

# **MENINGITIS & ENCEPHALITIS**

## **BACTERIAL MENINGITIS**

Acute bacterial meningitis is a life-threatening neurological emergency. Its estimated annual incidence is 2–5 per 100 000 people in the Western world and a figure that may be 10 times as high in the less developed countries. Bacterial meningitis is one of top 10 causes of infection-related death worldwide and 30–50% of its survivors have permanent neurological sequelae. Conditions that predispose patients to its development include systemic (especially respiratory) or parameningeal infection, head trauma, anatomic meningeal defects, previous neurosurgical procedures, cancer, alcoholism, and other immunodeficiency states. The etiologic organism varies with age and with the presence of predisposing conditions.

### **Pathogenesis**

Bacteria typically gain access to the central nervous system by colonizing the mucous membranes of the nasopharynx, leading to local tissue invasion, bacteremia, and hematogenous seeding of the subarachnoid space. Bacteria can also spread to the meninges directly, through anatomic defects in the skull or from parameningeal sites such as the paranasal sinuses or middle ear. Polysaccharide bacterial capsules, lipopolysaccharides, and outer membrane proteins may contribute to the bacterial invasion and virulence. Low levels of antibody and complement in the subarachnoid space are inadequate to contain the infection. The resulting inflammatory response is associated with the release of inflammatory cytokines, including interleukins 1 and 6 and tumor necrosis factor  $\alpha$ , that promote blood-brain barrier permeability, vasogenic cerebral edema, changes in cerebral blood flow, and perhaps direct neuronal toxicity.

Pathologically, bacterial meningitis is characterized by leptomeningeal and perivascular infiltration with polymorphonuclear leukocytes and an inflammatory exudate. These changes tend to be most prominent over the cerebral convexities in *Streptococcus pneumoniae* and *Haemophilus* infection and over the base of the brain when *Neisseria meningitidis* is the causative organism. Brain edema, hydrocephalus, and cerebral infarction may occur, although actual bacterial invasion of the brain is rare.

### **Clinical Findings**

**A. Symptoms and Signs.** At the time of presentation, most patients have experienced symptoms of meningitis for one to seven days. The symptoms include fever, confusion, vomiting, headache, and neck stiffness, but the full syndrome is often not present.

Physical examination may show fever and signs of systemic or parameningeal infection, such as skin abscess or otitis. A petechial rash is seen in

50-60% of patients with *N. meningitidis* meningitis. Signs of meningeal irritation are seen in about 80% of cases; they are often absent at the extremes of age or with profoundly impaired consciousness. The level of consciousness, when altered, ranges from mild confusion to coma. Focal neurologic signs, seizures, and cranial nerve palsies may occur.

**B. Laboratory Findings.** Blood counts may reveal polymorphonuclear leukocytosis related to systemic infection or leukopenia reflecting immunosuppression. In associated bacteremia, the causative organism can be cultured from the blood in 40-90% of cases. X-rays of the chest, sinuses, or mastoid bones may indicate a primary site of infection. A brain CT scan may show contrast enhancement of the cerebral convexities, the base of the brain, or the ventricular ependyma. The EEG is usually diffusely slowed, and focal abnormalities suggest the possibility of focal cerebritis, abscess formation, or scarring.

While these studies are helpful in some cases, the essential investigation in all cases of suspected meningitis is prompt lumbar puncture and CSF examination. CSF pressure is elevated in about 90% of cases, and the appearance of the fluid ranges from slightly turbid to grossly purulent. CSF white cell counts of 1000-10,000/ $\mu$ L are usually seen, consisting chiefly of polymorphonuclear leukocytes, although mononuclear cells may predominate in *Listeria monocytogenes* meningitis. Protein concentrations of 100-500 mg/dL (1-5g/L) are most common. The CSF glucose level is lower than 40 mg/dL (2.2 mmol/L) in about 80% of cases; it may be immeasurably low. Gram-stained smears of CSF identify the causative organism in 70-80% of cases. CSF culture, which is positive in about 80% of cases, provides a definitive diagnosis and allows determination of antibiotic sensitivity. The polymerase chain reaction, which amplifies viral DNA, has also been used with CSF specimens to diagnose bacterial meningitis, including *H influenzae*, *N meningitidis*, and *L monocytogenes* meningitis.

**C. Differential Diagnosis.** The signs of meningeal irritation may also be seen with subarachnoid hemorrhage, but the distinction is easily made when lumbar puncture shows bloody CSF. Early viral meningitis can produce polymorphonuclear pleocytosis and symptoms identical to those of bacterial meningitis, but a repeat lumbar puncture after 6-12 hours should demonstrate a shift to lymphocytic predominance, and the CSF glucose level is normal.

### **Treatment**

Unless the physical examination shows focal neurologic abnormalities or papilledema, lumbar puncture should be performed immediately; if the CSF is not clear and colorless, antibiotic treatment (see below) is started without delay. When focal signs or papilledema are present, blood and urine should be taken for culture, antibiotics begun, and a brain CT scan obtained. If the scan shows no focal lesion that would contraindicate lumbar puncture, the puncture is then performed.

Initial antibiotic treatment of bacterial meningitis should be parenteral (EFNS, 2008). Empirical antibiotic therapy in suspected bacterial meningitis: Ceftriaxone 2 g 12–24 hourly or Cefotaxime 2 g 6–8 hourly. Alternative therapy -

Meropenem 2 g 8 hourly or Chloramphenicol 1 g 6 hourly. If penicillin or cephalosporin-resistant pneumococcus is suspected, use Ceftriaxone or Cefotaxime plus Vancomycin 60 mg/kg/24 hourly (adjusted for creatinine clearance) after loading dose of 15 mg/kg. Ampicillin/Amoxicillin 2 g 4 hourly if *Listeria* is suspected.

