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Treatment of Adult Meningitis and Complications

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1. Introduction

The term meningitis implies inflammation of the leptomeninges and cerebrospinal fluid (CSF) in the subarachnoid space. Typically manifests as headache, neck stiffness, light sensitivity, and varying degrees of neurological symptoms and signs.

The most common and often most severe forms of meningitis are due to infections, including bacteria, viruses, fungi, and parasites. Noninfectious causes of meningitis include primary inflammatory syndromes such as vasculitis and connective tissue disease, neoplasms of solid tumor and hematologic forms, and chemical irritants including certain medications, subarachnoid blood, and biologic matter spilling into CSF from tumors.

Although a patient may present with symptoms of meningitis within days of onset, distinguishing acute from subacute or chronic meningitis may not always be possible early in the course. Nevertheless, the distinction is important because of the varying urgency, causes, and treatment strategy involved in each syndrome.

In this review we summarize the current concepts of the approach to the treatment of adult meningitis and management of neurologic complications.

2. Bacterial meningitis

Bacterial meningitis is a medical, neurologic and sometimes neurosurgical emergency that requires a multidisciplinary approach. Bacterial meningitis has an annual incidence of 4 to 6 cases per 100,000 adults, and *Streptococcus pneumoniae* and *Neisseria meningitidis* are responsible for 80 percent of all cases. Recommendations for antimicrobial therapy are changing as a result of the emergence of antimicrobial resistance. (Van de Beek et al., 2004; Schuchat et al., 2005; Van de Beek et al., 2006)

In adults presenting with community-acquired acute bacterial meningitis, the sensitivity of the classic triad of fever, neck stiffness, and altered mental status is low (44%), but almost all such patients present with at least two of four symptoms – headache, fever, neck stiffness, and altered mental status (as defined by a score below 14 on the Glasgow Coma Scale).

2.1 Antimicrobial treatment

The choice of antibiotic for empirical therapy is based on the possibility that a penicillin- and cephalosporin-resistant strain of *S. pneumoniae* is the causative organism, and on the patient's age and any associated conditions that may have predisposed to meningitis (table 1).

Predisposing factor	Common bacterial pathogens	Initial intravenous antibiotic therapy
Age: 2-50 years	<i>N meningitidis</i> <i>S pneumoniae</i>	Vancomycin plus ceftriaxone or cefotaxime*
Age: >50 years	<i>N meningitidis</i> <i>S pneumoniae</i> <i>L monocytogenes</i> , aerobic gram-negative bacilli	**Vancomycin plus ceftriaxone or cefotaxime plus ampicillin
With risk factor present (alcoholism or altered immune status)	<i>S pneumoniae</i> <i>L monocytogenes</i> <i>H influenzae</i>	**Vancomycin plus ceftriaxone or cefotaxime plus ampicillin
*In areas with very low penicillin-resistance rates monotherapy penicillin may be considered **In areas with very low penicillin-resistance and cephalosporin-resistance rates combination therapy of amoxiciclin and a third-generation cephalosporin may be considered		

Table 1. Recommendations for empirical antimicrobial therapy in suspected community-acquired bacterial meningitis (adapted from Van de Beek et al., 2006)

For adults up to 50 years old from countries with high rates of pneumococcal penicillin- or cephalosporin-resistance, this should be a combination of either a third- or fourth-generation cephalosporin plus vancomycin. In countries with very low rates of pneumococcal penicillin-resistance (such as The Netherlands) (Van de Beek et al., 2002), penicillin can still be used safely as a first-line agent. In the UK, the addition of vancomycin is also not considered necessary and is not recommended unless the patient presents from one of the geographic regions associated with high-level ceftriaxone resistance, such as Spain, Southern Africa, and certain parts of the USA. In adults older than 50 years, and in the immunocompromised patient, ampicillin should be added to this combination because of possible *Listeria meningitis*. (Nudelman & Tunkel, 2009; Schut et al., 2008; Van de Beek et al., 2006; Williams & Nadel, 2001)

Once the bacterial pathogen is isolated and the sensitivity of the organism to the antibiotic is confirmed by in vitro testing, antimicrobial therapy should be modified accordingly. Recommendations for antibiotic therapy in bacterial meningitis are summarized in table 2-4 and some important tips are:

- a. Bacterial meningitis due to *S. pneumoniae*, *H. influenzae* and group B streptococci is usually treated with intravenous antibiotics for 10–14 days.

- b. Meningitis due to *N. meningitidis* is treated for 5–7 days.
- c. Patients with clinically suspected meningococcal meningitis who are treated with penicillin must be isolated for the first 24 h after initiation of antibiotic therapy and also treated with Rifampin 600 mg orally every 12 h for 2 days to eradicate nasopharyngeal colonization (penicillin does not eradicate the organisms in the nasopharynx).
- d. Meningitis due to *L. monocytogenes* and *Enterobacteriaceae* is treated for 3–4 weeks.
- e. Gentamicin is added to ampicillin in critically ill patients with *L. monocytogenes* meningitis.

