Chapter 14
Central Nervous System Infections (Bacteria and Parasites)

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Abstract Infections of the central nervous system (CNS) are common in children and should be investigated and managed promptly, since delay may result in significant morbidity or mortality. This chapter provides an approach to a child with neurological features associated with infections and then discusses the most common infectious disease syndromes likely to be encountered in practice, e.g., meningitis. It also includes those infections that are not found in many neurological text books, e.g., tetanus, but which need to be considered in the differential diagnosis of other neurological conditions.

Keywords Central nervous system infections • Bacteria • Fungi • Parasites

14.1 Introduction

Infections of the central nervous system (CNS) are common in children and can mimic many other neurological conditions. Suspicion should be aroused in any child who presents with neurological features in conjunction with a history of fever or recent travel. Prompt assessment and investigation are required, since the child can deteriorate rapidly. Initial management is often empirical, based upon the epidemiology of infections in the area, since delay often leads to significant morbidity or mortality.

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14.2 Approach to the Febrile Child with Neurological Symptoms

Fever is the cardinal feature of infection, but not all children with CNS infections present with fever. A history of fever in the presence of neurological symptoms, which include many nonspecific features (e.g., vomiting, diarrhea, lethargy), should arouse suspicion of CNS infection. In these circumstances, history should focus on:

- Potential sources of infections, i.e., contact with adults and children with infections, pets, travel, and history
- Evolution of the illness: how quickly has the illness developed
- Appearance of complications
  - Impaired consciousness
  - Seizures

Examination should concentrate on:

- Identifying potential sources of infection, e.g., ears
- Assessing levels of consciousness
- Looking for evidence of focal neurological deficits

Management needs to include immediate assessment of the cardiovascular and neurological status of the child, to determine if there is adequate oxygenation and cardiac output, and provide a baseline from which to monitor changes in cardiac, respiratory, and neurological status. Supportive care is important. In particular:

- Maintaining blood pressure to ensure adequate cerebral perfusion.
- Managing fluids.
- Correction of hypoglycemia and electrolyte disorders.
- Respiratory support may be needed.
- Immediate administration of antimicrobials, usually starting with an empiric regimen including a broad-spectrum antibiotics (e.g., cephalosporin), an antiviral (e.g., acyclovir), and an agent to treat *Mycoplasma* sp.
- Detection and treatment of:
  - Seizures
  - Raised intracranial pressure

Immediate investigations should include:

- Complete blood count (CBC) and differential.
- Nonspecific tests for infections, e.g., C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR).
- Blood glucose.
- Electrolytes, urea or creatinine, and liver enzymes.
- Assays of coagulation in those with hemorrhages or petechiae.
- Cultures of blood and urine and any other fluids which are thought to be involved, e.g., nasopharyngeal aspirates.

Table 14.1 Lumbar puncture

Indications
1. Signs of meningitis
2. Impaired consciousness
3. Seizures
Contraindications
1. Raised intracranial pressure, suggested by the following signs:
Impaired level of conscious or agitation
Brainstem signs of herniation, particularly diplopia, abnormal pupillary responses
Motor posturing
Papilledema
Papilledema is not a sensitive sign for RICP and is often a late sign of RICP in meningitis
Bulging fontanelle in the absence of other signs of RICP is not a contraindication to LP
2. Signs of space occupying lesion
Focal neurological signs
Focal seizures
3. Cardiovascular compromise/shock
4. Respiratory compromise
5. Bleeding diathesis
6. Skin infection over the site of the LP
7. Febrile child with purpura where meningococcal infection is suspected. Give antimicrobials immediately
Complications
1. Failure to obtain or blood stained CSF (common)
2. Post-dural puncture headache up to 5–15 %
3. Transient/persistent paresthesia/numbness (very uncommon)
4. Respiratory arrest from positioning (rare)
5. Spinal hematoma or abscess (very rare)
6. Tonsillar herniation (extremely rare in the absence of contraindications above)

