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

<table>
<thead>
<tr>
<th></th>
<th>NEONATES AND INFANTS &lt; 3 MONTHS</th>
<th>INFANTS AND YOUNG CHILDREN 3 MONTHS TO 3 YEARS</th>
<th>OLDER CHILDREN AND ADULTS &gt; 3 YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Irritability</td>
<td>Headaches</td>
<td>Headaches</td>
</tr>
<tr>
<td></td>
<td>Poor feeding</td>
<td>Neck stiffness</td>
<td>Neck stiffness</td>
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<td></td>
<td></td>
<td></td>
<td>Photophobia</td>
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<tr>
<td>Signs</td>
<td>Bulging fontanelle</td>
<td></td>
<td>Rash: maculopapular or petechial</td>
</tr>
<tr>
<td></td>
<td>Hypothermia</td>
<td></td>
<td>Neck stiffness††</td>
</tr>
</tbody>
</table>

*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**

<table>
<thead>
<tr>
<th>Age</th>
<th>Birth</th>
<th>1 month</th>
<th>3 months</th>
<th>5 years</th>
<th>50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes</td>
<td></td>
<td></td>
<td></td>
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</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Neisseria meningitidis</td>
<td>Haemophilus influenzae</td>
<td><em>Streptococcus agalactiae</em></td>
<td><em>Escherichia coli</em></td>
<td><em>Listeria monocytogenes</em></td>
</tr>
</tbody>
</table>

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 ≤ 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 ≤ 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**

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.

<table>
<thead>
<tr>
<th>AGE</th>
<th>CAUSATIVE ORGANISM</th>
<th>EMPIRIC ANTIBIOTIC TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 month</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- S. agalactiae (group B streptococcus)
- E. coli
- L. monocytogenes
- Gram-negative bacilli

<p>| Age &lt; 1 week: 100 mg/kg IV 12 hourly |
| Age 1–4 weeks: 100 mg/kg IV 8 hourly |
| AND |
| Age &lt; 1 week: 2.5 mg/kg IV 12 hourly |
| Age 1–4 weeks: 2.5 mg/kg IV 8 hourly |
| OR |
| Ampicillin |
| Age &lt; 1 week: 100 mg/kg IV 12 hourly |
| Age 1–4 weeks: 100 mg/kg IV 8 hourly |
| AND |
| Cefotaxime |
| Age &lt; 1 week: 50 mg/kg IV 8 hourly |
| Age 1–4 weeks: 50 mg/kg IV 6–8 hourly |</p>
<table>
<thead>
<tr>
<th>AGE</th>
<th>CAUSATIVE ORGANISM</th>
<th>EMPIRIC ANTIBIOTIC TREATMENT</th>
</tr>
</thead>
</table>
| 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  
Nosocomial bacterial meningitis  
Risk factors:  
• Neurosurgery  
• Internal or external ventricular drains  
• Trauma (cranial fracture, especially basilar skull fracture) | • S. pneumoniae,  
• L. monocytogenes,  
• Gram-negative bacilli (including *P. aeruginosa*)  
• S. aureus  
• S. epidermidis  
• Other coagulase negative staphylococci  
• Aerobic Gram-negative bacilli including *Pseudomonas* | Cefepime 2 g IV 8 hourly  
**OR**  
Meropenem 2 g IV 8 hourly  
**AND**  
Ampicillin 2 g IV 4 hourly  
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) |
### 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 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

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Duration of Antimicrobial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neisseria meningitidis</td>
<td>7 days</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>7–10 days</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>10–14 days</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>14–21 days</td>
</tr>
<tr>
<td>Aerobic Gram-negative bacilli</td>
<td>21 days</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>21 days</td>
</tr>
<tr>
<td>Culture-negative meningitis</td>
<td>≥ 14 days</td>
</tr>
</tbody>
</table>

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 15 mg/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)
### STREPTOCOCCUS AGALACTIAE

<table>
<thead>
<tr>
<th><strong>NEONATES</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1: Benzylpenicillin G (600 mg = 1 000 000 units) 60 mg/kg (100 000 units/kg) IV 12 hourly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
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</tr>
</tbody>
</table>

| **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 7–10 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 ± gentamicin 2 mg/kg IV loading dose, then 1.7 mg/kg IV 8 hourly
Treat for at least 21 days

STAPHYLOCOCCUS AUREUS
S. aureus meningitis 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.

