Infections of the Nervous System

Chapter Eleven

BACTERIAL INFECTIONS

ACUTE PYOGENIC (BACTERIAL) MENINGITIS

DEFINITION
Inflammation of the leptomeninges (pia and arachnoid membranes) caused by bacterial infection.

EPIDEMIOLOGY
- Annual incidence: 1.9 per 100,000 for Neisseria meningitidis; 1.6 per 100,000 for Haemophilus influenzae; 1.0 per 100,000 for Streptococcus pneumoniae.
- Incidence rates are influenced by country, ethnic group, social class and deprivation, and immunization programmes.
- Lifetime prevalence: 1 (95% CI: 0.8–2) per 1000.
- Age: any age (see Table 33); most common in the first month of life.

<table>
<thead>
<tr>
<th>Table 33 Empirical therapy for suspected bacterial meningitis*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>0–4 weeks</td>
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<tr>
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<tr>
<td></td>
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<td>4–12 weeks</td>
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<tr>
<td>3 months–18 years</td>
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<tr>
<td></td>
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<tr>
<td>18–50 years</td>
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<tr>
<td>&gt;50 years</td>
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</tr>
</tbody>
</table>

*Applies only to the immunocompetent patient

**Add vancomycin to empirical regime when pneumococcal meningitis highly resistant to penicillin or cephalosporin is suspected

***Add if L. monocytogenes meningitis suspected (i.e. deficiencies in cell-mediated immunity)
PATHOLOGY
The fundamental process is inflammation of the leptomeninges (325, 326). Complications include vasculitis, cerebral infarction, hydrocephalus (327), brain abscesses, and cerebral oedema.

AETIOLOGY
The most common organisms causing meningitis are:
• Haemophilus influenzae: 45% of cases.
• Streptococcus pneumoniae (pneumococcus): 18%.
• Neisseria meningitidis (meningococcus): 14%.

However, there are important differences in the patterns of organisms encountered in different age groups (Table 11.1). Listeria monocytogenes, although uncommon, occurs especially during pregnancy and the neonatal period. Among neonates (<1 month of age), group B streptococci (S. agalactiae) and coliforms (particularly Escherichia coli, but also Proteus and Pseudomonas) predominate.

In the 1980s, H. influenzae was the most common cause of meningitis in children 1 month–4 years of age, N. meningitidis predominated in older children and young adults (5–29 years old) and S. pneumoniae in older adults.

During the 1990s widespread use of conjugate H. influenzae type b (Hib) vaccines, consisting of protein combined with the Hib polysaccharide capsule, has virtually eliminated Hib disease from several developed countries (and is now being introduced in developing countries). This reduction means that S. pneumoniae and N. meningitidis have become the predominant causes of meningitis in children. A second epidemiologic trend is the worldwide increase in infection with strains of S. pneumoniae that are resistant to penicillin and other β-lactam antibiotics, mediated by alterations in the penicillin-binding proteins involved in the synthesis of bacterial cell walls.

Risk factors
CSF leak due to:
• Recent craniotomy: risk of staphylococcal meningitis.
• Recent open skull fracture: risk of pneumococcal meningitis, and Gram-negative bacillary (coliform) pathogens, such as Klebsiella spp., E. coli and Pseudomonas spp.
PATHOGENESIS
Organisms may reach the meninges by direct spread from adjacent structures in the skull and spine (middle ear, paranasal sinuses, skull fractures) and via the blood stream.

Bacterial cell wall materials and bacterial products such as endotoxin stimulate the local release of proinflammatory cytokines such as tumour necrosis factor alpha, interleukin 1 and interleukin 6 from host cells and thereby initiate the inflammatory response. Hyperaemia of the meninges is followed by migration of neutrophils into the walls of blood vessels and into the subarachnoid space where the inflammatory infiltrate extends along cranial and spinal nerves. Foci of necrosis develop in vessel walls, sometimes with thrombosis sufficient to cause cerebral infarction and seizures. Fibrino-purulent exudate accumulates in the subarachnoid space and may block the flow of CSF at the base of the brain or in the arachnoid granulations causing hydrocephalus. Infection may become loculated to form abscesses. Cerebral oedema may develop also and raise intracranial pressure.

CLINICAL FEATURES
Meningeal inflammation
Fever, headache, meningismus (neck stiffness), and signs of cerebral dysfunction (confusion, delirium, vomiting or declining consciousness) are found in about 85% of patients at presentation. Meningismus is accompanied by Kernig’s and/or Brudzinski signs in about half of adults.

Complications
• Cranial nerve palsies, particularly nerves III, IV, VI and VII (30% of cases).
• Deafness due to cochlear damage either by a direct effect of bacterial toxins or by an indirect cytokine-mediated effect.
• Epileptic seizures (30%) or focal neurological signs (10–20% of cases), due to inflammation and thrombosis of cortical arteries and veins and venous sinuses (causing cerebral infarction), or subdural effusion.
• Signs of increased intracranial pressure (coma, cranial nerve III palsy, hypertension, bradycardia) due to hydrocephalus or cerebral oedema, or subdural effusion. Papilloedema is unusual at presentation (<1% of cases), and should suggest an alternative diagnosis at that time, but is more common among acutely ill patients who are deteriorating.

AETIOLOGICAL CLUES
• Sources of infection: evidence of suppuration may be present in the ears (otitis media), paranasal sinuses, skin, lungs, and heart (infective endocarditis).
• Skin rash: primarily on the limbs, that is typically erythematous and macular early in the infection, but may quickly evolve into a petechial phase with further coalescence into a purpuric form, is present in about 50% of patients with meningococcaemia, with or without meningitis (328, 329).
• Features of a rhombencephalitis, such as ataxia, cranial nerve palsies, and nystagmus early in the clinical course may indicate Listeria monocytogenes meningitis.

Atypical presentations
Neonates and infants
Change in affect or state of alertness, irritability, lethargy, listlessness, feeding difficulties, weak suck, high-pitched crying, fretfulness, vomiting, diarrhoea, respiratory distress, temperature instability (fever or hypothermia), or jaundice. Neck stiffness may be absent. A bulging fontanelle is found in one-third of cases and usually occurs late in the course of the illness.

Elderly patients (particularly with diabetes or cardiopulmonary disease)
May present insidiously with lethargy or obtundation, no fever, and variable signs of meningeal inflammation.

Neutropenic patients
Symptoms and signs may be subtle because of the impaired ability to mount an inflammatory response in the subarachnoid space.

328, 329 Purpuric skin rash. Rash in an unconscious child (328) and adult (329) with meningococcal meningitis and septicaemia. (Courtesy of Dr AM Chancellor, Tauranga, New Zealand.)
DIFFERENTIAL DIAGNOSIS

Meningitis due to non-bacterial causes

Aseptic meningitis (see p.291)
The physical signs are not so marked and the illness is not as severe and prolonged as bacterial meningitis. A CSF finding of >2000 white cells/µl, >1180 neutrophils/µl, protein >22 g/l (>220 mg/dl), glucose <1.9 mmol/l (<34 mg/dl), or a glucose ratio below 0.23 are individual CSF predictors of bacterial, rather than viral, meningitis, with 99% certainty or better.

Tuberculous meningitis
CSF white cell count predominantly lymphocytic and seldom >1000/mm³; CSF protein can be very high (>10 g/l [1000 mg/dl]).

Fungal meningitis (Cryptococcus neoformans, Candida, aspergillus, histoplasma)
Insidious onset, often immunosuppressed (HIV infection, lymphoma, leukaemia, other malignancies), with capsular antigen present in serum and CSF.

Protozoal meningitis
Toxoplasmosis causes meningo-encephalitis and brain abscesses in people who are usually immunosuppressed with HIV infection, malignancy or immunosuppressive therapy.

Other
- Subarachnoid haemorrhage (see p.249).
- Acute prolapsed cervical disc (see pp.545, 550).
- Brain abscess and subdural empyema (see p.284).
- Migraine (see p.95).
- Acute tonsillitis, parotitis, cervical lymphadenitis and pneumonia: may cause neck pain in children but meningism is uncommon.

INVESTIGATIONS

Brain imaging
The imaging modality of choice is either CT or MRI; typically neither will show any abnormality in the early stages of uncomplicated meningitis. The main reason for imaging in suspected meningitis is to exclude other causes of headache, focal neurological signs or papilloedema (such as a mass lesion), and to ensure that it is safe to do a lumbar puncture (LP).