Pathogen specific therapy. 1) Penicillin-sensitive Pneumococcal meningitis (and including other sensitive Streptococcal species) — Benzyl Penicillin 250 000 U/kg/day (equivalent to 2.4 g 4 hourly) or Ampicillin /Amoxicillin 2 g 4 hourly or Ceftriaxone 2 g 12 hourly or Cefotaxime 2 g 6–8 hourly. Alternative therapy - Meropenem 2 g 8 hourly or Vancomycin 60 mg/kg/24 hourly as continuous infusion (adjusted for creatinine clearance) after 15 mg/kg loading dose aiming for serum levels of 15–25 mg/l) plus Rifampicin 600 mg 12 hourly or, Moxifloxacin 400 mg daily. 2) Pneumococcus with reduced susceptibility to penicillin or cephalosporins — Ceftriaxone or Cefotaxime plus Vancomycin ± Rifampicin. Alternative therapy - Moxifloxacin, Meropenem or Linezolid 600 mg combined with Rifampicin. 3) Meningococcal meningitis — Benzyl Penicillin or Ceftriaxone or Cefotaxime. Alternative therapy - Meropenem or Chloramphenicol or Moxifloxacin 4) *Haemophilus influenzae* type B — Ceftriaxone or Cefotaxime. Alternative therapy - IV Chloramphenicol–Ampicillin/Amoxicillin. 5) Listerial meningitis — Ampicillin or Amoxicillin 2 g 4 hourly ± Gentamicin 1–2 mg 8 hourly for the first 7–10 days. Alternative therapy - Trimethoprim–Sulfamethoxazole 10–20 mg/kg 6–12 hourly or Meropenem. 6) Staphylococcal species — Flucloxacillin 2 g 4 hourly or Vancomycin if penicillin allergy is suspected. Rifampicin should also be considered in addition to either agent, and Linezolid for methicillin-resistant staphylococcal meningitis. 7) Gram-negative Enterobacteriaceae — Ceftriaxone or Cefotaxime or Meropenem 8) Pseudomonal meningitis — Meropenem ± Gentamicin.

Dexamethasone at a dose of 10 mg every 6 h for 4 days should be administered both in adults and in children with or shortly before the first dose of antibiotic in suspected cases of *Streptococcus pneumoniae* and *H. Influenzae* meningitis. The rationale for using corticosteroids was that the treatment would attenuate subarachnoid space inflammation and vasogenic oedema in meningitis that may have potentially serious and damaging effects.

### **Prognosis**

Complications of bacterial meningitis include headache, seizures, hydrocephalus, inappropriate secretion of antidiuretic hormone, residual neurologic deficits (including cognitive disturbances and cranial – especially VIII – nerve abnormalities), and death. A CT scan will confirm suspected hydrocephalus. Fluid and electrolyte status should be carefully monitored in patients with meningitis. *N meningitidis* infections may be complicated by adrenal hemorrhage related to meningococemia, resulting in hypotension and often death (Waterhouse-Friderichsen syndrome).

The morbidity and mortality rates of bacterial meningitis are high. Fatalities occur in about 20% of affected adults, but fatality rates are higher with some

pathogens (eg, *S pneumoniae*, gram-negative bacilli) than others (eg, *H influenzae*, *N meningitidis*). Factors that worsen prognosis include extremes of age, delays in diagnosis and treatment, a complicating illness, stupor or coma, seizures, and focal neurologic signs.

## **TUBERCULOUS MENINGITIS**

Tuberculous meningitis is an important diagnostic consideration in patients who present with a confusional state, especially if there is a history of pulmonary tuberculosis, alcoholism, corticosteroid treatment, HIV infection, or other conditions associated with impaired immune responses. It should also be considered if patients are from areas (eg, Asia, Africa) or groups (eg, the homeless and inner-city drug users) with a high incidence of tuberculosis. Tuberculous meningitis usually results from reactivation of latent infection with *Mycobacterium tuberculosis*. Primary infection, typically acquired by inhaling bacillus-containing droplets, may be associated with metastatic dissemination of blood-borne bacilli from the lungs to the meninges and the surface of the brain. Here the organisms remain in a dormant state in tubercles that can rupture into the subarachnoid space at a later time, resulting in tuberculous meningitis.

The principal neuropathologic finding is a basal meningeal exudate containing mainly mononuclear cells. Tubercles may be seen on the meninges and surface of the brain. The ventricles may be enlarged as a result of hydrocephalus, and their surfaces may show ependymal exudate or granular ependymitis. Arteritis can result in cerebral infarction, and basal inflammation and fibrosis can compress cranial nerves.

### **Clinical Findings**

**A. Symptoms and Signs.** Symptoms have usually been present for less than 4 weeks at the time of presentation and include fever, lethargy or confusion, and headache. Weight loss, vomiting, neck stiffness, visual impairment, diplopia, focal weakness, and seizures may also be noted. A history of contact with known cases of tuberculosis is usually absent.

Fever, signs of meningeal irritation, and a confusional state are the most common findings on physical examination, but all may be absent. Papilledema, ocular palsies, and hemiparesis are sometimes seen. Complications include spinal subarachnoid block, hydrocephalus, brain edema, cranial nerve palsies, and stroke caused by vasculitis or compression of blood vessels at the base of the brain.

**B. Laboratory Findings.** Only about one-half to two-thirds of patients show a positive skin test or evidence of active or healed tubercular infection on chest x-ray. The only investigation that can establish the diagnosis is CSF analysis. CSF pressure is usually increased, and the fluid is typically clear and colorless but may form a clot upon standing. Lymphocytic and mononuclear cell pleocytosis of 50-500 cells/ $\mu$ L is most often seen, but polymorphonuclear pleocytosis can occur early and may give an erroneous impression of bacterial meningitis. CSF protein is

usually more than 100 mg/dL (1 g/L) and may exceed 500 mg/dL, particularly in patients with spinal subarachnoid block. The glucose level is usually decreased and may be less than 20 mg/dL (1.1 mmol/L). A decreased chloride level, formerly thought to be specifically associated with tuberculous meningitis, is no longer considered diagnostically useful. Acid-fast smears of CSF should be performed in all cases of suspected tuberculous meningitis, but they are positive in only a minority of cases. Definitive diagnosis is most often made by culturing *M tuberculosis* from the CSF, a process that usually takes several weeks and requires large quantities of spinal fluid for maximum yield. However, the polymerase chain reaction has also been used for diagnosis. Finally, the CT scan may show contrast enhancement of the basal cisterns and cortical meninges, or hydrocephalus.

C. Differential Diagnosis. Many other conditions can cause a subacute confusional state associated with mononuclear cell pleocytosis, including syphilitic, fungal, neoplastic, and partially treated bacterial meningitis. These can be diagnosed by appropriate smears, cultures, and serologic and cytologic examinations.