Pathogen	Recommended therapy	Adult dosage (intravenous)	Days of therapy	Alternative therapy
<i>Streptococcus pneumoniae</i>			10 to 14	Meropenem, moxifloxacin or cloranfenicol
Penicillin MIC: < 0,1 mcg per mL	Penicillin	4 million units every four hours		
Penicillin MIC: 0,1 to 1 mcg per mL	Ceftriaxone	2g every 12 hours		
Penicillin MIC: ≥ 1 mcg per mL	Vancomycin plus Ceftriaxone	15 to 22,5 mg per kg every 12 hours 2 g every 12 hours		
<i>Neisseria meningitidis</i>	Ceftriaxone	2 g every 12 hours	5 to 7	Chloranfenicol, meropenem or moxifloxacin
<i>Haemophilus influenza</i>	Ceftriaxone	2 g every 12 hours	7 to 10	Chloranfenicol or moxifloxacin
<i>Streptococcus agalactiae</i> (group B streptococcus)	Ampicillin plus Gentamicin	Usually in children	14 to 21	Vancomycin or cefotaxime
<i>Listeria monocytogenes</i>	Ampicillin with or without Gentamicin	2 g every four hours 1 to 2 mg per Kg every eight hours	21 First 7 to 10 days	Trimethoprim/sulfamethoxazole
<i>Enterobacteriaceae</i>	Ceftriaxone, ceftazidime or cefepime	varies	21 to 28	Ciprofloxacin, meropenem or Trimethoprim/sulfamethoxazole
<i>Staphylococci</i>			7 to 10 days after shunt removal or cerebrospinal fluid sterilization	Daptomycin or linezolid. Consider adding rifampicin
Methicillin susceptible	Nafcillin	2 g every four hours		
Methicillin resistant	Vancomycin	15 to 22,5 mg per Kg every 12 hours		

Table 2. Pathogen-specific therapy for common causes of bacterial meningitis

Treatment	Dose
Penicilin	2 million units every 4 h
Amoxicilin or ampicillin	2 g every 4h
Vancomycin	15 mg/Kg every 8h
Third generation cephalosporins	
Ceftriaxone	2 g every 12h
Cefotaxime	2 g every 4-6h
Cefepime	2 g every 8h
Ceftazidime	2 g every 8h
Meropenem	2 g every 8h
Chloramphenicol	1-1, 5g every 6h
Fluroquinolones	
Gatifloxacin	400 mg every 24h
Moxifloxacin	400 mg every 24h
Trimethoprim-sulfamethoxazole	5 mg/kg every 6-12h
Aztreonam	2 g every 6-8 h
Ciprofloxacin	400 mg every 8-12h
Rifampicin	600 mg every 12-24h
Aminoglycoside (gentamicine)	1,7 mg/Kg every 8h

Table 3. General recommendations for intravenous empirical antibiotic treatment

Treatment	Dose
Rifampicin	600 mg twice daily for two days
Ceftriaxone	One dose 250 mg intramuscularly
Ciprofloxacin	One dose, 500 mg orally
Azithromycin	One dose, 500 mg orally

Table 4. General recommendations for chemoprophylaxis

2.2 Adjunctive dexamethasone

A large randomized trial showed that dexamethasone (10 mg IV 15–20 min before or with the first dose of antibiotic and given every 6 h for 4 days) is beneficial in adults with acute bacterial meningitis. It reduced unfavorable outcome from 25% to 15% and mortality from 15% to 7%. The benefits were most striking in patients with pneumococcal meningitis. Furthermore, patients on dexamethasone were less likely to have impaired consciousness, seizures and cardiorespiratory failure. Starting corticosteroids before or with the first dose of parenteral antimicrobial therapy appears to be more effective than starting corticosteroids after the first dose of antimicrobial therapy. For some adults with suspected meningitis, the beneficial effect of adjunctive dexamethasone is less certain, or may even be harmful. Therefore these patients should be carefully monitored throughout treatment. Steroids are not recommended in patients with postneurosurgical meningitis, those with a severe immunocompromised state, or in those who are hypersensitive to steroids. Patients with septic shock and adrenal insufficiency benefit from steroid therapy in physiological doses and longer duration. (Van de Beek et al., 2004; Van de Beek & de Gans, 2006; Fitch & Van de Beek, 2007; Nudelman & Tunkel, 2009; Schut et al., 2008; Van de Beek et al., 2006; Williams & Nadel, 2001; Weisfelt et al., 2006)

2.3 Monitoring of the patient and systemic complications

Patients who are diagnosed with acute bacterial meningitis are at risk of various neurological and systemic complications and to detect them, patients should be admitted to intensive care unit where the following should be monitored: vital signs (blood pressure, heart rate, respiratory rate, temperature), oxygen saturation, level of consciousness, presence or absence of focal neurological signs or symptoms, papillary diameter and certain laboratory parameters, like CRP, leukocyte count, electrolytes, urea and creatinine. Analysis of arterial blood gases and measurement of serum lactate are important in patients in whom septic shock is suspected and the platelet count and coagulation tests are important in those in whom disseminated intravascular coagulation is suspected. (Van de Beek et al., 2006)

Table 5 resumes the management of bacterial meningitis in Adults in the Intensive Care Unit.

Bacterial meningitis is often associated with septic shock, which is an important predictor of outcome. It may manifest in several ways: hypotension (systolic pressure < 90 mm Hg or a reduction of >40 mm Hg from baseline) despite adequate fluid resuscitation, tachycardia (>100/min), tachypnea (>20/min), core body temperature >38°C or <36°C, drowsiness and oliguria (Pfister et al., 1993).

Adrenocorticoid insufficiency in patients with septic shock must be treated with low doses of corticosteroids. Care should be taken to estimate and replace imperceptible fluid loss through the skin and lungs in patients who are febrile.

Dyspnea, labored breathing, agitation, followed by progressive drowsiness, tachycardia, scattered crackles on pulmonary auscultation and hypoxemia point to the diagnosis of adult respiratory distress syndrome (ARDS). The chest x ray usually reveals characteristic diffuse alveolar interstitial infiltrates in all lung fields.