In cases presenting later, or with proven bacterial meningitis, the following features may be seen:
- Hydrocephalus (dilated ventricles) (327), enlarged CSF spaces (basal cisterns and interhemispheric fissure).
- Sediment in the posterior horns of the lateral ventricles (pus) (330).
- Absence of the basal cisterns (due to inflamed meninges and pus).
- Areas of altered density in the brain parenchyma representing infarction (secondary to vasculitis) or cerebritis (these areas may enhance).
- After i.v. contrast, periventricular enhancement (indicating ventriculitis) or enhancement in the basal cisterns (from inflamed meninges).

<table>
<thead>
<tr>
<th>Infection</th>
<th>Cells/mm³</th>
<th>Protein (g/l [mg/dl])</th>
<th>Glucose (mmol/l [mg/dl])</th>
<th>Bacteriology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0–4 mononuclears</td>
<td>0.15–0.45 (15–45)</td>
<td>2.9–4.6 (52–83)</td>
<td>Negative</td>
</tr>
<tr>
<td>Bacterial meningitis: acute</td>
<td>10³ polymorphs</td>
<td>Increased</td>
<td>Markedly decreased</td>
<td>Bacteria +ve</td>
</tr>
<tr>
<td>Bacterial meningitis: partially treated</td>
<td>10²–10³ mononuclears or polymorphs</td>
<td>Normal or increased</td>
<td>Normal or decreased</td>
<td>Bacteria +ve or -ve</td>
</tr>
<tr>
<td>Aseptic meningitis*</td>
<td>10–10² mononuclears</td>
<td>Normal or increased</td>
<td>Normal**</td>
<td>Viruses</td>
</tr>
<tr>
<td>Meningoencephalitis</td>
<td>10–10² mononuclears</td>
<td>Normal or increased</td>
<td>Normal**</td>
<td>Viruses or -ve</td>
</tr>
<tr>
<td>Tuberculous meningitis</td>
<td>10–10² mononuclears</td>
<td>Increased</td>
<td>Decreased</td>
<td>Acid-fast bacilli +ve</td>
</tr>
<tr>
<td>Fungal meningitis</td>
<td>10–10² mononuclears</td>
<td>Increased</td>
<td>Decreased</td>
<td>Organism +ve</td>
</tr>
<tr>
<td>Carcinomatous meningitis</td>
<td>10–10² mononuclears</td>
<td>Increased</td>
<td>Normal or decreased</td>
<td>Malignant cells</td>
</tr>
<tr>
<td>Syphilitic meningitis</td>
<td>10–10² mononuclears</td>
<td>Increased</td>
<td>Normal**</td>
<td>Serological tests +ve</td>
</tr>
<tr>
<td>Subacute sclerosing panencephalitis</td>
<td>Normal raised gamma globulins</td>
<td>Increased</td>
<td>Normal</td>
<td>Measles antibody titre very high</td>
</tr>
<tr>
<td>Creutzfeldt–Jakob disease</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Progressive multifocal leucoencephalopathy</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
• MRI is more sensitive to the enhancement following contrast than CT.
• Evidence of local infection such as sinusitis or mastoiditis should be sought (opacified sinuses).
• Late complications include generalized atrophy, infarction, subdural empyema, mycotic aneurysms and loculated CSF collections.
• In cases of recurrent meningitis, a connection between the nasal or middle ear spaces and the CSF should be suspected and a contrast CT cisternogram performed to identify a leak when the patient is well.

CSF (and simultaneous blood glucose) (see Table 34)
If no focal neurological signs are present, LP should be performed immediately and the CSF examined for cell count, protein, glucose, polymerase chain reaction (PCR), and cultured:
• White cell count: usually 1000–5000/mm³ with a neutrophil predominance; lymphocyte predominance in 10%, particularly L. monocytogenes meningitis and newborns with Gram-negative bacillary meningitis. A very low CSF white cell count (0–20/mm³) in conjunction with high CSF bacterial concentrations indicates a poor prognosis.
• Gram stain: positive in 60–90% of untreated cases and 40–60% of partially treated patients. Specificity nearly 100%.
• Protein: raised (1–5 g/l [100–500 mg/dl]) in virtually all patients.
• Glucose: low (below 2.22 mmol/l [40 mg/dl]) in 60% of patients. The CSF: serum glucose ratio is below 0.31 in 70% of cases.
• Culture: positive in 70–85% of untreated and <50% of partially treated meningitis.

Latex agglutination test for bacterial antigen (H. influenzae type b, S. pneumoniae, N. meningitidis, Escherichia coli K1, and S. agalactiae)
• Indicated if clinical features and CSF profile are consistent with bacterial meningitis but CSF gram stain is negative.
• Sensitivity: 50–100%, specificity: high.

Polymerase chain reaction
The most sensitive method but frequently false positive results are obtained. Further refinements of this technique are required to confirm its usefulness in patients with bacterial meningitis in whom the CSF Gram stain, bacterial antigen tests and culture are negative.

Reagent strips
If no facilities for laboratory examination of CSF are available, the CSF can be tested with reagent strips that measure protein and glucose concentrations and leucocyte counts in the urine.

Blood
• Full blood count and ESR: a neutrophil leucocytosis and raised ESR are typical but not invariable nor specific: severe viral infections can cause similar changes.
• Blood cultures are essential because bacteria are often easier to isolate from the blood than the CSF.
• Culture (bacterial and viral) from septic sites, biopsy material, throat swab and feces.
• Acute and convalescent viral serology in blood and CSF, including HIV serum antibody in at-risk individuals.

Other
• Chest x-ray may show signs of infection by pneumococci, mycoplasma, legionella and tuberculosis (TB).
• Skin scrapings may identify meningococci that are present in the skin rash. The lesion is scraped with the point of a sterile needle until blood just starts to appear. The blood is then blotted on to microscope slides, allowed to dry, and examined for Gram-negative diplococci. This can provide results rapidly and, unlike examination of blood and CSF, is not greatly affected by prior antibiotic treatment.

DIAGNOSIS
The diagnosis is based on the finding of an increased number of white cells in the CSF (CSF pleocytosis) and demonstration of bacteria in the CSF whether by Gram stain, CIE, culture or PCR, in a patient with consistent clinical features.
**MANAGEMENT (331)**

**Antibacterial chemotherapy**

**Principles**
- The need to commence antibiotic treatment as soon as the diagnosis is suspected, even before admission to hospital or performing a lumbar puncture.
- The need for bactericidal activity in CSF.
- Factors influencing bactericidal activity in CSF:
  - Permeability of the blood–brain barrier.
  - Characteristics of the antibiotic (molecular size, protein binding, lipid solubility, degree of ionization).
  - CSF pH, protein concentration, temperature.
- Potential hazards of bactericidal activity in CSF: release of biologically active cell-wall products, increasing the production of cytokines in CSF, exacerbating inflammation and damaging the blood–brain barrier.

**Types of therapy**
- Empirical (see Table 33).
- Specific (see Table 35): an important epidemiologic trend is the worldwide increase in infection with strains of *S. pneumoniae* that are resistant to penicillin and other β-lactam antibiotics, mediated by alterations in the penicillin-binding proteins involved in the synthesis of bacterial cell walls.

**Supportive measures**
- General nursing care.
- Attention to the airway.
- Maintenance of adequate hydration: fluids should be replaced and maintained, and not restricted.
- Antipyretic measures.

**Adjunctive therapy**

**Dexamethasone**

Insufficient evidence exists to support the routine use of dexamethasone as an adjunct treatment in adults with bacterial meningitis. Selective use may be considered in patients at high risk with severely impaired mental status, cerebral oedema or substantially raised intracranial pressure.

**Lowering intracranial pressure**
- Elevate the head of the bed to 30° to maximize venous drainage with minimal compromise of cerebral perfusion.
- Hyperosmolar agents, such as mannitol and oral glycerol, increase the osmolality of the intravascular space with respect to the brain and facilitate diffusion of water from the brain to the intravascular space.
- Hyperventilation, to maintain arterial pCO₂ between 3.6 and 4 kPa (27 and 30 mmHg), but this may lead to a reduction in cerebral blood flow below ischaemic thresholds.
- Barbiturate therapy (pentobarbitone), in high-dose titrated to development of a burst-suppression pattern on the EEG, may help to protect the brain from ischaemic insult (by causing vasoconstriction in normal tissues, thus shunting blood to ischaemic tissue) and decrease metabolic demands of the brain. However, this is of unproven benefit in bacterial meningitis.

