Chapter 7

CENTRAL NERVOUS SYSTEM INFECTIONS

BACTERIAL MENINGITIS

CLINICAL FEATURES

Bacterial meningitis is a serious, life-threatening disease that results in high morbidity and mortality. The classical triad of acute bacterial meningitis consists of:

- Fever
- Neck stiffness
- Change in mental status (e.g. confusion, lethargy)

Headache is also common and is typically described as 'severe' and 'generalised'. The classic triad is found in only 41–51% of adult patients, but almost all patients present with at least two of the four symptoms of headache, fever, neck stiffness and altered mental status.

Childhood bacterial meningitis may typically present with fever, chills, vomiting, photophobia, neck stiffness and severe headache. The classical triad is less frequently present in infants compared to older children and adults. Clinical features of neonatal bacterial meningitis are often non-specific and include poor feeding, irritability, respiratory distress, pale or marbled skin, hyper- or hypotonia and a bulging fontanelle. The diagnosis of neonatal meningitis cannot be ruled out by clinical examination alone and therefore a low threshold to perform a lumbar puncture should be kept in neonates with suspected bacterial meningitis. Fever and seizures are present in the minority of patients.

TABLE 1: SIGNS AND SYMPTOMS OF ACUTE BACTERIAL MENINGITIS ACCORDING TO AGE GROUPS[1,2]

	NEONATES AND INFANTS < 3 MONTHS	INFANTS AND YOUNG CHILDREN 3 MONTHS TO 3 YEARS	OLDER CHILDREN AND ADULTS > 3 YEARS
Symptoms	Irritability Poor feeding	Headaches Neck stiffness	Headaches Neck stiffness Photophobia
Signs	Bulging fontanelle Hypothermia		Rash: maculopapular or petechial* Neck stiffness++

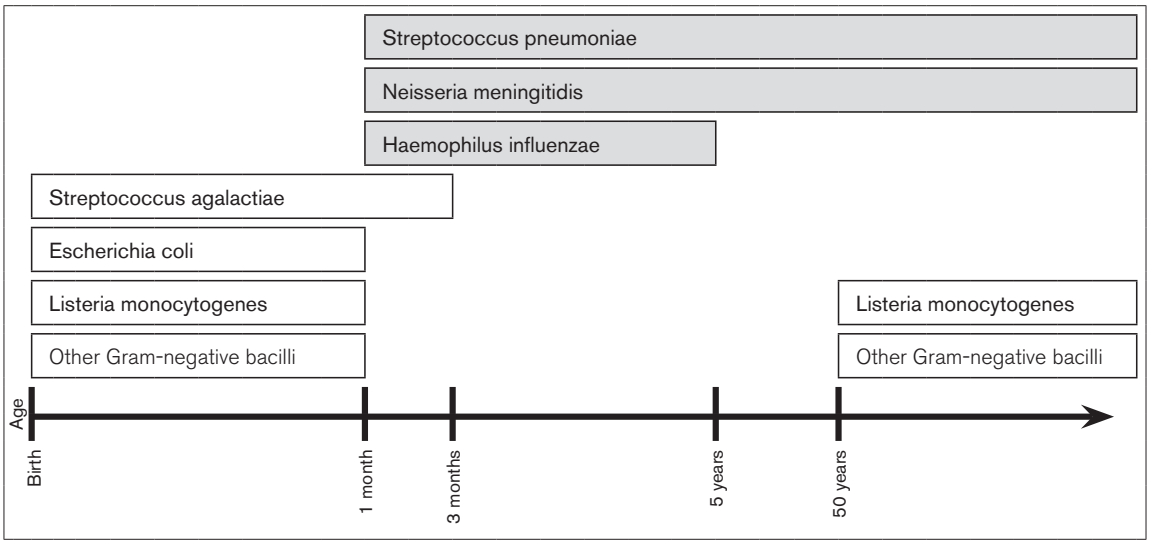
*Most common in Neisseria meningitidis infections, but may be noted in Streptococcus pneumoniae meningitis.

++The sensitivity in adults is only approximately 30%.

AETIOLOGY

The most common bacterial causes of acute meningitis vary with age (Figure 1). The incidence of meningitis due to *Streptococcus pneumoniae* and *Haemophilus influenzae* in children has decreased significantly after the introduction of conjugate pneumococcal and *H. influenzae* type b vaccines in routine childhood immunisation programmes. *Listeria monocytogenes* is an important causative pathogen in immunosuppressed patients or older adults (> 50 years) and in neonates (although uncommon in South Africa).

FIGURE 1: COMMON BACTERIAL CAUSES OF MENINGITIS ACCORDING TO AGE



LABORATORY INVESTIGATIONS

- **FBC:** white cell count is usually elevated, with a shift toward immature forms. Severe infection can be associated with a decreased white cell count (leucopaenia) and a low platelet count.
- **Serum glucose:** correlate with CSF glucose
- **Blood cultures:** positive in approximately 50–90% of patients and should be requested when contraindications for performing a lumbar puncture are present.
- **Procalcitonin (PCT) or CRP:** elevated PCT and CRP are suggestive of bacterial meningitis, although not diagnostic. Both have excellent negative predictive values.
- **CSF:** cell count and differential, MC&S, biochemistry, bacterial multiplex PCR

CSF examination is essential to establish a diagnosis of bacterial meningitis and to identify the causative organism and its susceptibility to various antibiotics so as to direct treatment. The Gram stain and culture can also help differentiate bacterial meningitis from other causes of meningitis. CSF abnormalities (cell count, glucose and total protein) may regularly be absent in neonates.