Patients with bacterial meningitis are at risk of acute hyponatremia, although most cases are mild. Hyponatremia (serum sodium <135 mmol/l) on admission to hospital is found in 30% of patients (Brouwer et al., 2007). Most episodes resolve within a few days without specific treatment and does not influence outcome. Severe hyponatremia (<130 mmol/l) is present in 6% of patients.

An exceptionally high frequency of hyponatremia is seen in meningitis due to *L. monocytogenes* (73%) and *S. pyogenes* (58%). This complication may be a result of cerebral salt wasting, the syndrome of inappropriate antidiuretic hormone secretion or exacerbation by aggressive fluid resuscitation. This lack of clarity about the mechanism has resulted in the clinical dilemma about the management of intravenous fluids in bacterial meningitis (restricted or not). The goal should be to maintain a normovolemic state, and in patients with severe hyponatremia to use fluid maintenance therapy then fluid restriction, although there is no clear evidence supporting this approach.

Hypertatremia (serum sodium >143 mmol/l) is less frequent and found on admission in only 7% of patients with culture-proven bacterial meningitis (Van de Beek et al., 2007). Patients with sodium levels >146 mmol/l (2% of patients) are more likely to have seizures before admission compared to those with lower levels. Sodium levels of >143 mmol/l are

<p>Neurocritical care</p> <p>In patients with a high risk of brain herniation, consider monitoring intracranial pressure and intermittent administration of osmotic diuretics (mannitol [25%] or hypertonic [3%] saline) to maintain an intracranial pressure of <15 mm Hg and a cerebral perfusion pressure of \geq60 mm Hg</p> <p>Initiate repeated lumbar puncture, lumbar drain, or ventriculostomy in patients with acute hydrocephalus</p> <p>Electroencephalographic monitoring in patients with a history of seizures and fluctuating scores on the Glasgow Coma Scale</p>
<p>Airway and respiratory care</p> <p>Intubate or provide noninvasive ventilation in patients with worsening consciousness (clinical and laboratory indicators for intubation include poor cough and pooling secretions, a respiratory rate of >35 per minute, arterial oxygen saturation of <90% or arterial partial pressure of oxygen of <60 mm Hg, and arterial partial pressure of carbon dioxide of >60 mm Hg)</p> <p>Maintain ventilatory support with intermittent mandatory ventilation, pressure-support ventilation, or continuous positive airway pressure</p>
<p>Circulatory care</p> <p>In patients with septic shock, administer low doses of corticosteroids (if there is a poor response on corticotropin testing, indicating adrenocorticoid insufficiency, corticosteroids should be continued)</p> <p>Initiate inotropic agents (dopamine or milrinone) to maintain blood pressure (mean arterial pressure, 70–100 mm Hg)</p> <p>Initiate crystalloids or albumin (5%) to maintain adequate fluid balance</p> <p>Consider the use of a Swan–Ganz catheter to monitor hemodynamic measurements</p>
<p>Gastrointestinal care</p> <p>Initiate nasogastric tube feeding of a standard nutrition formula</p> <p>Initiate prophylaxis with proton-pump inhibitors</p>
<p>Other supportive care</p> <p>Administer subcutaneous heparin as prophylaxis against deep venous thrombosis</p> <p>Maintain normoglycemic state (serum glucose level, <150 mg per deciliter), with the use of sliding-scale regimens of insulin or continuous intravenous administration of insulin</p> <p>In patients with a body temperature of >40°C, use cooling by conduction or antipyretic agents</p>

Table 5. Management of Bacterial Meningitis in Adults in the Intensive Care Unit.

associated with a higher heart rate, lower CSF protein and lower CSF glucose levels. Hypernatremia is independently predictive of unfavorable outcome and mortality, however it is unclear if it reflects severe disease or directly contributes to the poor outcome. Physicians should be aware of the potential importance of hypernatraemia in patients presenting with bacterial meningitis and care should be taken in the fluid management.

The coexistence of bacterial meningitis and arthritis has been described in several studies. It occurs in 7% of patients overall, more in meningococcal meningitis (12%) (Likitnukul et al., 1986; Weisfeit et al., 2006). It is caused either by haematogenous bacterial seeding of joints (septic arthritis) or by immune-complex deposition in joints (immunomediated arthritis). A patient with immunomediated arthritis during meningococcal infection typically develops symptoms from day 5 of the illness or during recovery from the infection, generally involving the large joints. A definitive diagnosis of septic arthritis requires identification of bacteria in the synovial fluid by Gram stain or culture. The treatment of acute bacterial arthritis requires antibiotics and joint drainage. Although with some limitation in the range of movement functional outcome is good in most of the patients.

2.4 Deterioration of consciousness

A common cause of a decline in consciousness in bacterial meningitis is clinical evidence of cerebral edema. The release of proinflammatory mediators in the subarachnoid space leads to an inflammatory response in the central nervous system that contributes to an increased permeability of the blood-brain barrier, cerebral edema and increased intracranial pressure. Several supportive therapies have been described, although no therapy has been proved to have clinical efficacy. Nevertheless, in patients with impending cerebral herniation, monitoring of intracranial pressure may be considered, but the outcome is expected to be poor. The use of osmotic diuretics to control intracranial pressure may be an option, although there are no definitive data on the efficacy of this approach. (Figure 1)

Seizures are other frequent cause of deteriorating consciousness with a higher mortality rate. They occur in about 20% of patients, that are older and more likely to have focal abnormalities on brain CT. *S pneumoniae* is the most usual causative micro organism. Patients with seizures or a clinical suspicion of prior seizure should receive anticonvulsant therapy, but the low incidence of this complication does not justify prophylaxis. A rare cause of the deterioration of consciousness in meningitis is nonconvulsive status epilepticus.