- Blood should be taken for serological assays.
- Lumbar puncture (Table 14.1) should be considered any children with:
  - Signs of meningitis
  - Seizures—if not typical of febrile seizures [1]
  - Impairment of consciousness
- Emergency neuroimaging should be considered in children with:
  - Impaired level of consciousness
  - Focal neurological deficits
  - Suspicion of raised intracranial pressure

Further investigations will be directed by possible etiologies.
When performing a lumbar puncture (LP), the following should be considered:

- Measure opening pressure using a manometer or an iv "giving set" and a tape measure.
- Take cerebrospinal fluid (CSF) in appropriate tubes for

Table 14.2 Interpretation of CSF usually immediately available

	White cell count		Biochemistry	
	Neutrophils	Lymphocytes	Protein	CSF: Blood ratio
Condition	$\times 10^6$/L	$\times 10^6$/L	g/L	
Normal neonate	0	<20	<1.0	>0.6, or CSF glucose >2.5 mol/L
Normal child	0	<5	<0.4	>0.6, or CSF glucose >2.5 mol/L
Viral meningitis	<100	10–1,000	<1.0	>0.6
Acute bacterial meningitis	Usually >100	50–1,000	>1.0, but may be normal	<0.4 but may be normal
Tuberculosis meningitis	Usually <100	10–1,000	1.0–5.0 but may be normal	<0.3 but may be normal
Fungal meningitis	May occur early in the illness	5–100	>1.0	>0.4
Encephalitis	<10	>20	>0.4	>0.6
Neuroborreliosis	<10	100–500	0.5–1.5	>0.4

  - Microbiology investigations (microscopy, culture, and sensitivity)
  - Glucose (with paired plasma sample)
  - Lactate
  - Protein

- Other CSF investigations include
  - Rapid antigen testing for *S. pneumoniae, N. meningitidis,* and *H. influenzae*
  - Polymerase chain reaction (PCR) for

    Bacteria (*S. pneumoniae, N. meningitidis, H. influenzae*)
    Viruses (enterovirus, adenovirus, and herpes simplex viruses)
    Mycobacterium tuberculosis

  - Ziehl-Neelsen staining and culture for *M. tuberculosis* (ideally a 2–5 mL is needed to improve yield)

- Save (freeze) a sample of blood and CSF for further investigations if needed.

The initial CSF findings may dictate the initial treatment (see Table 14.2).

Consider noninfective causes of abnormal CSF findings, in particular: drugs, autoimmune diseases, e.g., collagen vascular diseases or malignant meningitis, e.g., lymphomatous spread.

14.2.1 Radiology

X-rays, e.g., chest X-ray and isotope scans, may help determine the source of infection. For imaging the CNS, magnetic resonance imaging (MRI) is more sensitive than computerized tomography (CT), but often less available.

14.3 Definitions of the Syndromes of CNS Infections

Meningitis is the inflammation of the brain meninges, characterized by white blood cells in CSF. It can be caused by a wide range of organisms, particularly viruses, bacteria, and fungi. It may be associated with inflammation of the brain parenchyma (encephalitis), presenting as impairment of consciousness (meningoencephalitis).

Encephalitis is the inflammation of the brain parenchyma. This is a pathological diagnosis definitively made with a brain biopsy or at autopsy. However, surrogate markers such as CSF microscopy or the findings of neuroimaging (particularly MRI) are used. The child is febrile and encephalopathic with an altered level of consciousness or a behavioral change. They may also have signs of meningeal irritation and/or have focal neurological symptoms or signs.

Myelitis is the inflammation of the spinal cord, which usually presents as back pain, followed by paralysis, sensory disturbances, and incontinence of urine and/or feces. It may present acutely or in a slow progressive fashion, with asymmetry.

Infective space-occupying lesions (SOL) include brain abscesses and extra-axial collections of pus, e.g., subdural empyema. Lesions may be single or multiple depending on the cause. Typically the child is febrile and will have focal neurological symptoms or signs. They may have signs of meningeal irritation (depending on whether the meninges are involved) or be encephalopathic.