CSF is normally acellular but a certain amount of white blood cells (WBCs) may be considered normal depending on the age of the patient:

- Neonates: total WBC $\leq$ 20–30 cells/μL; up to 5% of the total WBC can be comprised of neutrophils, the remainder are lymphocytes
- Patients older than one month: total WBC $\leq$ 3 cells/μL (lymphocytes only)

A traumatic tap can introduce blood into CSF that can interfere with the interpretation of CSF cell counts. Certain formulas may be used to correct for this, however no formula has been identified to use with total confidence in correcting cell counts after a traumatic LP. As an aid in children and adults, one WBC can be subtracted from every 1000 red blood cells (RBCs) per μL if the CSF is not grossly bloody and the peripheral white cell count is within normal limits.

LABORATORY FEATURES OF ACUTE UNTREATED BACTERIAL MENINGITIS

- Elevated opening pressure
- CSF white cell count 100 to > 100 000 cells/μL with a neutrophil predominance (usually above 80%)
- CSF protein > 0.45 g/L
- CSF glucose concentration < 2.2 mmol/L

Bacterial meningitis multiplex PCR: useful when antibiotics were given prior to collecting CSF which may result in negative culture results. Two different multiplex PCR tests performed on CSF are available depending on the age of the patient:

- Neonatal bacterial meningitis multiplex PCR: detects *Streptococcus agalactiae* (group B streptococcus), *Escherichia coli* and *Listeria monocytogenes*
- Child and adult bacterial meningitis multiplex PCR: detects *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae*

CLINICAL SUBGROUPS AND EMPIRIC ANTIBIOTIC THERAPY [2,3,4]

Empiric antibiotic therapy must be started promptly and the patient must be transferred to a hospital. A delay in antibiotic treatment administration is associated with poor outcomes.

Clinical subgroups exist for patients with suspected bacterial meningitis. The choice of initial/empiric antibiotic therapy for these subgroups is based on the most common bacteria-causing disease according to the patient's age, clinical setting, and the patterns of antimicrobial susceptibility. After the results of the culture and susceptibility testing are available, antibiotic therapy can be modified for optimal treatment.

AGE	CAUSATIVE ORGANISM	EMPIRIC ANTIBIOTIC TREATMENT
< 1 month	• S. agalactiae (group B streptococcus) • E. coli • L. monocytogenes • Gram-negative bacilli	Ampicillin Age < 1 week: 100 mg/kg IV 12 hourly Age 1–4 weeks: 100 mg/kg IV 8 hourly **AND** Gentamicin Age < 1 week: 2.5 mg/kg IV 12 hourly Age 1–4 weeks: 2.5 mg/kg IV 8 hourly OR Ampicillin Age < 1 week: 100 mg/kg IV 12 hourly Age 1–4 weeks: 100 mg/kg IV 8 hourly **AND** Cefotaxime Age < 1 week: 50 mg/kg IV 8 hourly Age 1–4 weeks: 50 mg/kg IV 6–8 hourly

AGE	CAUSATIVE ORGANISM	EMPIRIC ANTIBIOTIC TREATMENT
1 month – 18 years	• S. agalactiae (group B streptococcus) • S. pneumoniae • N. meningitidis • H. influenzae	Cefotaxime 75 mg/kg IV 6–8 hourly (max dose 12 g/day) **AND** Vancomycin 10–15 mg/kg IV 6 hourly (to achieve serum trough concentrations of 15–20 μg/mL) OR Ceftriaxone 50 mg/kg IV 12 hourly (max dose 4 g/day) **AND** Vancomycin 10–15 mg/kg IV 6 hourly (to achieve serum trough concentrations of 15–20 μg/mL)
18 – 50 years	• S. pneumoniae • N. meningitidis • H. influenzae	Cefotaxime 2 g IV 6 hourly OR Ceftriaxone 2 g IV 12 hourly
> 50 years OR > 18 years with risk factors for L. monocytogenes	• S. pneumoniae • N. meningitidis • L. monocytogenes • Gram-negative bacilli	Cefotaxime 2 g IV 6 hourly **OR** ceftriaxone 2 g IV 12 hourly **AND** Vancomycin 15–20 mg/kg IV 8–12 hourly (to achieve serum trough concentrations of 15–20 μg/mL) **AND** Ampicillin 12 g/day IV in 6 divided doses (2 g every 4 hours)
Immunocompromised patients • HIV • Alcoholism • Diabetes mellitus • Cancer • Immunosuppressive drugs	• S. pneumoniae, • L. monocytogenes, • Gram-negative bacilli (including P. aeruginosa)	Cefepime 2 g IV 8 hourly **OR** meropenem 2 g IV 8 hourly **AND** Ampicillin 2 g IV 4 hourly
Nosocomial bacterial meningitis Risk factors: • Neurosurgery • Internal or external ventricular drains • Trauma (cranial fracture, especially basilar skull fracture)	• S. aureus • S. epidermidis • Other coagulase negative staphylococci • Aerobic Gram-negative bacilli including Pseudomonas	Ceftazidime 2 g IV 8 hourly (children: 150 mg/kg/day in 3 divided doses) **AND** Vancomycin 15–20 mg/kg IV 8–12 hourly (to achieve serum trough concentrations of 15–20 μg/mL) OR Cefepime 2 g IV 8 hourly (children: 50 mg/kg/dose 8 hourly) **AND** Vancomycin 15–20 mg/kg IV 8–12 hourly (to achieve serum trough concentrations of 15–20 μg/mL)