**Treatment of complications**

Specific treatment is indicated for specific complications such as seizures and hydrocephalus.

**Prophylactic treatment**

Prophylaxis prevents secondary cases by eradicating nasopharyngeal carriage in the short term.

**Meningococcal infections**

Rifampicin 10 mg/kg/day for 4 days is recommended for close contacts (usually household) and the patient.

**Haemophilus infections**

Rifampicin 20 mg/kg/day for 4 days is recommended for families and other close contacts with children <4 years of age (i.e. at high risk) and for the patient.

**PROGNOSIS**

- Overall case fatality rate is 25%.
- Case fatality rate varies according to the patient’s age and the type of bacteria: 31% for *S. pneumoniae* meningitis in adults over 60 years of age compared with 3% for children younger than 5 years of age. Overall case fatality is higher for *S. pneumoniae* (19%) than for either *N. meningitidis* (13%) or *H. influenzae* (3%).

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**Algorithm for the initial management of patients with acute bacterial meningitis.**

<table>
<thead>
<tr>
<th><strong>Bacterial meningitis suspected</strong></th>
<th><strong>Empirical antimicrobial therapy (Table 33)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consider empirical antibiotic therapy</strong></td>
<td><strong>Specific antimicrobial therapy (Table 35)</strong></td>
</tr>
<tr>
<td><strong>Obtain blood cultures</strong></td>
<td><strong>Empirical antimicrobial therapy (Table 33)</strong></td>
</tr>
<tr>
<td><strong>Obtain lumbar puncture immediately</strong></td>
<td><strong>Cranial CT scan</strong></td>
</tr>
<tr>
<td><strong>CSF consistent with bacterial meningitis</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td><strong>Gram stain or bacterial antigen test positive</strong></td>
<td><strong>No</strong></td>
</tr>
<tr>
<td><strong>Empirical antimicrobial therapy (Table 33)</strong></td>
<td><strong>Specific antimicrobial therapy (Table 35)</strong></td>
</tr>
<tr>
<td><strong>N.B.</strong> There is an increasing trend to administer antibiotics immediately after suspecting bacterial meningitis (i.e. before performing a lumbar puncture, and even before referral to hospital.)</td>
<td></td>
</tr>
</tbody>
</table>
Subacute and Chronic Meningitis and/or Encephalitis

**Definition**
A syndrome characterized by various combinations of fever, headache, lethargy, stiff neck, confusion, nausea, and vomiting with accompanying CSF pleocytosis, of greater than 4 weeks duration.

**Epidemiology**
- Incidence: uncommon.
- Age: any age.

**Aetiology and Pathophysiology**

**Infection**
- **De novo infection**
  - Bacterial:
    - Actinomyces.
    - Brucellosis.
    - Listeria.
    - Nocardia.
    - Whipple’s disease (see p.289).
  - Mycobacterial: TB.
  - Spirochaete:
    - *Borrelia burgdorferi* (see p.316).
    - Leptospirosis.
  - Syphilis (see p.312) (332).
- Viral:
  - HIV (see p.301).
  - Mumps.
  - Cytomegalovirus.
  - Lymphocytic choriomeningitis (LCM).
- Fungal:
  - Cryptococcus.
  - Coccidioides.
  - Histoplasma.
  - Candida.
  - Aspergillus.
  - Blastomyces.
- Protozoal: toxoplasmosis.
- Helminthic (cestode worms): cysticercosis.

**Bacterial meningitis** (see p.273): inadequately treated

**Chronic bacterial infection following**:
- Head injury.
- Intracranial surgery.
- Use of intracranial shunts.

**Parameningeal foci**
- Otitis.
- Mastoiditis.
- Sinusitis.
- Brain abscess.
- Subdural empyema.

**Non-infectious**
- Connective tissue/granulomatous diseases
  - Systemic lupus erythematosus.
  - Behçet’s syndrome (oral and genital ulcers, iritis, meningitis).
  - Sjögren’s syndrome.
  - Sarcoidosis (see p.350).
  - Systemic vasculitis.
  - Isolated granulomatous angiitis of the nervous system (see p.227).

**Malignant meningitis**
- Carcinoma: seeding of tumour cells in the CSF with, or more often without, a solid intracranial or spinal primary or secondary tumour. The common primary tumours are carcinoma of the breast, bronchus and nasopharynx; leukaemia, lymphoma and melanoma; primary intracranial tumours rarely seed through the CSF.
- Lymphoma (including intravascular lymphoma [neoplastic angioendotheliosis]).
- Leukaemia.
- Glioma.
- Melanoma.

**Chemical meningitis** (see p.291)
Cranioopharyngioma (see p.377), epidermoid cyst, drugs, dye.

**Mollaret’s meningitis** (see p.291)
Steroid-responsive chronic meningitis
Chronic benign lymphocytic meningitis

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**Table 35** Antimicrobial therapy for bacterial meningitis based on pathogen identification by positive Gram stain and/or bacterial antigen test

<table>
<thead>
<tr>
<th>Bacterial pathogen</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Haemophilus influenzae</em> type B</td>
<td>Third generation cephalosporin (cefotaxime or ceftiraxone): for 7 days</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>Penicillin or amoxicillin or third generation cephalosporin: for 7 days</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Vancomycin + third generation cephalosporin*: for 10–14 days</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>Amoxicillin or penicillin G**: for 14–21 days</td>
</tr>
<tr>
<td>Group B <em>Streptococci</em> (S. agalactiae)</td>
<td>Amoxicillin or penicillin G**: for 14–21 days</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>Third generation cephalosporin (cefotaxime or ceftiraxone): for 21 days</td>
</tr>
</tbody>
</table>

*Consider addition of rifampicin
**Consider addition of aminoglycoside

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**332** Skin rash on the sole of the foot of a patient with syphilitic meningitis.
CLINICAL FEATURES
Indolent onset and course.

Meningitis
- Headache.
- Fever.
- Malaise.
- Confusion.
- Weight loss.
- Meningism.

Associated syndromes
- Seizures.
- Hydrocephalus (obstructive or communicating).
- Confusion, dementia.
- Papilloedema.
- Syndrome of inappropriate antidiuretic hormone (SIADH).
- Migraine with CSF pleocytosis.
- Cranial neuropathies.
- Radiculopathies.
- Spinal root pain, weakness, sensory loss.
- Myelopathy.

INVESTIGATIONS

Blood
- Full blood count.
- ESR.
- Serum biochemistry (e.g. urea and electrolytes, liver function tests).
- Antinuclear antibodies, anti-DNA antibody.
- Rheumatoid factor.
- Serum protein electrophoresis.
- Serum immunoglobulins.
- Serum complements.
- Serum angiotensin-converting enzyme.

CSF
Testing should be repeated on several occasions:
- Microscopy, cell count, Gram stain, culture, protein, glucose, VDRL, TPHA, oligoclonal bands, IgG/albumin ratio, cytology for inflammatory and malignant cells, cryptococcal antigen and other antigens and antibodies as appropriate from the list above (see Aetiology, above).
- Malignant cells are more likely to be seen if the CSF is fresh and collected on several occasions.
- Lymphocytes usually predominate but occasionally neutrophils do.
- CSF lymphocytes should be typed if there is any suspicion of lymphoma.

Other
- Urine, sputum, and gastric washings for TB, fungi.
- Chest x-ray: if suspected TB, sarcoidosis or neoplasm.
- Ultrasound abdomen and pelvis: suspected hepatic metastases or pelvic infection.
- Cranial CT or MRI scan, or spinal MRI scan to exclude a focal parameningeal collection of pus such as an intracranial or spinal subdural empyema, or hydrocephalus.
- Biopsy with microscopy, cytology and culture of clinically involved extraneural sites (e.g. lymph nodes, liver) or clinically and radiologically involved leptomeninges and brain.

DIFFERENTIAL DIAGNOSIS

Chronic recurrent meningitis (vs. chronic persistent meningitis)
- Mollaret’s meningitis.
- Anatomic defects (e.g. skull fractures, post-operative).
- Congenital defects (e.g. meningomyelocele, dermal sinus).
- Parameningeal focus (e.g. otitis, mastoiditis, sinusitis, brain abscess, subdural empyema).
- Immunosuppression.
- Tumours (e.g. craniopharyngioma, epidermoid, ependymoma).
- SLE.

