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UPDATE

A Pragmatic Perspective to Meningitis and Encephalitis

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Abstract

Meningitis is an inflammation of the meninges, mostly manifested with headache and nuchal rigidity. The inflammation is usually caused by an infection of the fluid surrounding the brain and spinal cord and is diagnosed by cerebrospinal fluid examination. In contrast, encephalitis refers to inflammation of the brain parenchyma itself and often results in focal neurologic deficits or seizures. Review the differential diagnosis of meningitis and encephalitis, with an emphasis on infectious etiologies have been delineated by the authors. The recommended practical clinical approach focuses on early high-yield diagnostic testing and empiric antimicrobial administration. Etiology-specific testing based upon risk factors and clinical characteristics should be pursued if the initial work up does not yield a diagnosis. Efficacious treatment is available for many etiological factors of meningitis and encephalitis. The primary disease process along with associated potential complications should be addressed as well.

Keywords: Meningitis, Encephalitis, Infectious Disease, Meningoencephalitis, Autoimmune Encephalitis, Cerebrospinal Fluid

Introduction

Syndromes like Meningitis and encephalitis are syndromes are having broad differential diagnoses with substantial clinical and etiologic overlap. Though many etiological factors are treatable, both the condition is associated with high morbidity and mortality. The focus of early management should be mainly restricted to evaluation and treatment of acute bacterial meningitis and herpes simplex virus (HSV) meningoencephalitis. If initial diagnostics do not confirm either of these diagnoses, a more thorough evaluation process must be undertaken, prioritizing testing for treatable conditions. Infectious etiologies are initially emphasized given their high prevalence, but inflammatory, neoplastic, and toxic/metabolic causes should also be considered as well.

Acute Evaluation and Management

Initial history and physical examination should be targeted toward identification of the condition like acute bacterial meningitis or HSV meningoencephalitis. Empiric treatment for these entities should be initiated while awaiting results of early diagnostics. Fig. 1 provides a suggested algorithm to guide early diagnostic and therapeutic management.

Acute Bacterial Meningitis

Delayed treatment may result in significant morbidity and mortality in case of acute bacterial meningitis. Early initiation of empiric antibiotic and often corticosteroid treatment is therefore critical in management. Specific features on history

concerning for bacterial meningitis include headache, acute time course (usually hours to days), rapid progression, sick contacts, dormitory living, or recent systemic illnesses such as ear, sinus, or lung infection.