AGE	CAUSATIVE ORGANISM	EMPIRIC ANTIBIOTIC TREATMENT
Severe ß-lactam allergies Empiric treatment		Vancomycin 15–20 mg/kg/dose IV 8–12 hourly (to achieve serum trough concentrations of 15–20 μg/mL) **AND** Moxifloxacin 400 mg IV once daily **AND** Cotrimoxazole 5 mg/kg IV 6–8 hourly, if Listeria coverage is required

TREATMENT: CNS SHUNT INFECTIONS

Removal of the infected shunt and placement of an external ventricular catheter for drainage in combination with appropriate antibiotics appears to be the most effective treatment for CSF shunt infections. Success rates are lower when the CNS shunt infection is treated with the shunt in situ.

Ceftazidime 2 g IV 8 hourly (children: 150 mg/kg/day in 3 divided doses) **AND** vancomycin 15–20 mg/kg IV 8–12 hourly (to achieve serum trough concentrations of 15–20 μg/mL)

OR

Cefepime 2 g IV 8 hourly (children: 50 mg/kg/dose 8 hourly) **AND** vancomycin 15–20 mg/kg IV 8–12 hourly (to achieve serum trough concentrations of 15–20 μg/mL)

Direct instillation of antibiotics into the ventricles through either an external ventriculostomy or shunt reservoir is occasionally necessary in patients who have shunt infections that are difficult to eradicate via the parenteral route or when removal of the shunt is not possible. Preservative-free antibiotic must be used and the clamp/catheter closed for one hour post installation.

The recommended intraventricular doses are:

Vancomycin:	5–20 mg/day
Teicoplanin:	5–10 mg every second or third day
Gentamicin:	1–2 mg in children, 4–8 mg in adults
Amikacin:	5–50 mg/day
Colistin:	10 mg/day (125 000 IU/day)

ROLE OF DEXAMETHASONE

From the available evidence, dexamethasone treatment may be associated with a lower mortality in adults and fewer complications (e.g. hearing loss) in adults and children in high-income countries, in particular adults with pneumococcal meningitis as well as those with a Glasgow coma scale score of eight to 11. In contrast, studies conducted in developing countries have yielded less favourable results. Steroids are not recommended in infants younger than three months of age as there is insufficient evidence for their use and concerns as to their effect on neurodevelopment.

Dexamethasone (0.15 mg/kg/dose every six hours in children; 10 mg IV 6 hourly for adults) is recommended 15–20 minutes prior to, or given with, the first antibiotic infusion for suspected pneumococcal meningitis or meningitis due to *H. influenzae.* Continue for two to four days. Discontinue if not bacterial meningitis.

BACTERIAL MENINGITIS: PATHOGEN-SPECIFIC ANTIBIOTIC THERAPY[1,4]

DURATION OF ANTIMICROBIAL THERAPY BASED ON THE PATHOGEN ISOLATED

Neisseria meningitidis:	7 days
Haemophilus influenzae:	7–10 days
Streptococcus pneumoniae:	10–14 days
Streptococcus agalactiae:	14–21 days
Aerobic Gram-negative bacilli:	21 days
Listeria monocytogenes:	21 days
Culture-negative meningitis:	≥ 14 days

STREPTOCOCCUS PNEUMONIAE

The widespread emergence of penicillin-resistant pneumococci has made penicillin an inappropriate therapy without proof of in-vitro susceptibility. *Streptococcus pneumoniae* isolates from CSF are reported as either sensitive (MIC ≤ 0.06 μg/mL) or resistant. The following regimens are recommended:

PENICILLIN-SENSITIVE (MIC ≤ 0.06 μG/ML)

NEONATES

Week 1: Benzylpenicillin G (600 mg = 1 000 000 units) 60 mg/kg (100 000 units/kg) IV 12 hourly

Weeks 2–4: Benzylpenicillin G (600 mg = 1 000 000 units) 60 mg/kg (100 000 units/kg) IV 6–8 hourly (max 2.4 g)

INFANTS AND CHILDREN

Benzylpenicillin G (600 mg = 1 000 000 units) 60 mg/kg (100 000 units/kg) IV 4 hourly (max 2.4 g)

ADULTS

Benzylpenicillin G 4 million units IV 4 hourly

OR

Cefotaxime 2 g IV 4–6 hourly

OR

Ceftriaxone 2 g IV 12 hourly

PENICILLIN-RESISTANT (MIC ≥ 0.06 μG/ML)

NEONATES

Week 1: Cefotaxime 50 mg/kg IV 12 hourly

Add vancomycin 15 mg/kg IV 12 hourly if non-susceptible to cefotaxime or ceftriaxone (15–20 μg/mL trough target)

Weeks 2–4: Cefotaxime 50 mg/kg IV 8 hourly

Add vancomycin 15 mg/kg IV 8 hourly (15–20 μg/mL trough target) if non-susceptible to cefotaxime or ceftriaxone (MIC > 0.5 μg/mL)

INFANTS AND CHILDREN

Cefotaxime 50 mg/kg IV 6 hourly (max 2 g)