<table>
<thead>
<tr>
<th>TREATMENT: HERPES SIMPLEX ENCEPHALITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Start treatment immediately on suspicion of HSV encephalitis</strong></td>
</tr>
<tr>
<td><strong>CHILDREN &lt; 12 YEARS OF AGE</strong></td>
</tr>
<tr>
<td>Acyclovir 20 mg/kg 8 hourly IV by infusion over 1 hour</td>
</tr>
<tr>
<td><strong>ADULTS</strong></td>
</tr>
<tr>
<td>Acyclovir 10 mg/kg 8 hourly IV by infusion over 1 hour</td>
</tr>
<tr>
<td><strong>Treatment duration for HSV encephalitis is 14–21 days</strong></td>
</tr>
<tr>
<td>Refer to the chapter ‘Treatment of common viral infections’ for more detailed information</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>TREATMENT: VARICELLA ZOSTER ENCEPHALITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHILDREN ≥ 1 YEAR OF AGE AND ADOLESCENTS</strong></td>
</tr>
<tr>
<td>Acyclovir 1500 mg/m² IV per day in three divided doses OR</td>
</tr>
<tr>
<td>Acyclovir 10 mg/kg IV 8 hourly</td>
</tr>
<tr>
<td><strong>ADULTS</strong></td>
</tr>
<tr>
<td>Acyclovir 10 mg/kg IV 8 hourly</td>
</tr>
<tr>
<td><strong>Treatment duration of VZV encephalitis is 10 –14 days.</strong></td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>
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 RICKETSIAS

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

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

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

### BACTERIA

<table>
<thead>
<tr>
<th><strong>BACTERIA</strong></th>
<th><strong>SPECIMEN</strong></th>
<th><strong>DIAGNOSTIC METHOD(S)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartonella (Cat scratch disease)</td>
<td>Blood</td>
<td>Bartonella serology</td>
</tr>
<tr>
<td></td>
<td>Lymphnode/CSF</td>
<td>Bartonella PCR</td>
</tr>
<tr>
<td></td>
<td>Lymphnodes</td>
<td>Histology</td>
</tr>
<tr>
<td>Borrelia burgdorferi (Lyme disease)</td>
<td>CSF/blood</td>
<td>Borrelia antibodies</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>CSF</td>
<td>AFB, TB cultures and TB PCR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADA</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>CSF/NPA</td>
<td>M. pneumoniae PCR</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>M. pneumoniae serology</td>
</tr>
<tr>
<td>Rickettsia conorii and R. africae</td>
<td>Blood</td>
<td>Rickettsia specific serology</td>
</tr>
<tr>
<td>Treponema pallidum (Syphilis)</td>
<td>CSF/blood</td>
<td>VDRL and syphilis serology</td>
</tr>
<tr>
<td>PARASITES</td>
<td>SPECIMEN</td>
<td>DIAGNOSTIC METHOD(S)</td>
</tr>
<tr>
<td>-----------</td>
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<td>----------------------</td>
</tr>
<tr>
<td>Cysticercosis</td>
<td>CSF</td>
<td>Cysticercosis serology</td>
</tr>
<tr>
<td>Plasmodium falciparum</td>
<td>Blood</td>
<td>Thin and thick smears, malaria antigen test, QBC, malaria PCR</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>CSF</td>
<td>Toxoplasma PCR and Toxoplasma IgG</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>Toxoplasma IgG</td>
</tr>
<tr>
<td>Trypanosomiasis</td>
<td>Blood</td>
<td>Blood smears</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FUNGI</th>
<th>SPECIMEN</th>
<th>DIAGNOSTIC METHOD(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcus neoformans</td>
<td>CSF</td>
<td>Cryptococcal antigen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>India ink stain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fungal culture</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>Cryptococcal antigen</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>CSF/brain tissue/other</td>
<td>Fungal culture</td>
</tr>
<tr>
<td></td>
<td>Urine/blood</td>
<td>Histoplasma antigen</td>
</tr>
</tbody>
</table>

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

**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).

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**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.

<table>
<thead>
<tr>
<th>ANTIBIOTICS FOR THE TREATMENT OF NEUROSYPHILIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G 18–24 million units per day as a continuous infusion or as 3–4 million units IV 4 hourly</td>
</tr>
<tr>
<td>Treat for 10–14 days</td>
</tr>
</tbody>
</table>

**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.

**REFERENCES**