OVERVIEW OF ACUTE AND CHRONIC MENINGITIS

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DEFINITION

Meningitis is defined as inflammation of the meninges, the two membranes (pia and arachnoid mater) that surround the brain and spinal cord to form the subarachnoid space. This space is filled by cerebrospinal fluid (CSF). A hallmark of meningitis is the spillover of cells into the CSF to produce an increased cell count. Meningitis is the major infectious syndrome of the central nervous system (CNS). Meningitis can also be produced by several noninfectious causes. Sometimes involvement is more widespread than just the meninges. When meningitis is accompanied by obvious parenchymal involvement, it is more properly referred to as meningoencephalitis, meningomyelitis, or meningoencephalomyelitis. When there is nerve-root involvement it is a meningoradiculitis.

As is true of all the CNS infections, meningitis may produce significant morbidity and mortality. Several factors contribute to the severity of CNS infection. The CNS is a sequestered organ that is confined anatomically within a bony casement. There is little room for expansion during a localized inflammatory response without risking damage to intrinsic structures or even a herniation syndrome. Because the CNS lacks a fully developed and operational immune system to defend against invading pathogens, infection is harder to eradicate. It is also more difficult to deliver adequate concentrations of antimicrobials to the CNS. Because critical tissues are involved, meningitis produces unique sequelae with potentially devastating consequences. In some cases it is a true neurologic and medical emergency.

Meningitis is a syndrome with a wide spectrum. It can take several different forms. Each form has potential causes and a unique management strategy. An

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organized and logical approach to meningitis can optimize diagnosis and treatment and can minimize morbidity and mortality.

CLASSIFICATION

Meningitis can be divided based on time course, associated CSF profile, and underlying cause (Table 1). In acute meningitis, onset occurs within hours to days. There are two distinct types of meningitis. Aseptic meningitis implies that there is no obvious infectious cause after an initial evaluation for bacteria. Screening cultures and stains must be negative.[54] In cases in which an origin is ultimately established, the usual cause is a virus. Although bacteria are ultimately identified in some aseptic meningitis patients, they are not the agents that cause fulminant septic disease. In contrast, septic meningitis is always caused by bacterial infection. The CSF profiles of aseptic and septic meningitis are different. It is important to distinguish aseptic from septic meningitis because they have different management strategies and prognoses.

Acute meningitis is typically an isolated event that does not recur. In contrast, recurrent meningitis involves at least two and often multiple episodes of acute meningitis. To make a diagnosis of recurrent meningitis, however, the patient must return to normal between attacks. This requires not only that someone is clinically asymptomatic but also that CSF parameters are normal.

Chronic meningitis is arbitrarily defined as meningitis that persists for 4 or more weeks.[2,21] It is important to document that patients are not in a slow recovery phase; this distinguishes them from resolving acute meningitis cases.

EPIDEMIOLOGY

Of all the forms of meningitis, acute aseptic meningitis is the most common. In the United States, approximately 10,000 cases are reported each year.[11] This is probably a gross underestimation, because epidemiologic data suggest that there are more than 75,000 cases a year.[40] The incidence in Olmsted County, Minnesota

Table 1. CLASSIFICATION OF THE MENINGITIS SYNDROME

Type	Time Course	CSF	Origin
Aseptic	Acute episode, <4 wk duration	• Mild to moderate mononuclear pleiocytosis • Normal glucose	• Infectious (predominantly viral) • Noninfectious
Septic	Acute episode <4 wk duration	• Moderate to significant polymorphonuclear pleiocytosis • Low glucose	• Infectious (bacterial)
Recurrent	Multiple acute episodes, <4 wk duration	• Mild to significant mixed pleiocytosis • Variable glucose	• Infectious • Noninfectious
Chronic	Chronic episode, ≥4 wk duration	• Mild to moderate mononuclear pleiocytosis • Low glucose	• Infectious (predominantly mycobacterial, fungal) • Noninfectious

and Helsinki, Finland is reported at 10.9 to 26 per 100,000 persons per year.[5,31,35] Most aseptic meningitis cases are children who present during the summer months.[41]

In the past, septic meningitis cases in the United States ranged from 10,000 to 20,000 a year.[56] Immunocompetent children younger than age 5 were predominantly affected. *Hemophilus influenzae* was responsible for almost half of all meningitis cases and for more than 70% of infections in children younger than age 5.[44,56] The epidemiology of septic meningitis changed drastically after widespread use of conjugate vaccines for *H. influenzae*. Meningitis caused by this agent has decreased by 94%.[45] In 1986 there were a total of 12,960 septic meningitis cases in the United States. By 1995 this number had dropped by 55% down to 5755 cases a year. The median age of the typical meningitis patient over this same period rose from 15 months in the prevaccine era to 25 years in the postvaccine era. In the United States, septic meningitis shows a racial predisposition. Infection with the major bacterial pathogens (*Streptococcus pneumoniae, Neisseria meningitidis,* group B streptococcus) are significantly increased in African Americans; risks relative to non-African Americans range from 2.1 to 2.6.[45] There is also epidemiologic evidence that an increasing proportion of adult meningitis is caused by nosocomial rather than community-acquired infection. A recent review of 493 cases at a Massachusetts hospital noted that nosocomial infection accounted for 28% of all cases from 1980 through 1988.[15] Gram-negative bacilli accounted for 39% of nosocomial infections, compared with only 3% of community-acquired infections. During the 1960s gram negatives accounted for only 11% of all meningitis cases. By the 1980s this had increased to 24%. Risk factors for nosocomial infection include recent neurosurgery, indwelling neurosurgical device, or altered immune status.

