11.8
Meningitis and CNS infections

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Acute bacterial meningitis

Meningitis is an inflammation of the pia and arachnoid meninges and the cerebrospinal fluid (CSF) that surrounds the brain and spinal cord. The main causes are viral and bacterial. Meningitis is classified as acute or chronic. Acute meningitis occurs within hours or days and is classified as aseptic which is mostly viral in origin or septic which is caused by bacteria. Chronic meningitis by definition persists for 4 or more weeks and is mainly caused by tuberculosis and fungal infection. The aim of this chapter is to provide an overview of acute bacterial meningitis and to give a brief account of some other main central nervous system (CNS) infections encountered in clinical practice.

Epidemiology

The main causes of acute bacterial meningitis are *Neisseria meningitidis, Streptococcus pneumoniae, Listeria monocytogenes*, and *Haemophilus influenzae* type b (Hib). Each year, there are over 2000 new cases of acute bacterial meningitis in England and Wales giving an annual incidence rate of approximately 5 per 100 000 (Table 1). Similar rates have been reported in Europe with somewhat lower rates in the United States.(1) The epidemiology of acute bacterial meningitis has changed markedly in the last decade with a 95 per cent decrease in the incidence of Hib meningitis and a 75 per cent decrease in the incidence of serogroup C meningococcal infection. This decrease is mainly due to the introduction of the conjugated Hib vaccine and more recently the meningococcal conjugated C vaccine. Prior to this Hib was responsible for almost half the total annual cases of meningitis and the mean age of onset was 15 months.(2) Hib now accounts for only 1–2 per cent of overall cases of meningitis and the mean age has increased to 25 years.

Table 1 The approximate annual incidence of CNS infections in England and Wales (pop. 51 million)

	New cases per 100 000 pop. per annum	Years between two cases in a list of 2000 patients
Viral meningitis	20	2.5

Viral encephalitis	5–10	10–5
Bacterial meningitis	5	10
Meningococcal disease	5	10
Herpes encephalitis	0.2	250
CNS tuberculosis	0.2	250

The annual incidence of meningococcal disease in England and Wales is also approximately 5 per 100 000. This figure includes both cases of septicaemia and meningitis. In England and Wales, meningococcal meningitis is the major cause of acute bacterial meningitis accounting for 60 per cent of overall cases giving an incidence rate of 2–3 per 100 000.(3) A lower incidence rate of 0.6 per 100 000 has been reported in the United States where it accounts for about 25 per cent of overall cases.(2) In England and Wales, pneumococcal meningitis accounts for 13 per cent of meningitis cases giving an incidence rate of 0.5 per 100 000. In contrast, an incidence rate of 1.1 per 100 000 has been reported in the United States where it is the most common cause of bacterial meningitis.(2) Listeria meningitis (8 per cent) is the third most common cause, an incidence rate of 0.2 per 100 000 has been reported in the United States.(2)

Frequency in primary care

The frequency of the main CNS infections in the general population and in family practice in England and Wales is presented in Table 1.

Aetiology

Neisseria meningitidis

Neisseria meningitidis is a gram-negative diplococcus and infection results in meningococcal disease. The term meningococcal disease includes meningitis alone (45 per cent), meningitis and septicaemia (45 per cent), and septicaemia alone (10 per cent). The incubation period is 2–7 days. The peak incidence is in children aged 1–24 months with a second peak in teenagers aged 15–19 years, together accounting for 70–80 per cent of all cases. Most infections are sporadic and occur in winter but outbreaks can occur in households and schools. Risk factors for infection include household contact, asplenism,

influenza A, smoking in a household member, IgM, IgG and complement deficiencies, and travel to an endemic area. Meningococcus is classified into serogroups, including A, B, C, W135, and Y. Serogroup B is most common accounting for about two-thirds of cases and is on the increase. It occurs mostly in children and has no vaccine. Serogroup C mainly affects teenagers as clusters in schools and universities, causes most of the remaining cases and now has an effective vaccine. The incidence in this serogroup has rapidly declined since the introduction of a vaccine in 1999. Serogroup A is important worldwide causing large epidemics in Sub-Saharan Africa but is rare in Western countries. There are effective vaccines for serogroups A and C combined and more recently for the serogroup W135 which has occurred in pilgrims returning from Saudi Arabia. Serogroup Y is rare in the United Kingdom but common in North America.