Chronic persistent meningitis (see Aetiology, above)
CSF cell count: <50 cells/mm³
- Behçet’s syndrome.
- Benign lymphocytic meningitis.
- Carcinoma.
- Sarcoidosis.
- Vasculitis.

CSF cell type
- Neutrophils:
  - Bacterial meningitis.
  - Chemical (e.g. craniopharyngioma).
  - Fungal meningitis.
  - SLE.
- Eosinophils:
  - Chemical (e.g. intrathecal drugs).
  - Coccidioides.
  - Lymphoma.
  - Parasites.
- Lymphocytes: all other causes.

CSF glucose: low
- Bacterial meningitis.
- Carcinoma.
- Fungi.
- Syphilis.
- Sarcoid.
- Subarachnoid haemorrhage.
- Viral (mumps, herpes, LCM).
- Mollaret’s meningitis.
- Benign lymphocytic meningitis.
- Epidermoid cyst.

TREATMENT
- Specific treatment of underlying cause.
- Empirical:
  - Anti-TB (see p.282) and antifungal (see p.320) therapy: if no definite cause identified, and if the patient is unwell and deteriorating.
  - Corticosteroids: indicated if there is no favourable response clinically to empirical anti-TB and fungal therapy, and if fungi have not been identified, because some patients have a steroid-responsive chronic meningitis.
- Relapse may occur when treatment is withdrawn.
- Malignant meningitis and the primary tumour are seldom treatable, and death occurs in weeks or months.

PROGNOSIS
Depends on the underlying cause and response to treatment.
TUBERCULOUS MENINGO-ENCEPHALITIS

DEFINITION
Infection of the meninges and underlying brain by the acid-fast organism *Mycobacterium tuberculosis* and exceptionally by *Mycobacterium bovis*.

EPIDEMIOLOGY
- Incidence: increasing, concurrent with the HIV epidemic. Higher in developing countries, particularly the Indian subcontinent and sub-Saharan Africa, with higher prevalence of HIV infection.
- Age: any age.
- Gender: either sex.

PATHOLOGY
Macroscopic
- Discrete, small, white tubercles scattered over the convexities and base of the brain. The ependyma and choroid plexus are also studded with minute glistening tubercles.
- Thick, gelatinous exudate over the basal meninges, obliterating the pontine and interpeduncular cisterns and extending to the meninges in the floor of the third ventricle and subthalamic area, the optic chiasm, the under-surfaces of the temporal lobes, and around the medulla and spinal cord. The convexities are relatively spared.

Microscopic
- Meningeal tubercles: a central zone of caseation surrounded by epithelioid cells and some giant cells, lymphocytes, plasma cells, and connective tissue.
- Exudate: composed of fibrin, lymphocytes, plasma cells, and other mononuclear cells, some polymorphonuclear leucocytes and areas of caseation necrosis. The exudate is not confined to the subarachnoid space (as is the case with the pyogenic meningitides) but frequently spreads along the pial vessels and invades the underlying brain, leading to a pure meningoencephalitis. The inflammatory exudate involves the cranial nerves as they traverse the subarachnoid space. The arteries become inflamed and occluded, leading to focal brain infarction.
- The basal cisterns become blocked, resulting in a meningeal obstructive type of hydrocephalus.
- The CSF in the aqueduct, or fourth ventricle more rarely, becomes blocked by marked epudymitis, leading to obstructive hydrocephalus.

AETIOLOGY
*Mycobacterium tuberculosis* and exceptionally by *Mycobacterium bovis*.

Risk factors
- HIV infection: 500 times higher incidence of TB meningitis than in the general population; HIV increases the lifetime risk of developing TB to one in three.
- Alcohol abuse.
- Diabetes mellitus.
- Malignancy.
- Recent corticosteroid use.
- Populations with a high prevalence of pulmonary tuberculosis (i.e. poorer backgrounds, India, Africa).

PATHOGENESIS
Meningitis may occur as part of generalized TB with a single focus (tuberculoma) in the brain or as a terminal event in miliary TB. Two stages:
- Bacterial seeding of the meninges and subpial regions of the brain, forming tubercles.
- Rupture of one or more of the foci (tuberculomas) with discharge of bacteria into the subarachnoid space.

CLINICAL FEATURES
Subacute or chronic onset over weeks.

Syndromes
- Meningo-encephalitis:
  - Headache, lethargy, confusion, drowsiness, fever, stiff neck, Kernig and Brudzinski signs.
  - Cranial neuropathies: usually oculomotor palsy, less often facial palsies and deafness.
- Focal neurological deficit: due to brain infarction caused by infectious arteritis.
- Raised intracranial pressure: due to hydrocephalus.

Associated conditions
Systemic tuberculosis (two-thirds of patients): pulmonary, bone or renal.

OTHER FORMS
Tuberculous serous meningitis
- Due to a meningeal reaction to an adjacent tuberculous focus.
- Asymptomatic, or headache, lethargy and confusion with mild meningeal signs.
- CSF: modest pleocytosis in some, normal or elevated protein, normal glucose.
- Self-limiting usually, but may progress to fatal generalized TB meningitis.

Tuberculoma
- Tumour-like masses of tuberculous granulation tissue in the brain parenchyma.
- Asymptomatic or symptoms of a space-occupying lesion.
- CSF: mild pleocytosis and raised protein; normal glucose.
**Myeloradiculitis**
- Spinal cord or nerve root compression by an epidural mass of granulation tissue or angulation of the vertebral column (see Spinal epidural abscess, p.555).
- May accompany vertebral body disease (Pott’s paraplegia).

**DIFFERENTIAL DIAGNOSIS**
- Meningitis: fungal (e.g. cryptococcal, see p.318; see Chronic meningitis, p.279); pyogenic.
- Meningeal carcinomatosis (malignant meningitis).
- Brain tumour (e.g. brainstem glioma).

**INVESTIGATIONS**

**Blood**
Hyponatraemia is common due to inappropriate ADH secretion (SIADH) or TB of the adrenals.

**Brain imaging**
Similar features will be seen on CT or MRI, though MRI is more sensitive:
- Tuberculomas may be single or multiple, usually small (2–3 mm diameter) and can coalesce to form a larger lesion (334, 335). They may be low or high density on CT, may adhere to the dura, cause hyperostosis (mimicking a meningioma), and may calcify (<20%). They may produce symptoms from intracranial mass effect and oedema.
- Tuberculomas are hypo- or isodense on CT (as they are filled with exudate). They enhance intensely (particularly on MRI) with contrast. On MRI the basal cisterns may appear brighter than normal on T1W image because of the protein content of the exudate. The cisterns may calcify (best seen on CT).
- Tuberculoma and tuberculou meningoecephalovasculitis can simulate an infiltrating brainstem glioma radiologically.
- With treatment the tuberculomas may shrink and disappear (or calcify) but the hydrocephalus does not change.

**CSF (lumbar puncture)**
- Pressure: increased.
- Cells: 50–500 white cells/mm³; initially polymorphonuclear leucocytes and lymphocytes in equal numbers but after several days, lymphocytes predominate.
- Organisms: Ziehl–Neelsen stain of smears of CSF sediment reveals acid-fast tubercle bacilli in about 10–20% of patients; culture requires 3–4 weeks to become manifest (so treatment must be instituted on suspicion).
- Protein: 1.0–2.0 g/l (100–200 mg/dl); higher if CSF flow is blocked around the spinal cord.
- Glucose: <2.22 mmol/l (<40 mg/dl), but the glucose falls slowly over several days and rarely falls to the extremely low levels seen in pyogenic meningitis.

**Mantoux test**
10 tuberculin units are given intradermally on the flexor surface of the forearm. An area of induration measuring 5 mm or more read at 48–72 hours following the injection is a positive Mantoux. This indicates previous or recent exposure to *M. tuberculosis* and does not prove active TB; i.e. it may also indicate previous TB, healed infection, or BCG vaccination. The test may also be negative in active TB, if the test is done within 6 weeks of the patient acquiring the infection, or where the infection is overwhelming or the patient is immunosuppressed.