Recurrent meningitis is the least common form of meningitis with limited epidemiologic data; generalizations are not possible. Most recurrent meningitis patients are immunocompetent, although a significant minority have underlying immune deficits.

Chronic meningitis is also very uncommon and accounts for less than 10% of all meningitis cases (incidence and outbreaks).[2] It has the widest spectrum of causes and occurs in both immunocompetent and immunocompromised individuals.

ORIGIN

The different types of meningitis have distinct origins. Overall, most cases are caused by infection, and the most likely pathogens are quite predictable. This is an important observation because it helps to guide empiric therapy. It also has important implications for the community. Examples are the early identification of a sentinel case that predicts a potential epidemic or the identification of an agent that necessitates exposure prophylaxis. By definition, all cases of septic meningitis are caused by bacteria. In contrast, aseptic, recurrent, and chronic meningitis can be caused by many different pathogens as well as by noninfectious causes. When considering the origin of meningitis, it is useful to think in terms of infectious versus noninfectious causes and then to divide infectious causes by the type of pathogen.

Aseptic Meningitis

Although this syndrome has many causes, it is most often caused by viral infection[25]:

I. Infectious: Direct
   A. Viruses
      1. Enteroviruses
      2. Arboviruses
      3. Herpes viruses (Herpes simplex virus type 2 [HSV-2] > HSV-6 > HSV-1, varicella zoster virus, cytomegalovirus, Epstein–Barr virus)
      4. Mumps
      5. Lymphocytic choriomeningitis virus
      6. Human immunodeficiency virus type 1 (HIV-1)
      7. Miscellaneous (influenza, parainfluenza, measles, rotavirus, coronavirus, encephalomyocarditis virus, parvovirus)
   B. Bacteria
      1. Spirochetes
         a. *B. burgdorferi* (Lyme disease)
         b. *T. pallidum* (Syphilis)
         c. *Leptospira* species (Leptospirosis)
         d. *Borrelia* species (Relapsing Fever)
      2. Partially treated bacterial meningitis
      3. *Bartonella* species
      4. *Brucella* species
      5. *M. tuberculosis*
      6. *Chlamydia pneumoniae*
   C. Parasites
      1. Primary amoebic meningoencephalitis
      2. *Toxoplasma gondii*
   D. *Rickettsiae/Ehrlichiae*
   E. Mycoplasma
II. Infectious: Indirect
   A. Endocarditis
   B. Parameningeal infection
III. Noninfectious
   A. Autoimmune disease
   B. Behçet disease
   C. Drug induced
   D. Malignancy
   E. Mucocutaneous lymph node syndrome (Kawasaki disease)
   F. Vogt–Koyanagi–Harada disease

Enteroviruses (echovirus, coxsackie A and B viruses, polioviruses, and the numbered enteroviruses) are the major pathogens. They are responsible for at least 55% to 70% of all aseptic meningitis cases[6, 40] and for 85% to 95% of cases for which a pathogen is ultimately identified.[41]

Other viruses account for only a small proportion of aseptic meningitis cases. Arboviruses, which are transmitted by arthropod vectors, generally cause encephalitis. However, St. Louis encephalitis virus, California encephalitis virus, and the virus of Colorado tick fever also cause meningitis. Approximately 15% of St. Louis encephalitis infections result in meningitis.[41] This is especially true for children, in whom as much as 60% develop meningitis. Three California encephalitis

viruses (La Crosse, Jamestown Canyon, Snowshoe Hare) cause meningitis. The agent of Colorado tick fever, which infects *Dermacentor andersoni* ticks, is geographically restricted to western mountainous regions. The virus infects host red blood cells and can persist within these cells for weeks after clinical recovery.

Mumps was once the leading single pathogen responsible for aseptic meningitis, but the incidence of infection in the developed world rapidly declined after institution of the attenuated live virus vaccine. Nonetheless, worldwide, mumps remains an important cause of viral meningitis. Occult meningitis occurs in more than half of mumps parotitis cases[4] and is symptomatic in as much as 30%. Meningitis can also occur without parotitis.[3,27] Mumps meningitis is more common in males, with a male:female ratio of 3:1. Patients tend to be older than enteroviral meningitis patients and tend to cluster in winter and spring months. Lymphocytic choriomeningitis virus is a very rare cause of meningitis. This virus is transmitted by rodents (rats, mice, hamsters), and cases tend to present during winter months. Approximately 15% of clinical infections manifest as meningitis.[14,55]

Many herpes viruses are very rare causes of meningitis. The one exception is HSV, which accounts for 1% to 3% of all aseptic meningitis cases.[41] There are two types of HSV: type 1 (oral HSV) and type 2 (genital HSV). In particular, HSV type 2 (HSV-2) produces meningitis in 11% to 33% of people at the time of primary genital infection.[12] Human immunodeficiency virus (HIV) also causes aseptic meningitis, most commonly at the time of primary infection and seroconversion but also early in the course of HIV infection.[8,22]

Nonviral pathogens of aseptic meningitis include bacteria, parasites, rickettsiae, and mycoplasma.[25,52] These agents are not detected by Gram stain and are either difficult to culture or take weeks to culture. Although *Mycobacterium tuberculosis* typically causes chronic meningitis, on rare occasion it has been associated with a self-limited aseptic process.[16] Nonviral pathogens can also produce aseptic meningitis through indirect mechanisms (endocarditis, parameningeal infection). Finally, several noninfectious disorders can produce aseptic meningitis.[9,26,41] Many also produce recurrent meningitis.