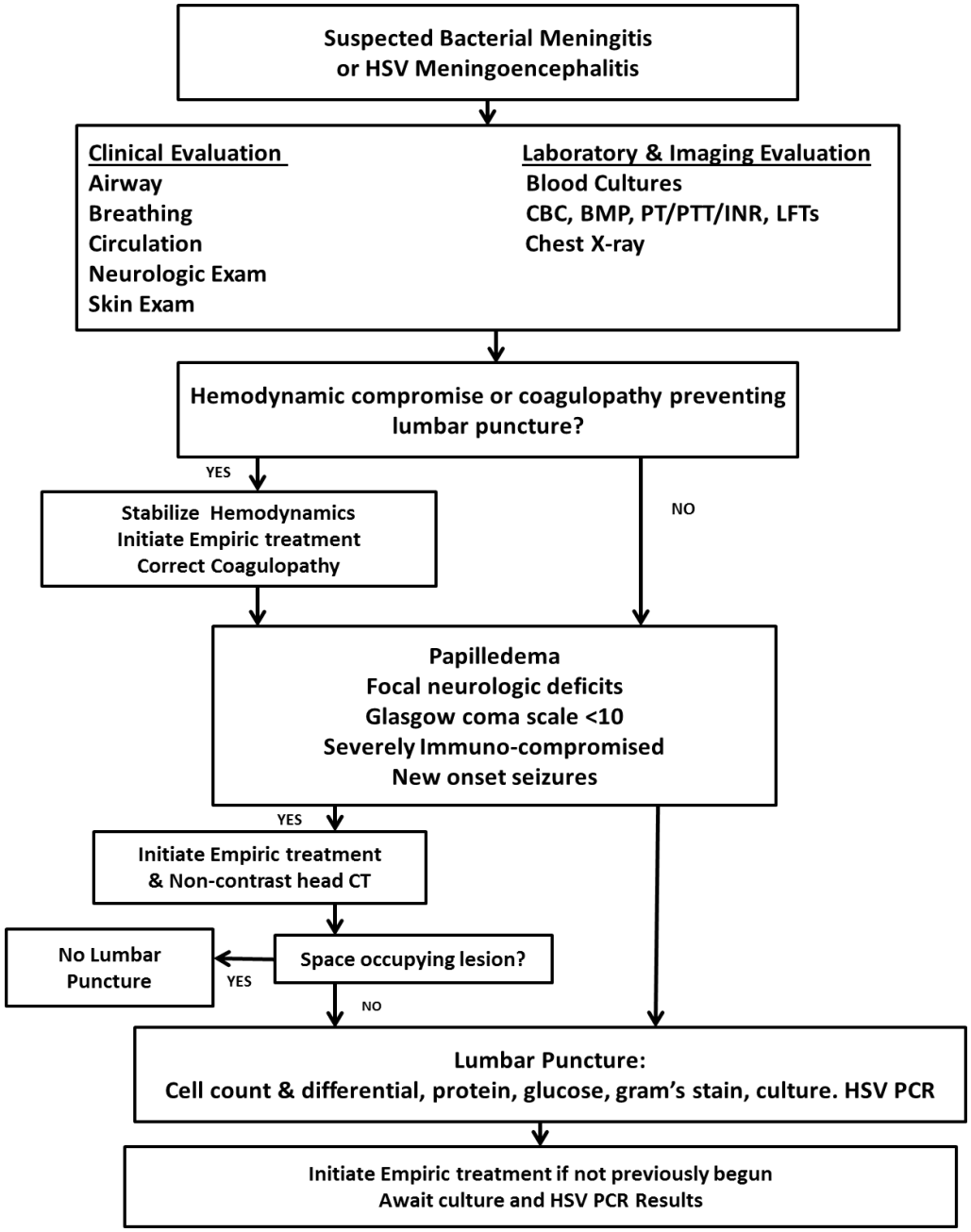

Fig 1: Management of acute bacterial meningitis and herpes encephalitis in adults. BMP, basic metabolic panel; CSF, cerebrospinal fluid; CBC,

In addition to fever and meningismus, concerning examination findings include mental state alteration, papilledema, cranial nerve palsies, or petechial rash characteristic of Neisseria meningitides. Empiric antibiotic therapy targets the most likely pathogens, taking into consideration age and other risk factors (Fig. 2).

Acute Bacterial Meningitis	Herpes Encephalitis
Dexamethasone 10 mg IV every 4 hours **With or Before** Vancomycin 15 mg/kg IV every 6-8 hours **And** Ceftriaxone 2 g IV every 12 hourly **OR** Cefotaxime 2 g IV every 8 hourly **Consider** Ampicillin 2 g IV every 4 hours If<3 months, > 50 years, immunocompromised	Acyclovir 10-15 mg/kg IV 8 hourly Especially in case of • Seizures • Altered mental states • Cortical deficits • Vesicular rash
Fig. 2: Empiric treatment for acute bacterial meningitis and herpes encephalitis. IV- intravenous	

Herpes Simplex Meningoencephalitis

The most common infectious cause of encephalitis is Herpes simplex virus infection and more than 70% mortality can be reduced by treatment with Acyclovir. Neurologic examination should focus on evaluating cortical function, including a detailed mental state evaluation. A thorough skin exam (including the tympanic membranes) should be performed to evaluate for the vesicular rash classically seen in HSV infection, although the neurologic syndrome often occurs without any systemic signs of the virus. Herpes simplex virus meningoencephalitis can be diagnosed with high sensitivity and specificity using viral deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) sent from CSF. Intravenous Acyclovir is the appropriate empiric treatment for HSV, but should be used cautiously in patients with renal dysfunction.