### **Treatment**

Treatment should be started as early as possible; it should not be withheld while awaiting culture results. The decision to treat is based on the CSF findings described above; lymphocytic pleocytosis and decreased glucose are particularly suggestive, even if acid-fast smears are negative. Four drugs are used for initial therapy, until culture and susceptibility test results are known. These are isoniazid, 300 mg; rifampin, 600 mg; pyrazinamide, 25 mg/kg; and ethambutol, 15 mg/kg, each given orally once daily. For susceptible strains, ethambutol can be discontinued, and triple therapy continued for 2 months, followed by 4-10 months of treatment with isoniazid and rifampin alone. Corticosteroids (eg, prednisone, 60 mg/d orally in adults or 1-3 mg/kg/d orally in children, tapered gradually over 3-4 weeks) are indicated as adjunctive therapy in patients with spinal subarachnoid block. They may also be indicated in seriously ill patients with focal neurologic signs or with increased intracranial pressure from cerebral edema. The risk of using corticosteroids may be high, however, especially if tuberculous meningitis has been mistakenly diagnosed in a patient with fungal meningitis. Therefore, if fungal meningitis has not been excluded, antifungal therapy (see below) should be added, together with corticosteroids. Pyridoxine, 50 mg/d, can be used to decrease the likelihood of isoniazid-induced polyneuropathy. Complications of therapy include hepatic dysfunction (isoniazid, rifampin, and pyrazinamide), polyneuropathy (isoniazid), optic neuritis (ethambutol), seizures (isoniazid), and ototoxicity (streptomycin).

Prognosis. Even with appropriate treatment, about one-third of patients with tuberculous meningitis succumb. Coma at the time of presentation is the most significant predictor of a poor prognosis.

## **SPIROCHETAL MENINGITIS & ENCEPHALITIS**

## Neurosyphilis

Syphilis is caused by the sexually transmitted spirochete, *Treponema pallidum*.

**A. Clinical manifestations.** Hematogenous spread of treponemes in the secondary phase of syphilis may lead to meningeal irritation or early syphilitic meningitis with cranial nerve palsies (basal meningitis). In the tertiary phase (usually one or two years after the primary infection and secondary seeding of treponemes), cerebrospinal syphilis mainly affects the mesenchymal structures (blood vessels, meninges) of the brain and, often, the spinal cord. Inflammatory changes of vascular walls, particularly in the arteries of the skull base and the middle cerebral a., cause stenoses and multiple ischemic strokes. Meningitis, mainly in the region of the skull base, presents with fluctuating headache and cranial nerve palsies. Occasionally, tertiary syphilis gives rise to polyneuropathic and polyradicular manifestations. In the rare gummous variant of tertiary syphilis, large granulomatous masses may form within the cranial cavity, producing mass effect and intracranial hypertension.

In the quaternary phase of syphilis, the inflammatory process extends into the parenchyma of the brain and spinal cord, producing tabes dorsalis (spinal cord involvement) and/or progressive paralysis (chronic meningoencephalitis). Tabes dorsalis appears in 7% of untreated syphilitics eight to 12 years after the primary infection. It is characterized, above all, by progressive degeneration of the posterior columns and posterior roots. Its clinical manifestations include progressively severe ataxia, lancinating pains, bladder dysfunction, diminished reflexes, loss of pupillary reactivity, diminished sensitivity to pain, hypotonia of the musculature, and joint deformities. Progressive paralysis appears 10–15 years after the primary infection and is caused by parenchymal meningoencephalitis with formation of caseating granulomas. Its major clinical sign is progressive dementia, with typical features including impaired judgment, lack of social inhibition, and, in some patients, expansive agitation (megalomania, nonsensical and delusional ideas). In other cases, patients may develop flattening of drive and affect, become depressed, or manifest schizophreniform phenomena (hallucinations, paranoia). The two late forms of neurosyphilis can also be present in combination.

**B. Diagnostic evaluation.** The diagnosis of neurosyphilis is established by various serologic tests: the TPHA and FTA–ABS tests for the demonstration of previous contact with *Treponema pallidum*, the VDRL test for the assessment of current disease activity (though this test is not specific for *Treponema pallidum*), and the 19-S-IgM–FTA–ABS test for the demonstration of treponeme-specific IgM antibodies, which indicate an active or florid infection. Neurosyphilis also causes an inflammatory CSF picture with elevated leukocyte count and protein concentration, a positive VDRL test in the CSF, and an elevated CSF concentration of treponeme-specific IgG.

**C. Treatment and prognosis.** All forms of neurosyphilis are treated with penicillin G; if the patient is allergic to penicillin, tetracycline or erythromycin can be given instead. The success of treatment depends on the time at which it is

begun: improvement is less likely if the brain and spinal cord parenchyma have already sustained considerable damage. The prognosis of early syphilitic meningitis is good. In the other phases of neurosyphilis, progression can be prevented by appropriate treatment, but residual deficits are common.

### **Lyme disease**

Lyme disease is a tick-borne disorder that results from systemic infection with the spirochete *Borrelia burgdorferi* (tick-borne borreliosis). The disease occurs in Europe, the northeastern and western United States, and Australia; most cases occur during the summer months.

**A. Clinical manifestations.** The early stage of infection (stage I), in which the infection is still local, is characterized by erythema chronicum migrans or, less commonly, by cutaneous erythema with lymphohistiocytic infiltration. Such skin changes are seen, however, in fewer than 25% of patients with borreliosis. The disseminated infection (stage II) makes itself known with headache, fever, musculoskeletal pain, arthralgias, and sometimes a generalized lymphadenopathy. Multifocal erythema may arise in this stage. 15% of patients with disseminated borreliosis suffer from neurologic syndromes including meningitis, cranial neuritis, radiculoneuritis, plexus neuritis, encephalitis, and combinations of these entities.

The most common form of neurologic involvement is a lymphocytic meningitis with uni- or bilateral facial palsy or radiculoneuritis. Uni- or multifocal encephalitis or vasculitis is rarer. Radiculoneuritis is typically very painful and may dominate the clinical picture. Within weeks of presentation, cardiac involvement may become evident in the form of intracardiac conduction abnormalities or, more rarely, myopericarditis with ventricular dysfunction. In the chronic, generalized stage of infection (stage III), arthralgias (60%) and cutaneous abnormalities (acrodermatitis chronica atrophicans) are typical. Late-stage neurologic abnormalities include a mild, nonspecific encephalopathy with mild memory loss and mood changes, or else leukoencephalopathy with spastic paraparesis and bladder dysfunction.

**B. Diagnostic evaluation.** Acute borreliosis is associated with a cerebrospinal fluid pleocytosis of up to 100 cells/ $\mu$ L. The cell count is lower, or even normal, in chronic borreliosis. The diagnosis is established by serological demonstration of IgG and IgM antibodies and is most reliable when seroconversion is found to have occurred over a time span of a few weeks. IgM titers are highest a few weeks after the onset of disease, IgG titers only months or years later. The presence of intrathecal antibodies is pathognomonic of neuroborreliosis. When interpreting positive findings, the diagnostician must remember that 10–15% of the normal population possesses IgG antibodies and will therefore have false-positive serology, that cross-reactions with other spirochetal diseases, such as syphilis, do occur, and that collagen-vascular diseases may also lead to falsely positive tests. If a test for serum antibody is positive, neuroborreliosis must be ruled in or out by lumbar puncture and cerebrospinal fluid serology.