Septic Meningitis

All cases of septic meningitis are caused by bacterial agents. In the post *H. influenzae* conjugate vaccine era, the most common causes of septic meningitis in the United States are *S. pneumoniae* (47%) and *N. meningitidis* (25%), followed by group B streptococcus (12%), *Listeria monocytogenes* (8%), and *H. influenzae* (7%).[45] The agents vary based on age of the host (Table 2). In general, children and young adults are most likely to be infected with *N. meningitidis*, whereas older adults are infected with *S. pneumoniae*. There are often other useful clues to suggest specific pathogens. Staphylococcal infection is seen with indwelling catheters, shunts, endocarditis, and head trauma and after neurosurgery. *Proteus* species, *Pseudomonas, Serratia,* and *Flavobacterium* may be pathogens when a patient is on an assisted ventilation device. *L. monocytogenes* infection occurs in association with diabetes, ethanol abuse, old age, and immunocompromise. Anaerobes may cause meningitis in the setting of ruptured brain abscess. Gram-negative bacterial infection occurs with head trauma and after neurosurgery, sepsis, immunocompromise, ruptured brain abscess, and systemic infection with the parasite *strongyloides. S. pneumoniae* infection, although the major pathogen overall, is particularly likely with pneumonia, sickle cell disease, cirrhosis, and myeloma.

Table 2. CAUSES OF THE SEPTIC MENINGITIS SYNDROME

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Recurrent Meningitis

Both infectious and noninfectious processes can cause recurrent meningitis[19,42]:

Anatomic defects (recurrent bacterial infection)
    Congenital
    Postoperative
    Traumatic
Autoimmune disease
Behçet disease
Chemical meningitis
    Endogenous (cyst, tumor)
    Exogenous (dye, drug)
Drug-induced hypersensitivity
Familial Mediterranean fever
Idiopathic (Mollaret's)
    HSV
    Other causes
Immune defects (recurrent bacterial infection)
    Antibody deficiency
    Complement deficiency
    Splenectomy
Migraine with pleocytosis
Parameningeal infection with seeding

Recurrent bacterial-viral infections
Sarcoidosis
Vogt–Koyanagi–Harada disease
Whipple's disease

On rare occasions drugs can trigger meningitis, which resolves once the provoking agent is removed. This is more likely to occur in patients who have a systemic autoimmune disease. Drugs that produce meningitis include antibody preparations (intravenous immunoglobulin, monoclonal antibody infusions), nonsteroidal anti-inflammatory agents (ibuprofen, naproxen, sulindac, tolmetin), antibiotics (ciprofloxacin, isoniazid, metronidazole, penicillin, phenazopyridine, sulfonamides, trimethoprim), carbamazepine, azathioprine, and cytosine arabinoside. Among infectious causes, viruses are the most likely pathogens to cause recurrent meningitis. Mollaret's meningitis is a rare cause of recurrent aseptic meningitis. A suggestive feature is the transient appearance of large fragile cells in the CSF that resemble endothelial cells but that are probably monocytes.[24] Based mainly on polymerase chain reaction (PCR) data, HSV-2 has been implicated in Mollaret's meningitis and in recurrent lymphocytic meningitis that does not meet the diagnostic criteria for Mollaret's meningitis.[53,57] Rare cases of Mollaret's meningitis have been associated with HSV-1 and Epstein–Barr virus.[20,50] In addition to herpes viruses, this idiopathic syndrome has been described with neuroepithelial or dermoid cysts and with immune, particularly complement, defects.[7,29]

Chronic Meningitis

Many infectious and noninfectious processes can result in the chronic meningitis syndrome:

I. Infectious
  A. Bacterial
    1. Mycobacterial (*M. tuberculosis, M. avium*)
    2. Spirochetal (*Borrelia burgdorferi, Leptospira interrogans, Treponema pallidum*)
    3. Agents causing sinus tracts (*Actinomycetes, Arachnia, Nocardia*)
    4. *Brucella*
    5. *Tropheryma whippelii*
    6. *L. monocytogenes*
    7. *N. meningitidis*
    8. *Francisella tularensis*
  B. Fungal
    1. *Cryptococcus neoformans*
    2. *Coccidioides immitis*
    3. *Histoplasma capsulatum*
    4. *Candida* sp
    5. Other mycoses (*Aspergillus, Blastomyces, Dematiaceous* sp, *Paracoccidioides, Pseudoallescheria, Sporothrix, Trichosporon beigelii, Zygomycetes*)
  C. Parasitic
    1. *Taenia solium* (cysticercosis)
    2. *Acanthamoeba* (granulomatous amebic meningoencephalitis)
    3. *Angiostrongylus* (eosinophilic meningitis)
    4. *Toxoplasma gondii*