Children who are immunocompromised may present with milder or atypical symptoms and signs for any of these CNS syndromes. Infants may not have a fever. A careful history should be taken to establish whether a child could be immunocompromised, particularly if their illness is unexplained, including asking the mother about risk factors for HIV.

14.4 Acute Bacterial Meningitis (ABM)

14.4.1 Background

The incidence of meningitis is highest during childhood, particularly during the neonatal and infancy periods. The incidence varies considerably throughout the world, with the highest in Africa and Asia, although it has reduced with the introduction of vaccines against *Haemophilus influenzae*, *Streptococcus pneumoniae,* and Meningococcus [2].

The causative organisms are dependent upon age, vaccination status, and immune status of the child. *H. influenza* and *S. pneumoniae* can occur before the child has reached the age for vaccination. *S. pneumoniae* is associated with more severe disease, greater morbidity, and sequelae. It is associated with pneumonia, otitis media, sinusitis, head injury, and sickle cell disease.

14.4.2 Presenting Signs and Symptoms

The typical features of ABM consist of fever, headache, photophobia, and neck stiffness, though most children with ABM do not have all these features. Infants may present with nonspecific signs of infection, including poor temperature control, lethargy, not interested in feeding, and a bulging fontanelle [2].

Signs include:

- Meningism (neck stiffness; Brudzinski and Kernig signs are rare in children).
- Altered level of consciousness in severe cases.
- Petechial or purpuric rash suggests meningococcus.
- Seizures (may be focal or generalized) in 30 %.
- Cranial nerve signs: 15 %.
- Other focal neurology: 10 %.
- Septicemic shock, multiorgan involvement, and abnormal clotting studies—particularly with meningococcus.

Infants or immunocompromised children may not display typical features, and an LP may be the only way to exclude meningitis.

14.4.3 Recommended Assessments

14.4.3.1 Lumbar Puncture

If ABM is suspected, an LP is essential to make the diagnosis, identify the organism, and determine the sensitivity of the organism to antimicrobials. It should be performed unless a specific contraindication exists (Table 14.1). It may be repeated if the initial CSF is normal.

14.4.3.2 Neuroimaging

In a child with suspected meningitis, brain imaging findings may be normal on admission. An MRI or CT scan may help in the differential diagnosis and should be performed acutely, particularly if there are any contraindications to an LP (see Table 14.1). Imaging may also be useful in the management of a child with definite meningitis if their condition deteriorates, and they become encephalopathic, develop focal deficits, or if a complication of the infection is suspected later, e.g., hydrocephalus.

Other investigations to consider include:

- Blood tests:
  - CBC and differential may show low or high white cell count, left shift, atypical white cells, low, or high platelets.
  - Blood culture.
  - CRP, renal, and liver enzyme.

Table 14.3 Organisms and treatment of acute bacterial meningitis

Age	Organisms	Initial empirical therapy	Notes
Neonates	*Group B streptococci, Escherichia coli, Listeria monocytogenes*	Ampicillin (50–100 mg/kg 6 h) plus gentamicin (2.5 mg/kg every 8 h) *or* cefotaxime (50 mg/kg every 6–8 h)	Vancomycin (15 mg/kg every 6 h) may be added in suspected staphylococcal meningitis
1–3 months	As above or *S. pneumoniae, N. meningitidis, H. influenzae*	Ampicillin (50–100 mg/kg every 6 h) plus cefotaxime (75 mg/kg every 6–8 h) *or* ceftriaxone (50 mg/kg every 12 h)	
3–6 months	*S. pneumoniae, N. meningitidis, H. influenzae*	Cefotaxime (75 mg/kg every 6–8 h, up to a maximum of 12 g daily) *or* Ceftriaxone (50 mg/kg every 12 h, up to a maximum of 4 g daily) plus vancomycin (15 mg/kg every 6 h, up to a maximum 1 g per dose)	Rifampicin may be added if dexamethasone is administered to prevent tuberculosis in patients at risk of tuberculosis
>6 months	*S. pneumoniae, N. meningitidis, H. influenzae*		

- Rapid antigen testing for several bacteria (*S. pneumoniae, N. meningitidis, H. influenzae*).
- Clotting/coagulation studies if child appears ill or has a petechial rash.
- Chest X-ray or imaging of the sinuses may be helpful depending on the history or clinical signs.

