Neurologic Infectious Disease Emergencies

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KEYWORDS

- Neurologic infectious diseases
- Central nervous system infections
- Bacterial meningitis • Encephalitis

Nearly 70 years after the discovery of penicillin, neurologic infectious diseases (NIDs) remain an important worldwide source of morbidity and mortality. The ongoing health threat from NIDs stems from several factors: (1) the emergence of large populations of immunocompromised patients, both from the acquired immunodeficiency syndrome (AIDS) and from aggressive treatment regimens with or without solid or hematopoietic cell transplantation (HCT) that have improved survival from many different kinds of malignancies and rheumatologic and neurologic disorders; (2) the increase in international travel allowing rapid global transmission of emerging infectious agents, presenting North American clinicians with illnesses unlikely to be seen with sufficient frequency to maintain diagnostic acumen; (3) the widespread use of antibiotics that have contributed to many clinical successes but that have also driven the emergence of resistant organisms; and (4) the recognition of an increasing number of "infectious mimes," including the immune reconstitution inflammatory syndrome (IRIS) and immune-mediated encephalitides (ADEM and NMDA receptor encephalitis).[1]

The clinician faced with a potential NID must consider 3 sets of data urgently:

1. Patient demographics: is the patient immunocompetent or immunocompromised and, if the latter, by what mechanism are host defenses altered (eg, HIV, corticosteroids, recent penetrating trauma or surgery, recent health care–related exposures)
2. Pace of illness and clinical syndrome (nonspecific altered mental status vs focal findings and associated extraneural infection sites)
3. Laboratory data, including neuroimaging and rapid detection tests to guide initial therapeutic strategy.

In keeping with the topics of this issue, initial emergency diagnosis and management are emphasized with appropriate references to relevant literature for subsequent longer-term interventions.

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EVALUATING THE PATIENT WITH SUSPECTED CENTRAL NERVOUS SYSTEM INFECTION

Major neurologic infections presenting in urgent care settings, such as emergency rooms or intensive care units, include meningitis, encephalitis, brain abscess, spinal epidural abscess, subdural empyema, and pyomyositis. When patients present with fever, headache, nuchal rigidity, altered mental status, and/or focal signs, emergent evaluation includes physical examination, serologic testing, neuroimaging, and cerebrospinal fluid (CSF) examination.[2] The order of testing depends on a process of triage dictated by the patient's epidemiologic risk factors and physical examination, which will sort the problem into one that best fits meningitis without focal signs, a brain parenchymal localization (focal findings consistent with mass lesion or characteristic infectious pattern), or a spinal cord or a peripheral nerve or muscle problem. **Fig. 1** outlines a broad overview of the urgent evaluation process of a patient with suspected infection.[3–7] The initial triage divides patients into those with minimal alteration in level of alertness and those with more impaired mental status with or without signs of brain parenchymal or specific focal signs. The first obligation is to exclude bacterial processes, most critically bacterial meningitis, and to proceed with imaging studies in those patients whose examination suggests intracranial processes that might preclude lumbar puncture (LP). Computed tomography (CT) of the head (performed as an initial rapid screen, often to be followed by magnetic resonance imaging [MRI]) should be performed before LP if any one of the following is present: depressed level of consciousness (<14 Glasgow Coma Scale), focal or lateralizing examination, new-onset seizures, immunosuppressed state (chronic corticosteroid use, chemotherapy, HIV), or history of central nervous system (CNS) pathology (tumor, stroke, demyelinating disease, previous infection).[8]

A useful strategy is to assume the worst-case, but treatable, scenario, which in most instances is bacterial meningitis, and to ask the following 4 critical questions in designing empiric regimens (**Table 1**):

1. Is *Streptococcus pneumoniae* a possibility (assume penicillin/cephalosporin resistance)?
2. Is coverage for gram negatives necessary?
3. Is *Listeria monocytogenes* a possibility (patients >50 years old, specific exposures)?
4. Is viral encephalitis or tick-borne disease coverage necessary?

BACTERIAL MENINGITIS

Risk Factors and Epidemiology

With the advent of effective vaccination for *Haemophilus influenzae*, community-acquired bacterial meningitis has ceased to be a disease of children and now is one more frequently seen at the extremes of age (elderly, infants and neonates). Other risk factors include crowding (dormitories, military recruits, household contacts), contiguous infection (otitis, sinusitis), bacterial endocarditis (either from intravenous drug abuse or on prosthetic valves), recent neurosurgery or head trauma, ventriculoperitoneal shunts, cochlear implants and other indwelling devices, and immunosuppression (splenectomy, sickle cell disease, thalassemia, malignancy, diabetes, alcoholism, complement and immunoglobulin deficiencies, and immunosuppressive regimens). Prior vaccination status does not preclude infection: patients who have received the 7-valent or 23-valent pneumococcal vaccine can still acquire pneumococcal meningitis, and patients who have received meningococcal vaccine can still be infected with serogroup B meningitis. **Table 1** lists the most common epidemiologic considerations with attendant empiric antibiotic regimen recommendations.

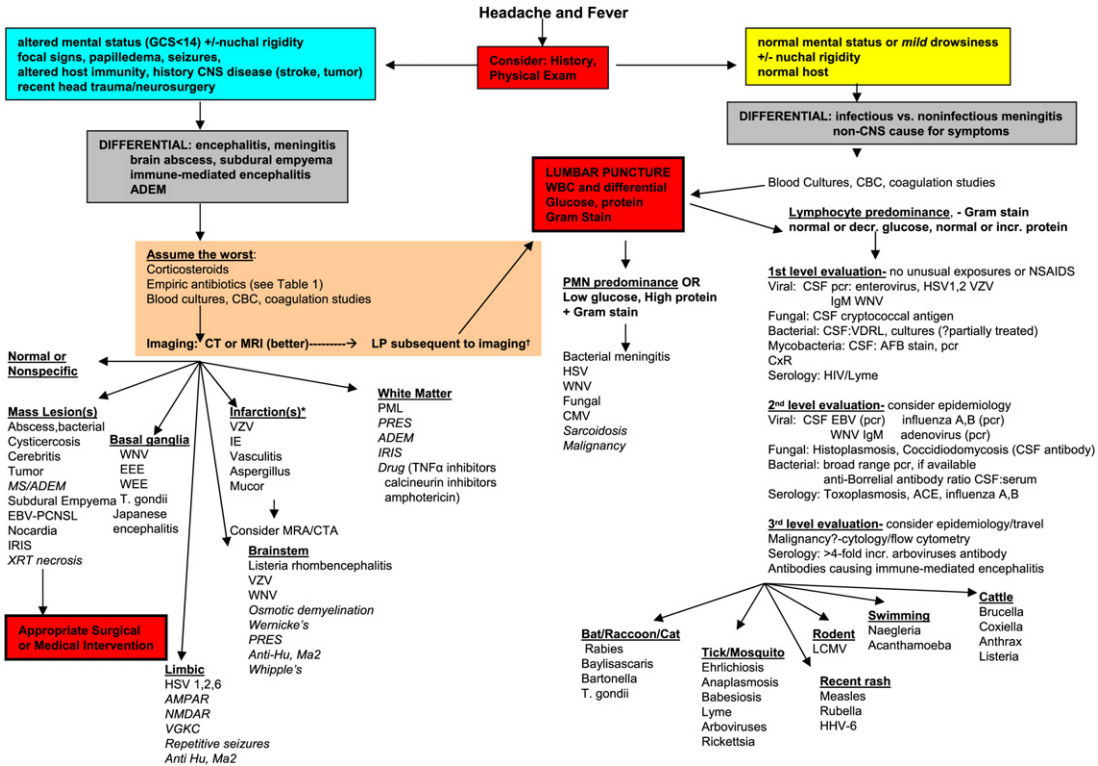

Fig. 1. Urgent evaluation of patient with suspected CNS infection. *Abnormal diffusion-weighted imaging (dwi); dwi also useful in diagnosis of Creutzfeldt-Jakob disease *Italics*, noninfectious processes that may mimic infection. † LP to be done *if* not contraindicated by findings on MRI. ADEM, acute disseminated encephalomyelitis; EBV/PCNSL, Epstein-Barr virus, primary central nervous system lymphoma; EEE/WEE, Eastern/Western equine encephalitis; GCS, Glasgow Coma Scale; IE, infective endocarditis; IRIS, immune reconstitution inflammatory syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs; PCR, polymerase chain reaction; PRES, posterior reversible encephalopathy syndrome; WNV, West Nile Virus; XRT, radiation therapy. (*Data from* Refs.[2–7])

Table 1
Initial empiric coverage for suspected bacterial meningitis or herpes simplex encephalitis by demographic factors

Clinical Setting	Child 1 mo to 17 y	Adults 18–50 y	Adults >50 y	Penetrating Trauma Neurosurgery Shunt, Ventricular Drain	Impaired T-cell Immunity (HIV, Corticosteroids Transplantation)
Potential organisms	*Streptococcus pneumoniae* *Neisseria meningitides*[a] Group B streptococcus *Haemophilus influenzae* (until age 2) *Escherichia coli*	*S pneumoniae* *N meningitidis*[a]	*S pneumoniae* *N meningitidis*[a] *L monocytogenes* Gram-negative bacilli	*Streptococcus aureus* Coagulase-negative staphylococci *Pseudomonas* *S pneumoniae* Streptococci	*S pneumoniae* *N meningitidis*[a] Gram-negative bacilli *Listeria* (consider TB risk by patient origin/ travel)
Empiric antimicrobial regimen[b]	Dexamethasone 0.15 mg/kg q6h for 4 d Ceftriaxone 20–25 mg/kg q6h OR Cefotaxime[c] 75–100 mg/kg q6–8h AND Vancomycin[c] 15 mg/kg q6h Acyclovir[c] 10 mg/kg q8h	Dexamethasone 10 mg q6h for 4 d Ceftriaxone 2 g q12h OR Cefotaxime[c] 2 g IV q6h PLUS Vancomycin[c] 15 mg/kg IV q8h Acyclovir[c] 10 mg/kg q8h Doxycycline PO 100 mg q12h if possibility of tick-borne disease	Dexamethasone 10 mg q6h for 4 d Ceftriaxone 2 g q12h OR Cefotaxime[c] 203 g/d q4–6h PLUS Ampicillin[c] 2 g q4h PLUS Vancomycin[c] 15 mg/k q8h PLUS Acyclovir[c] 10 mg/kg q8h PLUS Doxycycline PO 100 mg q12h if tick-borne disease Possible	Fourth-generation cephalosporin Cefepime[c] 2 g q8h PLUS Vancomycin[c] 15 mg/kg q8h PLUS Gentamicin[c] 1.0–1.3 mg/kg q8h ONLY if high suspicion High-risk MRSA: Vancomycin[c] 15 mg/kg q8h PLUS Rifampin 300 mg–400 mg IV/PO q8h	Ceftazidime[c] 2 g q12h PLUS Vancomycin[c] 15 mg/kg q8h PLUS Ampicillin[c] 2 g q4h High-risk MRSA regimen in previous column *First-Line TB*: Isoniazid 5 mg/kg PO qd; max 300 mg daily Pyridoxine 50 mg PO qd Rifampin 10 mg/kg/d PO; max 600 mg daily Pyrazinamide 15–35 mg/kg/d PO Ethambutol 15–25 mg/kg/d PO

Alternative regimens	Meropenem[c] 40 mg/kg q8h PLUS Vancomycin[c] 15 mg/kg q8h	Meropenem[c] 2 g IV q8h OR chloramphenicol 14–25 mg/kg q6h OR Moxifloxacin 400 mg IV daily PLUS Vancomycin[c] 15 mg/kg IV q8h	Ampicillin[c] 2 g q4h OR TMP 5 mg/kg every 6 h PLUS Vancomycin 15 mg/kg q8h PLUS Meropenem[c] 2 g IV q8h OR Moxifloxacin 400 mg IV daily	Vancomycin[c] 15 mg/kg q8h PLUS Ceftazidime 2 g q8h OR Meropenem[c] 2 g q8h OR Ciprofloxacin 400 mg q8h Metronidazole 400–500 mg q6h MRSA: Linezolid 600 mg IV/PO q12h	Meropenem[c] PLUS Vancomycin[c] PLUS Trimethoprim-sulfamethoxazole 5 mg/kg q6h See high-risk MRSA alternate in previous column TB: moxifloxacin 400 mg IV daily

Abbreviations: h, hour; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; PO, oral; q, every.