      5. *Coenuris cerebralis*
      6. *Schistosoma* sp
  D. Viral
      1. Retroviruses (HIV-1; HTLV-1, human T-cell lymphotrophic virus type 1)
      2. Enteroviruses (in the setting of hypogammaglobulinemia)
      3. Herpesvirus
II. Noninfectious
  A. Neoplastic
  B. Neurosarcoidosis
  C. Vasculitis
  D. Behçet's disease
  E. Chemical meningitis
      1. Endogenous
      2. Exogenous
  F. Fabry's disease
  G. Hypertrophic pachymeningitis
  H. Systemic lupus erythematosus
  I. Uveomeningoencephalitides
      1. Vogt–Koyanagi–Harada disease
      2. Sympathetic ophthalmia
III. Idiopathic
  A. Chronic benign lymphocytic meningitis

The major infectious causes are tuberculous (TB) meningitis and cryptococcal meningitis. Other fungal agents are rare causes, particularly in immunocompromised hosts. The major noninfectious causes are neoplastic disease, neurosarcoidosis, and vasculitis.

CLINICAL FEATURES

The hallmark clinical triad of meningitis is fever, headache, and stiff neck (meningismus). Headache, which may be quite severe, is often frontal or retroorbital. This classic triad may be accompanied by photophobia, nausea, vomiting, drowsiness, and generalized malaise. Significant fever suggests an infectious cause, and severe symptoms suggest bacterial rather than viral origin. Particularly with bacterial infection, there may be changes in mental status, irritability, or even seizures and focal deficits. Clinical features are more severe in the acute forms of meningitis, whereas chronic meningitis features may be subtle.

Aseptic Meningitis

Aseptic meningitis is a benign process with virtually no morbidity or mortality. Enteroviral meningitis is the most common form of aseptic meningitis. The typical patient is a young child who becomes ill during summertime. Other family members report a recent viral syndrome, and the meningitis patient may have experienced biphasic illness, with a preceding constitutional syndrome. The onset of meningitis is typically abrupt with high fever (38° to 10°C [100.4° to 104°F]) and severe headache. Patients may have nausea, vomiting, pharyngitis, diarrhea, meningismus, and photophobia. Parenchymal neurologic abnormalities occur in 5%

or less of cases. Suggestive features such as associated respiratory tract syndrome, rash (particularly with echovirus 9), or hand-foot-mouth syndrome (with enterovirus 71) strengthen the likelihood of diagnosis.[18,23,48] Recovery is typically rapid over a week, with no detectable morbidity and mortality. As opposed to children, adults may be ill for several weeks. The only exception to this benign pattern is perinatal infection, in which there is often a more severe encephalitic component.

Septic Meningitis

Septic meningitis is a neurologic emergency. The overall mortality rate of acute bacterial meningitis is 25%, with morbidity rates as much as 60%.[36] The classic features of septic meningitis are acute onset of fever, headache, and meningismus. Patients may be very ill and, at the most severe end of the spectrum, may lapse into stupor or coma within hours. Clinical features may differ based on the age of the host. The typical adult patient often presents in the setting of an acute respiratory tract infection. Neonates often appear septic rather than displaying obvious features of CNS involvement.[46] They show fever, gastrointestinal disturbances, respiratory problems, and lethargy, but meningismus is very unusual. At the other extreme, the elderly are more likely to show prominent mental status changes.[39] They have fever associated with confusion, stupor, or coma. Again, classic headache and meningismus may not be prominent.

Recurrent Meningitis

Most cases of recurrent meningitis resemble aseptic rather than septic meningitis, and there are no distinguishing clinical characteristics. Patients do not look as sick as those who have acute bacterial meningitis.

Chronic Meningitis

There are no pathognomic clinical features of chronic meningitis. Fever, headache, and meningismus may be extremely subtle and variable; any one feature may be absent. Signs of parenchymal involvement, such as mental status changes, seizures, or focal deficits, may be present to varying degrees. Unusual presentations include psychoses, movement disorders, and even a Parkinsonian syndrome. Chronic meningitis can slowly worsen, fluctuate, or remain static. Ultimately, many cases with no obvious cause remit. Their average duration of symptoms ranges from 17 to 43 months.[47]

DIAGNOSTIC APPROACH

Empiric therapy is often started before a definite diagnosis is made. The diagnostic goals are to confirm a meningitis, determine whether the origin is infectious, and decide on the most likely organism. CSF evaluation is critical for diagnosis in all the forms of meningitis. Other tests (blood tests, extraneural cultures, skin tests, neuroimaging, biopsy) may be indicated based on the type of meningitis and possible origins. Neuroimaging, for example, is important for investigating recurrent and chronic meningitis, but it generally is not helpful in establishing the cause of acute meningitis. In this setting it is most often used to determine the

safety of lumbar puncture. When a differential diagnosis is being considered, the various types of meningitis must be distinguished not only from each other but also from encephalitis. This is important because the causes are distinct.

