Meningitis

This disease is notifiable in the UK - see **NOIDs** article for more detail.

Meningitis is an inflammation of the meninges, the outer membranes covering the brain and spinal cord [1]. The inflammation may be caused by infection with viruses, bacteria, other micro-organisms, or non-infective causes. Viral meningitis is more common and usually more benign than bacterial meningitis but all cases of suspected meningitis should be managed as though having bacterial meningitis, until proven otherwise.

Meningococcal disease refers to meningitis and/or septicaemia caused by *Neisseria meningitidis* (the meningococcus). It presents as bacterial meningitis (15% of cases), septicaemia (25% of cases), or as a combination of the two presentations (60% of cases) [2]

See also the separate Sepsis (Septicaemia) article.

Epidemiology [1]

- The annual incidence of acute bacterial meningitis in developed countries is estimated to be 1-2 per 100,000.
- Public Health England publishes annual reports on laboratory-confirmed invasive meningococcal disease. In the epidemiological year (start of July to end of June) 2017-2018 there were 755 confirmed cases in England, similar to the 748 cases reported in 2016-2017 [3].
- Tables are also available for notified cases of acute meningitis in England and Wales - in 2017 there were 436 notifications, compared to 1,251 10 years previously in 2007 [4].

- The epidemiology of bacterial meningitis has changed in the UK over the past two decades with an evolving vaccination programme.
- Meningitis occurs in people of all age groups but infants are at most risk of bacterial meningitis and meningococcal disease, with another peak in teenagers and young adults.
- Viral meningitis is most common, accounting for over half of cases, but bacterial meningitis remains important, particularly as it has a high mortality[5]. Many cases of viral meningitis are thought to go unreported - in 2005-6, for example, there were ten times as many people admitted to hospital with a diagnosis of viral meningitis as there were notifications of the condition[6].
- It has been estimated that an average GP will only see one or two cases of bacterial meningitis in the course of their career.
- The incidence of culture-proven neonatal meningitis is estimated at 0.3 per 1,000 live births in developed countries[7].

Risk factors

- As above, young age is the most significant risk factor.
- Immune suppression.
- Smoking.
- Patients with CSF shunts or dural defects
- Patients having spinal procedures (eg, spinal anaesthetics) are at increased risk and *Pseudomonas* spp. may then be the cause.
- Other risk factors include bacterial endocarditis, diabetes mellitus, alcoholism and cirrhosis, intravenous drug abuse, renal insufficiency, adrenal insufficiency, malignancy (increased risk of listeria infection), hypoparathyroidism, thalassaemia major and cystic fibrosis.
- Splenectomy and sickle cell disease increase the risk of meningitis secondary to encapsulated organisms.
- Crowding (eg, military recruits and college students) increases the risk of outbreaks of meningococcal meningitis.

Aetiology

Viral causes are most common.

Bacterial meningitis [1] [2] [8]

Some of the more common causative organisms are listed below. This changes over time - the vaccination programme has been guided by this, and has had some impact on the subsequent epidemiology.

Age-specific common causes:

- Neonates: group B streptococci, *Listeria monocytogenes*, *Escherichia coli*.
- Infants and young children: *Haemophilus influenzae* type b, if younger than 4 years and unvaccinated; *Neisseria meningitidis*, *Streptococcus pneumoniae*.
- Adults and older children: *S. pneumoniae*, *H. influenzae* type b, *N. meningitidis*, Gram-negative bacilli (such as non-type b *H. influenzae*, *Klebsiella*, *Pseudomonas*, *Enterobacter*), staphylococci, enterococcus species, streptococci and *L. monocytogenes*.
- Elderly and immunocompromised: *S. pneumoniae*, *L. monocytogenes*, tuberculosis (TB), Gram-negative organisms.

Hospital-acquired and post-traumatic meningitis (may often be multidrug-resistant) tend to involve *Klebsiella pneumoniae*, *E.coli*, *Pseudomonas aeruginosa*, or *Staphylococcus aureus*.

N. meningitidis can cause local outbreaks among young adults; there is increased incidence in late winter or early spring. Meningococcal meningitis is endemic in parts of Africa, India and other developing nations. Periodic epidemics occur in sub-Saharan Africa as well as among religious pilgrims travelling to Saudi Arabia for the Hajj.

Syphilis and TB are rarer causes in those with relevant risk factors.

Neonatal meningitis [7]

See also the separate Congenital, Perinatal and Neonatal Infections article.