Store serum for specific antibody tests. A convalescent sample should be taken 3 weeks after the onset of the illness.

14.4.4 Recommended Interventions

Meningitis should be treated promptly. Since it is difficult to distinguish between viral meningoencephalitis and bacterial meningitis in neonates, antibiotics and antivirals, e.g., acyclovir, should be used. The antimicrobials used need to cover a wide range of organisms including the gram-positive and gram-negative organisms. Local information about the causative organisms and resistance patterns should inform the choice of antimicrobials.

Recommended antimicrobial regimens depend upon the age, most likely organisms and local resistance patterns. Initial therapy should be with empirical regimens (Table 14.3), until the organism has been identified. Antimicrobial treatment should last for 14–21 days in neonatal meningitis, and 7–14 days in older children, depending on the organism. Antimicrobials may need to be changed when the culture and sensitivity results are available. Repeating the lumbar puncture after 48–72 h after onset of treatment may help with management, recording the response to treatment.

Supportive care is important:

- Maintaining blood pressure to ensure adequate cerebral perfusion
- Careful fluid management
- Correction of electrolyte disorders
- Respiratory support may be needed
- Control of seizures with benzodiazepines, phenobarbital, phenytoin, or sodium valproate

Corticosteroids improve the outcome in meningitis in children in high-income countries [3], but there is little evidence in poor countries.

14.4.5 Complications

Raised intracranial hypertension and progression to a brainstem herniation syndrome, effusions and empyema, acute symptomatic seizures, cerebritis, abscess formation, hydrocephalus, electrolyte disturbances (particularly a low sodium or a metabolic acidosis), and venous sinus thrombosis leading to cerebral infarction are possible complications.

14.4.6 Outcome

Mortality is about 5 %, with neurological sequelae about 15 % [4]. Cognitive impairment/educational difficulties, behavioral problems, hemiplegia, spastic quadriplegia, dystonia, spasticity, hearing loss or visual loss, and epilepsy are the most common.

14.5 Viral (Aseptic) Meningitis

The epidemiology depends on geography, climate, and vaccination coverage. Epidemics occur and new viruses can emerge. Viral meningitis is common, but is rarely associated with shock.

The most commonly used agents are outlined in Table 14.4.

14.6 Presenting Signs and Symptoms

See section above on ABM. Headache is common in older children and impaired level of consciousness is very uncommon and if present suggests encephalitis.

Table 14.4 Viruses causing most CNS infections

Organisms	Meningitis	Encephalitis	Myelitis	Other clinical features	Comments
Adenovirus	Yes			Conjunctivitis, respiratory infection, or gastroenteritis	
Echovirus	Yes			Conjunctivitis, rash, myositis	
Enteroviruses	Yes	Yes		Rash	
Epstein-Barr virus (EBV)	Yes		Yes	Pharyngitis, lymphadenopathy, splenomegaly, atypical peripheral lymphocytes may have abnormal LFTs	
Coxsackie	Yes	Yes		Rash, hand, foot and mouth disease, myocarditis, pericarditis, pleurisy	
Cytomegalovirus (CMV)	Yes	Yes	Yes	Hepatitis and retinitis (uncommon unless immunocompromised)	
Herpes simplex virus type 1	Yes	Yes	Rare	May be associated with a cold sores or skin lesions, but rarely seen Suggested by focal seizures, personality changes, and aphasia	Transmitted orally
Herpes simplex virus type 2	Yes	Yes		Neonatal	Primarily sexual contact
Human herpes virus (HHV) 6	Yes			Roseola infantum (slapped cheek rash), febrile seizures	
Human herpes virus (HHV) 7	Yes			Similar to HHV-6	
Human immunodeficiency virus		Yes		May present with developmental delay, subacute encephalopathy, or opportunistic CNS infections	
Lymphocytic choriomeningitis virus	Yes			Orchitis, myocarditis, parotitis, alopecia	History of contact with rodents