**C. Treatment.** Acute neuroborreliosis are treated parenterally with ceftriaxone (2 g i.v./day), cefotaxime (2 g i.v. t.i.d.), or penicillin G (20–24million

units i.v./day) for 2weeks. Lymphocytic meningoradiculitis may also be treated with doxycycline 100mg p.o. b.i.d. for 2weeks. Chronic neuroborreliosis requires at least 3–4weeks of treatment with ceftriaxone, cefotaxime, or penicillin in the above doses. Isolated facial palsy can be treated with doxycycline 100mg p.o. b.i.d. or amoxicillin 500mg p.o. t.i.d. for 3weeks. Steroids are useful in the treatment of painful neuroborreliosis.

## **VIRAL MENINGITIS & ENCEPHALITIS**

Viral infections of the meninges (meningitis) or brain parenchyma (encephalitis) often present as acute confusional states. Children and young adults are frequently affected. Viral meningitis is most often caused by enteric viruses. Although the etiologic agent is not identified in most cases of viral encephalitis, childhood exanthems, arthropod-borne agents, and herpes simplex type 1 are the more commonly recognized causes.

**A. Pathology.** Viral infections can involve the central nervous system in three ways, through hematogenous dissemination of systemic viral infection (eg, arthropod-borne viruses); the neuronal spread of the virus (eg, herpes simplex, rabies) by axonal transport; and autoimmune responses causing postinfectious demyelination (eg, varicella, influenza).

Pathologic changes in viral meningitis consist of an inflammatory meningeal reaction mediated by lymphocytes. Encephalitis is characterized by perivascular cuffing, lymphocytic infiltration, and microglial proliferation mainly involving subcortical gray matter regions. Intranuclear or intracytoplasmic inclusions are often seen.

**B. Clinical findings.** Clinical manifestations of viral meningitis include fever, headache, neck stiffness, photophobia, pain with eye movement, and mild impairment of consciousness. Patients usually do not appear as ill as those with bacterial meningitis. Systemic viral infection may be reflected by skin rash, pharyngitis, lymphadenopathy, pleuritis, carditis, jaundice, organomegaly, diarrhea, or orchitis. Such associations often suggest a particular etiologic agent. Because viral encephalitis involves the brain directly, marked alterations of consciousness, seizures, and focal neurologic signs can occur. When signs of meningeal irritation and brain dysfunction coexist, the condition is termed meningoencephalitis.

**C. Laboratory findings.** CSF analysis is the most important laboratory investigation. CSF pressure is normal or increased, and a lymphocytic or monocytic pleocytosis is present, with cell counts usually less than 1000/ $\mu$ L. (Higher counts can be seen in lymphocytic choriomeningitis or herpes simplex encephalitis.) A polymorphonuclear pleocytosis can occur early in viral meningitis, while red blood cells may be seen with herpes simplex encephalitis. Protein is normal or slightly increased (usually 80-200 mg/dL). Glucose is usually normal; it may be decreased in mumps, herpes zoster, or herpes simplex encephalitis. Gram's stains and bacterial, fungal, and acid-fast bacillus (AFB) cultures are negative.

Oligoclonal bands and CSF protein electrophoresis abnormalities may be present. An etiologic diagnosis can often be made by virus isolation or by acute- and convalescent-phase CSF antibody titers.

Blood counts may show a normal white cell count, leukopenia, or mild leukocytosis. Atypical lymphocytes in blood smears and a positive heterophil (Monospot) test suggest infectious mononucleosis. Serum amylase is frequently elevated in mumps; abnormal liver function tests are associated with both hepatitis viruses and infectious mononucleosis. The EEG is diffusely slowed, especially if there is direct cerebral involvement; more characteristic findings can be found in encephalitis caused by herpes simplex infection.

**D. Differential diagnosis.** The differential diagnosis of meningitis with mononuclear cell pleocytosis includes partially treated bacterial meningitis as well as syphilitic, tuberculous, fungal, parasitic, neoplastic, and other meningitides. Evidence of systemic viral infection and CSF wet mounts, stained smears, cultures, and cytologic examination can distinguish among these possibilities. When presumed early viral meningitis is associated with a polymorphonuclear pleocytosis of less than 1000 white blood cells/ $\mu\text{L}$  and normal CSF glucose, one of two strategies can be used. The patient can be treated for bacterial meningitis until the results of CSF cultures are known, or treatment can be withheld and lumbar puncture repeated in 6-12 hours. If the meningitis is viral in origin, the second sample should show a mononuclear cell pleocytosis. The syndrome of viral encephalitis may clinically resemble that from metabolic disorders, but it can be distinguished by spinal fluid findings.

A disorder that may be clinically indistinguishable from viral encephalitis is the immune-mediated encephalomyelitis that may follow viral infections such as influenza, measles, or chickenpox. Progressive neurologic dysfunction typically begins a few days after the viral illness but can also occur either simultaneously or up to several weeks later. Neurologic abnormalities result from perivenous demyelination, which often severely affects the brain stem. The CSF shows a lymphocytic pleocytosis, usually with cell counts of 50-150/ $\mu\text{L}$ , and mild protein elevation.

**E. Treatment and prognosis.** Except for herpes simplex encephalitis, which is discussed separately (see below), no specific therapy for viral meningitis and encephalitis is available. Corticosteroids are of no benefit except in immune-mediated postinfectious syndromes. Headache and severe hyperthermia can be treated with acetaminophen; mild fever requires no treatment and may even contribute to the host response to the virus. Seizures usually respond to phenytoin or phenobarbital. Supportive measures in comatose patients include mechanical ventilation and intravenous or nasogastric feeding.

Symptoms of viral meningitis usually resolve spontaneously within 2 weeks regardless of the causative agent, although residual deficits may be seen. The outcome of viral encephalitis varies with the specific virus, however; eastern equine and herpes simplex virus infections are associated with severe morbidity and high mortality rates. Mortality rates as high as 20% have also been reported in immune-mediated encephalomyelitis following measles infections.