[a] Ciprofloxacin 500 mg oral one-time dose OR Rifampin 600 mg twice a day for 2 days prophylaxis for contacts.

[b] Doses IV unless otherwise indicated. See text for corticosteroid use. Once specific pathogen identified, local resistance patterns and nosocomial trends should be factored in with infectious disease consultation for definitive, pathogen-specific regimen.

[c] Adjust for renal insufficiency.

Data from Refs.[2–7,22,23,31]

Clinical Presentation

In a Dutch study of 696 episodes of adult community-acquired bacterial meningitis, only 44% of patients had the full triad of fever, altered mental status, and nuchal rigidity, but 85% of episodes had at least 2 of 4 symptoms of headache, fever, neck stiffness, and altered mental status.[9] Roos and Tyler[3] emphasize early vomiting as an important sign, even before headache or altered mental status. Up to one-third of patients with bacterial meningitis had focal signs and 14% were comatose in one study.[10] Immunocompetent patients with *Listeria* meningitis may present with the distinctive rhombencephalitis syndrome with focal cranial nerve and brainstem or other parenchymal deficits (**Fig. 2**).

Elderly patients, patients with partially treated meningitis, and patients on corticosteroids or other immunosuppressive drugs may not have any febrile response, and the clearest emergency distinction between viral and bacterial meningitis appears to be the severity of altered consciousness, seizures, focal neurologic findings, and shock.[11,12] Independent predictors of mortality are seizure activity, depressed level of consciousness (Glasgow Coma Score <13), and CSF white blood cell (WBC) count lower than 1000. Among the elderly with community-acquired meningitis, nearly one-third present in coma, and 16% have seizures. Pneumonia and diabetes are frequent predisposing conditions and additional poor prognostic indicators.[13] In community-acquired meningitis, about 50% of surviving patients have significant sequelae with case-fatality rate highest with *S pneumoniae*.[9]

Microbiology of Acute Bacterial Meningitis

The most common causes of community-acquired bacterial meningitis in adults are *S pneumoniae* and *Neisseria meningitidis* with *L monocytogenes* a consideration in patients older than 50 (see **Table 1**). *H influenzae* is a concern among asplenic or

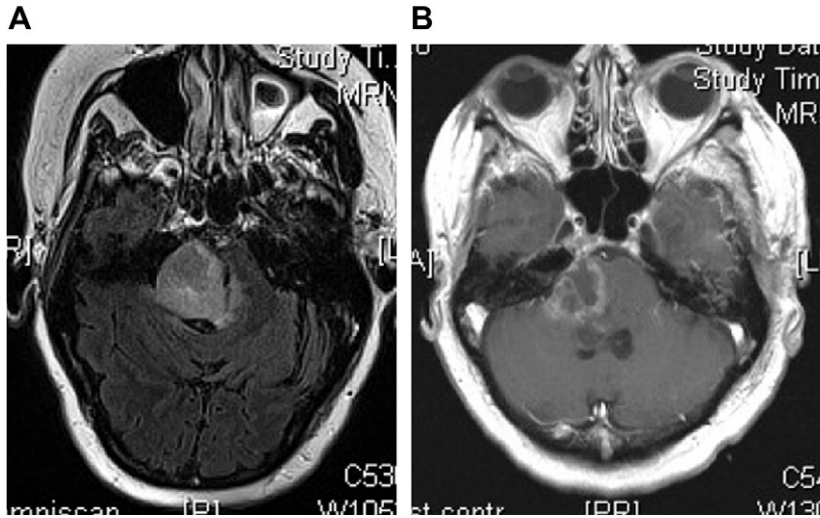

Fig. 2. FLAIR (*A*) and gadolinium-enhanced T1-weighted (*B*) MRI images of a patient with facial numbness, peripheral facial weakness, and rapid obtundation owing to *Listeria monocytogenes* rhombencephalitis. Although diffuse cerebritis predominates in immunocompromised patients, previously healthy patients may have this characteristic focal brainstem parenchymal involvement.

immune-compromised patients. Patients with nosocomially acquired bacterial meningitis occupy a growing number of beds in intensive care units. *Staphylococcus aureus* is a frequent pathogen and gram-negative bacilli (*Klebsiella*, *Serratia, Pseudomonas, Acinetobacter*) cause up to a third of nosocomial cases.[10,14,15]

Special Considerations in Vulnerable Populations

The risk of patients with HIV/AIDS for NIDs varies with CD4+ count less than 200/mm^3. These patients may present with meningitis caused by conventional bacterial pathogens but also caused by *Toxoplasma gondii*, Epstein-Barr virus (EBV), varicella zoster virus (VZV), *Cryptococcus neoformans,* and, more frequently outside North America, *Mycobacterium tuberculosis*. In such patients, the CSF WBC count and differential may be uninformative depending on the degree of immune suppression.[16] The full spectrum of transplantation-associated infections is beyond the scope of this article and is well covered elsewhere.[17,18] The clinician facing such a patient must cast a broad net to consider bacterial infections but also viral meningitides (VZV, EBV, cytomegalovirus [CMV], toxoplasmosis, and human herpesvirus 6 [HHV6]). For those who require ongoing immunosuppression of graft versus-host-disease, VZV remains a risk, and progressive multifocal leukoencephalopathy (PML) becomes a consideration with duration of immunosuppression.[19]

TREATMENT AND INVESTIGATION OF BACTERIAL MENINGITIS

First Step: Corticosteroids

Current guidelines and several meta-analyses support the use of dexamethasone administered concurrently with antimicrobial agents to abort the dysfunctional release of inflammatory cytokines triggered by bacterial lysis whose consequences include nearby tissue damage and a higher risk of venous infarctions and raised intracranial pressure.[20] A recent meta-analysis subsuming trials in patients who were HIV-positive and HIV-negative from many different parts of the world, suggested that the most solid corticosteroid benefit accrued to adults older than 55 largely in developed countries for whom steroid use decreased incidence of deafness and reduced mortality significantly in *S pneumoniae* cases. It was not clear that dexamethasone harmed any group.[21] Current guidelines recommend use of dexamethasone 10 mg every 6 hours intravenously.[22,23] Brouwer and colleagues[24] looked at 357 episodes of pneumococcal meningitis from 2006 to 2009 when 84% received steroids and compared them with a cohort from 1998 to 2002 when only 3% received steroids. Rates of death and hearing loss were lower in the recent group and, most impressively, mortality fell from 30% to 20%. Dexamethasone should be continued only in patients with cultures positive for pneumococci or with positive Gram stain for diplococci and should not be given to patients who previously received antibiotics. When doses are prescribed as indicated in **Table 1**, intrathecal vancomycin is not required to offset the effect of corticosteroids on CSF penetration.[25]

Other indications for corticosteroids in NID emergencies are control of edema in herpes simplex virus encephalitis[26] and control of initial edema with scolex lysis in cysticerosis.[27] Steroids convincingly reduce mortality in tuberculous meningitis, although the dose and duration of therapy are not fully established.[28–30]

Second Step: Empiric Antibiotics

Table 1 outlines recommendations, emphasizing the resistance of *S pneumoniae* to penicillin, the possibility of methicillin-resistant *S aureus* (MRSA), and the need to

cover possible viral encephalitis or tick-borne disease until further microbiologic data emerge.[31]

Third Step: Imaging

Any patient with significant altered mental status needs a CT or MRI before LP. Pyogenic abscesses exhibit several MRI characteristics that suggest infection rather than other etiologies (**Fig. 3**).[32–35]

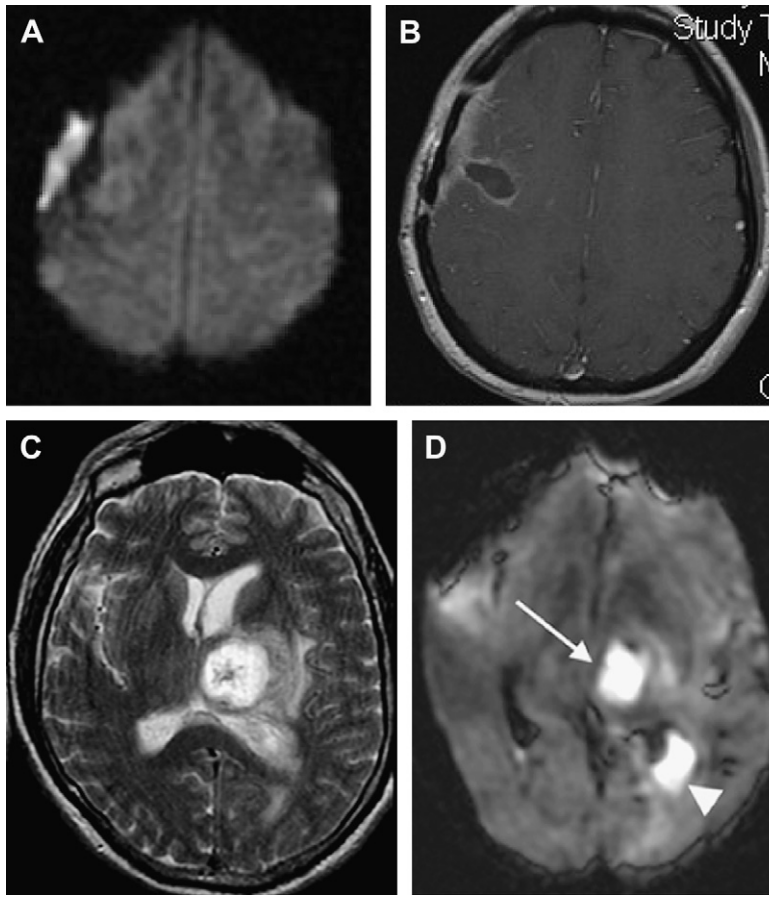

Fig. 3. Suspecting intracranial infection by MRI characteristics. Diffusion-weighted imaging (dwi) MRI (*A*) and gadolinium-enhanced T1-weighted MRI (*B*) in patient presenting with headache and fever 6 weeks after craniotomy for brain tumor. There is evidence of diffusion restriction of viscous purulent material, as well as cerebritis, indicated by parenchymal ring enhancement. Pyogenic abscesses exhibit characteristics suggesting infection rather than other etiologies, including T2 hyperintensity with isointense rim (*C*). (*D*) Another characteristic of purulent material in abscess, namely marked hyperintensity on diffusion-weighted images (*arrow and arrowhead*). Not shown in these figures, other characteristics suggestive of abscesses are increased mean transit time and decreased blood volume on perfusion-weighted images with increased flow in the periphery of the lesion consistent with reactive hyperemia and elevated lactate on proton magnetic resonance spectroscopy. Ventriculitis can be suspected by MRI as well, with decreased apparent diffusion coefficient values and increased signal of dependent intraventricular fluid on dwi. (*Data from* Refs.[32–35])

Fourth Step: Lumbar Puncture and Associated Serologies

Box 1 summarizes the pearls and pitfalls of infection diagnosis by lumbar puncture and serologic studies. A lymphocyte-predominant meningitis is usually seen in viral, tuberculous, fungal, or noninfectious entities, but the presence of lymphocyte predominance does not exclude bacterial meningitis. Decreased CSF glucose level to less than 40 mg/dL is highly suggestive of bacterial meningitis. Although Gram stain and reduced CSF glucose can be helpful in suggesting bacterial meningitis, cultures take several days and a rapid identification of common bacterial pathogens is greatly needed. Several broad-based multiprobe polymerase chain reactions (PCRs) that can detect bacterial DNA within 3 hours have been reported. Target organisms include *Neisseria*, *H influenzae, S pneumoniae, Streptococcus Agalactiae,* and *Listeria.*[36–38] PCR is not likely to replace culture, as cultures are needed for antimicrobial sensitivity testing; however, molecular methods have been developed to identify antibiotic resistance to penicillin G in *Neisseria meningitidis* strains.[39] Also, surrogate biomarkers, such as galactomannan, have potential as measures of response to antifungal therapy for *Aspergillus*.[40] C-reactive protein (CRP) is an acute-phase reactant that is a nonspecific marker of inflammation in serum or CSF. Although sensitive, it is not very specific for increased risk of bacterial meningitis. Similarly, elevated serum procalcitonin levels can be seen inconsistently in acute bacterial infection, and there is disagreement about their trustworthiness.[3,6]

Fifth Step: Complications of Meningitis

Acute hydrocephalus occurs in up to 8% of meningitis cases, most commonly in cryptococcal meningitis and other fungal infections (**Fig. 4**). *Listeria* is the bacterial pathogen most likely to cause acute hydrocephalus and this complication confers an unfavorable prognosis.[41] Hydrocephalus can be managed with repeated lumbar punctures or with a ventricular drain.