**Other**
- Sputum smears and cultures for acid-fast bacilli.
- Chest x-ray.
- Gastric washings.
- Urine examination.

**DIAGNOSIS**
Clinical and microbiological: demonstration of acid-fast bacilli, either on microscopy of smears of CSF sediment stained by the Ziehl–Neelsen method or by culture, in a patient with clinical evidence of meningoe-encephalitis.

**TREATMENT**

**Initial anti-TB chemotherapy treatment**
1 Rifampicin 600 mg daily as a single oral dose (15–20 mg/kg/day in children); plus
2 Pyrazinamide 30–50 mg/kg as a single oral dose (10 mg/kg/day in children); plus
3 Isoniazid 400 mg/day (5 mg/kg in adults; 10 mg/kg in children) as a single oral dose; plus
4 Pyridoxine 20–50 mg daily, oral should always be given with isoniazid to prevent peripheral neuropathy.

**Alternative initial treatments**
- Streptomycin 1 g i.m. daily (20–40 mg/kg/day in children) can be used instead of rifampicin if rifampicin causes intolerable adverse effects.
- Ethambutol may be substituted for pyrazinamide. The dose is 25 mg/kg day as a single oral dose for the first month, then 15 mg/kg/day. Ethambutol should be avoided in children, and patients with renal failure. It is given in divided doses, after meals, because of its tendency to produce gastric irritation. Visual acuity and red-green colour discrimination are regularly checked because of the risk of optic neuropathy.

**Additional treatments**
Dexamethasone (adults 12 mg/day; children <25 kg, 8 mg/day) given for 3 weeks (in conjunction with anti-TB therapy) then tapered over a further 3 weeks may reduce the incidence of sequelae in patients who are culture-positive, particularly those who have a decreased conscious level at presentation. Prednisolone, 60–80 mg/day tapering after 2 weeks to finish at 4–6 weeks, is an alternative.

**Treatment after 2 months**
If the mycobacterium is shown to be sensitive to all three antibiotics (rifampicin, pyrazinamide and isoniazid) in *vitro*, pyrazinamide can be discontinued, but rifampicin and isoniazid (and pyridoxine) should be continued together for about another 7 months; the dose of isoniazid can be reduced to 300 mg once daily. The duration of treatment depends on many factors, including the degree of supervision and compliance.

N.B. Intracranial tuberculomas require a similar course of chemotherapy as outlined above. The tuberculomas may transiently increase in size despite clinical improvement soon after the start of antimicrobial treatment, or disappear and calcify. If they persist, particularly exerting ‘mass effect’, surgical excision may be required.
Adverse effects
- Rifampicin:
  - Fever, skin rash, nausea, vomiting, diarrhoea, thrombocytopenia, hepatitis.
  - Saliva and urine turn orange-red and soft contact lenses may discolour.
  - An early transient rise in liver enzymes is common.
- Pyrazinamide: fever, urticaria, flushing, nausea, vomiting, arthralgia, hepatitis, hyperuricaemia.
- Isoniazid:
  - Skin rash, nausea, vomiting, arthralgia, peripheral neuropathy, confusional and psychotic states, seizures, hepatitis, pellagra.
  - If symptoms of hepatitis or abnormal liver function tests occur, stop the isoniazid.
- Streptomycin:
  - Skin rash, deafness, tinnitus, vertigo, ataxia, nephrotoxicity, and exacerbation of myasthenia gravis.
  - Serum levels of streptomycin should be monitored and if renal impairment occurs, the dose should be reduced.
- Ethambutol: blurred vision, optic atrophy, peripheral neuropathy, hepatitis.

**CLINICAL COURSE AND PROGNOSIS:**
- Untreated, the course is progressive and invariably fatal within weeks to months.
- Overall mortality: about 10%; higher in infants, the elderly and HIV-infected patients.
- Survival is enhanced by early diagnosis.
- Neurological impairments persist in 20–30% of survivors, most commonly cognitive dysfunction, epileptic seizures, visual and oculomotor disorders, deafness and hemiparesis.
- Focal weakness, Glasgow coma scale, and somatosensory evoked potentials are the best predictors of outcome at 6 months (in one recent study).

334, 335  CT brain scans with contrast showing calcified nodules (arrows) in the parenchyma (tuberculomas) and a degree of hydrocephalus.

336, 337  CT brain scans showing hydrocephalus due to tuberculous meningitis in a person from the Indian subcontinent. Note the dilated ventricles right down to the fourth where there is good communication with the basal cisterns, i.e. this is a communicating hydrocephalus.
INTRACRANIAL ABSCESS (BRAIN ABSCESS AND SUBDURAL EMPYEMA)

DEFINITION
- Brain abscess: a localized collection of pus within the brain, and usually supratentorial.
- Subdural empyema: a thin layer of pus between the dura and arachnoid membranes over the surface of one side of the brain, frequently spreading into the inter-hemispheric fissure (parafalcine) and over to the surface of the other side of the brain.

EPIDEMIOLOGY
- Incidence: uncommon.
- Point prevalence 2 per 100 000.
- Age: any age.
- Gender: M=F.

PATHOLOGY
Bacterial infection of a part of the brain causes inflammation and oedema around the periphery of the infected brain parenchyma (so-called ‘cerebritis’), which is followed by necrosis in the centre of the lesion, with the formation of pus in the abscess cavity.

PATHOPHYSIOLOGY
Local spread of infection/complications
- Trauma: penetrating head wounds with CSF leak.
- Suppurative middle ear, mastoid, paranasal sinus or dental infections (the most common local events leading to brain abscess formation).
- Bacterial meningitis.
- Orbital cellulitis.

Local spread of infection usually causes a subdural empyema or a single/solitary intracerebral abscess.

Haematogenous spread
- Septicaemia.
- Right to left shunt:
  - Intracardiac: cyanotic congenital heart disease.
  - Intrapulmonary: pulmonary arteriovenous malformation.
- Infective endocarditis.
- Suppurative chest infection (abscess, bronchiectasis, empyema).

Haematogenous spread of infection usually causes multiple intracerebral abscesses.

Other predisposing factors
Immune system compromise (e.g. HIV infection).

AETIOLOGY
Brain abscesses are often polymicrobial, particularly if they arise from a dental source.

Aerobic organisms
- *Streptococcus milleri* (causes suppurative dental and sinus infection in the middle-aged and elderly): up to 80% of cases of brain abscess are caused by a streptococcus.
- *Streptococcus pneumoniae* (pneumococcus): carried in the nasopharynx from where it can spread by droplets to cause sinusitis, otitis media and pneumonia. Severe infection tends to occur in patients who have had a splenectomy or have hypogammaglobulinaemia, complement deficiencies or sickle cell disease.
- *Enterobacter* /coliforms: increasing incidence (10–30% of cases).
- *Staphylococcus aureus* (head injury, neurosurgical procedure, ventricular shunt, CSF fistula): decreasing as a cause (10–30% of cases).
- *Fusobacterium* spp.: (<10% of cases).
- *Haemophilus* spp.: (<1%).
- Fungi (*Aspergillus and Candida* spp.): (especially if immunocompromised).
- *Mycobacterium tuberculosis*.
- Protozoa: *Toxoplasma gondii, helminths* (e.g. *Strongyloides stercoralis*): (especially if immunocompromised).
- *Amoeba*.

Anaerobic organisms
- Gram-negative rods: *Bacteroides, Prevotella, Porphyromonas* spp.: increasing incidence: comprise 20–50% of cases.
- *Peptostreptococcus* spp., particularly *P. micros*: (10–40% of cases).

Several bacterial strains are frequently present in a single abscess but sometimes nothing is seen on Gram stain or grown in aerobic or anaerobic culture.

CLINICAL FEATURES
Brain abscess
The usual presenting features are the subacute onset and progressive evolution of:
- Fever.
- Headache.
- Lethargy and malaise.
- Seizures.
- Focal neurological signs.
- Symptoms and signs of raised intracranial pressure, such as papilloedema, may follow as the abscess acts as an expanding space-occupying lesion.
- Meningism and systemic evidence of bacterial infection may be present.
- Features of the underlying source (e.g. dental or ear infection) may be present.

Subdural empyema
Supratentorial
- Severe headache, often unilateral.
- Dysfunction of, and focal seizures referable to, the underlying hemisphere.
- Cranial nerve III and VI palsies.