## **HERPES SIMPLEX VIRUS (HSV) ENCEPHALITIS**

Specific antiviral therapy is available for this disorder, which is the most common type of sporadic fatal encephalitis in the United States. About two-thirds of cases involve patients over 40 years of age. Primary herpes infections most often present as stomatitis (HSV type 1) or a venereally transmitted genital eruption (HSV type 2). The virus migrates along nerve axons to sensory ganglia, where it persists in a latent form – and may be subsequently reactivated. It is not clear whether HSV type 1 encephalitis, the most common type in adults, represents a primary infection or a reactivation of latent infection. Neonatal HSV encephalitis usually results from acquisition of type 2 virus during passage through the birth canal of a mother with active genital lesions. Central nervous system involvement by HSV type 2 in adults usually causes meningitis, rather than encephalitis.

**A. Pathology.** The pathologic picture of HSV type 1 encephalitis is that of an acute, necrotizing, asymmetric hemorrhagic process with lymphocytic and plasma cell reaction, which usually involves the medial temporal and inferior frontal lobes. Intranuclear inclusions may be seen in the neurons and glia. In patients who recover, the chronic state is characterized by cystic necrosis of the involved regions.

**B. Symptoms and signs.** The clinical syndrome may include headache, stiff neck, vomiting, behavioral disorders, memory loss, anosmia, aphasia, hemiparesis, and focal or generalized seizures. Active herpes labialis is seen occasionally, but its presence does not increase the likelihood that the encephalitis is due to HSV. The encephalitis is usually rapidly progressive over several days and may result in coma or death. The most common sequelae in patients who survive HSV encephalitis are memory and behavior disturbances, reflecting the predilection of the process for limbic structures.

**C. Laboratory findings.** The CSF in HSV type 1 encephalitis most often shows increased pressure, lymphocytic or mixed lymphocytic and polymorphonuclear pleocytosis (50-100 white blood cells/ $\mu$ L), mild protein elevation, and normal glucose. Red blood cells, xanthochromia, and decreased glucose are seen in some cases. The virus generally cannot be isolated from the CSF, but viral DNA has been detected by the polymerase chain reaction in some cases. The EEG may show periodic slow-wave complexes arising from one or both temporal lobes, and CT scans and MRI may show abnormalities in one or both temporal lobes. These can extend to frontal or parietal regions and are sometimes enhanced with the infusion of contrast material. It should be noted that imaging studies may also be normal. Definitive diagnosis is typically made by biopsy of affected brain areas, with the choice of biopsy site guided by the EEG, CT, or MRI findings.

**D. Differential diagnosis.** The symptoms and signs are not specific for herpes virus infection. The greatest diagnostic difficulty is distinguishing between HSV encephalitis and brain abscess. The latter is suggested by systemic bacterial

infection, a slower progression of deficits, less-marked CSF pleocytosis, a continuous polymorphic slow-wave disturbance in the EEG, and symmetric contrast enhancement of the rim of the lesion seen on CT scan. The two disorders often cannot be differentiated on clinical grounds alone, however. Final diagnoses in patients undergoing brain biopsy for suspected HSV encephalitis have included vasculitis, other viral infections, bacterial abscess, fungal infections, tumor, Reye's syndrome, parasitic infections, and tuberculosis. Because many of these conditions require specific therapy and none are favorably affected by the treatment used for HSV encephalitis, some clinicians argue that all patients with suspected HSV encephalitis should undergo brain biopsy to establish a definitive diagnosis. The most commonly accepted approach, however, is to treat patients with probable HSV encephalitis as described below and to reserve biopsies for those who fail to improve.

**E. Treatment and prognosis.** The most effective drug is acyclovir, given intravenously at a dosage of 30 mg/kg/d, divided into three daily doses, each given over 1 hour. Treatment is continued for 14-21 days. Complications reported include erythema at the intravenous infusion site, gastrointestinal disturbances, headache, skin rash, tremor, seizures, and encephalopathy or coma. Treatment is started as early as possible, since outcome is greatly influenced by the severity of dysfunction at the time treatment is initiated. Treatment is discontinued if a subsequent brain biopsy establishes another diagnosis.

Prognosis is influenced by the patient's age and level of consciousness at presentation and by the treatment. Patients under the age of 30 years and those who are only lethargic at the onset of treatment are more likely to survive than are older or comatose patients. Reported mortality rates are 44% at six months in vidarabine-treated patients and 28% at 18 months in patients given acyclovir. Acyclovir also increases the fraction of patients with no or only minor neurologic sequelae from 5% to 38%, compared with vidarabine. It is not known whether a combination of acyclovir and vidarabine has greater efficacy than either drug used alone.

## **ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)**

AIDS is a disorder caused by systemic infection with human immunodeficiency virus-1 (HIV-1) and characterized by opportunistic infections, malignant neoplasms (typically non-Hodgkin's lymphoma or Kaposi's sarcoma), and a variety of neurologic disturbances. Transmission occurs through sexual activity or by transfer of virus-contaminated blood or blood products. Individuals at particular risk of infection include homosexual and bisexual men, intravenous drug users who share needles, hemophiliacs who have received factor VIII transfusions, and the sexual partners of all the foregoing. Neurologic complications of AIDS include dementia, myelopathy, neuropathy, myopathy, and stroke. In addition, patients with AIDS are at increased risk for developing acute confusional states resulting from direct viral involvement of the nervous system, opportunistic infections, and tumors associated with AIDS.

**A. HIV-1 meningitis.** Patients infected with HIV-1 can develop a syndrome characterized by headache, fever, signs of meningeal irritation, cranial nerve (especially VII) palsies, other focal neurologic abnormalities, or seizures. This usually occurs at about the time of HIV-1 seroconversion. An acute confusional state is occasionally also present. HIV-1 meningitis is associated with mononuclear pleocytosis of up to about 200 cells/ $\mu$ L and may represent the initial immunologic response of the nervous system to HIV-1 infection. A similar CSF profile has been found in some asymptomatic patients undergoing lumbar puncture shortly after HIV-1 seroconversion. Symptoms usually resolve spontaneously within about 1 month. Other causes of pleocytosis associated with AIDS, including cryptococcal meningitis, herpes simplex encephalitis, and cerebral toxoplasmosis, must be excluded; specific treatments exist for these conditions.

**B. Cryptococcal meningitis.** It occurs in 5-10% of patients with AIDS. Clinical features include headache, confusion, stiff neck, fever, nausea and vomiting, seizures, and cranial nerve palsies. Because the CSF is otherwise normal in about 20% of patients with AIDS and cryptococcal meningitis, CSF cryptococcal antigen titers should always be obtained. Laboratory abnormalities and recommended treatment are discussed in the section on fungal meningitis.