Molecular techniques are providing major diagnostic advances. For example, for rapid and sensitive detection of organism nucleic acid to be made, PCR is being applied to infections for which it is difficult or even impossible to detect organisms.

Aseptic Meningitis

The classic CSF profile of aseptic meningitis is a mild to moderate mononuclear pleocytosis, with normal or minimally decreased glucose concentration. Protein concentration is normal or is mildly increased. Occasionally, there is an initial polymorphonuclear predominance, but this should convert to mononuclear cells within 8 to 48 hours.[41] The white blood cell (WBC) count is rarely over 1000 WBC/mm³. An exception is mumps meningitis; in this case 25% of patients have counts above this level. Seroconversion confirms recent infection. Culture is the gold standard for diagnosis but is not always positive. In the case of enterovirus infection, there is a reasonable chance of culturing virus from CSF, but it may take several days. Reverse transcriptase PCR is more sensitive than culture, almost 100% specific, and provides an answer within hours.[1,30,32,34,43] Virus can also be cultured from stool and oropharynx.[38] Mumps can be grown from CSF for as long as 1 week after presentation; serologic testing of CSF along with serum is also quite useful. In contrast, neuroimaging is normal and is not helpful for diagnosis.

In a recent prospective study of 2233 CSF specimens examined for viral infection, four viruses (enteroviruses, HSV, varicella zoster, and Epstein–Barr) accounted for 95% of all PCR positive samples.[37] Multiplex PCR allowed samples to be screened simultaneously for any one of several agents. In summary, the diagnosis of aseptic meningitis rests on CSF evaluation, supplemented with appropriate culture, PCR, and serologic studies in diagnosis. It is likely that PCR will play an increasing role in diagnosis.

Septic Meningitis

As is done for aseptic meningitis, the diagnosis of septic meningitis is made by CSF examination. Specific tests that document bacterial infection include culture (positivity rate 80%), Gram stain (positivity rate 60% to 90%), detection of bacterial antigens (positivity rate 50% to 100%), and detection of bacterial DNA by use of PCR.[39,46] Nonspecific but supportive findings include elevated opening pressure, moderate to significant polymorphonuclear pleocytosis, moderate to significant decrease in glucose concentration, and increased protein concentration. The CSF cell count is greater than 100 WBC/mm³ in 90% of patients; 65% to 70% of patients have cell counts greater than 1000 WBC/mm³. Occasionally (in as much as 10% of cases), there is an initial mononuclear pleocytosis, particularly with cell counts less than 1000. Combined CSF findings that have a predictive value of 99% for bacterial meningitis are glucose less than 34 mg/dL, CSF-to-serum-glucose ratio less than 0.23, and WBC cell count higher than 2000 WBC/mm³ or polymorphonuclear count higher than 1180 WBC/mm³.[49] Neuroimaging is not diagnostically useful in most cases. However, in a recent review, neuroimaging was recommended prior to lumbar puncture in patients who had coma, papilledema, or focal neurologic findings.[36] Neuroimaging is also obviously helpful to evaluate

possible complications of meningitis. Other useful tests for the diagnosis of septic meningitis include blood cultures, which are positive for the organism in as much as half of cases. Partial treatment of bacterial meningitis (with oral antibiotics for example) decreases the positivity rates of CSF culture and Gram stain and may decrease CSF protein and neutrophil cell count.[28] With appropriate intravenous antibiotics, culture and Gram stain should become negative after 24 hours, and CSF glucose approaches normal levels in 80% of patients within 3 days. Protein and cell count are less susceptible to rapid treatment. At 1 week the cell count is still increased, but at lower levels, in 50% of patients. The protein level remains elevated for 10 or more days.

Recurrent Meningitis

A careful history and physical and neurologic examination can detect suggestive drug exposure, structural lesion, or associated systemic disorder. The meningitis episodes must be documented by CSF examination confirming pleocytosis. CSF examination must also be carried out between discrete attacks to document that abnormalities return to normal. In general, unless there is an obvious origin, the entire neuraxis should be imaged to identify an anatomic defect. Because HSV-2 has been associated with most cases of Mollaret's meningitis, PCR, CSF, and serum antibody assays for this agent should be performed at the time of lumbar puncture. Dermatologic or ophthalmologic evaluation may be helpful for identification of skin lesions or for detection of uveitis. Complement and immunoglobulin studies may be used to document immune defects.

Chronic Meningitis

Many chronic meningitis patients come to medical attention before symptoms or signs have been present for 4 weeks.[21] At this stage it is important to differentiate them from patients who have acute meningitis, encephalitis, and recurrent meningitis. The typical patient who has acute meningitis, encephalitis, or recurrent meningitis presents abruptly and looks sicker than the patient with chronic meningitis. Encephalitis is marked by prominent mental status changes or focal features reflecting parenchymal involvement, with little meningismus. With the exception of acute septic meningitis, these other infection syndromes spontaneously improve within a few weeks. In contrast, the chronic meningitis syndrome may fluctuate but will not steadily improve. The CSF pattern is also helpful. A mildly decreased glucose in the setting of mononuclear pleocytosis should always raise the possibility of chronic meningitis.