Hyponatremia caused by salt-wasting, syndrome of inappropriate antidiuretic hormone (SIADH), adrenal insufficiency, or iatrogenic overhydration contribute to altered mental status and should be aggressively managed. Seizures occur in 5% of patients with bacterial meningitis before admission and in 15% during hospitalization. Continuous electroencephalogram (EEG) should be considered in selected patients to detect nonconvulsive status epilepticus, as purely electroencephalographic seizures may explain fluctuating level of consciousness in some patients. In one study, periodic epileptiform discharges were frequent in monitored patients, as were seizures, with one or the other occurring in 48% of patients: more than half of these had no clinical correlate.[42] Whether prophylactic antiepileptic drugs would improve outcome is unknown. Survivors of bacterial meningitis remain at risk for more indolent development of communicating hydrocephalus, cognitive impairment, and sensorineural hearing loss.

LYMPHOCYTE-PREDOMINANT MENINGITIS

It is prudent to retain a large differential for the many causes of lymphocyte-predominant meningitis, which is not exclusively caused by viruses. **Fig. 1** outlines a graduated approach to investigate the syndrome at different levels of likelihood given epidemiologic considerations.

Viral Meningitis

Summer and early autumn are the seasons for many viral meningitides, with enteroviral meningitis group (echo, Coxsackie, and enteroviruses types 68–71) and Lyme

Box 1
Cerebrospinal fluid and serologic diagnostic studies

I. Cerebrospinal Fluid (CSF) Standard: White blood cells with differential, glucose, protein, Gram stain, cryptococcal antigen, directed cultures

1. There is no definite cut off for viral versus bacterial meningitis, although >1000 polymorphonuclear leukocytes (PMNs) suggest bacterial etiology; persistent PMN predominance in some West Nile viruses (WNVs)
2. Procalcitonin and C-reactive protein (CRP) are nonspecific; treatment decisions should not be based on these parameters
3. Glucose <50% that of simultaneous serum glucose ominous: bacteria, some fungi (*Aspergillus*), some viruses (herpes simples virus [HSV], WNV), tuberculosis, cancer, neurosarcoidosis
4. Protein elevation reflects blood-brain barrier disruption and is very nonspecific
5. Gram stain may be negative in bacterial infections
6. Polymerase chain reaction (PCR) utility: good for: HSV 1, 2, 6; Epstein-Barr virus (EBV), cytomegalovirus (CMV), rapid enterovirus; untrustworthy for: varicella zoster virus (VZV), HIV, WNV (only very early), *Borrelia*
7. Broad range and specific meningeal pathogen PCR gaining acceptance
8. Tuberculous meningitis: adenosine deaminase (ADA) variably elevated and not reliable; PCR techniques improving
9. Antibody tests and antibody indices:

    Lyme antibody index

    WNV immunoglobulin (Ig) M, VZV IgM, and IgG antibody index

    Coccidioides immitis complement fixation antibody

    HSV serum: CSF antibody ratio <20:1
10. Antigen: *Histoplasma capsulatum, Cryptococcus neoformans*
11. Other special testing: Venereal Disease Research Laboratory: syphilis Galactomannan *Aspergillus*
12. 14-3-3 protein not specific for Creutzfeldt-Jakob disease: elevated in states of rapid neuronal death

II. Serology Standard: complete blood count and differential, retain acute sera for directed antibody testing

1. Viruses

    Measure IgM and IgG antibodies acute and convalescent (fourfold rise in IgG):

    St. Louis, West Nile, Eastern and Western Equine, Japanese encephalitis, Dengue fever

    EBV (antiviral capsid antigen IgM and IgG and EBV nuclear antigen [EBNA])

    VZV, HSV-1(IgM), rabies, HIV (RNA can be checked early when viral load high but enzyme-linked immunosorbent assay [ELISA] weakly positive or negative)

    Borrelia burgdorferi (see #9 in first part of this list)
2. Tick-borne bacterial

    IgG and IgM by indirect immunofluorescence for Rocky Mountain spotted fever (RMSF)

    Lyme ELISA: confirmatory Western blot

    Ehrlichia antibodies by indirect fluorescent antibody

3. Parasites:

Toxoplasma gondii

a. Absence of IgG or IgM antibodies does not exclude *Toxoplasma* encephalitis in patients with AIDS. If positive in a patient with HIV, treat with pyrimethamine/sulfadiazine and folinic acid (incidence reduced among people receiving prophylaxis with sulfadiazine or dapsone and pyrimethamine against *Pneumocystis jiroveci* pneumonia).

b. If toxoplasma serology negative, check CSF EBV PCR and consider brain biopsy of any accessible mass lesion for lymphoma

Taenia solium (cysticercosis)

ELISA, but 50% with solitary lesions will be seronegative

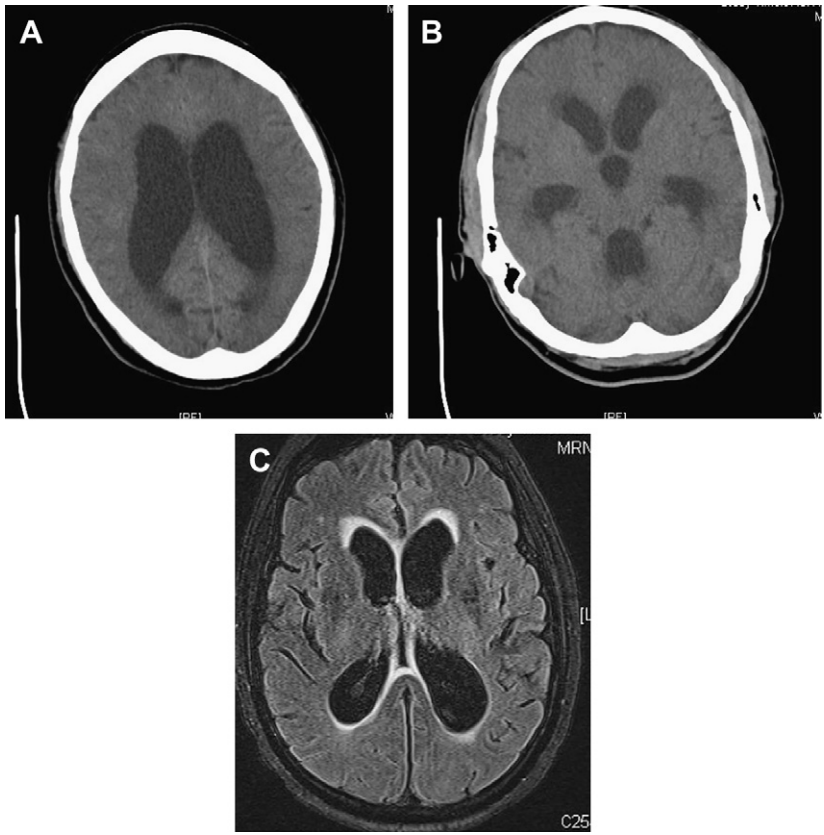

Fig. 4. Acute hydrocephalus complicating meningitis. CT scan of patient with *Coccidiodes immitis* meningitis. Like many such patients with fungal meningitis, this patient required ventriculoperitoneal shunting. The lateral ventricles on the unenhanced CT (*A*) are huge and there is transependymal spread of fluid across the ependymal surface. Lateral third and fourth ventricles are symmetrically enlarged (*B*), demonstrating that circulation of CSF is impeded at the level of the arachnoid villi. (*C*) FLAIR MRI of patient with community-acquired *S pneumoniae* meningitis also with acute hydrocephalus, a poor prognostic sign.

meningitis accounting for many North American cases. HIV seroconversion may be heralded by meningitis with persistent pleocytosis in some patients. Seasonal arthropod-borne viruses, such as West Nile virus (WNV), are concerns in many parts of the United States and the winter season raises the possibility of mumps and lymphocytic choriomeningitis virus (LCMV). Nonseasonal herpesvirus (HSV) type 2 and VZV account for many other cases. Fortunately, HSV type 2 and enteroviral PCRs are quite sensitive and specific and can be used to diagnose this common and usually self-limited illness efficiently.[43] VZV diagnosis is more complex and is summarized both for immunocompetent and immunocompromised patients in **Box 2**. Differential diagnosis includes several noninfectious entities, including sarcoidosis and drug adverse effects (particularly nonsteroidal anti-inflammatory drugs).

Treatment

Treatment of enteroviral meningitis is symptomatic, although in immunocompromised hosts with life-threatening symptoms, pleconaril can be considered.[58] A special group at risk for virulent enteroviral meningitis is patients treated with the monoclonal B-cell antibody rituximab.[59] Herpesviruses are treated with acyclovir 800 mg 5 times daily, famcyclovir 500 mg 3 times daily, or valacyclovir 1 gm 3 times daily for 2 weeks.

Recurring lymphocyte-predominant meningitis

The most common etiology is HSV type 2, often in association with genital herpetic eruption, although many patients are unaware of this infection. Herpes simplex virus (HSV) 2 is treated with acyclovir 100 mg 3 times daily for 5 days if genital herpes is known or 10 days for primary infection Alternatives are famcyclovir 500 mg 3 times daily for 7 to 10 days followed by 250 mg twice daily chronic prophylaxis *or* valacyclovir 500 mg twice daily.

Neuroborreliosis (Lyme Disease)

Neurologic Lyme disease is a potentially serious complication of *Borrelia burgdorferi*. Much confusion exists both in the professional and the lay community about the manifestations of neurologic Lyme disease, the appropriate duration of therapy, and the existence of long-term sequelae of infection. Therefore, this article features **Fig. 6**, a detailed illustration of the appropriate diagnostic process sanctioned by the American Academy of Neurology, to confirm and treat a neurologic syndrome attributable to this organism.[60–66] The most common neurologic sign of Lyme disease is facial palsy, often bilateral. **Table 2**, however, illustrates the myriad of other potentially infection-associated causes of facial palsy.[67,68] Meningitis and radiculitis are other common neurologic syndromes, but brain parenchymal involvement is *rare.* The decision to treat Lyme disease with intravenous (IV) antibiotics versus oral antibiotics is the subject of evolving recommendations, and each institution's infectious disease experts should be consulted for duration of IV treatment.

The current method for diagnosing Lyme neuroborreliosis is demonstration of abnormal CSF with increased leukocyte count, elevated protein, plus intrathecal synthesis of *Borrelia* antibodies. To discriminate between active and past infection can be difficult, as the antibody production can persist for years. Schmidt and colleagues[69] recently showed that measuring CXCL 13, a chemokine that attracts B and T lymphocytes, shows high sensitivity and specificity (100%/90.4%) for acute untreated Lyme disease, a finding that may help mark treatment response and distinguish atypical early cases.