Acute hydrocephalus can also complicate meningitis, because the purulent exudate interferes with CSF absorption by the arachnoid villi, resulting in communicating hydrocephalus. When the inflammatory exudate involves the basal cisterns and surrounds the cranial nerves at the base of the brain (basilar meningitis), it may block CSF flow at the foramina of Luschka and Magendie, resulting in obstructive hydrocephalus.

Repeated lumbar puncture or the placement of a temporary lumbar drain may effectively reduce intracranial pressure. In patients with mild enlargement of the ventricular system with no clinical deterioration, a spontaneous resolution may occur, and invasive procedures are therefore withheld.

Cerebral infarction due to arterial occlusion complicates bacterial meningitis in 10–15% of patients. Venous infarction due to septic venous thrombosis occurs in 3–5%. Cerebral

infarcts may involve large vascular territories and may cause brain swelling and a mass effect, which may result in a decline in consciousness. Arteritis of small and medium-sized arteries and inflammatory involvement of veins is probably caused by tissue destructive agents, such as oxidants and proteolytic enzymes, released by activated leukocytes. Treatment is mainly supportive and these patients have a poor outcome.

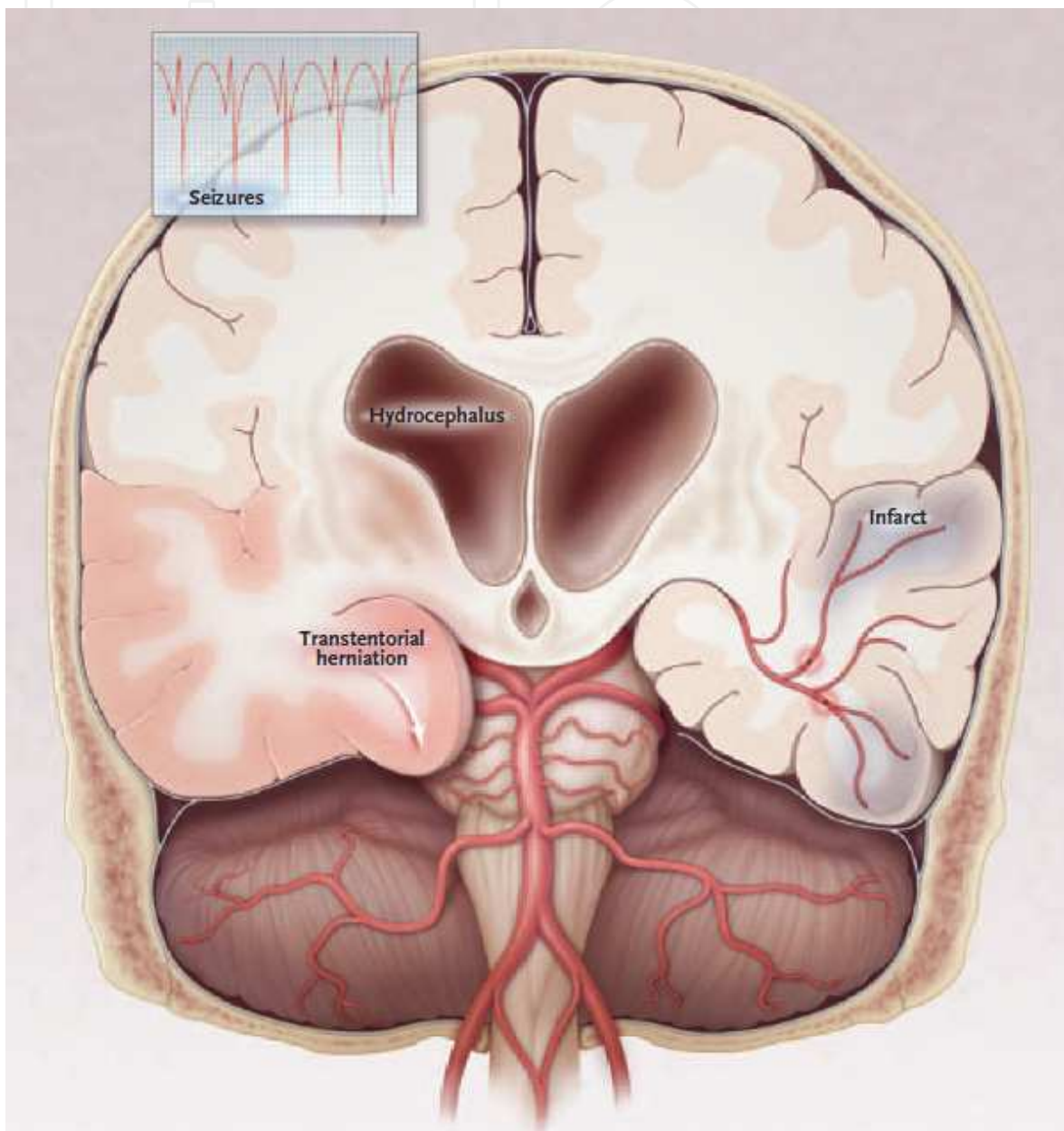


Fig. 1. Major Intracranial Complications in Bacterial Meningitis in Adults.

2.5 Focal neurological complications

In patients who develop focal neurological signs (hemiparesis, monoparesis, aphasia) some entities must be excluded: cerebral infarction (due to inflammatory occlusion of cerebral

arteries, septic venous thrombosis), seizures, subdural empyema or a combination of these causes. A brain CT scan is needed to rule out many of these causes.