The history is focused to identify previous systemic diseases and specific infections that can involve the meninges, to screen for suggestive exposures and geographic risk factors, to identify preexistent immunologic abnormalities, and to determine concurrent extraneural involvement. A history of TB; previous systemic fungal infection; malignancy; sarcoidosis; autoimmune disease; systemic vasculitis; or previous spirochetal, brucella, or parasitic infections are probably pertinent. Underlying diabetes predisposes to a specific fungal (zygomycetes) infection. Recognition of certain exposures is important because they can suggest certain origins (Table 3).

Immunocompromised hosts (HIV infection, cancer, chronic glucocorticoids, or immunosuppressive therapy) is susceptible to a specific set of pathogens.

Table 3. SUGGESTIVE CAUSAL EXPOSURES IN THE CHRONIC MENINGITIS SYNDROME

Cause	Exposure
Bacteria	
Mycobacterium tuberculosis	Contact with infected individual
Borrelia burgdorferi	Geographic (coastal Northeast, Minnesota and Wisconsin, Pacific coast); time spent out of doors, tick exposure
Treponema pallidum	Sexual contact
Leptospira interrogans	Animal exposure, pond water
Brucella	Dairy products, farm animals, laboratory exposure
Franciscella tularensis	Tick exposure, cats, rabbits
Viruses	
HIV, HTLV-1	Sexual contact, intravenous drug use, blood transfusion; geographic (HTLV-1: Caribbean, Tropics, Japan)
Fungi	
Pseudoallescheria	Near drowning
Sporothorix	Rose thorn prick
Coccidioides immitis	Geographic (arid Southwest)
Blastomyces dermatitidis	Geographic (Mississippi valley, mid-Atlantic states)
Histoplasma capsulatum	Geographic (Ohio and Mississippi river valleys)
Paracoccidioides	Geographic (Latin America)
Parasites	
Angiostrongylus cantonensis	Consumption of snails, raw fish, infected vegetables; geographic (Indo-Pacific)
Taenia solium	Geographic (Latin America, Poland, Portugal, China, Africa, India)

HTLV-1 = Human T-cell lymphotropic virus type 1.

Evidence for concurrent disease outside the nervous system can provide important clues to origin. For example, certain bacteria and fungi are associated with draining sinus tracts from the skin surface, whereas other agents frequently cause ocular problems (sarcoidosis, Behçet, uveomeningoencephalitides, lymphoma, angiostrongylus, leptospirosis, Lyme disease). Other causes are associated with frequent pulmonary involvement (TB, aspergillus, blastomyces, histoplasma, sarcoidosis), rheumatologic involvement (Behçet, Lyme disease), or skin lesions (Lyme disease, Vogt-Koyanagi-Harada disease).

The examination is focused on identifying the extraneural involvement, the pattern of neurologic involvement, and the potential biopsy sites. Dermatologic and ophthalmologic evaluations may be useful to screen for skin and eye lesions. A careful assessment is made for adenopathy, enlargement of liver or spleen, or other organ abnormality. The neurologic examination looks for evidence of spinal-cord involvement, cranial-nerve disease, focal lesions, hydrocephalus, peripheral nervous system involvement, or multilevel neuraxis involvement.

The laboratory investigation for chronic meningitis can be quite extensive (Table 4). In a Mayo Clinic study of 37 chronic meningitis patients who ultimately underwent leptomeningeal biopsy, there were 2295 CSF tests, 1289 serologic tests, 401 radiologic studies, 1152 other studies, and 82 extraneural biopsies.[10] Only 157 of these tests (3.3%) were abnormal. CSF was abnormal in all patients, neuroimaging was abnormal in 60%, and erythrocyte sedimentation rate was abnormal in 44%. Extraneural biopsies (bone marrow) were positive in less than 4%. On the average, each patient had five lumbar punctures.

Table 4. LABORATORY EVALUATION OF CHRONIC MENINGITIS

Blood Tests	Complete blood count, differential
	Chemistries, erythrocyte sedimentation rate, antinuclear antibodies
	HIV serology
	RPR
	Consider angiotensin-converting enzyme (ACE), antineutrophilic cytoplasmic antibodies, specific serologies, blood smears
CSF	Cell count with differential, protein, glucose
	Cytology
	VDRL
	Cultures (TB, fungal, bacterial, viral)
	Stain (Gram, acid fast, India ink)
	Cryptococcal antigen
	Oligoclonal bands, IgG index
	Consider ACE; PCR (viruses, mycobacteria, *T. whippelii*); histoplasma antigen, immunocytochemistry (*T. whippelii* and other selected agents); paired antibodies for *B. burgdorferi*, *Brucella*, histoplasma, *coccidioides*, other fungal agents; neoplastic markers
Neuroimaging	Brain MR imaging with contrast
	Consider CT, spinal MR imaging, angiography
Cultures	Blood (parasites, fungi, viruses, rare bacteria)
	Urine (mycobacteria, viruses, fungi)
	Sputum (mycobacteria, fungi)
	Consider gastric washings, stool, bone marrow, liver (mycobacteria, fungi)
Ancillary	Chest radiograph
	Electrocardiogram
	Selected testing (mammogram, CT chest/abdomen, etc.)
Biopsy	Extraneural sites (bone marrow, lymph node, peripheral nerve, liver, lung, skin, small bowel)
	Leptomeningeal/brain ($\pm$ special stains)

RPR = Rapid plasma reagin; VDRL = Venereal Disease Research Laboratory.