Streptococcus pneumonia

Streptococcus pneumonia is a gram-positive coccus. The incubation period is unknown. It affects mainly adults but can affect all age groups especially

infants aged 1–24 months and has a high mortality. The main source of infection is haematogenous from the respiratory tract. Risk factors for infection include basilar skull fractures, dural defects post-neurosurgery, chronic otitis media, sinusitis, asplenism, alcoholism, and chronic disease. A pneumococcal vaccine is recommended for those at increased risk and more recently for infants in the United States.

Listeria monocytogenes

Listeria meningitis is caused by *L. monocytogenes*, a small gram-positive rod that is commonly found in soil and water. The incubation period is 3–7 days. It can infect humans and animals and mainly leads to asymptomatic faecal excretion. Infection, however, can result in sepsis and meningitis. All age groups are affected but neonates, pregnant women, immunosuppressed, and the elderly are at increased risk. Sources of infection are contaminated vegetables, unpasteurized milk, soft cheeses, paté and chilled meats. The organism replicates at fridge temperatures and can survive heating up to 60°C. Prevention largely depends on adequate food hygiene, heating of chilled foods and avoidance of high-risk foods by those at risk.

Other less common causes of acute bacterial meningitis include Hib, *E. coli*, group B streptococcus, and *Staphylococcus aureus.*

Pathogenesis

With the exception of Listeria, all the main bacterial causes of meningitis colonize the nasopharynx of asymptomatic carriers. Colonization rates of around 10 per cent are common place with higher rates (20–50 per cent) in winter in children, young adults and case contacts. Spreads is by droplets or close physical contact with asymptomatic carriers (95 per cent) or occasionally direct from cases. Bacteria reach the meninges via the bloodstream or by direct invasion, and the presence of a polysaccharide capsule helps their survival in the blood stream. Clinical disease is rare and only occurs when there is septicaemia or penetration across the blood–brain barrier. The multiplication of bacteria in

the CSF triggers a massive host immune response with release of inflammatory cytokines and accumulation of cells and exudate. This leads to a further breakdown in the blood–brain barrier with resultant cerebral oedema, raised intracranial pressure, cerebral thrombosis, and infarction.

Clinical diagnosis

The classical clinical features of acute bacterial meningitis are headache, fever, and neck stiffness. When this triad is accompanied by alteration in consiousness or seizures the diagnosis of meningitis is usually not in doubt. Other common presenting symptoms include photophobia, nausea, vomiting, backache, and lethargy. The finding of a haemorrhagic rash is strongly suggestive of meningococcal infection. Progression occurs in most cases over 1–3 days, a small number have an acute fulminant course lasting hours while a third group progress rapidly over 24 hours. The cardinal signs of meningitis are *neck stiffness, Kernig's and Brudzinski's signs.* These are usually elicited with the patient in the supine position and should be checked for in all suspected cases of meningitis. Neck stiffness is the most important sign and is present when the neck resists passive flexion to bring the chin on to the chest. It is found in about 90 per cent of adults and 60–80 per cent of children with meningitis. *Kernig's sign* is elicited by passively attempting to straighten the leg with the hip and knee flexed to more than 90°. In cases of meningitis, there is resistance and pain caused by spasm in the hamstrings as a result of stretching inflamed nerve roots. Forward flexing the neck elicits Brudzinski's sign, and in cases of meningitis, there is involuntary hip and knee flexion. This sign is elicited mainly in young children. These signs are present in most cases of established meningitis but are less likely in the very young and the elderly. In infants, the combination of fever, respiratory distress, irritability, crying, vomiting, drowsiness, and failure to feed may be the only findings. The association of bulging fontanel, neck retraction, and seizures should however suggest the diagnosis. In older children and adults, there may be backpain and myalgia in addition to the classic features. In the elderly, an alteration in level of consiousness and fever may be the only findings. Seizures occur in about one-third of patients typically in children and may be the presenting complaint. Focal neurological abnormalities and coma occur mainly as complications. There may also be evidence of infection outside the CNS or an underlying condition predisposing to meningitis. The main differential diagnosis in primary care includes viral meningitis, viral childhood exanthema, encephalitis, and subarachnoid haemorrhage.