(continued)

Table 14.4 (continued)

Organisms	Meningitis	Encephalitis	Myelitis	Other clinical features	Comments
Measles	Yes	Yes	Rare	Morbilliform rash, conjunctivitis, lymphadenopathy, pneumonitis	
Mumps	Yes	Yes		Parotitis, pancreatitis (with elevated amylase and lipase), hearing loss	
Poliovirus	Yes	Rarely	Yes	Rash	
Rabies		Yes		Furious rabies with agitation, hydrophobia, or hypersalivation is much more common than the "paralytic" or "dumb" type with flaccid ascending paralysis	Most commonly dog and bat bites Endemic in Africa and Asia
Varicella zoster (VZV)	Yes			May have typical chicken pox rash with fluid-filled blisters	
Arboviruses					
Dengue	Yes	Yes		May occur during primary or secondary infections. High prevalence of sequelae	SE Asia
Equine encephalitis	Yes	Yes	Yes	High mortality	North and South America
Japanese encephalitis		Yes	Yes	Basal ganglia involvement	SE Asia
Lacrosse	Yes	Yes		Increased fever and hyponatremia associated with clinical deterioration	USA
St. Louis encephalitis	Yes	Yes		High prevalence of sequelae	Culex sp. Late summer early autumn in USA
West Nile		Yes	Yes	Guillain-Barre syndrome, multifocal chorioretinitis, hepatitis, myocarditis, nephritis, pancreatitis, and splenomegaly	Ubiquitous Culex sp.

14.6.1 Recommended Assessments

Assess the clinical state as above.

If viral meningitis is suspected, an LP is essential and the CSF may show typical changes (Table 14.2). Mild elevation of the liver enzymes or pancreatic enzymes can occur with some viruses.

Other investigations include swabbing the throat and rectum for viral isolation (viral culture medium needed). A serum sample should be saved to compare with a convalescent sample taken 3 weeks after the onset of the illness. Infants rarely need neuroimaging.

14.6.2 Outcome

Outcomes are generally good, although hearing should be tested.

14.6.3 Recommended Interventions

Ensure cardiovascular status is stable.

No specific treatment is needed. Full recovery usually occurs within 2 weeks, although some patients may have post-viral fatigue syndrome (rare in infancy). Test hearing after recovery.

14.7 Chronic Bacterial Meningitis

The major causes of chronic bacterial meningitis are *Mycobacterium tuberculosis* and fungi, in particular *Cryptococcus species*, *Candida albicans,* and *Coccidioides immitis*. Although tuberculosis meningitis occurs in immunocompetent children, tuberculosis and fungal meningitis should be considered particularly in immunocompromised children. These infections can be transmitted during pregnancy, although congenital meningitis is rare.

14.7.1 Tuberculosis Meningitis (TBM)

14.7.1.1 Presenting Signs and Symptoms

Tuberculosis meningitis may occur as a separate clinical syndrome or in young children as part of miliary tuberculosis. Most infants present with fever, vomiting,

cough, and impaired consciousness. Seizures are common. Bulging fontanelle is noticeable in younger infants. In older children cranial nerve palsies, hemiparesis, or opisthotonus may occur [5].

14.7.1.2 Recommended Assessments

Laboratory investigations:

- Hyponatremia is common.
- CSF: Pleocytosis with lymphocytic predominance (usually <1,000 cells 10^6/L); increased CSF protein and decreased CSF glucose.
- Acid-fast bacillus is rarely seen and culture often negative.
- PCR can be helpful in reliable laboratories.

Diagnosis is often based upon high index of suspicion, history of contacts, positive tuberculin test, and evidence of TB in other organs, particular in the lungs.

CT or MRI scans and cranial ultrasound commonly show hydrocephalus and less often basal enhancement and/or infarction of the basal ganglia. Chest X-ray is helpful in the diagnosis.