Early Management

Patient stabilization and information collections are mainly included as initial evaluation of suspected acute bacterial meningitis and HSV meningoencephalitis (Fig. 1). Once lumbar puncture has been either completed or deemed acutely inadvisable, empiric treatment should be initiated in all patients with suspected acute bacterial meningitis or HSV meningoencephalitis. The clinical symptoms indicates whether management should include acute bacterial meningitis, HSV meningoencephalitis, or both. If lumbar puncture is not performed prior to antibiotic treatment, CSF should still be sent as soon as possible for analysis. A CSF culture may remain positive up to 4 hours even after antibiotic administration, although treatment for greater than 8 hours generally leads to culture sterility. The remainder of the CSF profile is helpful even if cultures are sterile. Typical findings in bacterial meningitis include a polymorphonuclear predominant CSF pleocytosis, elevated protein, and low glucose (less than 40% of simultaneously sampled serum glucose). Even in patients on antibiotic therapy, pleocytosis and glucose only begin to normalize after 48 to 72 hours of treatment.

The typical CSF profile in HSV meningoencephalitis includes a mononuclear-predominant pleocytosis, normal or elevated protein, and normal glucose. Red blood cells may be variably elevated, but this feature is not diagnostic. Herpes simplex virus meningoencephalitis is best diagnosed with high sensitivity and specificity using CSF HSV 1 and 2 DNA PCR. Early in the course of disease (< 24 hours), HSV PCR may be falsely negative in over one-quarter of patients, and the CSF profile may be completely normal. Therefore, if there is a high suspicion for HSV meningoencephalitis, empiric treatment should be continued and a second lumbar puncture for repeat studies is required after at least 3 days' delay. A HSV PCR remains a useful test even after starting Acyclovir, as DNA titers typically begin to fall after 10 days of antiviral treatment.

After Definitive Diagnosis

After obtaining the lumbar puncture with CSF conformation of acute bacterial meningitis, the patient should be continued on antibiotics for 7 to 14 days, depending on the organism. In cases in which no organism is found despite clinical and

CSF features concerning for bacterial meningitis, an empiric 14-day course of broad-spectrum antibiotics is suggested. Blood cultures may also be positive in 50 to 80% of patients with bacterial meningitis if drawn prior to antibiotics, and it can be assumed that the causative organism has been identified based on positive blood cultures with an appropriate CSF profile. After 48 hours of treatment, patients who have not responded clinically should undergo repeat lumbar puncture to ensure that CSF pleocytosis is resolving. If HSV meningoencephalitis is confirmed, antibiotics for bacterial meningitis can be stopped and intravenous Acyclovir continued for 21 days. Patients should be monitored clinically for complications related to meningitis, such as hydrocephalus or stroke.

Diagnostic Approach to Meningitis and Encephalitis: After the Acute Evaluation

In many cases, a diagnosis is not made during the initial evaluation, and the practitioner must broaden the differential and direct further workup based upon risk factors, clinical characteristics, availability of testing, and potential for treatment. A neurologic exam provides information regarding localization, while brain magnetic resonance imaging (MRI) and electroencephalogram (EEG) are highly useful diagnostic tests.

First-Tier Diagnostic Testing

Lumbar puncture with CSF sent for cell count and differential, protein, glucose, Gram stain, and culture are performed on all patients with suspected meningitis or encephalitis. **Table 1** provides an overview of the typical CSF profile seen in subcategories of infectious meningitis and encephalitis. Opening pressure should be obtained when possible. In suspected encephalitis, CSF should be sent for HSV-1 and 2 and varicella zoster virus (VZV) PCR, although a negative VZV PCR does not exclude the diagnosis and may be supplemented with VZV serum and CSF immunoglobulin M (IgM) and IgG serologies. Depending on the clinical scenario, acid-fast bacilli smear and culture, Venereal Disease Research Laboratory (VDRL) and cryptococcal antigen testing may be indicated. **Table 2** provides a list of diagnoses to consider based upon CSF characteristics. Important serum studies in most patients include blood cultures, human immunodeficiency virus (HIV) serologies, rapid plasma reagin (RPR), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), with consideration for Quanti FERON-TB Gold testing when tuberculosis is on the differential. A nasopharyngeal swab for respiratory viruses is indicated, especially during influenza season. A chest radiograph is helpful when considering tuberculosis, fungal infection, and sarcoidosis.

