



# MENINGITIS – THE BASICS

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**Meningitis** is inflammation of the protective membranes covering the brain and spinal cord. The inflammation may be caused by infection with viruses, bacteria or other microorganisms, and less commonly by certain drugs. Meningitis can be life-threatening because of the inflammation's proximity to the brain and spinal cord; therefore the condition is classified as a medical emergency.

The most common symptoms of meningitis are headache and neck stiffness associated with fever, confusion or altered consciousness, vomiting, and photophobia or phonophobia. Sometimes, especially in small children, only nonspecific symptoms may be present, such as irritability and drowsiness. If a rash is present, it may indicate a particular cause of meningitis; for instance, meningitis caused by *Neisseria meningitidis* may be accompanied by a characteristic rash consisting of petechiae on the trunk, lower extremities, mucous membranes, conjunctiva, and (occasionally) the palms of the hands or soles of the feet. The rash is typically non-blanching.

## Causes

### • Bacterial

The types of bacteria that cause bacterial meningitis vary by age group. In premature babies and newborns up to three months old, common causes are group B streptococci and *Escherichia coli* (carrying K1 antigen). *Listeria monocytogenes* may affect the newborn as well as severely immunocompromised adults and may occur in epidemics. Older children are more commonly affected by *Neisseria meningitidis*, *Streptococcus pneumoniae* and those under five by *Haemophilus influenzae* type B (in countries that do not offer vaccination or amongst unvaccinated children). In adults, *N. meningitidis* and *S. pneumoniae* together cause 80% of all cases of bacterial meningitis, with increased risk of *L. monocytogenes* in those over 50 years old. Since the pneumococcal vaccine was introduced, however, rates of pneumococcal meningitis have declined in children and adults.

Recent trauma to the skull gives bacteria in the nasal cavity the potential to enter the meningeal space. Similarly, individuals with a cerebral shunt or related device are at increased risk of infection through the devices. In these cases, infections with staphylococci are more likely, as well as infections by pseudomonas and other Gram-negative bacilli.

Infection due to *Mycobacterium tuberculosis* is more common in countries where tuberculosis is common, but is also encountered in the immunocompromised.

### • Fungal

Fungal meningitis, e.g. due to *Cryptococcus neoformans*, is typically seen in people with immunodeficiencies such as AIDS.

### • Aseptic

The term *aseptic meningitis* refers loosely to all cases of meningitis in which no bacterial infection can be demonstrated. It is usually due to a viral infection, but it may be due to a partially treated bacterial infection with disappearance of the bacteria from the meninges, or by infection in a space adjacent to the meninges (e.g. sinusitis). Endocarditis may cause aseptic meningitis.

Aseptic meningitis may also result from:

- infection with spirochetes such as *Treponema pallidum* (the cause of syphilis) and *Borrelia burgdorferi* (the cause of Lyme disease).
- cerebral malaria
- amoebic meningitis, due to infection with amoebae such as *Naegleria fowleri*.

- **Viral**

Viruses that can cause meningitis include enteroviruses (approximately 80% of cases), herpes simplex virus type 2 (and less commonly type 1), varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus type 6, mumps virus, HIV and lymphocytic choriomeningitis virus (LCMV). Patients with rabies virus infection usually present with symptoms suggestive of encephalitis, but there may be confusion with meningitis-type symptoms, especially in children. Mollaret's meningitis is a syndrome of recurring episodes of meningitis thought to be caused by HSV-2.

- **Parasitic**

A parasitic cause is often assumed when there is a predominance of eosinophils in the CSF. The most common parasites implicated are *Angiostrongylus cantonensis* and *Gnathostoma spinigerum*. Amoebic meningitis due to infection with amoebae such as *Naegleria fowleri*, is contracted from freshwater sources.