Infratentorial (rare)
- Severe headache.
- Meningism.
- Cerebellar and brainstem signs.
- Features of raised intracranial pressure.
DIFFERENTIAL DIAGNOSIS
- Bacterial meningitis.
- Tuberculous meningitis.
- Encephalitis.
- Intracranial tumour: both abscess and tumour frequently appear as ring-enhancing lesions on neuroimaging studies. A raised C-reactive protein and increased uptake of tracer on 99mTc-HMPAO leucocyte scintigraphy raises the likelihood of abscess; steroid therapy should be discontinued for 48 hours prior to leucocyte scintigraphy.
- Cerebral infarction.

INVESTIGATIONS
Full blood count and other blood tests
In general, laboratory tests are of little value in the diagnosis of brain abscess. Only 30% of patients have peripheral leucocyte counts greater than 11 000 cells/ml. However, blood tests can be helpful in identifying the underlying cause or predisposing condition (e.g. HIV serology, toxoplasma serology, serum immunoglobulins, serum complement).

Cranial CT or MRI scan without and with contrast
Chronic sinusitis, mastoiditis, osteomyelitis, fracture.

Abscess
- CT or MR can be used, though MR is probably more sensitive particularly in the very early ‘cerebritis’ stage.
- CT shows a low density area (sometimes multiple) usually at the grey/white matter junction, and which may lie adjacent to an infected (opacified) nasal sinus or mastoid. It has some mass effect and surrounding white matter oedema, and shows enhancement in a thin walled ring after i.v. contrast (338, 339).
- MRI, T1W, reveals a central region of marked low intensity surrounded by a discrete ring that is isointense to mildly hyperintense. This area is surrounded by a region of mild hypointensity. These regions correlate with the necrotic centre, the abscess capsule, and surrounding oedema respectively. N.B. Some tumours can look very much like abscesses and vice versa, and abscesses do not always cause pyrexia. The only sure way of differentiating an abscess from a tumour is by biopsy which may be necessary prior to starting steroids. (Steroids may be acceptable for a brain tumour but not so good for abscesses!)

Subdural empyema
On CT or MRI:
- A collection in the subdural space which may be very difficult to see on the unenhanced scan as it is often isodense with brain or so thin that it is not visible.
- Often adjacent to an infected nasal sinus or mastoid.
- Swelling (oedema) of the adjacent underlying cerebral hemisphere is usually present, sometimes with effacement of cortical sulci, compression of horns of lateral ventricles, and midline shift. The appearance may be extremely subtle, for example only slight widening of the interhemispheric fissure as the only clue (if in doubt give contrast and preferably do an MRI).

(Continued overleaf)
On CT or MRI (continued):
- After intravenous contrast injection, a thin rim of intense contrast enhancement over the cerebral hemisphere may become evident, and enhancement in the brain if the infection has spread to cause cerebritis.
- Magnetic resonance imaging without and with gadolinium enhancement is superior to CT due to the absence of bone artefact; increased contrast between bone, CSF and brain parenchyma; and the ability to produce images in multiple planes. Furthermore, MRI can better characterize subdural collections, allowing differentiation of sterile, bloody and infected collections.
- Complications include meningitis (see above), cerebral infarction, cerebral abscess, venous thrombosis.

Radionuclide scan
Increased uptake by the collection of pus on 99mTc-HMPAO leucocyte scintigraphy.

Carotid angiography
Rarely required, but may be useful if a subdural empyema is suspected but not imaged on CT or MRI, to show the avascular gap between the skull and underlying cerebral hemisphere, or in the interhemispheric fissure.

Exploratory burr holes
These may be necessary when a subdural empyema is strongly suspected but not imaged by serial application of the above techniques.

Chest x-ray
- Heart abnormality (e.g. cyanotic congenital heart disease).
- Pulmonary arteriovenous malformation.
- Lung infection (e.g. abscess, bronchiectasis, empyema).

Blood cultures

Culture (aerobic and anaerobic) of pus
Pus is cultured from the abscess, sputum, sinuses and blood. Prolonged incubation of specimens under a wide range of cultural conditions is necessary to ensure isolation and identification of all organisms.

Lumbar puncture
LP is contraindicated when a brain abscess is suspected. If done inadvertently, the CSF may be normal or show no organisms, a mild CSF pleocytosis, mild elevation of CSF protein, and a normal glucose. Cultures of CSF are usually negative (i.e. similar to acute viral encephalitis, and viral or tuberculous meningitis).

DIAGNOSIS
The diagnosis of brain abscess is suggested but not confirmed by the presence of a suggestive clinical picture, and imaging evidence of an asymmetric capsule, multiple lesions, the location of the lesion at the corticomedullary junction, and associated leptomeningeal enhancement. Ultimately, aspiration and biopsy are often necessary to confirm the diagnosis of brain abscess. Isolation and identification of all organisms is vital to allow rational decision-making about optimal therapy.

TREATMENT
Small abscesses (<2.5 cm [<1 in])

Antibiotics
Antibiotics that enter the brain at high concentrations include chloramphenicol, selected third-generation cephalosporins, metronidazole, methicillin, nafcillin, penicillin, trimethoprim plus sulphamethoxazole, and vancomycin.

Despite bacteriocidal concentrations of these antibiotics, bacteria may still be cultured from abscess aspirates, probably because of the acidic environment favouring bacterial growth and inhibiting antibiotic action.

Initial empirical antibiotic therapy
- Benzylpenicillin 200 mg/kg/day intravenously (i.v.) in 4 hourly boluses (about 33 mg/kg every 4 hours); plus
- Chloramphenicol 5 g daily i.v. in 8 hourly doses (i.e. 1 g every 8 hours) (75 mg/kg/day in children); plus
- Metronidazole 2 g daily i.v. in 6 hourly boluses (i.e. 500 mg infused over 1 hour every 6 hours) (7.5 mg/kg 6 hourly in children).

If staphylococcal infection is suspected (i.e. post-neurosurgery, ventricular shunts, and so on), replace benzylpenicillin in the above regime with:
- Flucloxacillin 6 g daily i.v. in 4 hourly doses (i.e. 1 g every 4 hours) (children 50 mg/kg/day); or
- Fusidic acid, 1.5 g daily i.v. (i.e. 500 mg infused over 6 hours, every 8 hours), particularly if osteomyelitis is present.

Alternatives
- Cefotaxime + metronidazole (+ benzylpenicillin).
- Ampicillin + gentamicin + metronidazole.

Specific antibiotic therapy
Specific antibiotic therapy (choice of antibiotics and dose) will depend on bacterial culture, sensitivities and serum levels. Intravenous antibiotic therapy should be continued until the patient is at least neurologically stable, and preferably fully recovered. It should then be possible to change to oral therapy for several weeks.
Large abscesses (>2.5 cm [>1 in])
Rarely cured by antibiotics alone; indeed long-term combined use of several antibiotics may allow for the uncontrolled growth of resistant organisms or may lead to greater toxicity to the patient. Furthermore, because the clinical and radiological diagnosis of brain abscess is not always certain, be aware that antibiotic therapy may be given for a brain tumour that is mistaken as an abscess.

**Neurosurgery**
With the advent of image-guided stereotactic techniques, aspiration of a brain abscess can be performed quickly and safely under local anaesthesia.

Aspiration provides diagnostic material, immediate decompression, and removes acidic and hypoxic necrotic material, providing a more favourable environment for antibiotic therapy. Aspiration is indicated in the stages of cerebritis, multiple lesions, deep seated lesions, and lesions in eloquent areas of the brain.

Open surgical excision is limited to large superficial lesions at risk of causing herniation and which are well encapsulated and in non-eloquent lesions, fungal abscesses, multiloculated abscesses, and post-traumatic abscesses which often contain contaminated foreign bodies.

Pre-operative antibiotics are not given because they increase the risk of sterile cultures. Antibiotic therapy as directed by culture and sensitivity is given for 6 weeks. Neuroimaging studies are obtained at weekly intervals during therapy and monthly thereafter until the abscess has resolved.

**Subdural empyema**
At some stage it is usually necessary to drain surgically the purulent loculation, but the decision of when and whether to undertake burr hole drainage or a formal craniotomy should be made in conjunction with the neurosurgeon. The method of drainage probably matters less than its timing and adequacy.

The local instillation of antibiotics (e.g. amphotericin B) as an adjunct to the treatment of otherwise intractable brain abscess and subdural empyema appears to be promising.