Table 1 Typical cerebrospinal fluid profiles of infectious subcategories of meningitis and encephalitis

	Meningitis				**Encephalitis**
	Bacterial	Viral	Mycobacterial	Fungal	
Opening pressure	Elevated	Normal	Normal or elevated	Normal or elevated	Normal or elevated
White cells	Increased	Increased	Increased	Increased	Increased
Differential	Predominantly polymorphonuclear	Predominantly mononuclear	Predominantly mononuclear	Mononuclear ± eosinophils	Mononuclear
Glucose	Often decreased	Normal	Often decreased	Often decreased	Normal
Protein	Usually increased	Normal or increased	Usually increased	Usually increased	Normal or increased

Noninfectious causes are often high enough on the differential diagnosis at this point. Inflammatory causes should be investigated through serum rheumatologic studies and possibly autoimmune or para-neoplastic auto antibodies in the serum and CSF. CSF cytology and flow cytometry should be performed if neoplastic etiologies such as carcinomatous meningitis or lymphoma are being considered.

Table 2 Select diagnoses to consider based upon cerebrospinal fluid characteristics

CSF Profile		Suspect
Differential	**Glucose**	
PMNs	Low	Bacterial meningitis, amoebic meningitis
PMNs	Normal	Bacterial meningitis (partially treated), L. monocytogenes, C. albicans
Mononuclear	Low	Bacterial meningitis (partially treated), mycobacterial, fungal, carcinomatous meningitis
Mononuclear	Normal	B. Burgdorferi, mycobacterial, fungal, T. pallidum, most viruses, SLE, carcinomatous meningitis, chemical/iatrogenic
Variable		Sarcoidosis, Leptospira species
Atypical lymphocytes		EBV, CMV, JE, WNV, enteroviruses, VZV, Mollaret's
Abnormal cells		Carcinomatous meningitis, CNS lymphoma
Eosinophils		T. solium, C. immitis, Angiostrongylus cantonensis, Gnathostoma species, NMO, neurosurgical hardware, chemical/iatrogenic

CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; JE, Japanese encephalitis; LCMV, lymphocytic choriomeningitis virus; NMO, neuromyelitis optica; PMN, polymorphonuclear lymphocyte; SLE, systemic lupus erythematous; VZV, varicella zoster virus; WNV, West Nile virus.

A brain MRI scan is required in all patients with encephalitis and most patients with meningitis. Along with determining disease etiology, brain MRI also investigates complications of meningitis such as infarction or hydrocephalus. Head computed tomography (CT) with and without contrast is an alternative if MRI is not possible, although the sensitivity and specificity is significantly lower. In presence of myelopathy or radiculopathy, spinal MRI with contrast should be performed.

Electroencephalography is indicated in patients with encephalitis, coma, or a waxing and waning mental status to evaluate for subclinical seizure activity. Occasionally, an EEG may also help determine the etiology of illness. More commonly, EEG findings in meningitis and encephalitis are nonspecific, and may include epileptiform discharges, generalized or focal slowing, or intermittent rhythmic delta activity.

Second-Tier Testing: Clues to Elusive Etiologies

Environmental Factors: Differential diagnosis of meningitis and encephalitis are influenced by both season and geographic prevalence. During winter months, influenza viruses should be considered in patients with meningitis or encephalitis regardless of vaccination status, although generally neurologic complications of influenza are rare. In late summer and early fall, the differential diagnosis should include enteroviruses as well as tick- and mosquito-borne infections, the prevalence of which varies based upon geography. Certain fungal infections have geographic variability and may cause disease at any time of year. Coccidioides immitis is common in the Southwest and California whereas Histoplasma capsulatum in the Ohio and Mississippi River valleys.