OR

Ceftriaxone 50 mg/kg IV 12 hourly (max 2 g)

Add vancomycin 15mg/kg IV 6 hourly (15–20 μg/mL trough target) if non-susceptible to cefotaxime or ceftriaxone (MIC > 0.5 μg/mL)

ADULTS

Ceftriaxone 2 g IV 12 hourly

OR

Cefotaxime 2 g IV 4–6 hourly

Add vancomycin 15–20 mg/kg IV 8–12 hourly (15–20 μg/mL trough target) if non-susceptible to cefotaxime or ceftriaxone (MIC > 0.5 μg/mL)

Rifampicin (600 mg orally or IV once daily) may be added if the ceftriaxone or cefotaxime MIC is > 2.0 μg/mL

Treat for 10–14 days

NEISSERIA MENINGITIDIS

NEONATES

Week 1: Benzylpenicillin G (600 mg = 1 000 000 units) 60 mg/kg (100 000 units/kg) IV 12 hourly

Weeks 2–4: Benzylpenicillin G (600 mg = 1 000 000 units) 60 mg/kg (100 000 units/kg) IV 6–8 hourly (max 2.4 g)

INFANTS AND CHILDREN

Benzylpenicillin G (600 mg = 1 000 000 units) 60 mg/kg (100 000 units/kg) IV

4 hourly (max 2.4 g)

ADULTS

Penicillin G 4 million units IV 4 hourly

OR

Cefotaxime 2 g IV 4–6 hourly

OR

Ceftriaxone 2 g IV 12 hourly

Treat for 7 days

HAEMOPHILUS INFLUENZAE

NEONATES

Week 1: Cefotaxime 50 mg/kg IV 12 hourly

Weeks 2–4: Cefotaxime 50 mg/kg IV 8 hourly

INFANTS AND CHILDREN

Cefotaxime 50 mg/kg IV 6 hourly (max 2 g)

OR

Ceftriaxone 50 mg/kg IV 12 hourly (max 2 g)

ADULTS

Ceftriaxone 2 g IV 12 hourly

OR

Cefotaxime 2 g IV 4–6 hourly

Treat for 7–10 days

STREPTOCOCCUS AGALACTIAE

NEONATES

Week 1: Benzylpenicillin G (600 mg = 1 000 000 units) 60 mg/kg (100 000 units/kg) IV 12 hourly

Weeks 2–4: Benzylpenicillin G (600 mg = 1 000 000 units) 60 mg/kg (100 000 units/kg) IV 6–8 hourly (max 2.4 g)

INFANTS AND CHILDREN

Benzylpenicillin G (600 mg = 1 000 000 units) 60 mg/kg (100 000 units/kg) IV 4 hourly (max 2.4 g)

ADULTS

Ampicillin 2 g IV 4 hourly

OR

Ceftriaxone 2 g IV 12 hourly

OR

Cefotaxime 2 g IV 4–6 hourly

Treat for 14–21 days

LISTERIA MONOCYTOGENES

NEONATES

Week 1: Ampicillin 50 mg/kg IV 8 hourly **AND** gentamicin 2.5 mg/kg IV 12 hourly

Weeks 2–4: Ampicillin 50 mg/kg IV 6 hourly **AND** gentamicin 2.5 mg/kg IV 8 hourly

INFANTS AND CHILDREN

Ampicillin 50 mg/kg IV 4 hourly (max 2 g) **AND** gentamicin 2.5 mg/kg IV 8 hourly

ADULTS

Ampicillin 2 g IV 4 hourly ± gentamicin 2 mg/kg IV loading dose, THEN 1.7 mg/kg IV 8 hourly

Cotrimoxazole 5 mg/kg IV 6–8 hourly is an alternative agent if the patient is allergic to penicillin

Treat for at least 21 days

ENTEROBACTERIACEAE

NEONATES

Week 1: Cefotaxime 50 mg/kg IV 12 hourly **AND** gentamicin 2.5 mg/kg IV 12 hourly

Weeks 2–4: Cefotaxime 50 mg/kg IV 8 hourly **AND** gentamicin 2.5 mg/kg IV 12 hourly

INFANTS AND CHILDREN

Cefotaxime 50 mg/kg IV 6 hourly (max 2 g) **AND** gentamicin 2.5 mg/kg IV 12 hourly

OR

Ceftriaxone 50 mg/kg IV 12 hourly (max 2 g) **AND** gentamicin 2.5 mg/kg IV 12 hourly

Ceftazidime 150 mg/kg per day IV (maximum dose 6 g/day) in 3 divided doses should be used for P. aeruginosa infections

ADULTS

Ceftazidime/cefepime 2 g IV 8 hourly

OR

Meropenem 2 g IV 8 hourly ± gentamycin 2 mg/kg IV loading dose, then 1.7 mg/kg IV 8 hourly

Treat for at least 21 days

STAPHYLOCOCCUS AUREUS

S. aureus meninigitis is usually acquired nosocomially and may occur following neurosurgical procedures and the placement of CSF shunts.