The possibility of septic intracranial venous thrombosis should be considered in patients with an impaired level of consciousness, seizures, fluctuating focal signs and stroke in non-arterial distributions. MRI with venous-phase studies confirms the diagnosis. Treatment of cerebral thrombophlebitis in bacterial meningitis is directed toward the infection.

Subdural empyema should be suspected in patients who have concomitant sinusitis or mastoiditis or who have recently undergone surgery for either of these disorders. In most cases contrast-enhanced brain CT will reveal the hypodense subdural collections (Figure 2). Brain MRI is more sensitive than CT in detecting subdural empyema along the convexity, and especially for infratentorial subdural empyema. Currently, MRI with diffusion-weighted images (DWI) and apparent diffusion coefficient mapping (ADC) remains the preferred imaging modality for detecting subdural empyema. Subdural empyema should be surgically drained by craniotomy but the outcome is poor if the patient is unconscious.

Abnormalities of the cranial nerves are caused by the meningeal inflammatory process or by an increase in cerebrospinal fluid pressure. The most frequent cranial-nerve abnormality is the involvement of the eighth cranial nerve, which is reflected in a hearing loss in 14 percent of patients. A cochlear implant may eventually be needed by some severely affected patients.

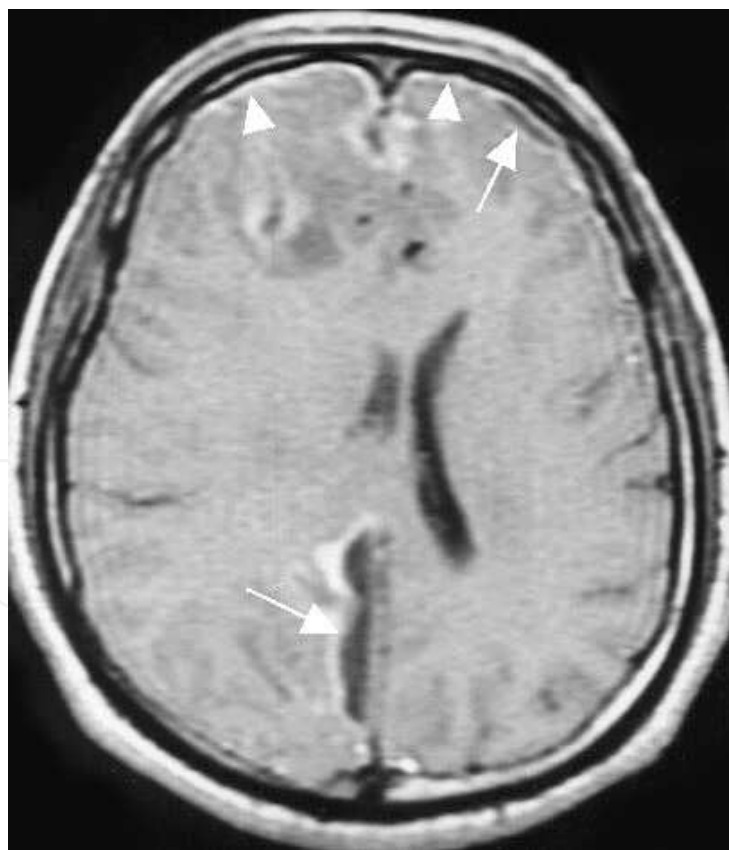


Fig. 2. Frontal sinusitis, empyema, and abscess formation in a patient with bacterial meningitis. This contrast-enhanced, axial T1-weighted magnetic resonance image shows a right frontal parenchymal low intensity (edema), leptomeningitis (arrowheads), and a lentiform-shaped subdural empyema (arrows).

3. Aseptic meningitis

Enteroviruses are the most common etiologic pathogens in persons with aseptic meningitis and do not require specific antimicrobial therapy. They can be diagnosed by CSF polymerase chain reaction testing (Kupila et al., 2006), which is not always needed, but a positive test may be useful in discontinuing antimicrobials initiated presumptively for bacterial meningitis.

Herpes Simplex Virus (HSV) aseptic meningitis is usually a self-limited infection that must be distinguished from HSV encephalitis based on clinical and radiographic features. Therapy with acyclovir can be lifesaving in patients with HSV encephalitis. (Bamberg, 2010)

In contrast with HSV encephalitis, most patients with HSV aseptic meningitis have normal mental status and neurologic function and do not have the temporal lobe enhancement observed on magnetic resonance imaging. Both forms of HSV central nervous system disease are diagnosed by CSF HSV polymerase chain reaction testing. Infection with HSV may cause recurrent disease (e.g., Mollaret meningitis).

Varicella zoster virus infection may cause aseptic meningitis in the absence of cutaneous manifestations. Although it has not been studied in clinical trials, therapy with acyclovir at 10 mg per kg every eight hours is suggested, based on expert opinion.