- Neonates are at greater risk of meningitis. Risk factors for the development of meningitis include low birth weight (below 2500 g), premature delivery, premature rupture of membranes, traumatic delivery, fetal hypoxia and maternal peripartum infection.
- Intrapartum prophylactic antibiotics in pregnant mothers who carry, or who are at risk of colonising, group B streptococci, have been effective in reducing the risk of early neonatal group B streptococcal meningitis, although it remains one of the most common causative organisms.
- *E.coli* is another common pathogen in this group, and particularly in very low-birth-weight babies.
- Caesarean section reduces the risk of transmission of herpes simplex virus (HSV) when present and active in the mother.
- In developed countries, overall incidence and mortality from bacterial meningitis among neonates has decreased but there has not been a significant decrease in long-term complications such as cerebral palsy, learning disability, seizures and hearing impairment.
- Mortality following HSV infection of the central nervous system is 4-14%. HSV-1 and HSV-2 have the same risk of mortality but HSV-2 is more often associated with long-term complications such as cerebral palsy, general learning disability, seizures, microcephaly and visual impairment [9].

Aseptic meningitis [5] [10] [11]

CSF has cells but is Gram-stain negative and no bacteria can be cultured on standard media. Causes include:

- Viral infection - eg, enteroviruses (echovirus, Coxsackievirus), mumps, HSV and herpes zoster virus, HIV, measles, influenza, arboviruses. Enteroviruses are the most common cause of meningitis in immunocompetent adults in the UK. Exact viral aetiology differs between countries [12].
- Fungal infection: fungal meningitis is rare but can be life-threatening. People with immunodeficiency (eg, AIDS, leukaemia, immunosuppressant medication) are at higher risk. Fungal causes of meningitis include infection with *Cryptococcus*, *Histoplasma* and *Coccidioides* species.

- Parasites - eg, eosinophilic meningitis caused by angiostrongyliasis.
- Other possible causative organisms include atypical TB, syphilis, Lyme disease, leptospirosis, listeriosis and brucellosis.
- Kawasaki disease.
- Mollaret's meningitis.
- Partly treated bacterial meningitis.

Non-infective meningitis

Meningeal inflammation can be caused by meningeal infiltration by:

- Malignant cells (leukaemia, lymphoma, other tumours).
- Chemical meningitis (intrathecal agents, contaminants).
- Medication (non-steroidal anti-inflammatory drugs (NSAIDS), trimethoprim).
- Sarcoidosis.
- Systemic lupus erythematosus.
- Behçet's disease.

Presentation[2]

See also the separate Ill and Feverish Child and Fever and Night Sweats articles.

Invasive meningococcal disease

Invasive meningococcal disease may present with septicaemia, meningitis or a combination of both. See the separate Meningococcal Disease article.

- A generalised non-blanching petechial rash, beyond the distribution of the superior vena cava, or a purpuric rash in any location, in an ill child, is strongly suggestive of meningococcal septicaemia and should lead to urgent treatment and referral to secondary care.
- The following features in an ill child should prompt consideration of a diagnosis of invasive meningococcal disease: petechial rash, altered mental state, cold hands and feet, extremity pain, fever, headache, neck stiffness, skin mottling.
- Meningococcal meningitis and/or septicaemia may also present with capillary refill time more than two seconds, unusual skin colour and hypotension.
- Meningococcal septicaemia without meningitis does not tend to present with stiff neck, back rigidity, bulging fontanelle, photophobia, Kernig's sign, Brudzinski's sign, paresis, focal neurological deficits or seizures.

Clinical presentation of meningitis may include:

- Non specific features: fever, headache, vomiting, nausea, lethargy, irritability, muscle or joint pains, refusing food/drink, respiratory symptoms. Less common nonspecific symptoms include chills, shivering, diarrhoea, abdominal pain, sore throat, coryzal symptoms.
- Stiff neck (generally not present in children under the age of 1 year or in patients with altered mental state).
- Non-blanching rash.
- Back rigidity.
- Bulging fontanelle (in infants).

- Photophobia.
- Leg pain.
- Capillary refill time >2 seconds, cold hands and feet.
- Unusual skin colour.
- Altered mental state, unconsciousness, toxic/moribund state.
- Shock: other signs of shock include tachycardia and/or hypotension, respiratory distress, poor urine output in addition to increased capillary refill time, altered mental state, leg pain, cold hands and feet and unusual skin colour.
- Kernig's sign (pain and resistance on passive knee extension with hips fully flexed).
- Brudzinski's sign (hips flex on bending the head forward).
- Paresis, focal neurological deficits (including cranial nerve involvement and abnormal pupils).
- Seizures.