Patient-Specific Risk Factors: The most common infections before 1 month of age are driven by perinatal transmission from mother to infant. Neonatal meningitis is most frequently due to Group B streptococcus, Escherichia coli, Klebsiella pneumoniae, and Listeria monocytogenes. Listeria monocytogenes may also cause encephalitis in this population, as can cytomegalovirus (CMV), HSV-2, rubella, Toxoplasma gondii, and Treponema pallidum (syphilis). Between 1 and 23 months of age, pneumococcus, N. meningitidis, and H. influenzae commonly cause meningitis, whereas influenza, La Crosse, Murray Valley, and Eastern equine encephalitis viruses cause encephalitis. Over age 50, L. monocytogenes and aerobic gramnegative rods join S. pneumoniae and N. meningitidis as common causes for bacterial meningitis. These patients are also at higher risk for WNV, St. Louis, and Eastern equine encephalitis, presumably due to waning immunity. The list of pathogens related to exposures such as animal contact, ingestion, or international travel is extensive. Coxiella burnetii, Bartonella henselae, and T. gondii are treatable causes of encephalitis related to cat exposure. International travel

is another risk factor for parasitic infection, even years prior to presentation. Taenia solium is found in Asia, and Central and South America, Trypanosoma species in Africa, and Leptospira species in tropical areas. Malaria, caused by protozoan Plasmodium species, is common worldwide in an equatorial band across areas with high rainfall and mosquito proliferation.

A broad range of infectious causes of meningitis and encephalitis should be considered in immune-compromised patients, including patients with HIV, hematologic malignancies, or those taking immunosuppressant therapy. In addition to the usual bacterial causes of meningitis, patients with decreased cell-mediated immunity are at higher risk for L. monocytogenes regardless of age. Cryptococcus neoformans is an important cause of meningitis in these populations; it may be diagnosed with high sensitivity and specificity using CSF or serum cryptococcal antigen and classically causes increased intracranial pressure requiring serial therapeutic lumbar punctures. Although fungal infection with Aspergillus species, B. dermatitidis, and C. immitis may occur in normal populations, neurologic involvement is more common in those with decreased immunity, as are other features of disseminated disease including infection of skin, soft tissue, and bone, and severe pulmonary symptoms including cavitary or reticulonodular pneumonia.

Many viral infections are also more common in immune-compromised hosts, including WNV and Epstein-Barr virus (EBV). Some are almost exclusively seen in those with depressed immune function, including CMV, human herpes virus 6 (HHV-6), and John Cunningham (JC) virus. Epstein Barr virus is difficult to determine as a causative agent of meningitis or encephalitis because the virus may be harbored in lymphocytes in the absence of active infection. A positive CSF EBV PCR may indicate central nervous system lymphoma rather than true infection, particularly in patients with HIV. John Cunningham virus causes progressive multifocal leukoencephalopathy (PML), classically presenting with areas of confluent, non-enhancing subcortical white matter T2 hyperintensity on MRI. Populations at risk for PML include those with HIV-acquired immunodeficiency syndrome (AIDS) or patients taking immune-suppressants such as Natalizumab, Rituximab, Methotrexate, Cyclophosphamide, or Azathioprine. Varicella zoster virus may cause meningitis or encephalitis in any host, but the characteristic rash may not be present in those with immunodeficiency, and disseminated disease is more common

Systemic Signs and Symptoms

Differential diagnosis of meningitis and encephalitis may be guided by systemic symptoms. Many viruses cause lymphadenopathy including HIV, EBV, CMV, HHV-6, WNV, Coltivirus (Colorado tick fever), measles, and rubella. Lymphadenopathy may also be seen in syphilis, B. henselae, T. gondii, and mycobacterial infections. Ophthalmologic evaluation may reveal retinitis in cases of CMV, WNV, B. henselae, or syphilis, and conjunctival suffusion in leptospirosis, Colorado tick fever, WNV, and St. Louis encephalitis. Pulmonary disease may be seen in all fungal infections, as well as pneumococcus, influenza, Mycoplasma pneumoniae, C. burnetii, and mycobacterial infections. In patients with diarrhea, clinicians should consider M. pneumoniae, L. monocytogenes, or viral encephalitides such as St. Louis, Japanese, La Crosse, and WNV.