The goals of the laboratory evaluation are to confirm the diagnosis and to identify the origin. Therefore the major focus is on CSF analysis. Several lumbar punctures are generally needed, and 25 mL can be removed from adults at one setting without problems. Infants and children have smaller CSF volumes; therefore less CSF should be removed.[38] The yield of CSF culture, cytology, and stains is increased with large volumes and multiple samples. When lumbar CSF is unrevealing, cisternal or intraventricular CSF may be helpful. This is particularly true when there is basilar meningitis or ventriculitis. With regard to neuroimaging, contrast magnetic resonance (MR) imaging of the brain is the study of choice. Cultures are done not only on CSF but also on blood, urine, sputum, and occasionally, other sites. Morning urine and deep sputum samples should be obtained. At least three cultures are sent from each site. The microbiology laboratory is notified that samples are from a chronic meningitis case, so that prolonged incubations and special techniques (anaerobic culture for actinomycetes and arachnia, increased CO_2 for brucella, Saboraud's agar for fungi) can be used.

There is a wide array of serologies that can be sent (Table 5). In general, useful information is obtained by doing paired (CSF, serum) antibody tests to look for intrathecal production. CSF studies can provide important clues regarding the cause of chronic meningitis:

Table 5. USEFUL SEROLOGIC TESTS IN THE CHRONIC MENINGITIS SYNDROME

Bacteria	*B. burgdorferi*
	Brucella
	Leptospira
	Treponema pallidum (RPR, VDRL, ±FTA-ABS)
Fungi	*Aspergillus* sp
	Coccidioides immitis
	Histoplasma capsulatum (50% cross-reactivity)
	Sporothrix schenckii
	Zygomycetes
Parasites	*Taenia solium*
	Toxoplasma gondii
Viruses	HIV-1
	HTLV-1

FTA-ABS = Fluorescent treponemal antibody absorption.

I. Cells
   A. <50 WBC/mm3
      1. Noninfectious
      2. Cryptococcus (with HIV-1 infection)
   B. Neutrophil predominance
      1. Bacterial (*Actinomycetes,* arachnia, *Brucella,* nocardia, early TB)
      2. Fungi (*Aspergillus* sp, zygomycetes, pseudoallescheria, *Blastomyces dermatitidis, Candida* sp, *Coccidioides immitis, Histoplasma capsulatum*)
      3. Parasites (acanthamoeba)
      4. Noninfectious (chemical, lupus, vasculitis)
   C. Eosinophil predominance
      1. *Coccidioides immitis*
      2. Parasites (*Angiostrongylus cantonensis, Taenia solium, Schistosoma* sp)
      3. Noninfectious (lymphoma, chemical, polyarteritis)
II. Protein
   A. High level
      1. TB

THERAPEUTIC APPROACH

The therapeutic approach to infectious meningitis involves antimicrobial therapy, supportive care, and the novel approach of controlling the host response to infection (adjunctive therapy). Meningitis patients who appear to have infection with a treatable pathogen should be started on appropriate therapy. The urgency of starting treatment varies, depending on the type of meningitis. Empiric choice of antimicrobials, based on predicting the most likely pathogen, is increasingly complicated in the current era because of antimicrobial resistance problems. Supportive care (hydration, control of symptoms such as headache and nausea) applies to all patients. Although most patients will need to be admitted to the hospital, aseptic meningitis patients (when it is clear that they do not need antimicrobial therapy) can usually be managed as outpatients. Adjunctive therapy is

aimed at treating host immune or inflammatory factors that accentuate the damage produced by meningitis. For now this treatment is confined to use of glucocorticoids.[13]

Aseptic Meningitis

For most viral causes of aseptic meningitis, there is no specific antiviral therapy and management is supportive. The major exceptions are certain herpes viruses and HIV. For the unusual cases of aseptic meningitis caused by a nonviral pathogen, specific treatment is indicated. All patients should have control of symptoms such as pain and nausea and should be hydrated if they are fluid depleted.

Septic Meningitis

Antibiotic treatment must be started as soon as the diagnosis of septic meningitis appears likely. If CSF is obtained immediately, then Gram stain should guide therapy. If CSF is not helpful or cannot be obtained quickly, then empiric treatment is based on the likely organism. Initial regimens can be modified once culture results are available. The patient's age and underlying health status can be used to select appropriate broad-spectrum coverage. The increasing resistance of *S. pneumoniae* to penicillin and cephalosporins must be considered. One of the new areas in septic meningitis therapeutics involves control of the damaging aspects of the host's immune and inflammatory response to infection. Such adjunctive therapy is still in its infancy, and current treatment is confined to glucocorticoids. Adjunctive therapy with dexamethasone may be indicated in a high infection load (positive Gram stain) or the increased intracranial pressure setting.[36] For all patients, appropriate supportive care and management of complications can help to minimize morbidity and mortality.