It often presents a diagnostic challenge in the early stages in primary care:

- In the early stage of meningitis, features can be vague and nonspecific, similar to other infectious conditions with less catastrophic outcomes than meningococcal disease, making diagnosis a challenge in primary care, and safety-netting information particularly important. The disease can progress very rapidly.
- Classic symptoms are not evident in infants and also not often seen in the elderly.
- Fever is not necessarily present, especially in neonates.
- Some children and young people will present with mostly nonspecific symptoms or signs and the conditions may be difficult to distinguish from other less important infections presenting in this way. Children and young people under the age of 16 with more specific symptoms and signs are more likely to have bacterial meningitis or meningococcal septicaemia and the symptoms and signs may become more severe and more specific over time.

- A study of children aged 16 years or younger with meningococcal disease found that classical signs such as haemorrhagic rash, meningism and impaired consciousness did not tend to appear until after 13-22 hours. However, more nonspecific features such as leg pain, cold hands and feet and abnormal skin colour appeared much earlier with a median onset of 7-12 hours. These earlier features are thus very important in early diagnosis and therefore earlier initiation of potentially life-saving treatment [13].
- Most patients with viral meningitis present with subacute neurological symptoms developing over 1-7 days. Chronic symptoms lasting longer than one week suggest meningitis caused by some viruses as well as TB, syphilis or fungi. Viral meningitis may be clinically indistinguishable from bacterial meningitis but features may be more mild and complications (eg, focal neurological deficits) less frequent. Any person presenting with suspected meningitis should be managed as having bacterial meningitis until proved otherwise.

Early recognition of bacterial meningitis/meningococcal disease is vital to improve prognosis.

Differential diagnosis

- Other causes of pyrexia and severe infection.
- Intracranial abscess.
- Other causes of altered mental state and coma - eg, encephalitis, subarachnoid haemorrhage, brain tumours.
- Other causes of petechial/purpuric rashes. (In the face this may occur due to coughing, sneezing, or vomiting.)

Investigations [2] [5] [8]

Investigations must not delay treatment. Diagnosis can only be confirmed in secondary care by lumbar puncture followed by laboratory examination of the CSF.

Lumbar puncture (LP)

See the separate Lumbar Puncture and Cerebrospinal Fluid articles for normal values and interpretation of abnormal CSF findings.

LP is performed immediately provided there are no signs of raised intracranial pressure (reduced consciousness, very bad headache, frequent fits), focal neurology, severe shock or sepsis. Ideally LP should be performed within an hour of arrival at hospital and treatment commenced immediately afterwards, with the rationale being that the LP is performed before starting antibiotics to allow the best chance of a definitive diagnosis of causative organism, and subsequently appropriate treatment. Samples of CSF are usually sent for white blood cell count and differential, Gram stain, glucose, protein, lactate, culture, and meningococcal and pneumococcal polymerase chain reaction (PCR). Further tests on saved CSF can be performed if no aetiology is found at first, such as virology, etc. CSF may be normal in the early stages of meningitis so the LP is usually repeated if symptoms and signs persist.

Tests performed in secondary care for children and young people

If a child or young person under the age of 16 years has an unexplained petechial rash and fever (or history of fever) the following investigations are often performed in secondary care:

- FBC.
- CRP.
- Coagulation screen.
- Blood culture.
- Whole-blood PCR for *N. meningitidis*.
- Blood glucose.
- Blood gases.

Other investigations for all ages

Apart from the above, other tests often required include:

- Renal function tests
- Coagulation profile: especially if disseminated intravascular coagulation is suspected.
- CXR (lung abscess).
- Culture urine, nasopharyngeal swabs and stool (virology).

- CT scan is usually reserved for those with specific adverse clinical features or when an underlying cause such as mastoiditis is suspected. It is not usually indicated or advisable before LP, as it may further delay appropriate treatment and is not reliable for identifying raised intracranial pressure. It may be used prior to LP where there are signs of brain shift such as focal neurology or a reduced Glasgow coma scale score. (The exact level of score is debatable and a recent study suggested that proceeding with an LP without a CT scan in patients with altered awareness may in fact reduce mortality [14].)
- Other possible investigations:
    - Serum cryptococcal antigen, especially if the baseline is known (less diagnostic than India ink and CSF cryptococcal antigen).
    - Serology of blood, urine and CSF for specific bacterial antigens is occasionally recommended if there is diagnostic doubt or in patients with partially treated meningitis.
    - Serum test for syphilis if neurosyphilis is suspected.