Neurosyphilis

Neurosyphilitic emergencies can present at any time in the course of neurosyphilis. Symptomatic syphilitic meningitis is seen weeks or months to a couple of years

Box 2
Encephalitis and meningoencephalitis

1. Etiology: A significant percentage of cases may remain idiopathic after all appropriate serologic and CSF studies (40%–50%)
2. Radiology: Magnetic resonance imaging (MRI) (fluid-attenuated inversion recovery [FLAIR]) abnormalities in the temporal lobe are found in at least 80% of patients with HSV 1 >48 hours from symptom onset

   VZV may show large/small vessel infarctions but MRI picture also may resemble HSV 1 (**Fig. 5**).

   Flaviviruses (WNV, Eastern Equine Encephalitis, St Louis, Japanese) may show T2 and FLAIR abnormalities in thalami, basal ganglia, and substantia nigra, but, unlike HSV 1, evolution of such abnormalities may be delayed several days
3. PCR Pitfalls:
   a. EBV DNA can be found in peripheral blood mononuclear cells and may be positive in the CNS in many inflammatory disorders; its presence in CSF of immunocompromised hosts *is* significant. EBV acute infection diagnosed by VCA IgM antibodies and absence of antibodies to virus-associated nuclear antigen (EBNA) IgG. In samples collected more than 5 weeks after onset of illness, there should be a decrease in VCA IgG antibody titer and an increase in anti-EBNA IgG.
   b. HSV PCR may be negative in the first 3 days of illness and then remains positive for 2–10 days. CSF antibody becomes positive 8–12 days after illness onset and persists for 30 days. Serum: CSF antibody ratio of less than 20:1 is diagnosis of recent HSV 1 encephalitis.
   c. HIV testing: viral load be very high early on, but PCR IS negative and ELISA weak early on
   d. detection of human herpesvirus 6 (HHV6) in CSF is not definitive evidence that HHV6 is the etiologic organism owing to chromosomal integration
4. Other CSF strategies:
   a. consider repeated cytologies and flow cytometry in suspected malignancy
   b. consider interleukin (IL)-10 in patients with suspected lymphoma (IL-6 elevated in infection and inflammation)
   c. angiotensin-converting enzyme (ACE) level in CSF is of very limited utility
5. Dermatology skin lesions should be biopsied (VZV vs herpes simplex, RMSF, cryptococcus, syphilis, WNV, noninfectious etiologies, such as intravascular lymphoma presenting with fever unknown origin)
6. "New Diseases": consider testing for autoimmune encephalopathies N-methyl-D-aspartate receptor (NMDAR), GluR1/2 alpha-amino3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), voltage-gated potassium channel (VGKC) antibodies in both children and adults; acute disseminated encephalomyelitis (ADEM) has a different distribution of antecedent infections: measles, group A streptococci, *Mycoplasma pneumoniae*
7. Global Medicine: Read the newspaper and consider travel history for emerging viral infections, often zoonotic pathogens, that cause encephalitis, of which 5 examples follow here:
   a. Toscana virus caused by bites of sand flies: common cause of summer viral meningitis in central Italy
   b. Japanese encephalitis (JE): most common acute viral encephalitis worldwide: half of world population lives where JE can infect; pigs, herons, egrets as amplifying hosts[57]
   c. Paralytic disease can occur with enterovirus 71.[57–59]
   d. Chikungunya virus (togavirus now endemic in India and La Reunion, Zimbabwe, Sri Lanka)

e. Nipah and Hendra viruses (henipavirus genus of paramyxovirus family: pig farmers, horse workers)

8. Ancillary Studies: Use electroencephalogram (EEG) if fluctuating mental status develops and continue long-term monitoring
9. Empiric Treatment:
   a. Acyclovir 10 mg/kg q8h while investigations under way (**Table 1** for specific therapeutic recommendations).
   b. Consider foscarnet for encephalitis of unknown etiology: 60 mg/kg q8h for 14–21 days.
   c. Consider pleconaril for life-threatening enteroviral meningoencephalitis in immune-compromised patients.

Data from Refs.[44–57]

following primary infection and sometimes causes cranial nerve palsies, including II, IV, VI, VII, and VIII, with acute hearing loss. Skin rash after penile or other genital ulceration and subsequent optic neuritis/neuropathy should raise concern for neurosyphilis, which is included among pathogens presenting with acute infectious visual loss

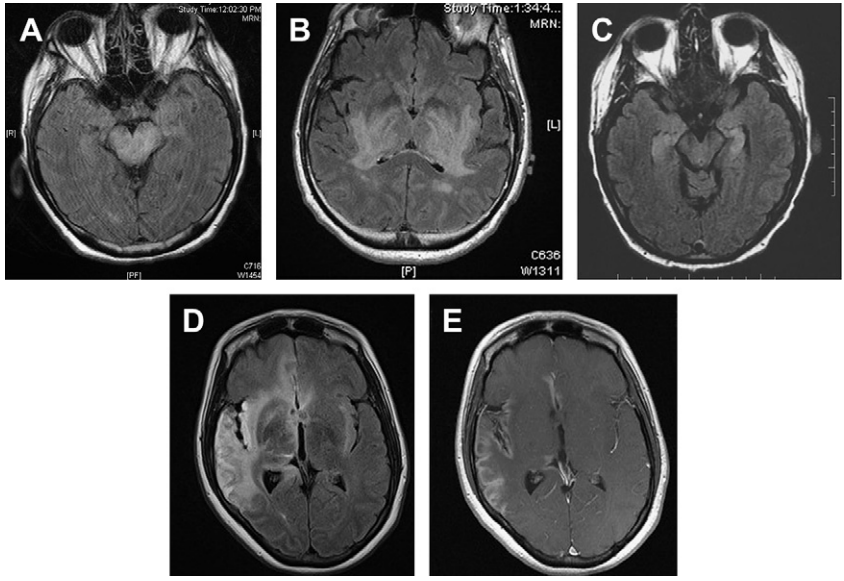

Fig. 5. MRI patterns of viral encephalitis. Although not definitive for specific pathogen and, in fact, as shown in panels *D* and *E*, sometimes misleading, MRI can be helpful. Different characteristic patterns in 3 patients show flavivirus (West Nile virus) or togavirus pattern of brainstem and basal ganglia pathology on FLAIR sequences (*A*, *B*) contrasted with HSV 1 encephalitis with bilateral hippocampal FLAIR abnormality (*C*); and FLAIR (*D*) and gadolinium-enhanced T1 sequences (*E*) of a patient thought to have HSV 1 but who had biopsy-proved varicella zoster virus encephalitis with small vessel vasculitis. There is extensive abnormal FLAIR signal in the right temporal and parietal lobes and genu of corpus callosum, along with sulcal increased FLAIR signal, suggesting proteinaceous fluid (*D*). Compared with the MRI with T1-weighted gadolinium images of *E*, cortical signal looked similar on T1 before gadolinium infusion (not shown), suggesting petechial hemorrhage.

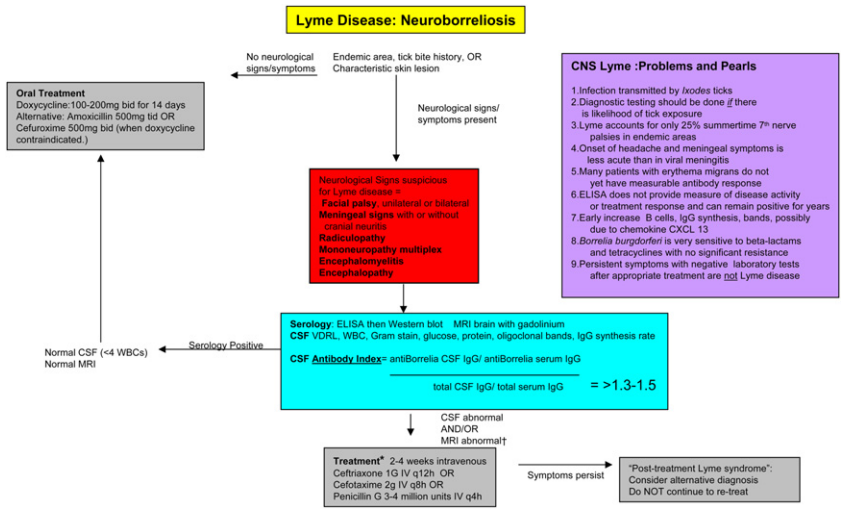

Fig. 6. Diagnosis and treatment of neuroborreliosis. *Some authorities now give 5 to 7 days of IV treatment and followed by change to oral doxycycline for meningitis, cranial neuritis. American Academy of Neurology guidelines recommend 2 weeks of oral or parenteral treatment regimens, but some authorities extend treatment to 4 weeks. †Consider alternative diagnoses if MRI shows only lesions that are nonspecific and CSF negative (see text). (*Data from* Refs.[60–66])

Table 2
Facial nerve palsies: differential diagnosis of infectious processes requiring specific treatment

Most Common Infectious Causes	
Herpes simplex ("Bell palsy"), Borrelia burgdorferi, Varicella zoster virus	
Less Common Infections	**Noninfectious Conditions**
Botulism	Carcinomatous meningitis
Cytomegalovirus[a]	Guillain-Barré syndrome
Epstein-Barr virus	Intranasal influenza vaccine
Diphtheria[b]	Lymphoma meningitis
Guillain-Barré syndrome	Pontine glioma
HIV[a]	Pregnancy
Human herpesvirus 6[a]	Sarcoidosis[b]
Leprosy	Schwannoma
Listeria (rhombencephalitis)	Sjogren
Parotitis/Otitis	
Mucormycosis[a]	
Mycoplasma pneumoniae	
Parotitis	
Syphilis (*Treponema pallidum*)	
Tetanus[b]	
Tuberculosis	

Most common causes are bolded, less common causes listed alphabetically.
[a] Immunocompromised patients.
[b] Often bilateral.

(*Bartonella*, HSV, VZV, CMV, Mucoraceae). Acute ocular manifestations include anterior and posterior uveitis or optic neuritis.[70] Visual deterioration following antibiotic treatment has been ascribed to a Herxheimer reaction, and may require steroids.[71] Among its protean manifestations are convulsive and nonconvulsive status epilepticus; thus, neurosyphilis should be considered in the differential diagnosis of rapidly progressive cognitive change and seizures.[72] Syphilitic meningovasculitis can cause stroke occurring 2 to 5 years after primary infection in patients who do not have HIV.

Diagnosis of neurosyphilis is made by finding a CSF pleocytosis greater than 20, or a reactive CSF-VDRL (Venereal Disease Research Laboratory). Treatment recommendations include penicillin G 3 to 4 μ IV every 4 hours for 2 weeks OR 2.4 procaine intramuscularly (IM) with 500 mg 4 times a day probenecid for 10 to 14 days. Ceftriaxone 2 g IV or IM daily for 10 to 14 days is an alternative. Treatment may be followed with 3 weekly IM injections of 2.4 million units of benzathine penicillin G. CSF should be rechecked at 6 weeks. Outcome is better for patients who are HIV-uninfected, whereas up to 30% of HIV-infected individuals may require retreatment and have residual symptoms.[73]

Cryptococcal Meningitis

Overwhelmingly a disease of the immunocompromised patient (chronic corticosteroids, HIV), immunocompetent individuals also may be at risk for infection with some varieties of the yeast, *Cryptococcus neoformans* var. *gattii*, found in the tropics in decaying heartwood of trees and responsible for recent outbreaks on Vancouver Island in British Columbia and Alberta.[74] Characteristic clinical manifestations in this most common cause of lymphocytic meningitis in patients with HIV are a marked rise in intracranial pressure (ICP) with rapid development of hydrocephalus and visual loss either from invasion of cranial nerves or from sustained elevated pressure. Lung and skin lesions may provide clues.