Rash may be a particularly helpful sign. Hemorrhagic purpura is highly suggestive of meningococcemia, although they may occasionally be seen with pneumococcus. A vesicular pattern may be seen in herpes virus infections such as VZV and HSV, whereas a nonspecific macular or maculopapular exanthem occurs with M. pneumoniae, EBV, HHV-6, rubella, WNV, and Colorado tick fever. Rickettsia rickettsii infection classically features a maculopapular rash that begins on the wrists and ankles and may spread to the palms and soles. Enterovirus is one cause of the vesicular hand, foot, and mouth disease; enteroviral rashes may also be maculopapular, morbilliform, hemorrhagic, or petechial. Disseminated fungal infections may also have skin manifestations, including pustules and abscesses. Skin manifestations of secondary syphilis are diverse, but may appear maculopapular or pustular, often involving the palms or soles.

Sub-acute, Chronic, or Recurrent Time Course

Subacute or chronic presentations are typical characteristic of many fungal infections. Fungal cultures or direct microscopic visualization are insensitive, posing a diagnostic challenge. Serum and CSF antigen are highly sensitive and

specific for C. neoformans, while serum and CSF serology for C. immitis is more reliable than for other fungal mycoses and are performed using complement fixation, immune-diffusion, or enzyme immunoassay. Further fungal testing includes urine antigen for B. dermatitidis and H. capsulatum, CSF serology for H. capsulatum, and serum or CSF β-d glucan and galactomannan for Aspergillus. A systemic source of culture should be requested by the clinician; often this will involve pulmonary, nasal, or cutaneous samples.

Mycobacterial infection is another consideration in patients with a subacute or chronic time course. Typical tuberculous meningitis is basilar-predominant, with cranial nerve involvement and striking enhancement on MRI. There may be associated vasculopathy and cerebral infarction. The characteristic CSF profile includes a mononuclear predominant pleocytosis, hypoglycorrhachia, and elevated protein. CSF microscopy and culture for acid-fast bacilli is specific, but slow and highly insensitive. Practitioners should therefore supplement the workup with pulmonary imaging, cutaneous tuberculin sensitivity testing, the serum Quanti-FERON-TB Gold test, and induced sputum testing for acid-fast bacilli, with the caveat that these tests may also have false-negative results and empiric treatment for tuberculosis may be warranted when there is high clinical suspicion. Secondary syphilis may also cause subacute meningitis, and tertiary syphilis causes chronic psychiatric or cognitive symptoms. Subacute cognitive decline is also associated with HIV, CJD, CMV, measles, Whipple's disease, neoplastic meningitis, and autoimmune encephalitis. Cysticercosis may cause chronic meningitis with CSF eosinophilia and characteristic cysts on MRI scan. Herpes simplex virus-2 may have a distinctive relapsing course in which patients experience recurrent lymphocytic meningitis (also known as Mollaret's meningitis) that may be shortened with antivirals or suppressed with prophylactic therapy. Recurrent bacterial meningitis should raise suspicion for a parameningeal focus of infection or CSF leak.

Special Laboratory Testing

Cellular targets unique to specific categories of infection can be chosen by the clinician. These tests results are unaffected by prior antibiotic therapy because of no requirement of live organisms. Latex agglutination is a rapid and specific test that uses antibodies to detect capsular polysaccharides present in bacterial infection; it has the disadvantages of high cost, low availability, and variable sensitivity. Polymerase chain reaction-based techniques utilize conserved genetic sequences to amplify and detect DNA or ribonucleic acid (RNA) from particular pathogens. The 16S component of ribosomal RNA is highly conserved among bacterial organisms and may be investigated using this method. Fungal infections may also be found by targeting 18S and 28S rRNA, and mycobacteria using 16s rRNA, heat shock protein- (Hsp-) 65, and rpoB. Although these PCR tests are highly specific, sensitivity depends on the concentration of the organism, and may be further lowered when blood is present.

Noninfectious Meningitis and Encephalitis

Many inflammatory, neoplastic, or toxic causes of meningitis and encephalitis are treatable. Investigating noninfectious etiologies requires additional first-tier CSF and serum studies including paraneoplastic and autoimmune antibody panels, and serum studies including ESR, CRP, antinuclear antibody (ANA), angiotensin converting enzyme (ACE), anti-double-stranded DNA, and anti-Sjögren'ssyndrome-related-antigen A or B (SSA, SSB). Neoplastic meningitis and encephalitis are best evaluated using three separate large-volumes, fresh CSF specimens sent for cytology, and flow cytometry if lymphoma is under consideration. Suspected autoimmune vasculitis should prompt vessel imaging. Computed tomography and full-body positron emitted tomography (PET) are helpful in the evaluation of sarcoidosis, granulomatosis with polyangiitis, neoplastic, and paraneoplastic etiologies. In many cases, biopsy and systemic imaging of affected organ will firm the diagnosis.