14.7.1.3 Recommended Interventions

Isoniazid, rifampicin, streptomycin, and pyrazinamide are the combination of choice. Corticosteroids improve outcome in HIV-negative children [6], but there is no evidence they improve outcome in HIV-positive children with TBM. Streptomycin, pyrazinamide, and dexamethasone are given for 2 months, and the isoniazid and rifampicin for 18 months. Ventriculoperitoneal shunting is often required for hydrocephalus.

Follow-up contacts with the family and neighbors.

14.7.1.4 Outcome

TBM is increasing and is associated with HIV infection. Mortality is high and neurological sequelae are common.

14.7.2 Fungal Meningitis

This commonly occurs in immunocompromised hosts and may be the first sign of an AIDS defining illness. It is reported from immunocompetent children as well.

14.7.2.1 Presenting Signs and Symptoms

The presentation may be more insidious than TBM. Infants present with respiratory distress, not tolerating feeds and/or abdominal distension. Older children have more typical features of meningitis. Fundoscopic examination may reveal disseminated Candida.

14.7.2.2 Recommended Assessments

Similar to TBM, but hyponatremia less common. The organisms may be seen with fungal stains of the CSF, but the organism is usually isolated from other parts of the body, and meningitis is suspected from the pleocytosis.

14.7.2.3 Recommended Interventions

Candida sp.: amphotericin B in combination with flucytosine

Cryptococcus sp.: amphotericin B and flucytosine for 6–10 weeks in HIV-negative patients. For HIV-positive patients, amphotericin B and flucytosine for 2 weeks and then fluconazole for 10 weeks.

14.7.2.4 Outcome

The mortality rate is very high and sequelae are common in those that survive.

14.8 Infective Space-Occupying Lesions

Brain abscesses or extra-axial collections can be caused by bacteria, fungi, or parasites with the most common causal organisms in infancy being Staphylococci, *Streptococcus* (aerobic and anaerobic), and *H. influenzae*. Anaerobic organisms such as *bacteroides*, *Streptococcus milleri,* and *Fusobacterium* are also commonly found. CNS tuberculosis presenting as a tuberculoma should be considered. Fungi (*Aspergillus* species) and parasites have also been reported. Many abscesses will contain mixed flora (approximately 40 %).

These lesions may be caused by hematogenous or local spread and should be considered in children with the risk factors outlined in Table 14.5. They may be single or multiple, with the site related to predisposing factor. Hematogenous spread is found mainly in the supply of the middle cerebral artery, but may also occur via the veins from the sinuses to the frontal lobes. Direct invasion from infections of the sinuses or middle ear cause abscesses in the temporal lobes or cerebellum.

Table 14.5 Risk factors for brain abscesses

Congenital heart disease
Sinus or ear infections
Poor dental hygiene
Immunosuppression
Complication of bacterial meningitis
Child with a ventriculoperitoneal shunt
Skull fracture
Congenital lesions of head and neck which communicate with the CNS, e.g., dermal sinuses
Aspiration of a foreign body

14.8.1 Presenting Signs and Symptoms

This depends on location of the lesion(s) in the CNS. It typically causes irritability, fever, and a focal neurological deficit. Brain abscess are more common in infants than older children [7]. In infancy, the fontanelle can bulge and the head circumference can increase rapidly. There may be lethargy or impaired level of consciousness. RICP and herniation syndromes can develop. If the abscess ruptures into the ventricular system, it causes an acute neurological decompensation with signs of meningitis.

14.8.2 Recommended Assessments

Elevated nonspecific markers of infection may occur. Blood cultures are rarely positive.

Cardiac assessment including echocardiography should be done.

LP is usually contraindicated due to the risk of brain herniation syndromes.

14.8.2.1 Neuroimaging

Cranial ultrasound may be useful in a neonate. CT is useful and will detect most SOL, except those in the posterior fossa. Contrast should be given as extra-axial collections can be missed on an unenhanced CT scan, and a ring enhancement of lesions is characteristic.