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

CHILDREN

Vancomycin 15 mg/kg/dose IV every 6 hours

OR

Children < 12 years of age: Linezolid 30 mg/kg/day in 3 divided doses

Children > 12 years of age: Linezolid 20 mg/kg/day in 2 divided doses (maximum of 1200 mg/day)

ADULTS

Vancomycin 15–20 mg/kg/dose IV every 8 to 12 hours, not to exceed 2 g per dose and to aim for a serum trough concentration of 15–20 μg/mL

OR

Linezolid 600 mg PO/IV twice daily (with vancomycin resistance or contraindications to vancomycin)

May add rifampicin 600 mg orally/IV once daily or 300–450 mg orally/IV twice daily to vancomycin

For CNS shunt infection, shunt removal is recommended, and it should not be replaced until CSF cultures are negative

METHICILLIN-SENSITIVE STAPHYLOCOCCUS AUREUS (MSSA)

Cloxacillin 150–200 mg/kg IV per day in four to six divided doses; maximum daily dose 12 g

At least 14 days of therapy recommended.

VIRAL MENINGITIS

Patients present with similar symptoms and signs as bacterial meningitis. Enteroviruses are the most common cause of viral meningitis. Other common causes include mumps virus, herpes viruses (herpes simplex virus, varicella zoster, cytomegalovirus, Epstein-Barr virus and human herpes virus-6), HIV, adenovirus and arboviruses.

LABORATORY INVESTIGATIONS

- CSF typically has 10 to < 1000 WBC/μL, which are mostly lymphocytes, (but polymorphonuclear leucocytes may be seen early in the course, e.g. enterovirus meningitis), elevated protein, a normal glucose, and negative Gram-stain and bacterial culture.
- The infectious agents associated with, and diagnostic approach to, aseptic (bacterial culture-negative meningitis) are the same as those seen in encephalitis.
- Viral meningitis multiplex PCR detects: HSV 1&2, enteroviruses, parechovirus, varicella-zoster virus and mumps virus.

TUBERCULOUS MENINGITIS

- CSF: lymphocyte predominance, a low CSF glucose and elevated CSF protein level
- Laboratory testing: CSF TB culture and TB PCR, CSF ADA

CRYPTOCOCCAL MENINGITIS

- CSF: elevated lymphocyte count, elevated protein level and low CSF glucose
- Laboratory testing: CSF India ink and cryptococcal antigen test (CrAg)

ENCEPHALITIS

Encephalitis is defined as an inflammatory process of the brain parenchyma in association with clinical evidence of neurological dysfunction. In most cases there is some concomitant meningeal inflammation in addition to the encephalitic component – a condition referred to as meningoencephalitis. Since it is often difficult to differentiate patients with encephalitis from those with meningitis, it is important to investigate both diagnoses.

A wide variety of pathogens have been reported to cause encephalitis, most of which are viruses. In general, the most commonly identified infectious aetiologies of encephalitis are herpes simplex virus (HSV), enteroviruses, parechovirus, mumps virus followed by the other herpes viruses (including varicella zoster virus, cytomegalovirus and Epstein-Barr virus), arboviruses, *Toxoplasma gondii* and *Mycoplasma pneumoniae*.

A subset of viruses including mumps, measles, varicella zoster virus (VZV), rubella and influenza have been associated with post-infectious encephalitis, an immune-mediated process (acute disseminated encephalomyelitis or ADEM) where the virus cannot be detected or recovered.

CSF associated with encephalitis or meningoencephalitis typically have 10 – < 1000 WBC/μL, which are mostly lymphocytes, (but polymorphonuclear leucocytes may be seen early in the course), elevated protein which rarely exceeds 2 g/L, a normal glucose, and negative Gram-stain and bacterial culture.

Additional diagnostic tests are guided by the clinical and epidemiological clues obtained during the evaluation of the patient. PCR assays are generally the most sensitive assays to detect the causative pathogen. Viral culture is very rarely used and brain biopsy has a limited role and is generally only used with a rapidly deteriorating clinical status despite aggressive antimicrobial and antiviral chemotherapy.

LABORATORY INVESTIGATIONS

- FBC, renal (U&E) and hepatic function(LFT), coagulation studies
- CSF analysis: Ideally 10 ml of CSF should be obtained
  - CSF opening pressure
  - CSF cell count and differential

  - CSF chemistry: protein and glucose
  - Gram-stain and bacterial cultures (MC&S)
  - Viral meningitis multiplex PCR: HSV, VZV, enterovirus, parechovirus and mumps
- HIV testing and if reactive, a CD4 count to determine the probability of certain opportunistic infections

NOTES ON SELECTED CAUSES OF ENCEPHALITIS

HERPES SIMPLEX VIRUS

- HSV PCR on CSF is the diagnostic test of choice. Of note, HSV PCR may be negative in the first 72 hours and repeat LP and PCR should be performed to exclude the diagnosis after three days in cases with an initial negative PCR.
- HSV serology: limited role as false positive IgM results are common; however, IgG seroconversion may be used to diagnose a primary infection.

TREATMENT: HERPES SIMPLEX ENCEPHALITIS

Start treatment immediately on suspicion of HSV encephalitis

CHILDREN < 12 YEARS OF AGE

Acyclovir 20 mg/kg 8 hourly IV by infusion over 1 hour

ADULTS

Acyclovir 10 mg/kg 8 hourly IV by infusion over 1 hour

Treatment duration for HSV encephalitis is 14–21 days

Refer to the chapter 'Treatment of common viral infections' for more detailed information

VARICELLA ZOSTER VIRUS

- VZV encephalitis can be due to either primary varicella infection (chickenpox), which usually involves the cerebellum, or reactivation (zoster/shingles), which may occur in the absence of skin manifestations.
- VZV may also cause a vasculopathy of the cerebral arteries in patients with a history of recent zoster often presenting as an altered mental state, or a transient ischaemic attack or stroke.
- VZV PCR on CSF is the diagnostic test of choice. In addition, intrathecal synthesis of VZV antibodies can be detected by requesting VZV serology on CSF.