Repeated lumbar punctures may be necessary to control ICP. Patients are treated with amphotericin 0.7 mg/kg/d or AmBisome (amphotericin B) 5 mg/kg/d with flucytosine 25 mg/kg 4 times daily and 8 to 10 weeks of 400 to 800 mg per day oral fluconazole, followed by 6 months of 200 mg per day in immunocompromised patients.[5,6]

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) refers to the often dramatic and frequently dysfunctional inflammatory response to recent infection after a rapid improvement in the host's immune system, either as a result of withdrawal of immunosuppression or treatment of the underlying immunosuppressive cause, such as AIDS. Thus, it is seen in patients with HIV, in the posttransplant period, or after withdrawal of intense chemotherapy. Neurologists are most likely to encounter IRIS with tuberculous meningitis, cryptococcal meningitis, toxoplasmosis, or PML. Two potentially confusing radiographic pictures should be recognized: (1) diffuse meningeal enhancement with elevated CSF pressure and pleocytosis of several hundred WBCs (**Fig. 7**A)[75] or (2) a mass lesion (see **Fig. 7**B) that can resemble tumor or tumefactive demyelination. Paradoxically, brief courses of corticosteroids can help suppress inflammation and improve outcome.

ENCEPHALITIS: BRAIN PARENCHYMAL DISEASE WITH OR WITHOUT FOCAL SIGNS

More than 100 different agents can cause encephalitis. In the United States, there are about 20,000 reported cases of encephalitis per year, although the actual number is likely larger.[44] The proportion of cases without established etiology in one literature analysis was greater than 50%.[45] Emergency clinical strategy is different from

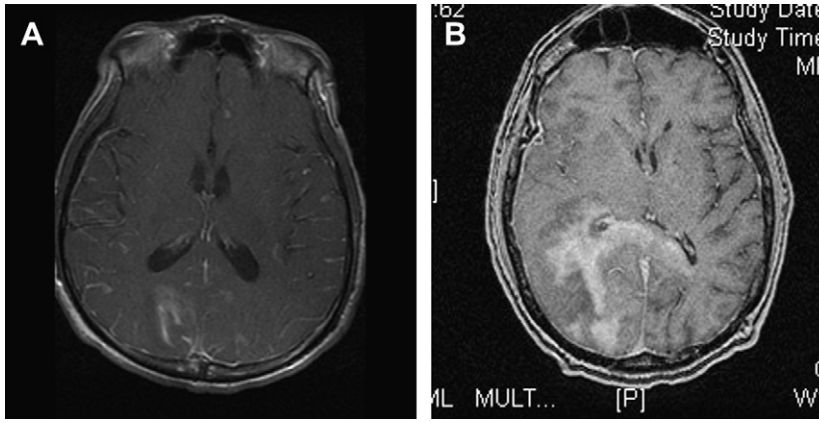

Fig. 7. Two patterns of immune reconstitution inflammatory syndrome (IRIS). (*A*) Gadolinium-enhanced T1-weighted MRI that shows intense leptomeningeal enhancement in a patient recently treated for cryptococcal meningitis who has had rapid rise in CD4 count on antiretroviral therapy and presents with seizures and marked rise in intracranial pressure. (*B*) Gadolinium-enhanced T1-weighted MRI that shows a different HIV-positive patient newly on antiretroviral therapy presenting with hemianopia and a mass lesion resembling high-grade tumor owing to PML with IRIS.

suspected bacterial meningitis, as there are fewer pathogen-specific therapeutic options. In treating a patient with possible encephalitis (defined as 2 or more of the following: fever, CSF pleocytosis, headache, altered mental status, seizures, or focal findings, with or without MRI abnormalities), the short-term goals should be as follows:

1. Treat what is treatable: cover for encephalitis sensitive to acyclovir (HSV, VZV, and possibly EBV) or other antivirals (**Table 3**); consider the possibility that a bacterial cause, such as *Listeria*, *Rickettsia*, or *Borrelia,* requires specific treatment.[46]
2. Provide supportive care with low threshold for continuous EEG monitoring.
3. Use imaging characteristics and epidemiology to dictate specific infectious workup, whereas brain biopsy should be a last resort.
4. Consider autoimmune encephalitis.
5. Save acute serum and CSF for subsequent studies (see **Box 2**).

Unlike bacterial meningitis, viral encephalitis at times can be distinguished by its particular pattern of brain involvement (see **Fig. 5**). Some viruses are likely to produce focal clinical and radiographic signs (John Cunningham [JC] virus, VZV, HSV 1, HHV6), whereas others produce diffuse inflammation. Specific neurotropisms of diagnostic relevance include the following:

1. *Basal ganglia and anterior horn cell infection* with paralytic syndromes and movement disorders are seen with WNV. Other flaviviruses and togaviruses involve preferentially the basal ganglia.
2. *Limbic encephalitis* with memory loss, confusion, and possible seizures or autonomic features is characteristic of HSV types 1 and 6. HSV 1 is the most common nonseasonal encephalitis in North America. HHV6 is associated with the period of engraftment of bone marrow or peripheral blood transplantation.[47] Also targeting mesial temporal structures are some of the antibody-mediated paraneoplastic syndromes such as anti-N-methyl-D-aspartate receptor encephalitis (NMDAR) and antivoltage-gated potassium channel antibody encephalitis

Table 3
Acute infectious encephalitis and possible antiviral treatments

Common	Uncommon
SEASONAL[a] **West Nile virus**	**Eastern equine encephalitis**
Japanese encephalitis[b]	**Western equine encephalitis**
Chikungunya[b]	**Powassan virus**
La Crosse[6]	**Colorado tick virus**
St Louis virus	Naegleria fowleri
Borrelia burgdorferi	Acanthamoeba (Balamuthia mandrillaris)
Rickettsia: Coxiella, *Ehrlichia, Babesia*	*Leptospirosis*
	LCMV[6]
NONSEASONAL **HSV type 1**[1]	**Rabies**[c]
Varicella zoster[1]	**Cytomegalovirus**[c,2–4]
Epstein-Barr[1,2]	**Mumps**
HIV	**Enteroviruses**[c,5]
Adenoviruses	**HHV6**[c,2+3]
Toxoplasma gondii[c]	*Bartonella henselae*
Cryptococcus neoformans[c]	

[d]*Treatment:* 1 acyclovir, 2 ganciclovir, 3 foscarnet, 4 cidofovir, 5 pleconaril, 6 ribavirin.

No evidence for oral therapy with acyclovir, famciclovir, or valacyclovir, although long-term supplemental oral valacyclovir for HSV encephalitis is in trial.

Bold, viruses; *Italics*, bacteria; Normal font, other (parasites, amoebae, fungi).

Abbreviations: HHV, human herpesvirus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus.

[a] Summer/fall except for LCMV in late fall/winter.

[b] Outside North America.

[c] Primarily in HIV or transplant recipient.

[d] Some investigators have recommended Foscarnet 60 mg/kg every 8 hours for 21 days for microbiologically undiagnosed encephalitis.

Data from Refs.[3,5,26,46,54,56,57]

(VGKC).[48] The California Encephalitis Project, as well as other groups, have identified numerous patients with NMDAR antibodies as the likely cause of what was previously deemed infectious encephalitis of unknown cause. Compared with enteroviral, rabies, and HSV 1 encephalitis, these patients were younger, non-white and had lower WBC median CSF cell counts.[49–51] In children, as many as one-third of cases of acute encephalitis are possibly immune-mediated.[52]

CURRENT IMPORTANT ENCEPHALITIC PATHOGENS: NORMAL OR IMMUNOCOMPROMISED HOSTS

West Nile Virus

Most WNV infections are asymptomatic, but 20% of patients develop an acute febrile illness and 1 in 150 develops neuroinvasive disease, including meningitis, encephalitis, and acute flaccid paralysis.[53] These are usually older patients (mean age 60 with vs 46 without neuroinvasive disease) or immunosuppressed patients. A rash may be present, possibly raising diagnostic confusion with Rickettsial diseases.[54] Acute flaccid paralysis, resembling poliomyelitis, is distinctive. Diagnosis is based on serologic testing. Immunoglobulin G (IgG) persists for life, and 18 months after infection, 20% of cases still have detectable IgM. Detection of IgM WNV antibodies in CSF is diagnostic.[55] There is no known specific treatment.[56,76]

Enterovirus 71

Enterovirus 71 is an emerging pathogen with expanding geographic range causing hand-foot-and-mouth disease mostly in children, and neurologic manifestations that include lymphocytic meningitis, encephalitis, and acute flaccid paralysis, as well as transverse myelitis and cerebellitis.[77] Because the geographic range of this RNA virus with a high spontaneous mutation rate is expanding, neurologists and emergency room physicians in North America should be aware of potential cases.[57]

Influenza

Seasonal and nonseasonal influenza is associated with uncommon neurologic complications, including seizures, encephalitis, myositis, and necrotizing encephalopathies. The spectrum and severity of complications of the 2009 H1N1 influenza pandemic are consistent with those of seasonal influenza. Neurologic illness was more frequently reported in children, many of whom had preexisting seizure disorders or other conditions.[78–80]

Varicella Zoster Virus

Varicella zoster virus (VZV) produces a host of neurologic symptoms, both in immunocompromised and in immunocompetent patients (**Box 3**). The most common manifestation is a dermatomal rash but rash is *not* necessary for other complications.[81] Other recognized syndromes include vascular events with a combination of large-vessel and small-vessel strokes and myelopathy. Detection of anti-VZV antibody IgG in the CSF with reduced serum-to-CSF ratio of anti-VZV IgG antibody is the preferred diagnostic test. Alternative tests include anti-VZV IgM in the serum or CSF VZV PCR. CSF IgG antibody is a more sensitive indicator of VZV-related vasculopathy than is PCR.[82,83] Ocular complications can result from trigeminal VZV infection or from retinal necrosis or delayed optic neuropathy.[84,85]

Epstein-Barr Virus

EBV has been associated with a variety of putative neurologic complications in healthy hosts, including meningitis, myelitis, brachial plexitis, and cranial neuritis. A positive EBV PCR in the CSF of healthy hosts does not necessarily represent causal association, although it is significant in immunocompromised patients.[4] Infection usually occurs within weeks of hematopoietic cell transplantation but can present years after transplantation as fulminant lymphoma with multiple contrast-enhancing mass lesions (**Fig. 8**).[86]

An important entity to consider in diffuse or focally abnormal brain MRIs with rapid onset of altered mental status is the posterior reversible encephalopathy syndrome (PRES). Multifocal abnormalities in white matter that resemble encephalitis can occur. The cardinal features include subacute headache, confusion, and seizures, often with cortical visual loss. The MRI picture is consistent with vasogenic edema, primarily in the occipital and parietal lobes, but there are diffuse radiographic presentations, including hemorrhagic lesions and spinal cord involvement. Clinical context dictates evolving diagnostic considerations, as illustrated in **Fig. 8**. The lengthening list of drugs predisposing to PRES includes calcineurin inhibitors, antiangiogenesis agents, and chemotherapeutic drugs.[87]

APPROACH TO THE PATIENT WITH FOCAL CEREBRAL SIGNS OF POSSIBLE INFECTIOUS ORIGIN

Although the bulk of syndromes discussed previously demonstrate presentations dominated by meningeal signs with less prominent focality, much of the differential diagnosis in this section follows from pathogen-suggestive neuroimaging abnormalities outlined on the left-hand side of **Fig. 1**. Of course, many pathogens, notably VZV, assume both patterns.