MRI is the modality of choice. Contrast should be given since ring enhancement of lesions is more commonly seen than on CT scans. Enhancement may be seen in single demyelinating lesions (v uncommon in infancy). Diffusion-weighted and MR spectroscopy can also be helpful in differentiating a single parenchymal lesion from a tumor.

Brain biopsy may be helpful, but is rarely performed. Differential diagnoses include brain tumors, tuberculomas, lymphoma, single demyelinating lesion, and intraparenchymal hemorrhage.

14.8.3 Recommended Interventions

Antimicrobials may be used for small lesions (<2 cm) or those in whom the causative organism has been identified. Most brain abscesses require surgical drainage, followed by prompt initiation of empirical broad-spectrum antimicrobial therapy, usually for 6 weeks but longer in immunocompromised children. Surgical specimens should be sent for histology and for microbiology. The first choice antibiotics would include a third-generation cephalosporin and metronidazole, but advice should be sought from microbiologists or infectious disease team. If an associated foreign body, e.g., central line or ventriculoperitoneal shunt, is found, it should be removed.

14.8.4 Outcome

Depends of severity and location of parenchymal damage. Up to 40 % of children have neurological sequelae and 25 % have epilepsy.

14.9 Encephalitis

Encephalitis can be caused by a wide range of viruses (Table 14.4), many of which have specific geographical distributions. See Chap. 16 for more details.

14.9.1 Presenting Signs and Symptoms

The clinical manifestations of encephalitis vary according to the site and severity of parenchymal involvement. In neonates, encephalitis generally presents with nonspecific symptoms and signs of systemic sepsis including fever, poor feeding, irritability, lethargy, seizures, or apnea. History of maternal fever in the peripartum may be present in some cases of enterovirus or adenovirus infections. History of maternal genital herpes is seen in only 20–27 % of infants with herpes infection. Hence, an absence of parental history of HSV infection does not exclude neonatal HSV infection. Skin lesions in the neonate are seen in some cases of neonatal herpes encephalitis. Focal neurological signs may be present.

In older children, the usual presentation of encephalitis in older children is with acute onset fever, headache, seizures, behavioral changes, and impairment of consciousness leading to coma. A prodromal illness with myalgias, fever, anorexia, and lethargy, reflecting the systemic viremia, may occur. Seizures are common and may be generalized or focal. Cortical involvement may lead to disorientation and

confusion, basal ganglia involvement to movement disorders, and brainstem involvement to cranial nerve dysfunction. Associated spinal cord involvement (myelitis) may cause flaccid paraplegia with abnormalities of the deep tendon reflexes.

14.9.2 Recommended Assessments

Early in the illness, the CSF is clear and colorless; the opening pressure may be high. CSF cell count may be normal or slightly elevated, with a mixed pleocytosis (neutrophils and mononuclear cells), which later becomes lymphocytic. Lack of cells in the CSF does not exclude the diagnosis, and a repeat lumbar puncture after 1–2 days may subsequently demonstrate pleocytosis. Red blood cells in the CSF may be seen in late stages of HSV encephalitis or from vasculitis or tissue necrosis.

Confirmatory diagnosis is performed by culture, rapid diagnostic tests including antigen detection and PCR, demonstration of rise in specific antibody titer, and/or direct visualization of virus.

EEG helps distinguish generalized (diffuse slowing with high voltage slow waves; occasionally, spikes and spike) from focal encephalitis (focal slow waves or spikes), but can be normal. The EEG is particularly helpful in HSV encephalitis, since characteristic periodic lateralizing epileptiform discharges (PLEDS) may be seen.

MRI is a sensitive method of diagnosing well-established encephalitis, but may be normal early in the illness (particularly neonates). It detects inflammation and edema in the cerebral cortex, gray-white matter junction, basal ganglia, or cerebellum. Specific areas of involvement may suggest an etiology: inferomedial temporal lobe and frontal lobes involvement in HSV; bilateral thalamic and basal ganglia in Japanese encephalitis; hippocampal, cerebellar, and mesencephalic areas in rabies; and disseminated lesions in brainstem and basal ganglia in eastern equine encephalitis. MRI can differentiate acute encephalitis from ADEM.