**C. Herpes simplex and varicella-zoster encephalitis.** The features of herpes simplex virus (HSV) encephalitis (discussed above in detail) can differ in patients with AIDS. While HSV encephalitis in immunocompetent adults is almost always due to type 1 virus, either type 1 or type 2 HSV can produce the disorder in patients with AIDS. The focal neurologic signs and CSF abnormalities usually associated with HSV encephalitis may be absent in AIDS, and the disorder may follow a more indolent course. Varicella-zoster virus, a herpesvirus that rarely causes encephalitis in immunocompetent individuals, may do so in patients with AIDS. Treatment is as described above for HSV encephalitis.

**D. Cytomegalovirus encephalitis.** Cytomegalovirus, another herpesvirus, has been implicated as a cause of retinitis and polyradiculomyelitis in patients with AIDS. Cytomegalovirus can also be identified in CSF and biopsy specimens from patients with AIDS who are neurologically asymptomatic, acutely confused, or demented. In some symptomatic cases, autopsy shows microglial nodules and cytomegalovirus inclusions. Death usually occurs within a few weeks, although therapeutic responses to antiviral treatment with ganciclovir and foscarnet have been reported.

**E. Cerebral toxoplasmosis.** Cerebral toxoplasmosis produces intracerebral mass lesions in patients with AIDS, although its frequency appears to be declining as anti-toxoplasma drugs such as trimethoprim-sulfamethoxazole are widely used for prophylaxis against *Pneumocystis carinii* pneumonia in patients with AIDS. A confusional state lasting days to weeks exists at the time of presentation in about 30% of patients. Other clinical features include fever, focal neurologic abnormalities such as cranial nerve palsies or hemiparesis, seizures, headache, and signs of meningeal irritation. Serologic tests for toxoplasmosis are unreliable in patients with AIDS. CT scanning typically reveals one or more lesions, which

often show a contrast enhancement of the rim and are commonly located in the basal ganglia; MRI is more sensitive than CT in revealing the lesions. Because toxoplasmosis is readily treatable, patients with AIDS and intracerebral mass lesions that are not obviously due to stroke should be treated for presumed toxoplasmosis, as described in the section on parasitic infections (below). Up to 90% of patients respond favorably to therapy within the first few weeks and the majority survive longer than 6 months.

## FUNGAL MENINGITIS

In a small fraction of patients with systemic fungal infections (mycoses), fungi invade the central nervous system to produce meningitis or focal intraparenchymal lesions. Several of these fungi are opportunistic organisms that cause infection in patients with cancer, patients receiving corticosteroids or other immunosuppressive drugs, and other debilitated hosts. Intravenous drug abuse is a potential route for infection with *Candida* and *Aspergillus*. Diabetic acidosis is strongly correlated with rhinocerebral mucormycosis. In contrast, meningeal infections with *Coccidioides*, *Blastomyces*, and *Actinomyces* usually occur in previously healthy individuals. *Cryptococcus* (the most common cause of fungal meningitis in the United States) and *Histoplasma* infection can occur in either healthy or immunosuppressed patients. Cryptococcal meningitis is the most common fungal infection of the nervous system in AIDS, but *Coccidioides* and *Histoplasma* infections can also occur in this setting. Geographic factors are also important in the epidemiology of certain mycoses.

**A. Pathogenesis and pathology.** Organisms reach the central nervous system by hematogenous spread from the lungs, heart, gastrointestinal or genitourinary tract, or skin or by direct extension from parameningeal sites such as the orbits or paranasal sinuses. Invasion of the meninges from a contiguous focus of infection is particularly common in mucormycosis but may also occur in aspergillosis and actinomycosis. Pathologic findings in fungal infections of the nervous system include a primarily mononuclear meningeal exudative reaction, focal abscesses or granulomas in the brain or spinal epidural space, cerebral infarction related to vasculitis, and ventricular enlargement caused by communicating hydrocephalus.

**B. Clinical findings.** Fungal meningitis is usually a subacute illness that clinically resembles tuberculous meningitis. A history of such predisposing conditions as carcinoma, hematologic cancer, AIDS, diabetes, organ transplantation, treatment with corticosteroids or cytotoxic agents, prolonged antibiotic therapy, or intravenous drug use increases the suspicion of opportunistic infection. Questions should be asked about recent travel through areas where certain fungi are endemic.

Common symptoms include headache and lethargy or confusion. Nausea, vomiting, visual loss, seizures, or focal weakness may be noted, while fever may be absent. In a diabetic patient with acidosis, complaints of facial or eye pain, nasal

discharge, proptosis, or visual loss should urgently alert the physician to the likelihood of *Mucor* infection.

Careful examination of the skin, orbits, sinuses, and chest may reveal evidence of systemic fungal infection. Neurologic examination may show signs of meningeal irritation, a confusional state, papilledema, visual loss, ptosis, exophthalmos, ocular or other cranial nerve palsies, and focal neurologic abnormalities such as hemiparesis. Because some fungi (most commonly *Cryptococcus*) can cause spinal cord compression, there may be evidence of spine tenderness, paraparesis, pyramidal signs in the legs, and loss of sensation over the legs and trunk.

Fungal meningitis may mimic brain abscess and other subacute or chronic meningitides, such as those due to tuberculosis or syphilis. CSF findings and contrast CT scans are useful in differential diagnosis.

**C. Laboratory findings.** Blood cultures should be obtained. Serum glucose and arterial blood gas levels should be determined in diabetic patients. The urine should be examined for *Candida*. Chest x-ray may show hilar lymphadenopathy, patchy or miliary infiltrates, cavitation, or pleural effusion. The CT scan or MRI may demonstrate intracerebral mass lesions associated with *Cryptococcus* or other organisms, a contiguous infectious source in the orbit or paranasal sinuses, or hydrocephalus.

CSF pressure may be normal or elevated, and the fluid is usually clear. It may be viscous in the presence of numerous cryptococci, but the presence of alcohol (once considered indicative of cryptococcal infection) is not a reliable finding. Lymphocytic pleocytosis of up to 1000 cells/ $\mu$ L is common, but a normal cell count or polymorphonuclear pleocytosis can be seen in early fungal meningitis and normal cell counts are common in immunosuppressed patients. *Aspergillus* infection typically produces a polymorphonuclear pleocytosis. CSF protein, which may be normal initially, subsequently rises, usually to levels not exceeding 200 mg/dL. Higher levels ( $<1$  g/dL) suggest possible subarachnoid block. Glucose is normal or decreased but rarely below 10 mg/dL. Microscopic examination of Gram-stained and acid-fast smears and India ink preparations may reveal the infecting organism. Fungal cultures of CSF and other body fluids and tissues should be obtained, but they are often negative. In suspected mucormycosis, biopsy of the affected tissue (usually nasal mucosa) is essential. Useful CSF serologic studies include cryptococcal antigen and *Coccidioides* complement-fixing antibody. Cryptococcal antigen is more sensitive than India ink for detecting *Cryptococcus*, and should always be looked for in both CSF and serum when that organism is suspected (in patients with AIDS, for example).

