Most Common Bacterial Pathogen	Initial intravenous therapy
Neonates, < 1 week	*S. agalactiae, E. coli, L. monocytogenes*	Ampicillin (50 mg/kg every 8 hrs) AND Cefotaxime (50 mg/kg every 8 hrs)
Neonates, > 1 week and < 6 weeks	*L. monocytogenes, S. agalactiae*, Gram-negative bacilli	Ampicillin (50 mg/kg every 6 hrs) AND Cefotaxime (50 mg/kg every 6 hrs)
Infants and children	*S. pneumoniae, N. meningiditis*	Cefriaxone (80–100mg daily) OR Cefotaxime (75 mg/kg every 6 hrs)
Adults	*S. pneumoniae, N. meningiditis*	Ceftriaxone (2g every 12 hrs) OR Cefotaxime (3 g every 6 hrs) AND Vancomycin (15–20 mg/kg every 8 hrs)
Elderly	*S. pneumoniae, N. meningiditis, L. monocytogenes*	Ceftriaxone (2g every 12 hrs) OR Cefotaxime (3 g every 6 hrs) AND Vancomycin (15–20 mg/kg every 8 hrs) AND Ampicillin (2 g every 4 hrs)
Immunocompromised	*S. pneumoniae, N. meningiditis, H. influenzae*	Ceftriaxone (2g every 12 hrs) OR Cefotaxime (3 g every 6 hrs) AND Vancomycin (15–20 mg/kg every 8 hrs) AND Ampicillin (2 g every 4 hrs)
Nosocomial	*S. aureus, S. epidermidis*, aerobic Gram-negative bacilli	Vancomycin (15–20 mg/kg every 8 hrs) AND Ceftazidime (2 g every 8 hrs) OR Cefepime (2 g every 8 hrs) OR Meropenem (2 g every 8 hrs)

Table 4

Demographics, clinical presentation, and treatment of select etiologies of viral encephalitis

Pathogen	Demographics	Neurologic Symptoms (Headache, fever, altered mental status and…)	Non-neurologic symptoms	Diagnostic Test	Treatment (Adult dosing)
Herpes simplex virus (HSV)	Usually young and elderly; no seasonal predilection	Seizures, olfactory/gustatory hallucinations, aphasia, personality changes, hemiparesis (face/arm>leg), upper visual field cut	Rash	HSV-1, HSV-2 PCR (CSF)	Acyclovir 10 mg/kg every 8 hrs (adjust for renal function)
Varicella-zoster virus (VZV)	Most common in immunocompromised	Cranial nerve palsies, cerebellitis	Shingles	VZV PCR (CSF)	Acyclovir 10 mg/kg every 8 hrs (adjust for renal function)
Cytomegalovirus (CMV)	Immunocompromised	Behavior changes, coma	Pneumonitis, retinitis, myelitis	CMV PCR (CSF)	Ganciclovir 5 mg/kg every 12 hrs
Enterovirus	Usually young	Rhombencephalitis (myoclonus, tremors, ataxia, cranial nerve palsies), polio-like acute flaccid paralysis, neurogenic shock	Hand-Foot-Mouth disease, rash, myocarditis, pericarditis, conjunctivitis, pulmonary edema	Enterovirus PCR (CSF)	Supportive Care
Arboviruses	Summer months			IgG and IgM (CSF and serum)	Supportive care
Flaviviridae West Nile Virus (80% infecions asymptomatic)	US, Africa, Europe, Middle East, Asia	Tremors, parkinsonism, asymmetric flaccid paralysis	Insect bite, myalgias, hepatitis, pancreatitis, myocarditis, rhabdomyolysis, orchitis, rash		
St. Louis encephalitis virus	Widespread in US; Adults (> 50 yo_	Vomiting, confusion, disorientation, stupor, coma	Insect bite, malaise, myalgias, syndrome of inappropriate antidiuretic hormone secretion (SIADH) Myalgias, malaise		
Togaviridae Eastern equine encephalitis virus	Eastern and gulf coasts of USA, Caribbean and South America; children and adults	Seizures			
Western equine encephalitis virus	West, Midwest USA and Canada; infants and adults	Seizures	Myalgias, malaise		
Rabies virus	Exposure to infected animal	Agitation, bizarre behavior, coma, stupor	Hydrophobia, fever, malaise, anxiety, pain or itching at site of the bite wound	Rabies virus RNA by rtPCR (saliva)	Post-exposure vaccination, once infected supportive care but universally fatal.