TREATMENT: VARICELLA ZOSTER ENCEPHALITIS

CHILDREN ≥ 1 YEAR OF AGE AND ADOLESCENTS

Acyclovir 1500 mg/m^2 IV per day in three divided doses

OR

Acyclovir 10 mg/kg IV 8 hourly

ADULTS

Acyclovir 10 mg/kg IV 8 hourly

Treatment duration of VZV encephalitis is 10 –14 days.

Patients with VZV vasculitis should receive antiviral therapy for a minimum of 14 days. Longer treatment may be necessary if the patient does not improve clinically, develops new MRI lesions or has persistent pleocytosis.

EPSTEIN BARR VIRUS

- CNS manifestations occur in five to 15% of primary EBV infections, and usually affect the cerebellum.
- Primary EBV infections are diagnosed by EBV serology and not EBV PCR: EBV NA (EBNA) IgG negative, EBV VCA IgM and IgG positive are the typical serological findings.
- CSF EBV PCR has a poor specificity for diagnosing EBV encephalitis as EBV DNA is frequently detected in the CSF of patients with a non-intact blood-brain barrier.

CYTOMEGALOVIRUS

- CMV may cause encephalitis in immunocompetent persons during a primary infection.
- In our setting, most CNS CMV infections are encountered in severely immunocompromised HIV-infected patients as encephalitis, ventriculitis, radiculopathy or a mass lesion.
- CMV PCR/viral load on CSF is the diagnostic test of choice.
- Refer to the chapter 'Treatment of common viral infections' for details on antiviral therapy.

TICK-BORNE RICKETTSIAS

In South Africa: *R. conorii* and *R. africae*

- Serological testing, using specific rickettsial assays, remains the gold standard for the diagnosis of tick bite fever. However, elevated IgM or IgG results are present in only 35% of acute samples, and therefore the diagnosis is made retrospectively by resubmitting serum samples for repeat rickettsial serology two to three weeks after acute presentation.
- Rickettsia PCR on blood may be positive during the acute infection. However, a negative PCR does not exclude the diagnosis.

NEUROSYPHILIS

- Although the CSF VDRL is the method of choice, VDRL reagent is not available in South Africa.
- The CSF-FTA is a more sensitive test, with a negative result essentially excluding the diagnosis of neurosyphilis.

TABLE 3: RECOMMENDED LABORATORY INVESTIGATIONS TO DIAGNOSE THE COMMON INFECTIOUS CAUSES OF ENCEPHALITIS

VIRUSES	SPECIMEN	DIAGNOSTIC METHOD(S)
Arboviruses (e.g. West Nile, Rift Valley fever and Dengue	CSF/blood	Virus-specific antibodies and PCR
Cytomegalovirus (CMV)	CSF	CMV PCR or viral load
Enterovirus and parechovirus	CSF	Enterovirus PCR/Parechovirus PCR
Epstein-Barr virus (EBV)	CSF	EBV PCR/viral load
	Blood	EBV serology
Herpes simplex virus (HSV)	CSF	HSV PCR
HIV	CSF	HIV viral load
	Blood	HIV antibodies

VIRUSES	SPECIMEN	DIAGNOSTIC METHOD(S)
Human Herpes virus-6 (HHV-6)	CSF	HHV-6 PCR
JC virus (PML – progressive multifocal leucoencephalopathy)	CSF	JC virus PCR
Measles	CSF	Measles virus PCR
	Blood	Measles serology with suspected primary infection
Mumps	CSF	Mumps virus PCR
	Blood	Mumps serology with suspected primary infection
Rabies	Saliva/CSF/ nuchal skin biopsy/corneal scraping	Rabies PCR
	Blood	Rabies serology is of limited value for the diagnosis of rabies encephalitis
Varicella zoster virus (VZV)	CSF	VZV PCR (preferred) ± VZV serology
	Blood	VZV serology with suspected chickenpox OR VZV PCR on vesicle fluid

BACTERIA	SPECIMEN	DDIAGNOSTIC METHOD(S)
Bartonella (Cat scratch disease)	Blood	Bartonella serology
	Lymphnode/CSF	Bartonella PCR
	Lymphnodes	Histology
Borrelia burgdorferi (Lyme disease)	CSF/blood	Borrelia antibodies
Mycobacterium tuberculosis	CSF	AFB, TB cultures and TB PCR ADA
Mycoplasma pneumoniae	CSF/NPA	M. pneumoniae PCR
	Blood	M. pneumoniae serology
Rickettsia conorii and R. africae	Blood	Rickettsia specific serology
Treponema pallidum (Syphilis)	CSF/blood	VDRL and syphilis serology

PARASITES	SPECIMEN	DIAGNOSTIC METHOD(S)
Cysticercosis	CSF	Cysticercosis serology
Plasmodium falciparum	Blood	Thin and thick smears, malaria antigen test, QBC, malaria PCR
Toxoplasma gondii	CSF	Toxoplasma PCR and Toxoplasma IgG
	Blood	Toxoplasma IgG
Trypanosomiasis	Blood	Blood smears