Box 3
Spectrum of neurologic manifestations of varicella zoster virus

Epidemiology:

- Immunocompetent: usually >60 years
- Immunocompromised: glucocorticoid use, natalizumab, fingolimod, antirejection regimens: calcineurin inhibitors, tumor necrosis factor-α inhibitors

Clinical presentation

- Dermatomal rash or disseminated skin lesions (40% with VZV encephalitis have no history of rash)
- Zoster sine herpete (no rash) occurs in 37% of cases with stroke or meningoencephalitis
- Vasculopathy: transient ischemic attack, ischemic or hemorrhagic stroke
- Segmental motor weakness
- Polyneuritis (cranial nerves [Ramsay Hunt, involving V3 and VII]), lower cranial neuritis (glossopharyngeal, vagus)
- Cerebellar ataxia
- Transverse myelitis
- Necrotizing (acute or progressive outer retinal retinitis, Zoster keratitis)
- Delayed ischemic optic neuropathy after ophthalmic VZV
- Postherpetic neuralgia

Diagnosis:

- Biopsy skin lesions if present
- There may not be CSF pleocytosis
- PCR sensitivity only 30%
- Anti-VZV IgM in serum or CSF, *or*
- VZV DNA by PCR in blood or CSF, *or*
- Anti-VZV IgG in CSF (more often positive in chronic vasculopathy than is PCR) intrathecal synthesis VZV IgG present if: ratio (anti-VZV IgG in CSF/anti-VZV IgG in serum) to (total IgG in CSF/total IgG in serum) $\geq$1.5

Treatment:

- Acyclovir 10 mg/kg IV q8h $\times$ 2 weeks
- Retinal necrosis: ganciclovir and foscarnet
- Postherpetic pain: topical lidocaine, gabapentin, amitriptyline, nortriptyline, desipramine, prega balin, duloxetine; retreatment with IV acyclovir then oral valacyclovir
- Post-VZV encephalitis: check CD4+ count; if <500, consider valacyclovir 500 mg bid chronically

Immunocompetent patients usually have only skin rash in $\leq$3 dermatomes.

Data from Refs.[81–85]

Progressive Multifocal Leukoencephalopathy

PML, a progressive viral illness caused by papovavirus JC infection, has emerged as an important pathogen. Clinicians should be alert to its varied physical and radiographic manifestations and appropriate workup.[88] Diagnosis is made after suspicious

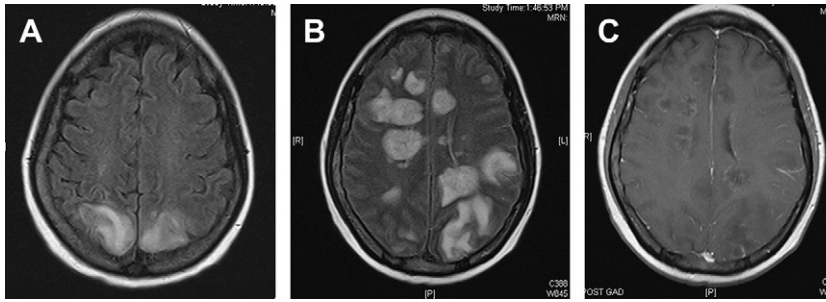

Fig. 8. PRES or infection? Diagnostic confusion illustrated by (*A*), which looks like posterior reversible encephalopathy syndrome (PRES) in a patient 18 days after hematopoietic cell transplantation for acute myelogenous leukemia on cyclosporine. The patient was switched to tacrolimus but continued to worsen over the next month with cytomegalovirus reactivation, graft–versus-host disease, and multifocal FLAIR lesions that enhanced throughout brain ([*B*] FLAIR and [*C*] gadolinium-enhanced T1 sequences) owing to aggressive monoclonal Epstein-Barr virus proliferation producing multicentric lymphoma that was rapidly fatal.

MRI findings lead to CSF PCR for JC virus and brain biopsy is infrequently necessary. Although patients with HIV continue to account for more than 80% of all cases, patients with solid organ and hematopoietic cell transplantation, particularly those taking mycophenolate, and a wide array of patients on immunosuppressives, such as rituximab, natalizumab, and efalizumab for rheumatologic, neurologic, and other conditions, are now recognized as being at risk for PML.[89] Even patients with no discernible prior immunosuppression can develop PML, and the amount of inflammation in such patients may lead to radiographic diagnostic confusion (**Fig. 9**).[90] PML-IRIS further adds to unusual inflammatory lesion development by MRI that can mimic brain tumor (see **Figs. 7** and **9**). Although withdrawal of immune suppression is first-line therapy, emerging strategies include mirtazapine and mefloquine.[85,91]

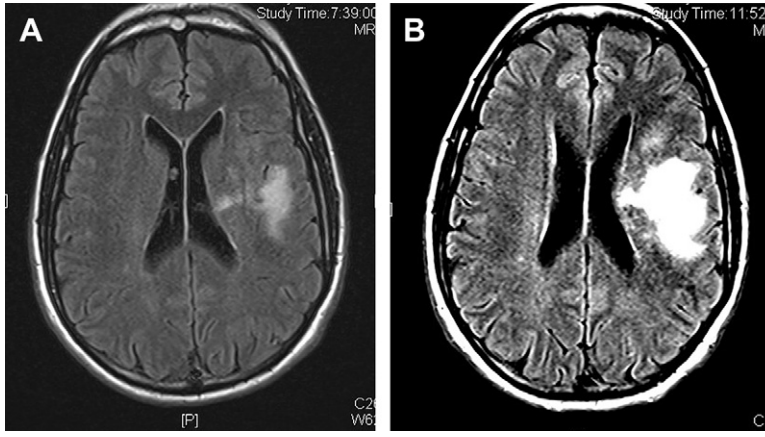

Fig. 9. Rapid progression of progressive multifocal leukoencephalopathy with characteristic white matter abnormality that does not enhance (not shown) in a patient 1 year after HCT for AML. Eighteen days separate (*A*) from (*B*), both FLAIR MRI images. Patient was JC virus positive in CSF.

Brain Abscess

Less common now than in the pre-antibiotic era, brain abscesses are associated, however, with a wider range of organisms than in previous decades. Nonbacterial and uncommon bacterial organisms likely to cause abscess formation in appropriate epidemiologic circumstances include parasites: *T gondii, Taenia solium;* fungi: *Aspergillus*, Mucoraceae, *Histoplasma*, *Candida* species; and bacteria: *Listeria*, *Nocardia*, and *M tuberculosis*. Several of the more common diagnostic and therapeutic emergencies in this category are summarized in the following sections.

Toxoplasma gondii

The most common cause of mass lesions in patients with HIV, this parasitic disease is quite treatable.[16] MRI shows multiple deep microabscesses. Treatment is pyrimethamine 75 to 100 mg/d for 3 to 4 weeks after a 200-mg loading dose, sulfadiazine 1.5 g 4 times a day for 3 to 4 weeks, and folinic acid 10 to 25 mg per day for 3 to 4 weeks. Patients with HIV should continue once-daily trimethoprim/sulfadiazine prophylaxis until the CD4 count exceeds 200.

Neurocysticercosis

Infection of the brain by the larval stage of *T solium* disease is widely prevalent in India, China, and Central and South America, as well as increasingly in the Southwestern United States owing to increasing immigration from seroprevalent areas. MRI is usually suggestive of a scolex (**Fig. 10**). Solitary cysticercus granuloma treatment and steroid use are ongoing areas of therapeutic controversy. The duration of antiseizure treatment may depend on persistence of enhancing lesions and long-term seizure outcome is generally good. If there is residual calcific residue, anti-epileptic drugs likely should be continued.[92] Phenytoin and carbamazepine should be avoided, as they increase metabolism of praziquantel and albendazole.

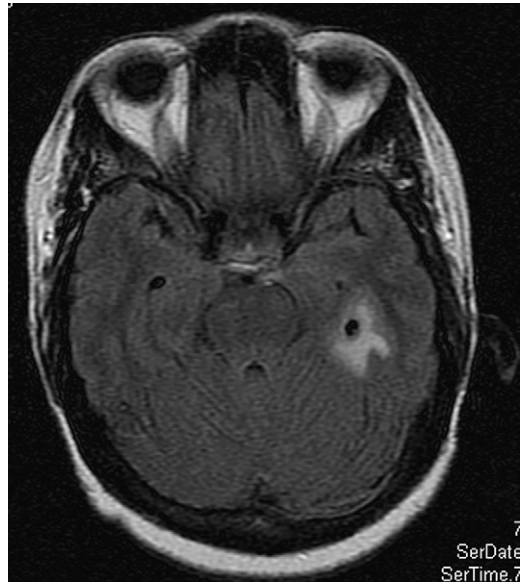

Fig. 10. A 46-year-old patient with new-onset seizure. A Haitian native, the patient was last there more than a decade earlier. Isolated cysticercus scolex seen with small amount of surrounding vasogenic edema on FLAIR MRI image.

Bacterial brain abscess

Postoperative bone infections or paranasal, ear, and pharyngeal infections, as well as pulmonary arteriovenous malformations, dental surgery, endometrial biopsy, and sepsis are all predisposing conditions.[93] Microbiology depends on source: *S aureus* is the most common pathogen postoperatively or after trauma. When the source is hematogenous spread from endocarditis, or urosepsis, *Streptococcus anginosus* (formerly *Streptococcus milleri*), and *Streptococcus viridans* are the culprits, whereas anaerobes (*Bacteroides*, *Peptostreptococcus*, *Actinomyces*, *Fusobacterium*) predominate in lung sources. Enteric gram-negative bacilli often recovered with gastrointestinal or urologic sources. *Pseudomonas* should be considered when ear infections are the source.[4] Empiric coverage should cover gram-positive, gram-negative, and anaerobic organisms (third-generation or fourth-generation cephalosporins and metronidazole). Vancomycin and carbapenems can be used in place of cephalosporins and metronidazole. Surgical intervention is considered in lesions of larger than 2.5 cm, although some abscesses may be drained without open craniotomy.[94] Some authorities believe steroids can be used briefly to control edema.[95] Prophylactic antiepileptic drugs are not recommended.

Subdural empyema, a surgical emergency, is defined as purulent infection between the dura and arachnoid membranes and has risk factors and pathogenesis similar to those of brain abscess.[4] Clinical signs include headache and rapid deterioration in mental status, and CT and/or MRI are often suggestive (**Fig. 11**). Risk factors are similar to those of brain abscess.[96] Lumbar puncture is generally inadvisable because of the risk of raised intracranial pressure.

Infective Endocarditis

Infective endocarditis (IE) in the twenty-first century remains a disease of high morbidity and mortality. In much of the world, IE is no longer a subacute or chronic disease of patients with rheumatic valvular damage, but targets those with degenerative valve disease or prosthetic valves and drug abusers. An important emerging population at risk is patients with health care contact. Current in-hospital mortality

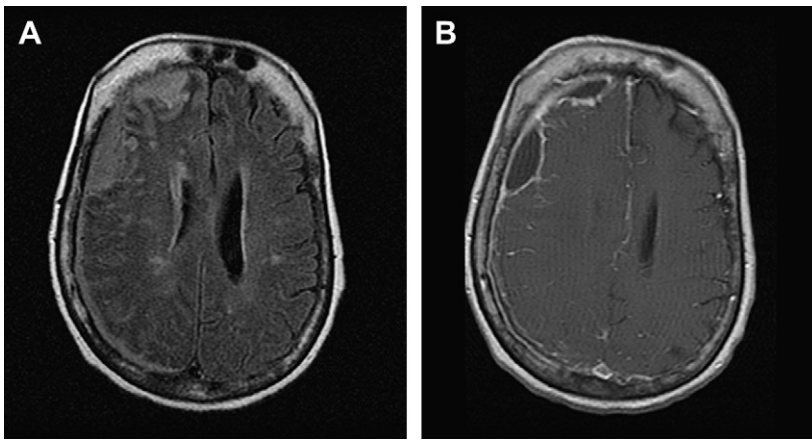

Fig. 11. Patient with long-standing systemic lupus erythematosus on prednisone and azathioprine presented with headache and fever. MRI FLAIR (*A*) shows extradural signal hyperintensity layering along the subdural space. There is intense dural enhancement on the gadolinium image (*B*).