CSF = cerebrospinal fluid

Table 5

The Rochester Criteria for identifying the febrile neonate at low risk for Serious Bacterial Infection (SBI)

Rochester Criteria	
1	Infant appears generally well
2	Infant has been previously healthy:
	- born at≥ 37 wks gestation
	- did not receive perinatal antimicrobial therapy
	- was not treated for unexplained hyperbilirubinemia
	- had not yet received antimicrobial agents
	- had not been previously hospitalized
	- had no chronic or underlying illness
	- was not hospitalized longer than the mother
3	No evidence of skin, soft tissue, bone, joint, or ear infection.
4	Laboratory values:
	- WBC between > 5,000 and < 15,000/mm^3
	- absolute band count ≤ 1500/mm^3
	- ≤ 10 WBC per high-power field on urine micro
	- ≤ 5 WBC per high-power field in microscopic examination of stool smear for infants presenting with diarrhea

WBC = white blood cell

Data from Pantell RH., Newman TB., Bernzweig J., et al. Management and outcomes of care of fever in early infancy. JAMA 2004;291(10):1203–12

Table 6

Clinical presentation, diagnosis and treatment of opportunistic infections in HIV disease

Infection	Typical $CD4^+$ cell count at presentation (cells per μl)	Clinical presentation	Temporal evolution	Special CSF tests [Sensitivity/Specificity]	Typical radiographic appearance	Treatment = anti-retroviral therapy AND
Cytomegalovirus (CMV) encephalitis	< 50	Altered mental status, seizures	Days	CMV PCR [>90%/>90%]	Usually normal; may have evidence of ventriculitis with ventriculomegaly and periventricular enhancement on MRI	Ganciclovir
Cryptococcal meningitis	< 50 (rarely up to 200)	Fever, headache, altered mental status, vomiting	Days	Elevated opening pressure; Cryptococcal Antigen	May be normal; “Punched-out” cystic lesions on MRI if cryptococcocomas develop	Amphotericin B and flucytosine
Progressive multifocal leukoencephalopathy (PML)	< 100	Altered mental status, focal neurologic deficits	Weeks to months	JC virus PCR [50–90%/90–100%]	Hyperintense areas in white matter on T2-FLAIR imaging	–
Central nervous system (CNS) lymphoma	< 100	Altered mental status, focal neurologic deficits, headache	Weeks to months	EBV PCR [100% /50% specific]	Usually solitary, heterogeneously-enhancing lesions with mass effect	–
Toxoplasma encephalitis	< 200	Fever, headache, altered mental status	Days	*Toxoplasma gondii* PCR [50–80%/100%]	Multiple ring-enhancing lesions with mass effect	Pyramethamine, folinic acid, and sulfadiazine OR trimethoprim-sulfamethoxazole
Tuberculous meningitis	< 200	Altered mental status, cranial neuropathies	Days to Weeks	Culture and acid-fast bacilli stain [> 80%]	Rarely basilar enhancement; possibly abscesses or tuberculomas	Rifampin, isoniazid, pyrazinamide, ethambutol
Acute syphilitic meningitis	<350	Headache, photophobia, emesis. Ocular manifestations (CN palsies, uveitis, optic neuritis) commonly associated.	Within 12 months (chronic neurosyphilis 5–20 years)	CSF VDRL [CSF FTA-ABS more sensitive but less specific]	No pathognomonic findings	Pencillin-G 3–4 million units q 4 hrs × 10–14 days

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; PCR = polymerase chain reaction