Management

Management includes supportive treatment (including fluids, antipyretics, antiemetics), treatment of the causative organism and treatment of any complications - eg, seizures, raised intracranial pressure. See also the articles on specific infections for management of rarer causes of meningitis such as tuberculosis, fungi and parasites.

Management of viral meningitis [5] [6]

- The general principles of management for all viral meningitis include supportive therapy - eg, analgesia, antipyretics, nutritional support and hydration. There is no specific treatment for viral meningitis.
- Enteroviral meningitis: usually self-limiting and no specific therapy is required unless there is hypogammaglobulinaemia (immunoglobulins required).

- Aciclovir is considered beneficial in treating herpetic viral infections but only if given very early in the course of the infection and evidence for benefit is limited. Intravenous aciclovir should be started immediately if there is any suspicion of herpes simplex encephalitis. Evidence for benefit is for encephalitis, not for meningitis.
- Ganciclovir is effective for cytomegalovirus (CMV) infections but it has significant renal toxicity and close monitoring is mandatory.

Management of bacterial meningitis [2] [8]

Management in primary care

- The priority is urgent transfer to hospital.
- Transfer any patient with suspected bacterial meningitis or suspected meningococcal septicaemia to secondary care as an emergency by telephoning (if in the UK) 999.
- National Institute for Health and Care Excellence (NICE) guidelines for those under the age of 16 years advises that intramuscular or intravenous benzylpenicillin should be given before urgent transfer to hospital only if there is suspected meningococcal septicaemia with a non-blanching rash.
- Benzylpenicillin should not be given if there is a history of anaphylaxis associated with penicillins or if giving antibiotics will delay urgent transfer to hospital.
- If urgent transfer to hospital is not possible (eg, remote locations or adverse weather conditions), antibiotics should be given to any person with suspected bacterial meningitis.
- UK guidelines for management in adults advise that benzylpenicillin (or a third-generation cephalosporin) is given immediately to those with signs of severe sepsis (hypotension, altered mental state, poor capillary refill time) or where it will take more than an hour to get the person to hospital.
- Dose of immediate benzylpenicillin (where there is suspected meningococcal disease with a non-blanching rash or urgent transfer is not possible):
  - Children younger than 1 year of age: 300 mg.
  - Children 1-9 years of age: 600 mg.
  - Adults and children 10 years of age or older: 1200 mg.

Management in secondary care

- Management includes supportive treatment with analgesia, antipyretics, nutritional support and hydration. Metabolic and circulatory disturbances should be anticipated, monitored and corrected where necessary (hypoglycaemia, acidosis, hypokalaemia, hypocalcaemia, hypomagnesaemia, dehydration, anaemia and coagulopathy).
- Fluids should not be restricted unless there is evidence of raised intracranial pressure or increased antidiuretic hormone (ADH) secretion.
- The choice of antibiotics and the duration of therapy should be guided by the microbiological diagnosis but initial 'blind' antibiotic therapy must be started immediately (see below).
- The NICE recommendation for children (over 3 months old) is for dexamethasone to be given for suspected or confirmed bacterial meningitis as soon as possible (0.15 mg/kg to a maximum dose of 10 mg, four times daily for four days). Similarly adult guidelines recommend intravenous dexamethasone 10 mg four times a day, to be continued for four days if pneumococcal infection is confirmed, but stopped if another cause is found or suspected. This is based on balancing risks and benefits and the findings of a Cochrane review on the use of steroids in meningitis [15].

Initial 'blind' therapy

- Children 3 months and older, young people and adults under the age of 60 should be given intravenous ceftriaxone as empirical treatment before identification of the causative organism. If calcium-containing infusions are required at the same time, cefotaxime is preferable. Those aged over 60 and those who are immunocompromised should also receive intravenous ampicillin or amoxicillin in addition.
- Children younger than 3 months should be given intravenous cefotaxime plus either amoxicillin or ampicillin. **NB**: ceftriaxone should *not* be used in premature babies or in babies with jaundice, hypoalbuminaemia or acidosis, as it may exacerbate hyperbilirubinaemia.