Lyme disease, a systemic disease with dermatological, rheumatological, neurological, and cardiac manifestations, is caused by *Borrelia burgdorferi* and transmitted by the hard-shelled deer ticks: *Ixodes dammini* in the eastern United States, *Ixodes pacificus* in the western United States, and *Ixodes ricinus* in Europe. The existence of both early and late neurological manifestations, diagnostic uncertainty, and potential for relapse despite therapy have fueled continuing debate over the spectrum of Lyme-related neurological disease. Best agreement exists for the early neurological syndromes, which include lymphocytic meningitis, cranial neuropathy (commonly unilateral or bilateral Bell's palsy), and painful radiculoneuritis, which can occur alone or in combination. Optic neuritis, mononeuritis multiplex, and Guillain-Barré syndrome are other infrequent manifestations of early neurological involvement. Neurological complications of more advanced Lyme disease include encephalomyelitis, with predominant white matter involvement and peripheral neuropathy. Lymphocytic meningitis is usually acute, but may cause chronic or relapsing meningitis and communicating hydrocephalus. Radiculoneuritis, beginning as a painful limb disorder, may continue with exacerbations and remissions for up to 6 months. Encephalopathy with memory or cognitive abnormalities, confusional states, accelerated dementia, and normal CSF study results may occur. Other psychiatric or fatigue syndromes appear less likely to be causally related to Lyme disease.

Borreliosis is treated with parenteral antibiotics if there is evidence that infection has crossed the blood-brain barrier. Ceftriaxone (2 g once daily intravenously) or penicillin (3 to 4 million units intravenously every 3 to 4 hours) for 2 to 4 weeks are first-line drugs. Tetracycline and chloramphenicol are alternatives in penicillin- or cephalosporin-allergic patients. Routine use of corticosteroids is not indicated. Recommendations for the use of corticosteroids in neuroborreliosis generally have been limited to patients treated aggressively with intravenous antibiotics with evidence of severe inflammation that fails to improve. CSF examination should be performed toward the end of the 2- to 4-week treatment course to assess the need for continuing treatment and again 6 months after the

conclusion of therapy. Intrathecal antibody production may persist for years following successful treatment and in isolation does not indicate active disease. Patients in whom CSF pleocytosis fails to resolve within 6 months, should be retreated. Peripheral or cranial nerve involvement without CSF abnormalities may be treated with oral agents, either doxycycline, 100 mg twice daily for 14 to 21 days, or amoxicillin, 500 mg every 8 hours for 10 to 21 days.

Up to one third of untreated patients with syphilis develop late syphilis (tertiary syphilis), a slowly progressive inflammatory disease that includes gummatous (granulomatous), cardiovascular, and neurological forms. Early neurological manifestations of tertiary neurosyphilis include pure meningeal or meningovascular disease, with a 3- to 10-year latency period from primary infection, and parenchymal forms, which occur 10 to 30 years after initial infection. General paresis refers to parenchymal cerebral involvement and tabes dorsalis to syphilitic myeloneuropathy. Syphilitic gummas, granulomas that present as space-occupying lesions in brain or cord, may occur at any stage of disseminated disease.

Neurosyphilis spans all stages of disseminated disease. Meningeal, meningovascular, and parenchymal syndromes are perhaps best viewed as a continuum of disease, rather than as discrete disorders. Syphilitic meningitis, meningovascular syphilis, general paresis, and tabes are different clinical expressions of the same fundamental pathological events, specifically meningeal invasion, obliterative endarteritis, and parenchymal invasion. Especially in the antibiotic era, symptomatic neurosyphilis may present, not as one classic syndrome, but as mixed, subtle, or incomplete disease. All of the neurological complications of syphilis have been reported in HIV disease, which may accelerate the onset and progression of neurosyphilis.

Syphilitic meningitis typically occurs earlier than other forms of neurosyphilis and is often asymptomatic. Rare complications of acute syphilitic meningitis include cranial neuropathy, hydrocephalus, myelitis, or lumbosacral radiculitis. Meningovascular syphilis usually occurs 4 to 7 years after primary infection (range, 6 months to 12 years). In addition to stroke, involvement of large and small cerebral vessels also causes headache, vertigo, insomnia, and psychiatric or personality disorders.

Adequate treatment of neurosyphilis is based largely on achieving treponemicidal levels of penicillin in the CSF. *Treponema pallidum* is highly susceptible to penicillin, which is the drug of choice for all stages of syphilis. Serum levels of penicillin should be maintained for many days because treponemes divide slowly in early syphilis (30-33 per hour in experimental settings) and penicillin acts only on dividing cells.

Therapy that is considered standard for non immunocompromised individuals with syphilis meningitis should remain the standard for immunocompromised individuals even with asymptomatic neurosyphilis. Either of the following is acceptable treatment:

- a. Aqueous (crystalline) penicillin-G at 2-4 million U intravenously every 4 hours; alternatively, continuously for 10-14 days, or
- b. Procaine penicillin-G at 2.4 million U/d intramuscularly plus probenecid at 500 mg orally 4 times per day for 10-14 days (probenecid increases brain concentrations of penicillin less than it increases CSF concentrations, but avoid using it if the patient has a history of serious allergy to sulfonamides)

Contraindications include documented hypersensitivity, use of penicillin in pregnant patients (usually safe but benefits must outweigh the risks), and impaired renal function (use caution).

Other antibiotics, as alternative regimens, have not been studied sufficiently, and their routine use is not recommended. If patients are allergic to penicillin, either tetracycline or doxycycline probably is effective. Pregnant women should not receive doxycycline. Typically, tetracycline hydrochloride at 500 mg orally 4 times per day or doxycycline at 100 mg orally twice daily for 4 weeks is prescribed. Defining the efficacy of azithromycin for early syphilis may simplify therapy. Incidentally, the emergence of azithromycin-resistant *T pallidum* has been reported.

4. Tuberculous and cryptococcal meningitis

A high index of suspicion is needed to diagnose tuberculous meningitis because culture results are often delayed and stains are often negative. Empiric therapy may be lifesaving. Polymerase chain reaction testing may be useful. Death may occur as a result of missed diagnoses and delayed treatment.