FUNGI	SPECIMEN	DIAGNOSTIC METHOD(S)
Cryptococcus neoformans	CSF	Cryptococcal antigen India ink stain Fungal culture
	Blood	Cryptococcal antigen
Histoplasma capsulatum	CSF/brain tissue/other	Fungal culture
	Urine/blood	Histoplasma antigen

NON-INFECTIOUS DISEASES	SPECIMEN	DIAGNOSTIC METHOD(S)
Collagen vascular disorders and vasculitis	Blood	ANA (ANF), anti-ENA antibodies ANCA
Paraneoplastic syndrome	Blood	Paraneoplastic/cerebellar antibodies
Autoimmune (limbic) encephalitis	CSF	Anti-NMDA antibodies
	Blood	Anti-NMDA antibodies Neuronal and GAD65 antibodies

BRAIN ABSCESS

In 80–90% of brain abscesses, multiple organisms are found. Streptococci (especially *S. milleri*) are the most common single organisms identified (30–50%), but anaerobic or other aerobic organisms can predominate. Fungal causes include *Candida*, *Aspergillus* and zygomycetes, but these are rare.

LABORATORY INVESTIGATIONS

The gold standard is aspiration of pus and collection of a biopsy. Send these specimens for:

- Gram-stain, aerobic and anaerobic bacterial culture (MC&S)
- AFB stains, TB cultures and TB PCR
- KOH smear, fungal culture
- Histopathological examination
- *Toxoplasma gondii* PCR (in immunosuppressed patients with risk factors)

EMPIRIC TREATMENT: BRAIN ABSCESS

Cefotaxime 2 g IV 4 - 6 hourly **AND** metronidazole 500 mg IV 8 hourly

OR

Ceftriaxone 2 g IV 12 hourly **AND** metronidazole 500 mg IV 8 hourly

OR

Cefepime 2 g IV 8 hourly (or given as 2 g stat, 6 g daily over 24 hr as an extended infusion) **AND** metronidazole 500 mg IV 8 hourly

NOTE: Patients with endocarditis or following neurological procedures or head trauma add vancomycin 15–20 mg/kg/dose IV every 8–12 hours (not to exceed 2 g per dose and to aim for a serum trough concentration of 15–20 μg/mL) OR linezolid 600 mg IV 12 hourly.

If *Pseudomonas aeruginosa* is suspected (e.g. postsurgical/post trauma), substitute cefotaxime or ceftriaxone with cefepime.

Duration of therapy is unclear. Treat until a response by neuroimaging (CT/MRI) is observed. Course of treatment is usually 4–6 weeks for surgically treated abscesses, and 6–8 weeks if not drained or multiple abscesses are present.

ADJUNCTIVE AND SURGICAL THERAPY

- Surgical options: Generally either stereotactic aspiration of abscess by burr hole placement, or surgical drainage by craniotomy.
- Dexamethasone (10 mg IV loading dose, then 4 mg 6 hourly) may be needed if there is significant mass effect and/or there is neurological decline.
- Concern regarding elevated intracranial pressures may require additional neurosurgical consideration for ventriculostomy or shunt placement.
- Phenytoin or other anticonvulsant therapy may be required to prevent seizures.

BRAIN ABSCESS: PATHOGEN-SPECIFIC ANTIBIOTIC THERAPY

STREPTOCOCCI (PENICILLIN-SENSITIVE)

Penicillin G 4 MU IV 4 hourly

OR

Ampicillin 2 g IV 4 hourly

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

Vancomycin 15–20 mg/kg/dose IV every 8 to 12 hours, not to exceed 2 g per dose and to aim for a serum trough concentration of 15–20 μg/mL. Children: 15 mg/kg/dose IV every 6 hours

May add rifampicin 600 mg orally/IV once daily or 300–450 mg orally/IV twice daily to vancomycin

OR

IV Linezolid 600 mg PO/IV twice daily [children: < 12 years: 30 mg/kg/day in 3 divided doses; > 12 years 20 mg/kg/day in 2 divided doses (max. 1200 mg/day)]

METHICILLIN-SENSITIVE STAPHYLOCOCCUS AUREUS (MSSA)

Cloxacillin 150–200 mg/kg per day IV in 4–6 divided doses; maximum daily dose 12 g

HAEMOPHILUS INFLUENZAE

Cefotaxime 2 g IV 4–6 hourly

OR

Ceftriaxone 2 g IV 12 hourly

ANAEROBES

Metronidazole 500 mg IV 6 hourly **AND** clindamycin 600–1200 mg IV 6–8 hourly

GRAM-NEGATIVE BACILLI

Meropenem 2 g IV 8 hourly
OR
Cefepime 2 g IV 8 hourly

NOCARDIA

Cotrimoxazole 15 mg/kg/day IV of the trimethoprim component in 2–4 divided doses **AND** imipenem 1 g IV 6 hourly.

If multi-organ involvement, consider adding amikacin 7.5 mg/kg 12 hourly to the above regimen.

After 3 weeks of IV therapy, switch to combination oral therapy (based on susceptibility results) and continue for a minimum of 3 months (immunocompetent patients) or 1 year (immunosuppressed patients).

SPINAL CORD INFECTIONS

There are a variety of pathologies that affect the spinal cord, including autoimmune, neoplastic, vascular and hereditary-degenerative diseases. This section will cover the common infectious pathologies of the spinal cord.