**Orbital, ear, mastoid and sinus infection**
These must be treated accordingly.

**Antiepileptic therapy**
Institute if recurrent seizures.

**PROGNOSIS**
**Brain abscess**
- **Case fatality rate:**
  - Pre-CT era: up to 30%, together with a high morbidity rate among survivors.
  - Post-CT era: <6%, due to: improvements in microbiological isolation techniques, more effective antibiotics, availability of CT and MRI that have resulted in earlier diagnosis and more effective treatment at stages when patients are relatively well neurologically.
- **Predictors of a poor outcome in terms of morbidity and mortality:**
  - Severely impaired mental status and neurological impairment on admission.
  - Brain abscesses in infants, particularly those that are large (>5 cm [>2 in]) or multiple.
  - Epilepsy is a complication in more than 50% of survivors.

**TETANUS**

**DEFINITION**
A serious preventable disease caused by infection of the skin and deep and necrotic wounds by *Clostridium tetani*, a Gram-positive bacillus, which secretes a neurotoxin.

**EPIDEMIOLOGY**
- Incidence: 1 million cases annually worldwide. Rare in developed countries because of immunization; only 36 cases were reported (of an estimated 170 cases) in the United States in 1994.
- Age: more than half of cases occur in people 60 years of age or older.

**AETIOLOGY AND PATHOPHYSIOLOGY**
The source of infection is usually a wound (about 65%), often a minor one such as a thorn, splinter of wood, or a piece of metal. Chronic skin ulcers account for about 5% of cases, and there is no obvious source in the remainder. *Clostridium tetani* are Gram-positive, spore-forming bacilli that exist primarily in soil. Their prevalence in soil samples ranges from 2–23%.

Under anaerobic conditions, the spores germinate and produce two toxins: tetanolysis (a haemolysin with recognized pathological activity) and tetanospasmin, which is responsible for tetanus. Tetanospasmin is synthesized as a single 151-kd chain and cleaved to two chains joined by a single disulphide bond. The heavy chain (100 kd) is responsible for specific binding to neuronal cells and transport proteins. The light chain (50 kd) is a zinc endopeptidase that cleaves an integral membrane protein of small synaptic vesicles, synaptobrevin, at a single site and blocks the release of neurotransmitters.

Once the toxin is synthesized it moves from the contaminated site to the spinal cord or brainstem. The toxin reaches the CNS by intra-axonal transport, moving at a rate of 75–250 mm (3–10 in) per day. So, the process takes 2–14 days. With facial injuries the interval is short. Once the toxin reaches the CNS, local or cephalic tetanus may occur initially, followed by generalized tetanus. The toxin produces presynaptic blockade of the synapses of inhibitory Renshaw cells and 1a fibres of alpha motor neurones that handle the transmission of γ-aminobutyric acid and glycine, but not of the synapses of Renshaw cells that handle acetylcholine transmission. Instability of the autonomic nervous system also occurs. The toxin binding appears to be irreversible; recovery depends on the sprouting of new axonal terminals.

**CLINICAL FEATURES**
As described by Gowers (1888):

‘Tetanus is ... characterized by persistent tonic spasm with violent brief exacerbations. The spasm almost always commences in the muscles of the neck and jaw, causing closure of the jaws (trismus, lockjaw) and involves muscles of the trunk more than those of the limbs.’

Initially, within days or weeks of the injury, the patient complains of stiffness, pain and rigidity in the voluntary muscles of the jaw, face and abdomen. The disease may be mild and progress no further or the muscle stiffness, pain and rigidity may spread to involve the neck, pharynx, back and sometimes limbs. Involuntary spasms of the affected muscles
may occur and be painful, frightening and cause difficulty opening the jaw (trismus), a grimacing facial appearance ‘risus sardonicus’ due to contraction of the facial muscles (341), and difficulty swallowing, sometimes prompting the patient to complain of a ‘sore throat’. The patient is usually afebrile unless there is concurrent local infection.

With severe tetanus, all muscles contract, with the stronger overpowering the weaker. There is opisthotonos, flexion of the arms, extension of the legs, periods of apnoea due to spasm of the intercostal muscles and diaphragm, and rigidity of the abdominal wall. Spasms are precipitated by startle, cough, touch, and a full bladder. Laryngeal spasm can be precipitated by swallow or the passage of a nasogastric tube. Late in the disease autonomic dysfunction develops with tachycardia and hypertension alternating with bradycardia and hypotension, cardiac arrhythmias, sweating, fever, salivation and gastric stasis. Ophthalmoplegia and facial weakness are rare.

**DIFFERENTIAL DIAGNOSIS**

- Dystonic reactions to neuroleptic drugs (which typically involve lateral turning of the head, often with protrusion of the tongue (symptoms that are rarely, if ever, seen in tetanus).
- Strychnine poisoning.
- Local infection in the pterygomandibular space (e.g. dental or in the masseter muscle) with trismus.
- Dislocation of the mandible leading to ‘lockjaw’.
- Facial or jaw trauma.
- Rabies.
- Hysteria.

**INVESTIGATIONS**

- Laboratory tests are of virtually no value except to exclude strychnine poisoning.
- Blood counts and blood biochemistry findings are unremarkable.
- Imaging studies of the head and spine reveal no abnormalities.
- A LP is not necessary; the CSF is normal except for a raised opening pressure, particularly during spasms.

**DIAGNOSIS**

Clinical.

**TREATMENT**

- Nurse in quiet surroundings.
- Excise and debride any wound.
- Control muscle spasms: benzodiazepines are the mainstay of treatment; intravenous diazepam 10–40 mg every 1–8 hours may be required to prevent spasms that last more than 5–10 seconds. At high doses, lactic acidosis can occur, possibly as a result of the solvent vehicle, propylene glycol. There are γ-aminobutyric acid agonists that indirectly antagonize the toxin, but they do not restore glycinergic function.
- Maintain ventilation and oxygenation and prevent pulmonary aspiration of gastric contents:
  - Control the muscle spasms.
  - Tracheostomy is indicated if rigidity and spasms cannot be controlled and interfere with swallowing or breathing.
  - Paralysis and ventilation are required if spasms become severe.
- Maintain nutrition and fluid balance with oral feeds if mild, or i.v. line or nasogastric tube if spasms are moderate but not severe. If severe, the patient must be intubated and ventilated.
- Human antitetanus immunoglobulin (500 units) is recommended, although its efficacy is controversial.
- Antitetanus toxin.
- Antimicrobial chemotherapy: metronidazole (0.5 g every 6 hours or 1.0 g every 12 hours intravenously) is as good as, or better than, penicillin G which is no longer the drug of choice. Also, penicillin is an antagonist of γ-aminobutyric acid, just as is tetanus toxin.
- Prevent gastric stress ulcers: H2 receptor antagonists.
- Prevent deep vein thrombosis: low dose heparin 5000 units subcutaneously twice daily.
- Control autonomic dysfunction: beta-blockade or combined alpha and beta-blockade as necessary for labile blood pressure and heart rate.

**PROGNOSIS**

- The disease progresses over about a week, stabilizes for another week, and then recovers over several weeks.
- The severity is very variable.
- Case fatality ranges from 10 to >50% worldwide. At least half of deaths from tetanus worldwide occur in neonates. These deaths are preventable through antepartum maternal immunization.
- In the USA, 75% of deaths occur in people who are 60 years of age or older (who make up 59% of all cases of tetanus).

**PREVENTION**

Tetanus is a serious preventable disease that remains a threat even in developed countries, particularly in older people. A case of tetanus reflects the failure of our health care delivery system to provide immunization. Routine boosters every 10 years should be emphasized in older people.

About 70% of a random sample of Americans aged 6 or more years had protective levels of tetanus antibodies. The prevalence of protective antibodies is less than 50% in people aged 60–69 years, and about 30% in people aged 70 years and older.
WHIPPLE’S DISEASE

DEFINITION
A rare, chronic, relapsing, multisystem granulomatous disorder that is caused by infection by *Tropheryma whippelii*, a Gram-positive bacillus; it primarily involves the intestine causing chronic diarrhoea, together with fever and migratory polyarthralgias. About 5% of patients present with neurological manifestations and 6–43% eventually develop symptomatic CNS involvement.