Most of the guidelines follow the model of short-course chemotherapy of pulmonary tuberculosis: an "intensive phase" of treatment with four drugs, followed by treatment with two drugs during a prolonged "continuation phase". Initial treatment is a combination of isoniazid (5 mg per kg per day); rifampin (10 mg per kg per day, up to 600 mg); pyrazinamide (15 to 30 mg per kg per day, up to 2 g); and ethambutol (15 to 25 mg per kg per day). Streptomycin (20 to 40 mg per kg per day, up to 1 g) should be used instead of ethambutol in young children.

Evidence concerning the duration of treatment is conflicting. The duration of conventional therapy is 6-9 months, although some investigators still recommend as many as 24 months of therapy. No guidelines exist as to the components and duration of treatment in the case of multidrug-resistant TBM.

The use of corticosteroids in adults is controversial; they may be indicated in the presence of increased intracranial pressure, altered consciousness, focal neurological findings, spinal block, and tuberculous encephalopathy. Adding dexamethasone to the treatment regimen seems to improve mortality rate in patients older than 14 years with tuberculous meningitis. Cochrane systematic review concluded that overall adjunctive therapy with corticosteroids reduces the risk of death (relative risk (RR), 0.78).

The potential complications include associated elevated intracranial pressure, hydrocephalus, vasculitis, acute seizures, and hyponatremia. Aggressive and appropriate treatment of these complications can minimize the secondary brain injury and improve the chance of a good outcome. Disturbances of sodium, intravascular volume and water are common in tuberculous meningitis. Hyponatremia occurs in 35% to 65% of patients. Acute seizures occur in about 50% of children and in 5% of adults.

In these patients, associated space-occupying tuberculoma(s) may be the substrate for increased intracranial pressure (Figure 3). Growing evidence suggests that most tuberculomas resolve with antituberculous treatment. However, surgical excision is indicated in: tuberculoma causing obstructive hydrocephalus and significant increased

intracranial pressure; tuberculoma causing obstructive hydrocephalus and not resolving on medical treatment; large space-occupying tuberculomas with increased intracranial pressure; and tuberculomas with associated compartmental shifts and not resolving with medical treatment. (Marais, 2010; Murthy, 2010)

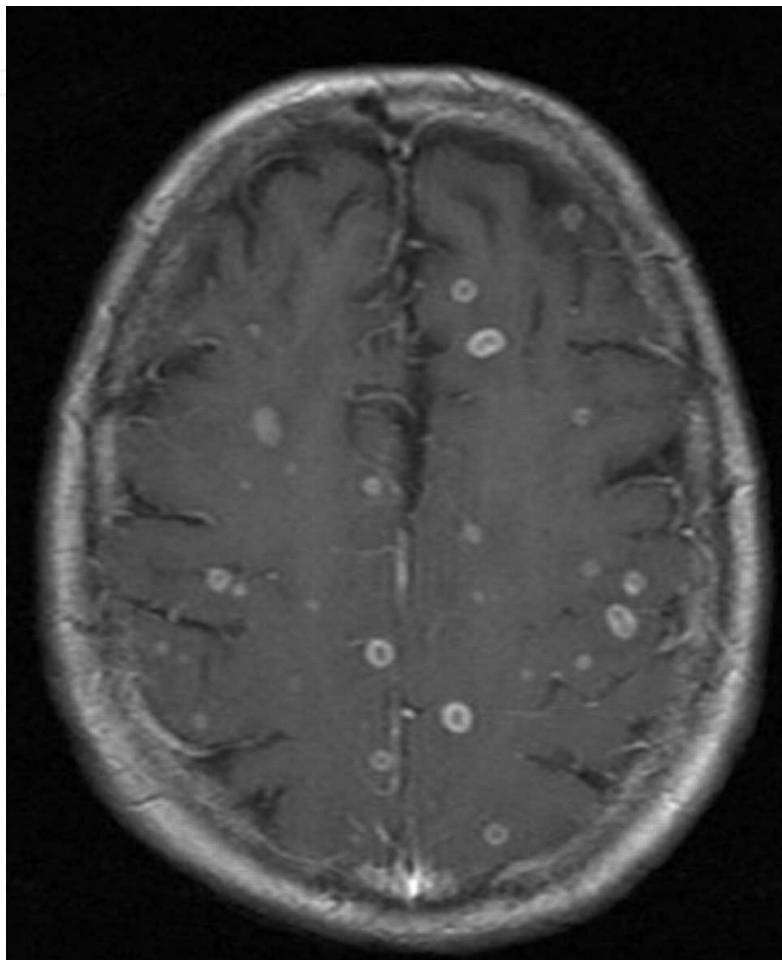


Fig. 3. MRI with contrast showing classical ring enhancing lesions of tuberculomas

Cryptococcal meningitis is the most common fungal meningitis, and usually occurs in patients with altered cellular immunity. It is estimated that the global burden of HIV-associated cryptococcosis approximates 1 million cases annually worldwide. It is relevant that, despite access to advanced medical care and the availability of highly active antiretroviral therapy, the 3-month mortality rate during management of acute cryptococcal meningoencephalitis approximates 20%. Furthermore, without specific antifungal treatment for cryptococcal meningoencephalitis in certain HIV-infected populations, mortality rates of 100% have been reported within 2 weeks after clinical presentation to health care facilities. (Perfect et al., 2010; Saag et al., 2000)

Usually presents with headache, fever, stiff neck and photophobia. However, meningeal symptoms and signs may be minimal or absent in over one half of the cases, and the rather broad clinical spectrum includes personality change, cognitive impairment, cranial neuropathy, altered consciousness and coma.