for patients with IE is 14% to 20%.[97] In a recent international survey of 2781 adults with definite IE from 2000 to 2005, the median age was 57.9. Native valve involvement was seen in 72%, recent health care exposure history was elicited in one-quarter of these patients, and *S aureus* was the most common pathogen, whereas culture results were negative in 10%. The most common predisposing conditions were valvular heart disease and about 10% were associated with IV drug abuse. *S aureus* was the causative organism in 68% of drug abusers. *S aureus* and *viridans* streptococci accounted for 28% and 21% of cases respectively in nondrug users.[98]

Neurologic complications continue to contribution to the morbidity and mortality of IE. In the study described above[98], the 16.9% stroke incidence remained stable compared with studies from more than 3 decades ago.[99] We now know, however, that MRI abnormalities are extraordinarily common, as recently demonstrated in a study in which all patients with suspected IE had an admission MRI. Eight-two percent of MRIs done in the first 5 days in hospital were abnormal. MRI helped to diagnose IE by Duke criteria or alter therapeutic decision making in a substantial proportion of patients, although whether this altered the course or outcome of IE remains to be seen.[100] We recommend at least CT or preferably MRI in any patient with suspected IE and altered mental status or focal findings. CT angiography can be done if renal function permits, and MR angiography also may disclose aneurysms. Early surgery decreases mortality.[101]

APPROACH TO THE PATIENT WITH FOCAL FINDINGS SUGGESTIVE OF SPINAL CORD OR PERIPHERAL PROCESSES

Emergency neurologic consultations for rapid onset of dysfunction localizing to the spinal cord raise extensive diagnostic considerations for infection-associated processes with cord tropisms.[102] These include myelitis or postinfectious demyelination with an array of etiologies that can include EBV, *Mycoplasma pneumoniae*, *Treponema pallidum*, and unidentified viruses. Cytomegalovirus can produce a cauda equina inflammatory syndrome. WNV produces an anterior horn syndrome, enterovirus 71 produces a similar picture, and schistosomiasis can invade the cord. Important viral myelitis pathogens include acute VZV and HSV 2, whereas longitudinally extensive intramedullary enhancing lesions of neuromyelitis optica (NMO) and sarcoidosis may mimic infection. Treatment with intravenous acyclovir (see **Table 1**) during workup for causes of myelitis is prudent.

Bacterial spinal epidural abscess is a medical and surgical emergency. Patients present with back pain and point tenderness with or without fever and sometimes in the absence of neurologic abnormalities on initial examination. Patients at risk for spinal epidural abscess often have underlying illnesses, such as diabetes, chronic renal failure, or malignancy. Main routes of infection are hematogenous (prior soft tissue infections or urinary tract or pulmonary infections), contiguous spread from osteomyelitis or muscle abscess, skin punctures through intravenous drug abuse or furuncles, and iatrogenic through invasive procedures on the spine, such as epidural catheters and spinal surgery.[103,104] Common organisms are *S aureus*, gram-negative rods, streptococci, and, *M tuberculosis*.

Management

Lumbar puncture should be avoided because of infection dissemination risk. Four to 6 weeks of antibiotics after immediate decompressive laminectomy are required with vancomycin and antibiotics targeting gram-negative bacilli (piperacillin-tazobactam, cefotaxime, and meropenem). If patients have sensitivity to beta lactam agents,

then levofloxacin or aztreonam may be used[83] with subsequent choice of grafting procedure by the neurosurgeon.[105] Prognosis is guarded, with mortality still at 5% to 20%, and complete recovery without neurologic impairments in only 45% of patients.[106] Negative prognostic factors include MRSA infection, motor deficits, elevated CRP, age older than 50, cervical and thoracic as opposed to lumbar area involvement, sepsis, delayed diagnosis and treatment, diabetes, and rheumatoid arthritis, as well as prior spinal surgery.[107]

Pyomyositis

Since the first reports 40 years ago, recognized cases of pyomyositis have increased rapidly and come to neurologists' attention because of pain and weakness. Pyomyositis is heralded by cramping and pain followed by signs of localized tenderness and edema, often in a febrile neutropenic patient and usually without muscle enzyme elevation. Originally described in the tropics, it usually involves transient bacteremia in the setting of preexisting or concurrent muscle injury elicited in more than one-third of the patients. Nearly half have at least one underling disease, such as HIV, diabetes, hematologic malignancies with or without stem cell transplantation, solid cancers, rheumatologic disorders, cirrhosis, or renal insufficiency, it also can be seen in previously healthy patients, often with a history of prior skin infection and in these instances muscle pain in back, buttocks, thighs, or calves can be a critical clue to sepsis.[108] *S aureus* is the most commonly implicated pathogen, and now up to three-fourths of community-acquired strands may be methicillin-resistant (MRSA, strain USA 300), producing an array of new presentations, such as pneumonia with early cavitation, and crops of pustular or vesicular skin lesions.[109] *Escherichia coli*, often fluoroquinolone-resistant, is the most common cause of nosocomial gram-negative bacteremia, both among patients with and those without cancer.[110] This pathogen is emerging as a major myositis culprit in patients with hematologic malignancies.[111] Compared with previously healthy patients, patients with pyomyositis with underling medical conditions have a higher rate of gram-negative infections.[112] MRI shows diffusely abnormal T2 in muscles consistent with edema and aids with rapid diagnosis, leading to prompt debridement and aggressive antimicrobial therapy.

SUMMARY

1. Neurologic infectious diseases remain a significant cause of morbidity and mortality, affecting both healthy hosts and those with HIV and immunosuppression from chemotherapy. There is a growing spectrum of pathogens and their clinical presentations. Timely diagnosis is essential to ensure good-quality survival.
2. Bacterial meningitis etiology differs by age group and site of acquisition. *Streptococcus pneumoniae* remains both the most common community-acquired pathogen in adults and the form with the highest mortality. Dexamethasone reduces mortality in adults with this pathogen.
3. More than half of encephalitis cases remain without definitive etiology and many may be caused by immune-mediated mechanisms, such as NMDAR or VGKC encephalitides.
4. PRES and IRIS are 2 mimes of infection that should be considered in the differential diagnosis of PML, itself a disease now diagnosed in many immune-suppressed patients beyond the HIV population.
5. Indications for neurosurgical intervention for NID treatment include acute hydrocephalus in bacterial or fungal meningitis, brain abscess drainage, subdural

empyema, epidural spinal abscess, and suspected infection of unknown etiology after appropriate serologic and CSF studies.

REFERENCES

1. Tan K, Patel S, Gandhi N, et al. Burden of neuroinfectious diseases on the neurology service in a tertiary care center. Neurology 2008;71:1160–6.
2. Ziai WC, Lewin JJ III. Update in the diagnosis and management of central nervous system infections. Neurol Clin 2008;26:427–68.
3. Roos K, Tyler KL. Meningitis, encephalitis, brain abscess and empyema. In: Hauser SL, Josephson SA, editors. Harrison's neurology in clinical medicine. 2nd edition. New York: McGraw-Hill; 2010. p. 451–83.
4. Honda H, Warren DK. Central nervous system infections: meningitis and brain abscess. Infect Dis Clin North Am 2009;23:609–23.
5. Mace SE. CNS infections as a cause of an altered mental status? What is the pathogen growing in your CNS? Emerg Med Clin North Am 2010;28:535–70.
6. Fitch MT, Abrahamian FM, Moran GJ, et al. Emergency department management of meningitis and encephalitis. Infect Dis Clin North Am 2008;22:33–52.
7. Rincon F, Badjatia N. CNS infections in the neurointensive care unit. Curr Treat Options Neurol 2006;8:135–44.
8. Hasbun R, Abrahams J, Jekel J, et al. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. N Engl J Med 2001;345: 1727–33.
9. Van de Beek D, de Gans J, Spanjaard L, et al. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med 2004;351:1849–59.
10. Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults. A review of 493 episodes. N Engl J Med 1993;328:21–8.
11. Brivet FG, Ducuing S, Jacobs F, et al. Accuracy of clinical presentation for differentiating bacterial from viral meningitis in adults: a multivariate approach. Intensive Care Med 2005;31:1654–60.
12. Safdieh JE, Mead PA, Sepkowitz A, et al. Bacterial and fungal meningitis in patients with cancer. Neurology 2008;70:943–7.
13. Cabellos C, Verdquer R, Olmo M, et al. Community-acquired bacterial meningitis in elderly patients: experience over 30 years. Medicine 2009;88:115–9.
14. Kourbeti IS, Jacobs AV, Koslow M, et al. Risk factors associated with postcraniotomy meningitis. Neurosurgery 2007;60:317–25.
15. Pizon AF, Bonner MR, Want HE, et al. Ten years of clinical experience with adult meningitis at an urban academic medical center. J Emerg Med 2006;30:367–70.
16. Walker M, Zunt JR. Parasitic CNS infections in immunocompromised hosts. Clin Infect Dis 2005;40:1005–15.
17. Saiz A, Graus F. Neurologic complications of hematopoietic cell transplantation. Semin Neurol 2010;30:287–95.
18. Rosenfeld MR, Pruitt AA. Neurologic complications of bone marrow, stem cell, and organ transplantation in patients with cancer. Semin Oncol 2006;33:352–61.
19. Pruitt AA. Central nervous system infections in cancer patients. Semin Neurol 2010;30:296–310.
20. Van de Beek D, de Gans J, McIntyre P, et al. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev 2007;1:CD004405.
21. Van de Beek D, Farrar JJ, de Gans J, et al. Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data. Lancet Neurol 2010;9: 254–63.

22. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267–84.
23. Nudelman Y, Tunkel AR. Bacterial meningitis: epidemiology, pathogenesis and management update. Drugs 2009;69:2577–96.
24. Brouwer MC, Heckenberg SG, de Gans J, et al. Nationwide implementation of adjunctive dexamethasone therapy for pneumococccal meningitis. Neurology 2010;75:1533–9.
25. Ricard JD, Wolff M, Lacherade JC, et al. Levels of vancomycin in CSF of adult patients receiving adjunctive corticosteroids to treat pneumococcal meningitis: a prospective multicenter observational study. Clin Infect Dis 2007;44:250–5.
26. Kamei S, Seikizawa T, Shiota H, et al. Evaluation of combination therapy using acyclovir and corticosteroids in adult patients with HSV encephalitis. J Neurol Neurosurg Psychiatry 2005;76:1544–9.
27. Abba K, Ramaratnam S, Ranganathan LN. Antihelmintics for people with neurocysticercosis. Cochrane Database Syst Rev 2010;3:CD000215.
28. Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 2004;351: 1741–51.
29. Sinner SW. Approach to the diagnosis and management of tuberculous meningitis. Curr Infect Dis Rep 2010;12:291–8.
30. Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev 2008;1:CD002244.
31. Chapman AS, Bakken JS, Folk SM, et al. Diagnosis and management of tickborne rickettsial diseases: rocky mountain spotted fever, ehrlichioses, and anaplasmosis—United States: a practical guide for physicians and other health-care and public health professionals. MMWR Recomm Rep 2006; 55(RR-4):1–27.
32. Cahill DP, Barker FG, Davis KR, et al. Case 10-2010: a 37-year-old woman with weakness and a mass in the brain. Case records MGH. N Engl J Med 2010;362: 1326–33.
33. Kastrup O, Wanke I, Maschke M. Neuroimaging of infections of the central nervous system. Semin Neurol 2008;28:511–22.
34. Ben Salem D, Peruse de Montclos E, Couaillier JF, et al. Urgences neuroradiologiques en pathologie infectieuse. J Neuroradiol 2004;31:301–12.
35. Hong JT, Son BC, Sun JH, et al. Significance of diffusion-weighted imaging and apparent diffusion coefficient maps for the evaluation of pyogenic ventriculitis. Clin Neurol Neurosurg 2008;110:137–44.
36. Van Gastel E, Bruynseels P, Verstrepen W, et al. Evaluation of a real-time PCR assay for the diagnosis of pneumococcal and meningococcal meningitis in a tertiary care hospital. Eur J Clin Microbiol Infect Dis 2007;26:651–3.
37. Rothman R, Ramachandran P, Yang S, et al. Use of quantitative broad-based polymerase chain reaction for detection and identification of common bacterial pathogens in cerebrospinal fluid. Acad Emerg Med 2010;17:741–7.
38. Hedberg ST, Olcen P, Fredlung H, et al. Real-time PCR detection of five prevalent bacteria causing acute meningitis. APMIS 2009;117:856–60.
39. Taha MK, Vazquez JA, Hong E, et al. Target gene sequencing to characterize the penicillin G susceptibility of *Neisseria meningitides*. Antimicrobial Agents Chemother 2007;51:2784–92.
40. Chen SC, Kontoyiannis DP. New molecular and surrogate biomarker-based tests in the diagnosis of bacterial and fungal infection in febrile neutropenic patients. Curr Opin Infect Dis 2010;23:567–77.