EPIDURAL ABSCESS

Spinal epidural abscess is a rare infection that occurs either via contiguous spread from skin or soft tissue infection or as a complication of spinal surgery or other invasive procedure such as epidural catheter placement. It may also occur as a result of haematogenous spread from a distant infection. Two distinct varieties of epidural abscess occur: spinal and intracranial.

Staphylococcus aureus infections account for about two thirds of cases with *Mycobacterium tuberculosis*, Gram-negative bacilli, streptococci, coagulase-negative staphylococci and anaerobes being responsible for the rest. Routine laboratory investigations are not usually helpful in the diagnosis of spinal epidural abscesses and imaging of the spinal column by means of MRI is the preferred test. Once identified, it is important to isolate the causative organism from the abscess content or from the blood. Two sets of blood cultures should be collected and pus should be collected by means of CT guided needle aspiration.

Management typically involves a combination of antibiotic and surgical therapy. Antibiotic management should be tailored according to the organism isolated and the duration of therapy is determined on a case-by-case basis, typically between four and eight weeks.

EMPIRIC TREATMENT: EPIDURAL ABSCESS

Cefotaxime 2 g IV 6 hourly **AND** vancomycin IV 15–20 mg/kg/dose every 8–12 hours (not to exceed 2 g per dose and to aim for a serum trough concentration of 15–20 μg/mL)

OR

Ceftriaxone 2 g IV 12 hourly **AND** vancomycin IV 15–20 mg/kg/dose every 8–12 hours (not to exceed 2 g per dose and to aim for a serum trough concentration of 15–20 μg/mL)

OR

Cefepime 2 g IV 8 hourly **AND** vancomycin IV 15–20 mg/kg/dose every 8–12 hours (not to exceed 2 g per dose and to aim for a serum trough concentration of 15–20 μg/mL)

OR

Ceftazidime 2 g IV 8 hourly **AND** vancomycin IV 15–20 mg/kg/dose every 8–12 hours (not to exceed 2 g per dose and to aim for a serum trough concentration of 15–20 μg/mL)

Cefepime or ceftazidime is preferred when *Pseudomonas aeruginosa* is considered a possible pathogen.

ACUTE VIRAL MYELITIS

Viral infections can cause two distinct syndromes of spinal cord involvement:

- Viral infection of the anterior horn cells as part of an acute viral illness such as enteroviruses (polio virus, coxsackie virus), and flaviviruses (West Nile and Japanese encephalitis). This results in a lower motor neuron disease and asymmetrical flaccid weakness. CSF typically shows a moderate pleocytosis and the causative virus can be identified by means of virus-specific PCR on CSF or serological testing on blood and CSF.
- A viral myelitis similar to transverse myelitis. The viruses associated with this presentation include CMV, varicella zoster, herpes simplex and EBV. In some cases the virus may be directly related to the myelitis and in others it may represent a post infectious immune-mediated complication.

HIV MYELOPATHY

HIV may produce a vacuolar myelopathy (HIV/AIDS myelopathy) and most often presents in patients with advanced AIDS. HIV-related dementia is often present in these patients and may obscure the diagnosis. The pathogenesis of this disorder is not known and the pathology includes demyelination of the dorsal and lateral columns with prominent vacuoles within the myelin sheath.

MRI of the spine is typically normal and the CSF may show non-specific abnormalities such as an elevated protein. Antiretroviral therapy may improve symptoms and intravenous immunoglobulin has been used in one case series with neurologic improvement.

HTLV-1 MYELOPATHY

Human T-cell lymphotropic virus type 1 (HTLV-1) causes a progressive neurological disorder known as tropical spastic paraparesis (TSP) or HTLV-1 associated myelopathy (HAM). This disorder is endemic in Japan, the Caribbean, central and parts of southern Africa and South America.

MRI of the spinal cord may show spinal atrophy. CSF examination typically shows a mild lymphocytosis and elevated protein. Serology on blood and CSF is positive for anti-HTLV antibodies with a high CSF/serum ratio. HTLV-1 DNA can also be detected in CSF and whole blood by means of a PCR. There is no specific antiviral treatment available.

SYPHILIS

Tabes dorsalis is a form of tertiary neurosyphilis in which the dorsal or posterior columns are affected. CSF may be normal or show an elevated protein level, lymphocytosis and a positive VDRL/FTA. Syphilitic meningoencephalitis and meningovascular myelitis represent earlier forms of syphilis infections whereby meningeal infection affects the adjacent spinal cord.

ANTIBIOTICS FOR THE TREATMENT OF NEUROSYPHILIS

Penicillin G 18–24 million units per day as a continuous infusion or as 3–4 million units IV 4 hourly

Treat for 10–14 days

TUBERCULOSIS

Tuberculosis infection of the vertebral body leads to tuberculous spondylitis or Pott's disease which can result in spinal cord compression. Tuberculomas within the intramedullary, intradural and extradural space may also result in a myelopathy.

BILHARZIA INFECTION

Schistosoma mansoni and *Schistosoma haematobium* may infect the spinal cord producing a transverse myelitis. CSF shows a pleocytosis and elevated protein, with eosinophilia occurring in about half of patients. *Schistosoma* DNA may be detected in CSF by means of a PCR. Treatment is with glucocorticoids and praziquantel.

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