The CSF profile ranges from striking protein elevation, mononuclear pleocytosis, and hypoglycorrhachia to minimal abnormalities that overlap with those attributable to HIV infection alone. Fungal CSF culture is the gold standard, but the time wasted before a positive result is obtained, limits its clinical utility. India ink smear is helpful when positive, but is too insensitive to exclude the diagnosis if negative. Fortunately, CSF cryptococcal antigen (CrAg) testing is a rapid, specific test with a sensitivity exceeding 90%. The diverse clinical presentations of cryptococcal meningitis enforce CrAg to be performed routinely in CSF of patients with AIDS.

It is apparent that insightful management of cryptococcal disease is critical to a successful outcome. We should divide the treatment in three situations, as follows:

- a. **In HIV infected individuals**, the initial treatment (induction regimen) includes amphotericin B (0.7 to 1.0 mg/kg per day IV) with or without flucytosine (25 mg/kg every six hours orally) for 2 to 3 weeks. Renal insufficiency, hypokalemia, and hypomagnesemia may complicate amphotericin B therapy, and the hematological toxicity of flucytosine sometimes precludes its use in patients with AIDS, in whom pancytopenia is common. Patients who are doing well can be switched to fluconazole, 200 mg twice a day for 8 to 10 weeks (maintenance therapy), and then placed on prophylactic therapy of 200 mg daily to prevent relapse. Alternatively Itraconazole can be used (200 mg twice per day orally; drug-level monitoring strongly advised). Active antiretroviral therapy should be initiated 2-10 weeks after the beginning of initial antifungal treatment. Consider discontinuing suppressive therapy during active antiretroviral therapy in patients with a CD4 cell count >100 cells/mL and an undetectable or very low HIV RNA level sustained for >3 months (minimum of 12 months of antifungal therapy); but consider reinstatement of maintenance therapy if the CD4 cell count decreases to <100 cells/mL (B-III).
- b. **In organ transplant recipients**, the treatment includes liposomal amphotericin B (3-4 mg/kg per day IV) or amphotericin B lipid complex (5 mg/kg per day IV) plus flucytosine (100 mg/kg per day in 4 divided doses) for at least 2 weeks for the induction regimen, followed by fluconazole (400-800 mg [6-12 mg/kg] per day orally) for 8 weeks initially, and (200-400 mg per day orally) for 6-12 months afterwards.
- c. **Non-HIV Infected, Non transplant Hosts**, the treatment includes amphotericin B (0.7-1.0 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for at least 4 weeks for induction therapy. The 4-week induction therapy is reserved for persons with meningoencephalitis without neurological complications and negative cerebrospinal fluid (CSF) yeast culture results after 2 weeks of treatment. For amphotericin B toxicity issues, lipid formulations of amphotericin B may be substituted in the second 2 weeks. In patients with neurological complications, consider extending induction therapy for a total of 6 weeks, and lipid formulations of amphotericin for the last 4 weeks of the prolonged induction period. Then, start consolidation with fluconazole (400 mg per day) for 8 weeks.

Regarding neurological complications, some of them had already been described in complications of bacterial meningitis, as cerebral edema, increased intracranial pressure, acute hydrocephalus and abnormalities of the cranial nerves. Their management was described above. Poor prognostic features at presentation include impaired level of consciousness, CSF cell count less than 20 cells/ μ L, and CSF CrAg greater than 1:1024.

Another possible complication is the presence of cerebral cryptococcomas. The treatment consists of induction with amphotericin B (0.7–1 mg/kg per day IV), liposomal amphotericin B (3–4 mg/kg per day IV), or amphotericin B lipid complex (5 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for at least 6 weeks. Then consolidation and maintenance therapy with fluconazole (400–800 mg per day orally) for 6–18 months. Adjunctive therapies include corticosteroids for mass effect and surrounding edema and/or surgery for large masses (>3 cm lesion).

5. Conclusions

The management approach to patients with suspected or proven bacterial meningitis includes emergent CSF analysis, and initiation of appropriate antimicrobial and adjunctive therapies. The choice of empirical antimicrobial therapy is based on the patient's age and underlying disease status; once the infecting pathogen is isolated, antimicrobial therapy can be modified for optimal treatment.

The most important priority to reduce the burden of bacterial meningitis throughout the world must include the introduction and availability of effective vaccines against the common meningeal pathogens.

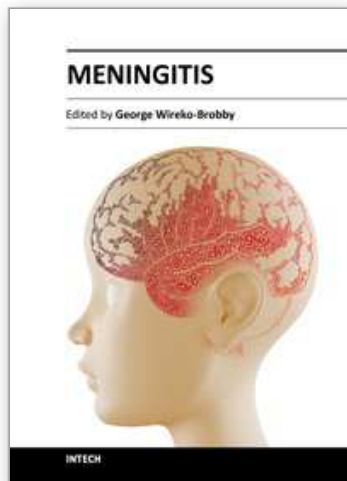
Finally a higher index of suspicion is needed to diagnose tuberculous meningitis because culture results are often delayed, stains are often negative and empiric therapy may be lifesaving. A prompt diagnosis of meningitis is specially important in immunosuppressive patients, with high rates of mortality.

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Meningitis is a medical emergency requiring a rapid diagnosis and an immediate transfer to an institution supplied with appropriate antibiotic and supportive measures. This book aims to provide general practitioners, paediatricians, and specialist physicians with an essential text written in an accessible language, and also to highlight the differences in pathogenesis and causative agents of meningitis in the developed and the developing world.

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