41. Kasanmoentalib ES, Brouwer MC, Van der Ende A, et al. Hydrocephalus in adults with community acquired bacterial meningitis. Neurology 2010;75:918–23.
42. Carrera E, Claassen J, Oddo ML, et al. Continuous electroencephalographic monitoring of critically ill patients with CNS infections. Arch Neurol 2008;65: 1612–8.
43. Kost CB, Rogers B, Oberste S, et al. Multicenter beta trial of the GeneXpert enterovirus assay. J Clin Microbiol 2007;45:1081–6.
44. Granerod J, Cunningham R, Zuckerman M, et al. Causality in acute encephalitis: defining aetiologies. Epidemiol Infect 2010;138:783–800.
45. Granerod J, Tam CC, Crowcroft NS, et al. Challenge of the unknown: a systematic review of acute encephalitis in non-outbreak situations. Neurology 2010;75: 924–32.
46. Tunkel AR, Glaser CA, Bloch KC, et al, Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47:303–27.
47. Seeley WW, Marth FM, Holmes TM, et al. Post-transplant acute limbic encephalitis. Neurology 2007;69:156–65.
48. Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain 2004;127(pt 3):701–12.
49. Prüss H, Dalmau J, Harms L, et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. Neurology 2010;75:1735–9.
50. Gable MS, Gaval S, Radner A, et al. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. Eur J Clin Microbiol Infect Dis 2009;28:1421–9.
51. Glaser CA, Honarmand S, Anderson L, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis 2006;43:1565–77.
52. Florance NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009;66:11–8.
53. Petersen LR, Hayes EB. West Nile virus in the Americas. Med Clin North Am 2008;92:1307–22.
54. Reznicek JE, Mason WJ, Kaul DR, et al. Avoiding a rash diagnosis. N Engl J Med 2011;364:466–71.
55. Davis LE, DeBiasi R, Goade DE, et al. West Nile virus neuroinvasive disease. Ann Neurol 2006;60:286–300.
56. Solomon T, Hart IJ, Beeching NJ. Viral encephalitis: a clinician's guide. Pract Neurol 2007;7:288–305.
57. Tyler KL. Emerging viral infections of the CNS parts I and II. Arch Neurol 2009; 66:939–48, 1065–74.
58. Desmond RA, Accortt NA, Talley L, et al. Enteroviral meningitis: natural history and outcome of pleconaril therapy. Antimicrobial Agents Chemother 2006;50: 2409–14.
59. Ganjoo KN, Raman R, Sobel RA, et al. Opportunistic enteroviral meningoencephalitis: an unusual treatable complication of rituximab therapy. Leuk Lymphoma 2009;50:673–5.
60. Halperin JJ, Shapiro ED, Logigian EL, et al. Practice parameter: treatment of nervous system Lyme disease. Neurology 2007;69:91–102.
61. Halperin JJ. Nervous system Lyme disease. J R Coll Physicians Edinb 2010; 40(3):248–55.
62. Blanc F, Jaulhac B, Fleury M, et al. Relevance of the antibody index to diagnose Lyme neuroborreliosis among seropositive patients. Neurology 2007;69:953–8.

63. Lantos PM, Charini WA, Medoff G, et al. Final report of the Lyme disease review panel of the Infectious Diseases Society of America. Clin Infect Dis 2010;51:1–5.
64. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006;41:1089–134.
65. Fallon BA, Keilp JG, Corbera KM, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology 2008;70: 992–1003.
66. Feder HM, Johnson BJ, O'Connell S, et al. A critical appraisal of chronic Lyme disease. N Engl J Med 2007;357:422–30.
67. Gleeson T, Etienne M. Cranial nerve VII palsy as the first sign of cephalic tetanus after an earthquake. Arch Neurol 2011;68:536–7.
68. Yis U, Kurul SH, Cakmakci H, et al. *Mycoplasma pneumoniae*: nervous system complications in childhood and review of the literature. Eur J Pediatr 2008;167: 973–8.
69. Schmidt C, Plate A, Angele B, et al. A prospective study on the role of CXCL13 in Lyme neuroborreliosis. Neurology 2011;76:1051–8. Accompanying editorial: Tuman H, David D. Are high CSF levels of CXCL 13 helpful for diagnosis of Lyme neuroborreliosis? Neurology 2011;76:1036–7.
70. Pless ML, Korshinsky D, LaRocque RC, et al. Case records of the MGH. Case 26-2010: a 54-year-old man with loss of vision and a rash. N Engl J Med 2010;363:865–74.
71. Kiss S, Damico FM, Young LH. Ocular manifestations and treatment of syphilis. Semin Ophthalmol 2005;20:161–7.
72. Marra CM. Update on neurosyphilis. Curr Infect Dis Rep 2009;11:127–34.
73. Ghanem KG, Moore RD, Rompalo AM, et al. Neurosyphilis in a clinical cohort of HIV-1-infected patients. AIDS 2008;22:1145–51.
74. Bestard J, Siddiqi ZA. Cryptococcal meningoencephalitis in immunocompetent patients: changing trends in Canada. Neurology 2010;74:1233–4.
75. Airas L, Paivarinta M, Roytta M, et al. Central nervous system immune reconstitution inflammatory syndrome (IRIS) after hematopoietic stem cell transplantation. Bone Marrow Transplant 2009;34:1–4.
76. Granwehr BP, Lillibridge KM, Higgs S, et al. West nile virus: where are we now? Lancet Infect Dis 2004;4:547–56.
77. Ooi MH, Wong SC, Pidin Y, et al. Human enterovirus 71 disease in Sarawak, Malaysia: a prospective clinical, virological and molecular epidemiological study. Clin Infect Dis 2007;44:646–56.
78. Ekstrand JJ, Herener A, Rawlings J, et al. Heightened neurologic complications in children with pandemic H1N1 influenza. Ann Neurol 2010;68:762–6.
79. Kedia S, Stroud B, Parsons J, et al. Pediatric neurological complications of 2009 pandemic influenza A (H1N1). Arch Neurol 2011;68:455–62.
80. Augarten A, Aderka D. Alice in wonderland syndrome in H1N1 influenza. Pediatr Emerg Care 2011;27:120.
81. Nagel MA, Gilden DH. The protean neurologic manifestations of varicella-zoster virus infection. Cleve Clin J Med 2007;74:489–94.
82. Nagel MA, Cohrs RJ, Mahalingam R, et al. The varicella zoster virus vasculopathies: clinical, CSF, imaging and virologic features. Neurology 2008;70:853–60.
83. Gilden D, Cohrs RJ, Mahalingam R, et al. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. Lancet Neurol 2009;8:731–40.

84. Nakamoto BK, Dorotheo EU, Biousse V, et al. Progressive outer retinal necrosis presenting with isolated optic neuropathy. Neurology 2004;63:2423–5.
85. Salazar R, Russman AN, Nagel MA, et al. Varicella zoster virus ischemic optic neuropathy and subclinical temporal artery involvement. Arch Neurol 2011;68: 517–20.
86. Ahmad I, Cau NV, Kwan J, et al. Preemptive management of Epstein-Barr virus reactivation after hematopoietic stem-cell transplantation. Transplantation 2009; 8:140–5.
87. Fugate JF, Claasen DO, Cloft HJ. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. Mayo Clin Proc 2010;85:427–32.
88. Aksamit AJ. Progressive multifocal leukoencephalopathy. Curr Treat Options Neurol 2008;10:178–85.
89. Carson KB, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009; 113:4834–40.
90. Gheuens S, Pierone G, Peeters P, et al. Progressive multifocal leukoencephalopathy in individuals with minimal or occult immunosuppression. J Neurol Neurosurg Psychiatr 2010;81:247–54.
91. Brickelmaiaer M, Lugovskoy A, Kartikeyan R, et al. Identification and characterization of mefloquine efficacy against JC virus in vitro. Antimicrobial Agents Chemother 2009;53:1840–9.
92. Singh G, Rajshekhar V, Murthy JM, et al. A diagnostic and therapeutic scheme for a solitary cysticercus granuloma. Neurology 2010;75:2236–45.
93. Bernardini GL. Diagnosis and management of brain abscess and subdural empyema. Curr Neurol Neurosci Rep 2004;4:448–56.
94. Tseng JH, Tseng MY. Brain abscess in 142 patients: factors influencing outcome and mortality. Surg Neurol 2006;65:557–62.
95. Hakan T, Cerana N, Erdem I, et al. Bacterial brain abscesses: an evaluation of 96 cases. J Infect 2006;52:359–66.
96. Osborn MK, Steinberg JP. Subdural empyema and other suppurative complications of paranasal sinusitis. Lancet Infect Dis 2007;7:662–7.
97. Cabell CH, Jollis JG, Peterson GE, et al. Changing patient characteristics and the effect on mortality in endocarditis. Arch Intern Med 2002;162:90–4.
98. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology and outcome of infective endocarditis in the 21st century. Arch Intern Med 2009; 169:463–73.
99. Pruitt AA, Rubin RH, Karchmer AW, et al. Neurological complications of bacterial endocarditis. Medicine (Baltimore) 1978;57:329–43.
100. Duval X, Lung B, Kelin I, et al. Effect of early clinical MR imaging on clinical decisions in infective endocarditis. Ann Intern Med 2010;152:497–504.
101. Vikram HR, Buencosejo J, Hasbun R, et al. Impact of valve surgery on 6-month mortality in adults with complicated, left-sided native valve endocarditis: a propensity analysis. JAMA 2003;290:3207–14.
102. Jacob A, Weinshenker BG. An approach to the diagnosis of acute transverse myelitis. Semin Neurol 2008;28:105–20.
103. Darouiche RO. Spinal epidural abscess. N Engl J Med 2006;355:2012–20.
104. Pradilla G, Nagahama Y, Spivak AM, et al. Spinal epidural abscess: current diagnosis and management. Curr Infect Dis Rep 2010;12:484–91.
105. Sendi P, Bregenzer T, Zimmerli W. Spinal epidural abscess in clinical practice. QJM 2008;101:1–12.

106. Reihsaus E, Waldbaur H, Seeling W. Spinal epidural abscess: a meta-analysis of 915 patients. Neurosurg Rev 2000;23:175–204.
107. Pradilla G, Ardila GP, Hsu W, et al. Epidural abscesses of the CNS. Lancet Neurol 2009;8:292–300.
108. Moellering RC Jr, Abbott GF, Ferraro MJ. Case Records of the MGH. Case 2-2011: a 30-year-old woman with shock after treatment of a furuncle. N Engl J Med 2011;364:266–75.
109. Moellering RC Jr. The growing menace of community-acquired methicillin-resistant *Staphylococcus aureus*. Ann Intern Med 2006;144:368–70.
110. Wisplinghoff H, Bischoff T, Tallent SM, et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309–17.
111. Vigil KJ, Johnson JR, Johnston BD, et al. *E coli* pyomyositis: an emerging infectious disease among patients with hematologic malignancies. Clin Infect Dis 2010;50:374–80.
112. Crum NF. Bacterial pyomyositis in the United States. Am J Med 2004;117:420–8.