Meningococcal disease

The main clinical features of meningococcal disease are outlined in Table 2. The onset is typically abrupt and disease develops in most patients over 24–48 h. The pathognomonic feature is the haemorrhagic rash, which is non-blanching and present in around 80 per cent of cases. About 10 per cent of cases have a maculopapular rash, which is non-haemorrhagic, erythematous, and blanching while the remainder have no rash at all. The rash of meningococcaemia may begin as a diffuse pink maculopapular rash in 20–25 per cent of children. It has a characteristic ‘flea bitten’ appearance on the limbs and trunk. Associated symptoms at this stage may be non-specific resembling influenza; and the diagnosis of meningitis is extremely difficult. In a matter of hours, a petechial and purpuric

rash develops in about 80–90 per cent of children and 60–70 per cent of adults. This appears first as small flat red or purple spots over the trunk, buttocks or lower limbs before becoming more widely distributed on the arms and soles of feet. The lesions do not blanch under pressure and this can be confirmed by gentle pressure with a glass when the rash can be seen to persist. Parents are encouraged to use this '*tumbler test*'. A common error is failure to examine the concealed areas such as buttocks groins and axillae. In dark-skinned patients, the conjunctiva, palate, soles, and palms should be examined particularly. Pethechiae may later progress to larger confluent purpuric areas with central necrosis in a condition called purpura fulminans.

Table 2 Presenting clinical features of meningococcal disease

Non-specific features	%	Major clinical features	%
Fever	71–100	Petechial/purpuric rash	48–71
Nausea/vomiting	34–69	Neck stiffness	71–79
Upper respiratory tract infection	10–27	Altered level of consciousness	65–91
Any rash	71–93	Seizures	4–21
Headache	34		

Based on review of five series of admission hospital records, Granier, et al. (1998).

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The clinical features of meningococcal septicaemia may vary from mildly symptomatic patients with positive blood cultures to acute fulminant infection, which is one of the most feared of all infections. Symptoms can progress rapidly from drowsiness and rash to circulatory failure, toxic shock, coma, and death within hours of onset. Complications

include skin necrosis, serositis, gangrene, arthritis, and Waterhouse–Friderichson syndrome of adrenal failure.

Pneumococcal meningitis typically presents with marked meningism. It generally lacks a rash but pneumonia may be present. Patients tend to progresses rapidly in 24–48 hours to drowsiness, confusion, coma, and seizures. Listerial infection is frequently asymptomatic in the normal host but causes acute sepsis and meningitis in the neonate and a subacute meningitis in the at risk adult. Hib meningitis has a characteristic slow onset over several days often starting with fever or respiratory tract infection. The onset of drowsiness, vomiting, and convulsions in an infant in this setting may suggest the diagnosis.

Meningitis in primary care

The average doctor in primary care will encounter only one new case of acute bacterial meningitis every 10 years (Table 1). While the diagnosis of the classical case is relatively straightforward the main difficulty in primary

care is discriminating between the rare patient with a life-threatening meningitis and the majority with similar symptoms but self-limiting viral illnesses.(4) Failure to make the correct diagnosis most often occurs in the early stages, in the young and elderly. Symptoms and signs that are strongly suggestive of meningitis in the hospital setting may be non-specific or be absent altogether in primary care. In one primary care study on patients presenting with new onset headache, only 0.4 per cent had meningitis,(5) whereas on average 2 per cent of the population consult their doctor annually for headache. Notably, about half the cases of meningitis are missed at the time of first examination mainly because of the absence of meningism and a rash.(6,7,8 and 9) The rash has been identified as one of the most important factors in primary care in the decision to refer to hospital.(10,11) Primary care doctors therefore need a high index of clinical suspicion and vigilance and need constantly to be aware of the possibility of meningitis. They need to examine for signs of meningitis in any ill or febrile patient particularly where the diagnosis is in doubt. Every effort should be made to revisit or recall ‘sick patients’ with puzzling findings especially if clinical deterioration or a rash develops or parents become concerned. There should also be a low threshold for using prophylactic antibiotics and hospital referral.

Key messages in primary care

- Half of all cases of acute bacterial meningitis are missed at first visit.
- The signs of meningitis may be absent in the early stages and in infants and the elderly.
- The characteristic haemorrhagic rash may be absent in meningococcal disease.
- The diagnosis of meningitis requires a high index of clinical suspicion.
- Doctors should re-examine febrile sick patients with puzzling symptoms and trust parents' instincts.
- The mainstay of management is early recognition, prompt antibiotics and urgent

transfer to hospital.

- *Neisseria meningitidis* infection is the leading infectious cause of death in children and young adults.
- All children who recover should have a formal hearing test.

Outcome

Bacterial meningitis is the leading infectious disease cause of death in children and young adults in western countries. Nearly 20 per cent of patients with bacterial meningitis die and this figure has changed little in the last 20 years. Poor prognostic factors include coma, short duration of symptoms, lack of meningism, shock, extensive purpura, and seizures.(12) The overall mortality in meningococcal disease is 8–10 per cent. It ranges from 2 to 4 per cent in uncomplicated meningitis to over 20 per cent in septicaemia and 50 per cent in shock. By age group, mortality rate is lowest in those aged 5–9 years with higher rates in young children and teenagers. It reaches 40–50 per cent in neonates and the elderly. By organism, it ranges from 3 to 6 per cent in meningococcal and Hib infection to 15–20 per cent in *S. pneumonia* and *N. meningitidis.* Permanent neurologic deficits persist in 10–20 per cent of adults, 10–30 per cent of children, and 15–50 per cent of neonates. These include deafness, cranial nerve palsies, seizures, paralysis, cognitive impairment, and sometimes blindness. They are more common after *S. pneumococcus* and Hib infection.