HISTORY
Described in 1907 by George Whipple. The patient was a missionary who had weight loss, diarrhoea, and abdominal pain associated with polyarthralgia and lymphadenopathy. At autopsy, numerous argyrophilic rod-shaped organisms were present in mesenteric lymph nodes. In 1949 Black-Schaffer showed that the bacilli gave a strongly positive result when stained with periodic acid Schiff reagent. In 1991 and 1992 specific DNA sequences were amplified from affected tissue. The nucleotide sequence had phylogenetic similarities to the actinomyces group, and the organism was named *T. whippelii*.

EPIDEMIOLOGY
- Incidence: rare; fewer than 800 cases have been reported (<10 cases per year).
- Age and gender: usually presents in middle-aged men.

PATHOLOGY
- Symptomatic neurological involvement occurs in at least 10% (6–43%) of patients at some stage in their illness. Autopsy more frequently reveals brain involvement, even in the absence of neurological symptoms.
- Sites of predilection are the basal ganglia, insular cortex, midbrain, pons and cerebellum.
- Microscopic examination of the brain reveals widespread inflammation (encephalitis) throughout the cerebral hemispheres and brainstem (particularly the striatum, other basal nuclei and pons) characterized by mononuclear cell perivascular cuffing and infiltration of white and grey matter, marked astrocytosis, proliferation of microglia, and focal necrosis of many nerve cells.
- With hematoxylin and cosin (H-E) stain some nerve cells appear swollen and the cytoplasm has a very fine, granular, bluish-purple staining appearance.
- Fat stains demonstrate nerve cells containing numerous, rather coarse, varying-sized pale granules and globules of fat.
- PAS stain shows that the cytoplasm of neurones, astrocytes and perivascular inflammatory cells contain abundant foamy macrophages filled with masses of coalescent PAS-staining granules.
- Electron microscopy shows numerous bacilli in the distended macrophages and in the intercellular spaces. The bacilli measure 1.5–3.0 µm in length and 200 nm in diameter. The bacilli are lined by a thin surface membrane and a thick (20 nm) cell wall. Whipple’s bacteria are most frequently found in microglial and ependymal cells in the brain but they are also found within astrocytes, pericytes, and choroid plexus cells. The internal layers of the retina also show many large, pale, granule-containing cells.

AETIOLOGY AND PATHOPHYSIOLOGY
Infection by *T. whippelii*, a Gram-positive bacillus.

CLINICAL FEATURES
The most common clinical presentation is the insidious onset of a malabsorption syndrome (e.g. diarrhoea), sometimes preceded by migratory polyarthralgia and fever. Cardiac (pericarditis, myocarditis, marantic endocarditis) and CNS involvement is also common, and a few present with primarily neurological manifestations.

Neurological triad
- Dementia, apathy and personality change: progressive.
- Myoclonus (facial) and tonic-clonic seizures; oculomasticatory myorhythmia (facial myoclonus) is pathognomonic: the eyes converge synchronously (convergent nystagmus) with involuntary jaw, palatal and tongue movements. Rhythmic spinal myoclonus has also been described.
- Supranuclear opthalmoplegia (voluntary vertical and, less so, horizontal gaze palsy; not caused by cranial nerve involvement but by lesions in the brainstem).

Other features
- Ataxic gait.
- Hypothalamic dysfunction (sleep [hypsomolence], drinking [polydipsia], and eating [hyperphagia] disorder).
- Coma.
- Chronic meningitis.
- Blurred vision or visual loss due to vitritis, uveitis, retinitis, retinal haemorrhage, choroiditis, papilloedema, optic atrophy or keratitis.
- Progressive peripheral neuropathy and myopathy are rare.

DIFFERENTIAL DIAGNOSIS
Depends on the clinical features:
- Progressive supranuclear palsy.
- Pituitary tumour.
- Alzheimer’s disease.
- Vascular dementia.
- Cerebral tumour: primary or metastatic.
- Sarcoïdosis.
- Syphilis.

INVESTIGATIONS

**Full blood count, ESR and other blood tests**
Minimal neutrophil pleocytosis, ESR and serum ACE may be raised.

**Molecular DNA analysis**
Amplification of sequences of bacterial 16S ribosomal RNA (rRNA) specific for Whipple bacillus (*T. whippelii*) from peripheral blood mononuclear cells using PCR.

**Cranial CT scan**
May be normal, show cortical atrophy, areas of low attenuation with or without contrast enhancement, areas of mixed density with multifocal enhancement and regions of vasogenic oedema.

**MRI brain**
May be normal in the early stages or show diffuse abnormalities on T2W images. Areas of increased T2W signal intensity on MRI scans are a sensitive indicator of disease activity and the lesions may enhance intensely with contrast medium.
The lesions may be seen in the hypothalamus, midbrain and basal ganglia and may have slight mass effect (342, 343).

CSF
CSF is normal or more commonly contains excess white cells and protein, oligoclonal banding and increased IgG. It may reveal sickle-particle-containing cells. Staining of the CSF with periodic acid Schiff reagent may give a positive result. PCR can be used to amplify sequences of bacterial 16S rRNA specific for Whipple bacillus (*T. whippelii*) in the CSF.

Other
• EEG: non-specific.
• Biopsy of jejunal mucosa, lymph nodes, vitreous or brain.

**DIAGNOSIS**

**Definite CNS Whipple’s disease**
Must have any one of the following three criteria:
• Oculomasticatory myorhythmia (OMM: pendular vergence oscillations of the eyes that are synchronous with masticatory myorhythmia) and oculo-facial-skeletal myorhythmia (OFSM: similar to OMM, also involves myorhythmia of non-facial skeletal muscle).
• Positive tissue biopsy: ultrastructural findings of distinctive periodic acid Schiff-positive bacillary rods and sickle-shaped inclusion bodies in macrophages in the CSF, vitreous or in a jejunal or brain biopsy.
• Positive PCR amplification of sequences of bacterial 16S rRNA gene corresponding to the Whipple’s disease bacillus (*T. whippelii*) in infected tissues.
• If histological or PCR analysis is not performed on CNS tissue, then the patient must also demonstrate neurological signs. If histological or PCR analysis is performed on CNS tissue, then the patient need not demonstrate neurological signs (i.e. asymptomatic CNS infection).

**Possible CNS Whipple’s disease**
Must have any one of four systemic symptoms, not due to another known aetiology:
• Fever of unknown aetiology.
• Gastrointestinal symptoms (steatorrhoea, chronic diarrhoea, abdominal distension, or pain).
• Chronic migratory arthralgias or polyarthralgias.
• Unexplained lymphadenopathy, night sweats, or malaise.
• Also must have any one of four neurological signs, not due to another aetiology:
  – Supranuclear vertical gaze palsy.
  – Rhythmic myoclonus.
  – Dementia with psychiatric symptoms.
  – Hypothalamic manifestations.
• A favourable response to trimethoprim-sulphamethoxazole or chloramphenicol therapy helps to confirm the diagnosis.

**TREATMENT**

**Antimicrobial treatment**
• Oral trimethoprim (160 mg) and sulphamethoxazole (800 mg) twice daily for 1 year plus folate supplementation.
• If allergic: intravenous penicillin G (2 million units, 4 hourly) and oral doxycycline (100 mg bd).

The choice of antimicrobial treatment is based mainly on taxonomy, which has been known for only the past few years. The organism has not been cultured, and therefore *in vitro* susceptibilities are not available. There are no data on comparison of antibiotics. However, empirical clinical experience suggests that patients initially treated with drugs that do not penetrate the blood–brain–barrier are at risk of neurological relapse.

**Myoclonus**
• Valproate 500 mg bd.
• Clonazepam 0.5 mg nocte, increasing up to 8 mg per day (or tolerance).

**PROGNOSIS**
• The clinical course is usually one of progression to death within 6–12 months but can be fulminant, leading to death within weeks, in spite of treatment with appropriate antibiotics.
• Involvement of the neuraxis carries a poor prognosis, even when the intestinal disease has been eradicated.
• Relapses are most common with CNS Whipple’s disease and are often resistant to antibiotics.

342, 343  T2W axial (342) and T1W axial (343) post contrast MRI in a patient with biopsy-proven Whipple’s disease. Note the areas of increased signal with mass effect and some enhancement in the basal ganglia. The lesion was initially mistaken for an infarct but, because it involves the carotid and basilar territory, this would be distinctly unusual.