Therapeutic approach

Even after a wide range of diagnostic evaluation, a specific cause of meningitis and encephalitis remains inconclusive in more than 50% cases. Additional empiric therapy for atypical bacterial, fungal, and inflammatory disorders should be considered in patients who are deteriorating or failing to improve after initial treatment with antimicrobials and Acyclovir. Table 3 depicts bacterial causes of meningitis and encephalitis along with their associated features

Table 3: Features of atypical bacterial causes of bacterial meningitis and encephalitis

	Meningitis	Meningo-encephalitis	Clinical features	Treatment
L. monocytogenes	++	++	Brainstem signs, cranial neuropathies, ataxia	Ampicillin or Trimethoprim-Sulfamethoxazole
B. burgdorferi	++	+	Cranial neuropathies, radiculitis, targetoid rash, erythema migrans, arthritis, arrhythmia	Ceftriaxone or Penicillin G
R. rickettsii		+	Seizures, coma, maculopapular petechial rash on wrists/ankles hands/feet, periorbital and extremity edema	Doxycycline
B. henselae		+	Seizures, neuroretinitis, regional lymphadenopathy, anemia, pneumonia, endocarditis	Doxycycline
C. burnetii	+	++	Brainstem signs, ataxia, cerebral edema, seizures, flu-like syndrome, hepatitis, pneumonia	Doxycycline + Fluoroquinolone + Rifampin
Brucella species	++	+	Cranial neuropathy, radiculopathy, encephalopathy, seizures, stroke, flu-like syndrome, arthritis	Doxycycline + Rifampin
Leptospira species	+	++	Myalgias, headache, uveitis conjunctivitis, nephritis, cholecystitis	Penicillin G or Doxycycline

Complications

Many complications are associated with meningitis and encephalitis, which require acute intervention. Seizures are common in both; patients with a fluctuating mental status or coma should undergo an EEG to evaluate for subclinical seizure activity. Vasculitic or vasculopathic processes may cause strokes (arterial or venous). Meningitis may lead to poor CSF reabsorption and hydrocephalus due to obstruction at the level of the arachnoid granulations, possibly requiring external ventricular drainage or ventriculoperitoneal shunting. Encephalitis can lead to cerebral edema necessitating hyperosmolar therapy, hyperventilation, strict control of serum sodium (usual goal 140–155 depending on severity), or neurosurgical intervention such as hemicraniectomy. Appropriate follow-up is critical in cases of meningitis and encephalitis. Patients may require repeat lumbar puncture to ensure that CSF pleocytosis is resolving, particularly if symptoms are progressing, failing to improve, or if the original diagnosis was insecure. Patients with known MRI abnormalities should have repeat scanning to document improvement over time. In patients who have received empiric corticosteroids, interval imaging is particularly important so that a subclinical infectious process does not blossom following initial improvement. At times, positive serologies should be repeated 6 to 12 weeks later; if titers have risen by fourfold, the originally positive titer was likely due to an acute infection, securing the diagnosis.

Conclusion

Because of broad differential diagnosis and high potential for morbidity and mortality, the clinical approach to meningitis and encephalitis is challenging. Hence systematic and stepwise patient management should be preferred by the clinician. Foremost, probability of acute bacterial meningitis and HSV meningoencephalitis should be assessed and pursued using diagnostic studies along with simultaneous initiation of empiric treatment. If a diagnosis is not made, the results of first-tier studies such as lumbar puncture and brain MRI scan should be used to generate a broader differential. Further second-tier etiology-specific testing should be performed based upon patient risk factors and clinical features, with a bias toward finding treatable causes. If no diagnosis is made, further empiric treatment should be considered, especially when the patient is deteriorating. Vigilance is essential for complications including seizure, hydrocephalus, and stroke.