- **Non-infectious**

Meningitis may occur as the result of several non-infectious causes: spread of cancer to the meninges (*malignant meningitis*) and certain drugs (mainly non-steroidal anti-inflammatory drugs, antibiotics and intravenous immunoglobulins). It may also be caused by several inflammatory conditions such as sarcoidosis, connective tissue disorders such as systemic lupus erythematosus, and certain forms of vasculitis such as Behçet's disease. Epidermoid cysts and dermoid cysts may cause meningitis by releasing irritant matter into the subarachnoid space. Rarely, migraine may cause meningitis, but this diagnosis is usually only made when other causes have been excluded.

## Diagnosis

**Table 1:** CSF findings in different forms of meningitis

Type of Meningitis	Glucose	Protein	Cells
Acute bacterial	Low	High	Neutrophils often higher than lymphocytes
Viral	Normal	Normal/High	Lymphocytes often higher than neutrophils
Tuberculosis	Low	High	Lymphocytes present
Fungal	Low	High	Lymphocytes often present
Malignant	Low	High	Variable

The most important test for identifying or ruling out meningitis is analysis of the cerebrospinal fluid. However, lumbar puncture is contraindicated if there is a mass in the brain (tumour or abscess) or the intracranial pressure (ICP) is elevated, as it may lead to brain herniation. If someone is at risk for either a mass or raised ICP (recent head injury, a known immune system problem, localizing neurological signs or evidence on examination of raised ICP), a CT or MRI scan is recommended prior to the lumbar puncture.

The "opening pressure" of the CSF is measured using a manometer. The pressure is normally between 6 and 18cm H<sub>2</sub>O. In bacterial meningitis the pressure is typically elevated. The initial appearance of the fluid may prove an indication of the nature of the infection: cloudy CSF indicates higher levels of protein, white and red blood cells and/or bacteria, and therefore may suggest bacterial meningitis.

The CSF sample is examined for presence and types of white blood cells, red blood cells, protein content and glucose level. Gram staining of the sample may demonstrate bacteria in bacterial meningitis, but absence of bacteria does not exclude bacterial meningitis as they are only seen in 60% of cases and in only 40% if antibiotics were administered before the sample was taken. Gram stain is also less reliable in particular infections such as listeriosis. Microbiological culture of the sample is more sensitive, identifying the organism in 70–85% of cases, but results can take up to 48 hours to become available. The predominant type of white blood cell present suggests whether meningitis is likely to be bacterial (usually neutrophil-predominant) or viral (usually lymphocyte-predominant), although in the beginning of the disease this is not always a reliable indicator.

The concentration of glucose in CSF is normally 40% higher than that in blood. In bacterial meningitis it is typically lower. The CSF glucose level is divided by the blood glucose level to give the CSF glucose:serum glucose ratio. A ratio  $\leq 0.4$  is indicative of bacterial meningitis; in the newborn, glucose levels in CSF are normally higher and a ratio below 0.6 (60%) is considered abnormal in this age group.

A latex agglutination test may be positive in meningitis caused by *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Escherichia coli* and group B streptococci. Sensitivities of agglutination tests vary widely.

Polymerase chain reaction (PCR) detects the presence of bacterial or viral DNA/RNA in cerebrospinal fluid. It is highly sensitive and specific. It may assist in distinguishing the various causes of viral meningitis.

If tuberculous meningitis is suspected, the sample is processed for Ziehl-Neelsen stain, which has a low sensitivity, and tuberculosis culture, which takes a long time to process. PCR testing is being increasingly used.

Diagnosis of cryptococcal meningitis can be made at low cost using an India ink stain of the CSF; however, testing for cryptococcal antigen in blood or CSF is more sensitive, particularly in individuals with AIDS.

## Prevention

For some causes of meningitis, prevention can be provided in the long term with vaccination or in the short term with antibiotics. Since the 1980s, many countries have included immunization against *Haemophilus influenzae* type B in their routine childhood vaccination schemes. This has practically eliminated this pathogen as a cause of meningitis in young children in those countries. In the countries where the disease burden is highest, however, the vaccine is still too expensive. Similarly, immunization against mumps has led to a sharp fall in the number of cases of mumps meningitis, which prior to vaccination occurred in 15% of all cases of mumps.