Recurrent Meningitis

Recurrent meningitis is a self-limited syndrome. Patients recover spontaneously, with the exception of the unusual cases of recurrent bacterial meningitis caused by anatomic defects, parameningeal infection, or immune defects. Such patients require appropriate antibiotics. Optimal therapy is aimed at the underlying cause of the recurrent meningitis. This includes correction of an anatomic neuraxis defect or endogenous chemical source, treatment of an underlying systemic disease, or withholding a precipitating drug or other exogenous chemical source. In cases of recurrent HSV infection, antiviral therapy may be helpful. If there is a possibility of septic meningitis at initial evaluation, then empiric antimicrobial therapy for 24 to 48 hours until cultures are reported as negative may be reasonable.

Chronic Meningitis

Management of chronic meningitis starts with an aggressive, rapid, and thorough diagnostic workup. Decisions about empiric therapy depend on severity of illness, whether a presumptive cause can be established, and toxicity of the pro-

posed empiric therapy. If the patient is in somewhat good condition and there is no presumptive cause, one can wait for initial study results before committing to therapy. If an origin appears highly likely, then appropriate therapy should be started early. If the patient is very ill or deteriorating, empiric therapy must be started (Table 6).

Empiric therapy is chosen to cover the most likely cause, on the basis of data generated from the initial evaluation. In general, TB therapy is given first. Antifungal therapy is used only when there is strong evidence of fungal infection. Although glucocorticoids may worsen fungal and certain TB infections, they have a therapeutic role in chronic meningitis. Glucocorticoids are a reasonable option when culture studies remain negative. The usual starting dose is 60 to 80 mg of prednisone a day. In a recent series of patients who had undiagnosed chronic meningitis, 52% (11 of 21) improved with steroid treatment, generally within 1 week[2]; in individual cases, there was drastic improvement of very sick individuals within 2 to 3 days.

Symptomatic and supportive treatments are important. Therapy includes careful attention to and management of vital signs and metabolic status. Potential complications of chronic meningitis, such as hydrocephalus, seizures, cerebrovascular events, or intracranial hypertension, require appropriate and aggressive symptomatic therapy.

PREVENTION

For infectious meningitis, the ultimate treatment is prevention. Strategies include immunoprophylaxis, chemoprophylaxis, and environmental control.

Aseptic Meningitis

Vaccines have been helpful in reducing infection caused by mumps. No vaccine is available for enteroviruses, with the exception of the polioviruses. Because there are over 71 different enterovirus serotypes, development of a comprehensive vaccine will be difficult. However, most cases of enteroviral meningitis in a given region are caused by a limited number of serotypes. In the United States, for

Table 6. EMPIRIC THERAPEUTIC TRIALS IN THE CHRONIC MENINGITIS SYNDROME

Cause	Therapy
TB	Triple therapy (isoniazid + vitamin B_6, rifampin, pyrazinamide) Multidrug resistant strains require 4–5 drugs
Unusual bacteria	Broad-spectrum antibiotics • penicillin, ceftriaxone, (*Actinomycetes*, spirochetes) • doxycycline, rifampin (*Brucella*) • streptomycin, gentamycin (*F. tularensis*)
Fungal	Antifungal agents • amphotericin B • flucytosine • fluconazole • miconazole, ketoconazole, itraconazole
Noninfectious	Glucocorticoids ± immunosuppressants

example, 15 serotypes account for more than 80% of CSF isolates.[51] Environmental control measures have been used to treat arbovirus infection, but they have not provided definitive prevention.

Septic Meningitis

The value of immunoprophylaxis is clearly demonstrated by the success of the second generation *H. influenzae* conjugate vaccines, which reduced infections with this agent by 85% to 90%. With regard to *S. pneumoniae,* there are over 84 *S. pneumoniae* serotypes, but 5 serotypes (6, 14, 18, 19, 23) account for 67% of meningitis cases in the United States. There is a first-generation vaccine for *S. pneumoniae,* but it is not very effective for meningitis.[33] A second-generation vaccine is being tested. With regard to *N. meningitidis,* most meningitis cases are caused by Group C, although organisms from Groups A, B, D, X, Z, 29E, W135, and Y are occasional pathogens. *N. meningitidis* also has an inadequate first-generation vaccine, but conjugate vaccines are being tested.[33] Chemoprophylaxis is used for close contacts of patients who have *N. meningitidis* or *H. influenzae* meningitis.

Recurrent Meningitis

Anecdotal data suggest that attacks of Mollaret's meningitis that are caused by HSV-2 may be prevented with chronic antiviral suppressive therapy.[17] Oral acyclovir treatment is given for months or for a year or more.

Chronic Meningitis

TB meningitis, the major infectious cause of chronic meningitis, is potentially preventable. In the United States identification and tracking of cases and contacts, early diagnosis, prophylactic as well as curative therapies, and directly observed therapy are helping to eliminate this infection.[58] On a global basis the Bacille Calmette–Guerin (BCG) vaccine is 80% to 90% effective in preventing meningitis, but societal issues will make worldwide control difficult.[58] With regard to fungal meningitis, experimental vaccines as well as antifungal chemoprophylaxis (particularly in the HIV-positive population) are under evaluation.

SUMMARY

Meningitis can be produced by many different organisms. Morbidity and mortality range from negligible to significant. CSF evaluation remains the cornerstone of diagnosis. The most likely pathogens are predictable based on the type of meningitis, host factors, and an accurate history and examination. An informed approach to meningitis helps assure timely diagnosis and optimal management.

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