**D. Treatment and prognosis.** For most organisms causing fungal meningitis, treatment is begun with amphotericin B deoxycholate, 1 mg intravenously as a test dose given over 20-30 minutes, followed the next day by 0.3 mg/kg intravenously in 5% dextrose, given over 2-3 hours. The dose is then increased daily in 5- to 10-mg increments until a maximal dose of 0.5-1.5 mg/kg/d is reached. Treatment is usually continued for 12 weeks. Nephrotoxicity is common with amphotericin B and may force interruption of therapy for 2-5 days. Newer, lipid-based

formulations (eg, amphotericin B lipid complex, amphotericin B cholesteryl sulfate, liposomal amphotericin B) are less nephrotoxic, and can be used in patients who develop such toxicity on amphotericin B deoxycholate.

In patients with *Coccidioides* meningitis or those not responding to intravenous therapy, intrathecal amphotericin B (usually administered via an Ommaya reservoir) is added. The drug is given as a 0.1-mg test dose diluted in 10 mL of CSF, with or without added corticosteroids, and increased to 0.25-0.5 mg every other day. Because administration of amphotericin into the CSF may produce side effects, may require instillation at multiple sites, and may be unsuccessful, another approach is to give fluconazole, 400-600 mg/d, or itraconazole, 200 mg twice daily with meals, by the oral route. In this case, treatment must be continued indefinitely.

In cryptococcal meningitis, flucytosine, 100 mg/kg/d orally, added to amphotericin B and given in four divided doses, reduces the duration of therapy from 12 to 6 weeks. The dose of flucytosine must be reduced in renal failure; the major side effect is bone marrow suppression, which is usually reversible. Because of this toxicity, flucytosine is usually omitted when treating cryptococcal meningitis in patients with AIDS. For patients with AIDS and cryptococcal meningitis who do not respond to amphotericin B alone, fluconazole can be added at an initial dose of 400 mg, followed by 200 mg/d, orally or intravenously, for at least 10-12 weeks after CSF cultures are negative. Long-term maintenance therapy with fluconazole, 100-200 mg/d orally, may also reduce the likelihood of recurrence following successful treatment of cryptococcal meningitis in patients with AIDS.

Rapid correction of hyperglycemia and acidosis must be combined with amphotericin B treatment and surgical debridement of necrotic tissue in diabetics with mucormycosis. Mortality rates remain high in fungal meningitis. The complications of therapy are frequent, and neurologic residua are common.

## PARASITIC INFECTIONS

Protozoal and helminthic infections are important causes of central nervous system disease, particularly in immunosuppressed patients (including those with AIDS), and in certain regions of the world. Rickettsias, the parasitic bacteria that cause Rocky Mountain spotted fever, rarely affect the nervous system.

### **Malaria**

Malaria is caused by the protozoan *Plasmodium falciparum* or another *Plasmodium* species that is transferred to humans by the female *Anopheles* mosquito. Clinical features include fever, chills, myalgia, nausea and vomiting, anemia, renal failure, hypoglycemia, and pulmonary edema. Although malaria is, worldwide, the most common parasitic infection of humans, cerebral involvement is rare. Plasmodia reach the central nervous system in infected red blood cells and cause occlusion of cerebral capillaries. Neurologic involvement becomes apparent

weeks after infection. In addition to acute confusional states, cerebral malaria can produce seizures and, rarely, focal neurologic abnormalities. The diagnosis is made by finding plasmodia in red blood cells of peripheral blood smears. The CSF may show increased pressure, xanthochromia, mononuclear pleocytosis, or mildly elevated protein.

Malaria prophylaxis is recommended for travelers to areas where the disease is endemic and consists of chloroquine phosphate, 500 mg orally, weekly. If exposure to chloroquine-resistant strains is expected, mefloquine (250 mg orally weekly for 4 weeks, then every other week for 4 weeks) should be given instead. Both regimens are started one week before the initial exposure and continued for 4 weeks after exposure ends.

Chloroquine-sensitive cerebral malaria is treated with chloroquine, 10 mg base/kg by continuous intravenous infusion over 8 hours followed by 15 mg base/kg over 24 hours, or 3.5 mg base/kg by the intramuscular or subcutaneous route every 6 hours to a cumulative dose of ~25 mg base/kg. Chloroquine-resistant cerebral malaria is treated with quinidine, 10 mg base/kg by intravenous infusion over 1 hour followed by 0.02 mg base/kg/min, or with quinine dihydrochloride, 20 mg/kg by intravenous infusion over 4 hours followed by 10 mg/kg infused over 2-8 hours every 8 hours. Each of these regimens is continued until oral therapy with chloroquine, amodiaquine, or sulfadoxine and pyrimethamine (for chloroquine-sensitive malaria) or with mefloquine, quinine, or quinidine (for chloroquine-resistant malaria) can be substituted. Cerebral edema is not a consistent finding in cerebral malaria, and corticosteroids are not helpful and may, in fact, be deleterious. The mortality rate in cerebral malaria is 20-50% and reaches 80% in cases complicated by coma and seizures.

### **Toxoplasmosis**

Acquired (as opposed to congenital) toxoplasmosis results from ingestion of *Toxoplasma gondii* cysts in raw meat or cat excrement and is usually asymptomatic. Symptomatic infection is associated with underlying malignant disease (especially Hodgkin's disease), immunosuppressive therapy, or AIDS. Systemic manifestations include skin rash, lymphadenopathy, myalgias, arthralgias, carditis, pneumonitis, and splenomegaly. Central nervous system involvement can take several forms.

**Clinical findings.** The CSF may be normal, or it may show mild mononuclear cell pleocytosis or slight protein elevation. A CT scan may show one or more ring-enhancing lesions, especially if a double dose of contrast material is used. Lesions revealed by CT scan may fail to enhance, however, and autopsy-proved lesions may not be detected by CT. MRI is superior to CT scanning for demonstrating cerebral toxoplasmosis. The diagnosis is made by blood tests demonstrating a high ( $\geq 1:32,000$ ) or rising Sabin-Feldman dye test titer or IgM antibodies to *Toxoplasma* by indirect immunofluorescence techniques. Accurate diagnosis requires appropriate serologic studies in the immunosuppressed patient who develops neurologic symptoms.