Meningococcus vaccines exist against groups A, C, W135 and Y. Development of a vaccine against group B meningococci has proven much more difficult, as its surface proteins (which would normally be used to make a vaccine) only elicit a weak response from the immune system or cross-react with normal human proteins. In Africa, the current approach for prevention and control of meningococcal epidemics is based on early detection of the disease and emergency reactive mass vaccination of the at-risk population.

Routine vaccination against *Streptococcus pneumoniae* with the pneumococcal conjugate vaccine (PCV), which is active against seven common serotypes of this pathogen, significantly reduces the incidence of pneumococcal meningitis. The pneumococcal polysaccharide vaccine, which covers 23 strains, is only administered in certain groups (e.g. those who have had a splenectomy). It does not elicit a significant immune response in all recipients, e.g. small children.

Childhood vaccination with BCG has been reported to significantly reduce the rate of tuberculous meningitis.

Short-term antibiotic prophylaxis is a method of prevention for meningococcal meningitis. Prophylactic treatment of close contacts with antibiotics (e.g. rifampicin 10mg/kg 12 hourly for 2 days, ciprofloxacin 500mg stat or ceftriaxone 250mg IMI stat) can reduce the risk of infection, but does not protect against future infections.

## Treatment

### • Initial treatment

Bacterial meningitis is potentially life-threatening and has a high mortality rate if untreated; delay in treatment has been associated with a poorer outcome. Treatment with wide-spectrum antibiotics plus acyclovir if HSV infection is suspected should not be delayed while awaiting laboratory results.

### • Bacterial meningitis

Empiric antibiotics must be started immediately. The choice of initial treatment consists of a third-generation cephalosporin such as cefotaxime (adults: 2gm IV 4 – 6 hourly; children: 50mg/kg/dose 6 hourly – max 3g; neonates: 50mg/kg/dose 12 hourly in the first week of life, 8 hourly from 1 – 3 weeks old and 6 hourly thereafter) or ceftriaxone (adult: 4g/day as a single dose or 2 divided doses; children: 75mg/kg as a single dose or 2 divided doses). For young children and those over 50 years of age, as well as those who are immunocompromised, addition of ampicillin (adults: 1 – 2 g 3-4 hourly; children: 50mg/kg/dose 6 hourly; neonates: 100mg/kg/dose 12 hourly in the first week, 8 hourly from 1 – 3 weeks old and 6 hourly thereafter) is recommended to cover *Listeria monocytogenes*.

The results of the CSF culture are generally available after 24–48 hours. At this stage, empiric therapy may be switched to specific antibiotic therapy targeted to the known causative organism and its antibiotic sensitivities.

Tuberculous meningitis requires prolonged treatment with antibiotics, typically requiring treatment for a year or longer.

- **Viral meningitis**

Viral meningitis not due to HSV, VZV or CMV typically requires supportive therapy only. Viral meningitis tends to run a more benign course than bacterial meningitis.

As the clinical features of encephalitis can overlap with those of meningitis, all patients with an acute onset of fever with a change in their mental status or new onset of seizures (excluding simple febrile seizures) should be treated for suspected herpes simplex encephalitis. Acyclovir dosing schedule for children and adults: 10 mg/kg 8 hourly by IV infusion over 1 hour for 21 days.

- **Fungal meningitis**

Fungal meningitis, such as cryptococcal meningitis, is treated with long courses of high dose antifungals, such as amphotericin B and fluconazole. Patients with HIV and cryptococcal meningitis: amphotericin B 1mg/kg IV and fluconazole 800mg PO daily for 14 days, then fluconazole 400mg PO daily for another 8 weeks followed by fluconazole 200mg PO daily until the CD4 count is > 200cell/ $\mu$ l, on antiretroviral therapy for a minimum of 6 months with a suppressed HIV viral load.

## References

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