- Antibiotic choice may be modified once a causative organism has been identified.

Meningitis caused by meningococci *(N. meningitidis)*

- Intravenous ceftriaxone for at least seven days is usually used. Adult guidelines advise cefotaxime may be used as an alternative.
- Prevention of secondary cases for close contacts of those with meningococcal meningitis is usually with ciprofloxacin or rifampicin.

See also the separate Meningococcal Disease article.

Meningitis caused by *S. pneumoniae*

- In children over the age of 3 months, ceftriaxone for 14 days is recommended.
- In adults, benzylpenicillin may be given if the organism is penicillin-sensitive, but depending on sensitivities, ceftriaxone, cefotaxime, vancomycin and rifampicin may also be used.

Meningitis caused by *H. influenzae* type b

- Children aged 3 months and older and young people - intravenous ceftriaxone for 10 days in total unless directed otherwise by the results of antibiotic sensitivities.
- In adults, cefotaxime or ceftriaxone is recommended first line.

Meningitis caused by group B streptococci
This mainly occurs in babies between the ages of 7-90 days. Intravenous cefotaxime for at least 14 days should be given.

Meningitis caused by listeriosis
For children under the age of 3 months, intravenous amoxicillin or ampicillin for 21 days in total, plus gentamicin for at least the first seven days. In adults, amoxicillin is recommended as first-line, with co-trimoxazole as an alternative option.

Complications

- Immediate: septic shock, including disseminated intravascular coagulation, coma with loss of protective airway reflexes, cerebral oedema and raised intracranial pressure, septic arthritis, pericardial effusion and haemolytic anaemia (*H. influenzae*).
- Subdural effusions are a common complication in young children. Risk factors include young age, rapid onset of illness, low peripheral white cell count and high CSF protein.
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH).
- Seizures: occur more commonly during the acute stage of the disease.
- Delayed: decreased hearing, or deafness; other cranial nerve dysfunction, multiple seizures, focal paralysis, hydrocephalus, intellectual deficits, ataxia, visual impairment, Waterhouse-Friderichsen syndrome and peripheral gangrene.
- 30-50% of survivors of acute bacterial meningitis have permanent neurological sequelae, and over recent years the reduction in overall mortality has not been matched by a reduction in rate of complications [1].

Prognosis

- Meningitis is one of the top ten causes of infection-related death worldwide, and NICE guidance states that it is the leading infectious cause of death in children in the UK [1] [2].
- Prognosis depends on the pathogen, the patient's age and condition and the severity of acute illness.
- Patients with severe neurological impairment on presentation or with extremely rapid onset of illness, even if treated immediately, have a very high mortality rate and an even higher rate of morbidity.

- There is a significant risk of death in bacterial meningitis, but this is very low for other causes. Meningococcal disease has a better prognosis when meningitis accompanies the septicaemia than when it does not. Up to 57% of those with meningococcal sepsis do not survive, and 7% who have meningococcal meningitis without sepsis do not survive [5]. 30% of those with pneumococcal meningitis without sepsis die. Pneumococcal meningitis is associated with a higher rate of mortality and morbidity than other bacterial causes [10].
- Poor prognostic factors in those under 18 years include symptoms lasting more than 48 hours before admission, coma/impaired consciousness, prolonged seizures, prolonged fever, shock, peripheral circulatory failure, respiratory distress, absence of petechiae, young age, and *S. pneumoniae* being the causative organism [1].
- The prognosis for viral meningitis is usually excellent, with complete resolution usually within 10 days. There may be longer-term sequelae, including headaches, and cognitive and psychological issues [5].

Prevention

See the separate Immunisation Schedule (UK), Hib Vaccination, Meningococcal Vaccination and Pneumococcal Vaccination articles.

- Vaccination programme. In the UK, this currently includes [16]:
  - Childhood vaccination against *H. influenzae* type b, meningococcus groups B and C and *S. pneumoniae*.
  - Quadrivalent vaccine (meningococcus groups A, C, W, Y) for teenagers.
  - Pneumococcal vaccination in those aged 65 years.
- Intrapartum screening for Group B streptococcus and antibiotic prophylaxis.
- Meningitis and meningococcal sepsis are notifiable diseases in the UK. Appropriate antibiotic prophylaxis of people in close contact with those diagnosed is arranged by the local public health team.

Further reading

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- Resources for health professionals and their patients; Meningitis Research Foundation

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