Management

The mainstay of effective management of suspected meningitis is early recognition, immediate use of antibiotics and rapid referral to hospital.(13) Family practitioners are advised to carry benzylpenicillin in their bag at all times. There is evidence that preadmission parenteral penicillin reduces mortality in meningococcal disease. The aim is that all cases should have benzylpenicillin within 30 minutes of suspected diagnosis. The preferred route is intravenously or failing that intramuscularly. Recommended dosages are 300 mg for children under 1 year, 600 mg for children aged 1–9 years, and 1200 mg for children aged 10 years and adults. A history of anaphylaxis is a contraindication for penicillin but a history of a rash following penicillin is not. Alternative antibiotics include cefotaxime and ceftriaxone especially in countries with penicillin-resistant *S. pneumoniae.* Attention to airway, oxygen administration, and seizure control on route to hospital may also be necessary.

Prevention

Meningococcal disease is a notifiable disease. All suspected cases should be reported immediately to the Public Health Authority. Chemoprophylaxis is required for household contacts and close contacts of the index case within the previous 7 days.(13) Adults and children over 12 years should receive Rifampicin 600 mg orally twice daily for 2 days or Ciprofloxacin 500 mg orally as a single dose. For children 1–12 years use Rifampicin 10 mg/kg twice daily for 2 days or ceftriaxone 125 mg IM as a single dose. Infants require lower doses. Contacts of vaccine preventable strains should also be offered vaccination in

addition to chemoprophylaxis. For Hib meningitis, Rifampicin 20 mg/kg daily (maximum 600 mg daily) as a single dose for 4 days is recommended for all household and nursery contacts when other children below age 4 years are present. Chemoprophylaxis is not recommended for those fully vaccinated against Hib. Chemprophylaxis is not usually indicated for close contacts of pneumococcal meningitis, however asplenic patients should receive long-term penicillin prophylaxis in addition to vaccine.

During the last decade we have witnessed the very effective primary prevention of Hib and *N. meningitidis* serogroup C meningitis. However, it should be noted that the overall incidence of meningitis has not declined and there are still no vaccines available against common causes of bacterial meningitis. There is also a dearth of community-based research on the early recognition and management of bacterial meningitis in primary care. Any future recommendations must include more research in these two key areas.

Other CNS infections

Viral meningitis

Viruses are the leading cause of meningitis worldwide and the commonest cause of meningitis encountered in primary care. Viral meningitis is usually a benign disease with less than 1000 cases reported annually in the United Kingdom. This is considered a gross underestimate as most cases go unreported (Table 1).(14) The overall annual incidence in the United Kingdom is estimated to be about 20 per 100 000. It is commonest in the age groups 0–1 years and 4–15 years but can affect all age groups. The *enteroviruses, echo and coxsackie* viruses account for over 90 per cent of cases. Other viruses include *arboviruses, adenoviruses*, and more recently, *HSV-2.* Young children are the usual source with spread via the faecal oral route within families. Outbreaks frequently occur in hospitals, nurseries, schools, and residential homes. It occurs throughout the year with a seasonal peak in summer. There may be a history of a viral like illness with rash. The onset can be acute or subacute with severe headache, photophobia and fever occur in most patients. Neck stiffness is frequently mild and only present in half the cases. Neurologic abnormalities are rare but febrile convulsions may occur in children. The illness can last over a week in children and longer in adults. The prognosis is generally excellent. Clinically, at onset it can be indistinguishable from bacterial meningitis and often requires provisional emergency antibiotics followed by prompt hospital

referral. A lumbar puncture and CSF examination are usually diagnostic. Treatment is mainly symptomatic and mild cases can be observed at home and the diagnosis reviewed. Suspected *HSV-2* infection may be treated with acyclovir.