Treatment is with pyrimethamine, 25-100 mg/d orally and sulfadiazine, 1-1.5 g orally four times daily, and is continued for 3-4 weeks in immunocompetent patients and for at least several months in patients with AIDS or other immunodeficiency states. Clindamycin, 600 mg orally four times a day, may be substituted for sulfonamides in patients who develop drug sensitivity rashes. Folinic acid (leucovorin), 10 mg orally daily, is added to prevent pyrimethamine-induced leukopenia and thrombocytopenia.

### **Primary amebic meningoencephalitis**

The free-living ameba *Naegleria fowleri* causes primary amebic meningoencephalitis in previously healthy young patients exposed to polluted water. Amebas gain entry to the central nervous system through the cribriform plate, producing a diffuse meningoencephalitis that affects the base of the frontal lobes and posterior fossa. It is characterized by headache, fever, nausea and vomiting, signs of meningeal irritation, and disordered mental status. Seizures and focal neurologic signs are rare. The CSF shows a polymorphonuclear pleocytosis with elevated protein and low glucose; highly motile, refractile trophozoites can be seen on wet mounts of centrifuged CSF. The disease is usually fatal within 1 week, although treatment with amphotericin B, 1 mg/kg/d intravenously, may be effective, as may a combination of amphotericin B, rifampin, and chloramphenicol or ketoconazole.

### **Granulomatous amebic encephalitis**

Granulomatous amebic encephalitis results from infection with the *Acanthamoeba/Hartmanella* species and commonly occurs in the setting of chronic illness or immunosuppression. The disorder typically lasts for periods from 1 week to 2 or 3 months and is characterized by subacute or chronic meningitis and granulomatous encephalitis. The cerebellum, brain stem, basal ganglia, and cerebral hemispheres are affected. An acute confusional state is the most common clinical finding. Although fever, headache, and meningeal signs are less common than in primary amebic meningoencephalitis (each occurring in only about half of patients), seizures and hemiparesis are more common. Cranial nerve palsies, cerebellar ataxia, and aphasia may occur. Pleocytosis may be primarily lymphocytic or polymorphonuclear; protein is elevated, and glucose is low or normal. Sluggishly motile trophozoites may be seen on wet mounts. Successful treatment has not been reported.

### **Cysticercosis**

Cysticercosis is common in Mexico, Central and South America, and certain regions of Africa, Asia, and Europe. Is caused by the pork tapeworm (cestode), *Taenia solium*. Man is the only known definitive host for the adult form of the organism (the tapeworm itself, which resides in the intestine). Man may also be infected as an intermediate host, harboring the larvae of the organism in skeletal muscle and in the brain (cerebral cysticercosis).

The commonest intermediate hosts are domestic animals such as pigs, dogs, cats, and sheep. When a human being eats the flesh of an infected animal that contains larvae, an intestinal infection with the adult tapeworm results. The worm produces eggs, which then develop into embryos; the latter penetrate the intestinal wall and spread through the bloodstream to the distant soft tissues, including the brain, where they mature further to larvae (cysticerci).

The cysticerci may be several millimeters to 2 cm in size. Their clinical manifestations are a function of their size, number, localization, and stage of development, together with the reaction of the surrounding cerebral tissue. They most commonly cause epileptic seizures, headache, papilledema, and vomiting, and more rarely hydrocephalus, meningitis, or spinal cord involvement (myelopathy).

Peripheral blood eosinophilia, soft tissue calcifications on x-ray, or the presence of parasites in the stool suggests the diagnosis. The CSF typically shows a lymphocytic pleocytosis ( $< 100$  cells/ $\mu\text{L}$ ), with eosinophils usually but not always present. Opening pressure is often increased but may be decreased with spinal subarachnoid block. Protein is increased to 50-100 mg/dL, and glucose is 20-50 mg/dL in most cases. Complement fixation and hemagglutination studies can assist in the diagnosis. The CT scan may show contrast-enhanced mass lesions with surrounding edema, intracerebral calcifications, or ventricular enlargement. Myelography should be performed in suspected spinal subarachnoid block.

The indications for treatment of cerebral cysticercosis are controversial. However, patients with symptomatic neurologic involvement (usually seizures) and either meningitis or one or more noncalcified intraparenchymal cysts should be treated. Intraventricular, subarachnoid, and racemose cysts respond poorly to treatment, and calcified cysts do not require treatment. Albendazole, 15 mg/kg/d in three doses taken with meals, and continued for 8 days, is the preferred therapy. Praziquantel, 50 mg/kg/d in three divided doses, can also be used, but blood levels are reduced by anticonvulsants and corticosteroids, which are often also required in these patients. Patients with seizures should also receive anticonvulsants. Corticosteroids are indicated for increased intracranial pressure or lesions near the cerebral aqueduct or intraventricular foramina; these may progress to cause obstructive hydrocephalus. Single accessible intraparenchymal lesions can be removed surgically, and shunting is required for intraventricular lesions causing hydrocephalus.

### **Angiostrongylus cantonensis meningitis**

*Angiostrongylus cantonensis* is endemic to Southeast Asia and to Hawaii and other Pacific islands. Infection is transmitted by ingestion of infected raw mollusks and produces meningitis with CSF eosinophilia. Most patients complain of headache, and about half report stiff neck, vomiting, fever, and paresthesias. Most patients have a CSF leukocytosis of 150-1500/ $\mu\text{L}$ , mild elevation of protein, and normal glucose. The acute illness usually resolves spontaneously in 1-2 weeks, although paresthesias may persist longer. Levamisole, albendazole, thiabendazole, mebendazole, and ivermectin have been used for treatment, and mebendazole 100

mg twice daily orally for 5 days may be preferred. Analgesics, corticosteroids, and reduction of CSF pressure by repeated lumbar punctures may be of value.

### **Rocky Mountain spotted fever**

Rocky Mountain spotted fever is caused by *Rickettsia rickettsii*, an intracellular parasite transmitted to humans by tick bites. *R. rickettsii* damages endothelial cells, leading to vasculitis, microinfarcts, and petechial hemorrhage. Initial symptoms include fever, headache, and a characteristic rash that involves the palms and soles and spreads centrally. Neurologic involvement, which is uncommon, produces a confusional state and, less often, coma or focal neurologic abnormalities. The CSF is normal or shows a mild mononuclear pleocytosis. Treatment is with chloramphenicol, 25-50 mg/kg/d orally or intravenously in four divided doses, or doxycycline, 200 mg/d orally or intravenously, and is continued for 7 days. Neurologic residua may occur.