Viral encephalitis

Encephalitis is inflammation of the brain. It is predominantly a disease of children. The incidence of encephalitis ranges from 8 to 30 per 100 000 in children to approximately 5 per 100 000 in adults (Table 1).(14) The causes of encephalitis include the *epidemic viruses, enteroviruses* and the *arthropod-borne viruses. Herpes simplex type 1, (HSV1)* an endemic herpes virus is the most common sporadic cause of encephalitis in adults in

Western countries. It occurs mostly in the over-50s, but can affect all age groups. Fewer than 100 cases are reported annually in the United Kingdom but this is considered an underestimate. Clinically HSV encephalitis usually begins as a non-specific febrile illness characterized by headache often unilateral, malaise, and altered mental status. Most patients go on to experience confusion, personality change, dysphasia, focal neurological findings and temporal lobe seizures. Symptoms typically evolve over several days and often take 2–3 weeks to reach their maximum severity. Suspected cases are transferred urgently to hospital and treated with intravenous acyclovir. The prognosis is particularly poor in coma. The case fatality rate in treated cases is around 20 per cent, in untreated cases it is 50–70 per cent. Morbidity is over 50 per cent and includes memory loss, cognitive impairment, and seizures.

Tuberculosis

Each year an estimated 8 million people worldwide develop clinical tuberculosis, of whom less than 1 per cent go on to develop CNS involvement. Tuberculous meningitis (TBM), tuberculoma, and spinal cord disease are the main clinical presentations. *Mycobacterium tuberculosis* is the main cause. One hundred to 200 cases of TBM are reported annually in England and Wales mostly in adults (Table 1). Risk factors include alcoholism, drug abuse, homelessness, malnutrition, and residence, or travel to endemic area and more recently HIV. TBM typically has a slow onset over 2–3 weeks presenting with chronic unrelenting headache, low-grade fever, tiredness, and mild meningism. Cranial nerve palsies, seizures and confusion develops in half the cases. Coma and death inevitably follow if left untreated. Rarely, the presentation is more acute over a few days. A history of TB exposure or disease is found in about half the cases. The diagnosis is confirmed by demonstrating mycobacterium in the CSF. The case fatality rate is 20–25 per cent. Morbidity (25–40 per cent) includes seizures, hydrocephalus, cranial nerve palsies and paralysis. Spinal cord disease results from spinal tuberculosis or Potts disease.

Brain abscess

Brain abscess is a focal pyogenic infection within the brain, subdural or epidural space. The majority are caused by bacteria including *Streptococcus viridans, S. aureus*, and *bacteroides fragilus.* In immunocompromised patients, toxoplasmosis and fungal infections are the main causes. Each year, approximately 200 cases are reported in the United Kingdom half of whom have a known risk factor. These include otitis media, mastoiditis, sinusitis, dental abscess, recent skull fracture or neurosurgery, bronchiectasis, cyanotic heart disease, and more recently, HIV. They are more common in males with the majority in the third or fourth decade. Over half the patients present with headache, fever, and focal neurological deficits. The fever is usually low grade and seizures occur in about a quarter of patients. The duration from onset to complications takes 1–2 weeks in half the cases. The main differential diagnosis is a brain tumour. The diagnosis is usually suggested by neuroimaging and occasionally by brain biopsy. Management is based on antibiotics, anticonvulsants and surgical drainage. The case fatality rate varies from 10 per cent in uncomplicated cases to 50 per cent in patients with coma. Morbidity is about 30 per cent and includes epilepsy and focal neurological deficits.

HIV

HIV disease and syphilis are worldwide venereal diseases caused by the *human immunodeficiency virus* and the spirochete *Treponema pallidum*, respectively. Neurosyphilis is now extremely rare in western countries and has largely been replaced by HIV disease as a cause of neurological disorders. Neurological disorders occur at all stages of HIV infection and about 10 per cent of AIDS patients will develop a major neurological disorder. These are caused mainly by opportunistic infections including *Toxoplasma gondii, Cryptococcoccus neoformans, Mycobacterium tuberculosis* and tumours including CNS lymphoma. The main clinical presentation is that of a space occupying lesion secondary to toxoplasmosis or lymphoma with headache, confusion, focal neurological deficit, or seizures evolving over 1–2 weeks. *Cryptococcus neoformans* and tuberculosis infection present mainly as chronic meningitis. Other presentations include retinitis caused by *cytomegalovirus* infection and shingles caused by *herpes zoster.* AIDS dementia complex develops in about a fifth of patients, mainly those with advanced disease. This is caused by direct HIV virus and is characterized by difficulty concentrating and remembering and general slowing of mental and motor tasks. Later, frank dementia may set in. The use of highly active antiretroviral treatment has decreased its severity. Peripheral manifestations occur in over half of AIDS patients. These include polyneuropathies, mononeuropathies, myelopathy and myopathy. The diagnosis of HIV is confirmed by serology.

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