14.9.3 Recommended Interventions

Children with acute encephalitis need to be monitored closely and thus are often admitted to the intensive care to observe and manage complications and for diagnostic work-up. Some viruses have specific antiviral agents: acyclovir for treatment of HSV encephalitis, ganciclovir or foscarnet for CMV encephalitis, and oseltamivir and zanamivir for either influenza A and B. No specific antiviral therapy is available for enteroviral and arboviral encephalitis.

Seizures are common and need to be treated aggressively. Continuous EEG may detect nonconvulsive seizures. Passive immunity in the form of intravenous immune globulin may be helpful in immunocompromised individuals who cannot mount an effective immune response. The role of corticosteroids has not been established.

14.9.4 Outcomes

The outcome in encephalitis is determined by etiology, host factors (age and immune status, severity of illness), level of consciousness at presentation, early intensive management, and institution of specific therapy [8]. Most arboviral encephalitis except eastern equine encephalitis and Japanese encephalitis have a good prognosis in children. The prognosis of HSV encephalitis has improved significantly with the use of early acyclovir therapy. Children with severe encephalitis and/or delayed therapy may be left with permanent neuro-deficits.

14.10 Lyme Neuroborreliosis

14.10.1 Presentation

There are three clinically defined stages of Lyme disease. Localized early Lyme disease consists of a single primary erythema migrans skin lesion at the site of the tick bite. The second stage, disseminated early Lyme disease, can include multiple erythema migrans lesions, carditis, meningitis, and cranial nerve palsies. Arthritis is a manifestation of the third stage (late Lyme disease). Different tick and Borrelia species exist in North America and Europe.

In general, neurologic manifestations are more common in European cases. However, whereas painful radiculitis (Bannwarth's syndrome) is much more common in adults in Europe compared to the North America, children in both regions typically present with meningitis and facial nerve palsy [9, 10]. Although CNS Lyme disease rarely causes frank acute encephalitis in children and therefore is unlikely to be confused with other CNS infectious and inflammatory disorders discussed here, we included it in this chapter as it still causes significant morbidity in endemic regions. The issue of chronic Lyme encephalopathy and post-Lyme disease syndrome are beyond the scope of this chapter [9].

14.10.2 Assessment

Although a matter of some debate among clinicians, patients with isolated facial palsy without meningeal symptoms or signs in whom Lyme disease is suspected most likely do not require LP. If meningeal symptoms or signs, or, less commonly, findings suggestive of parenchymal involvement, are present in the setting of suspected CNS Lyme disease, LP is mandatory. Culture and PCR of cerebrospinal fluid are insensitive tests for the diagnosis of CNS Lyme disease. Therefore, the diagnosis of CNS Lyme disease is usually made on the basis of typical neurological symptoms in the setting of positive serology. In interpreting the results of serologic

tests, it is important to remember that the high background prevalence of seropositivity in endemic areas requires a careful approach in determining causality. However, in general, CSF pleocytosis in the presence of positive peripheral Lyme serology and suggestive symptoms should be presumed to represent neuro-Lyme and treated as such, unless an alternative etiology is identified.

A two-step approach for serologic testing using a sensitive enzyme immunoassay (EIA) or immunofluorescent assay (IFA) followed by a standardized Western immunoblot is the algorithm of choice. The principal role of the Western blot is to differentiate false- from true-positive serologies, particularly when ELISA values are in the low-positive or borderline/equivocal range.

Brain MRI typically does not show parenchymal lesions, but can show nonspecific leptomeningeal enhancement, cranial or peripheral nerve root enhancement, and less commonly white matter lesions.

14.10.3 Intervention

Isolated facial nerve palsy due to Lyme disease can be treated with amoxicillin 50 mg/kg/day for 21–28 days in children younger than 8 years and doxycycline 100 mg twice a day for older children. Lyme meningitis or encephalitis requires treatment with intravenous ceftriaxone 100 mg/kg daily (up to 2 g) for 14–28 days. Given the controversies surrounding chronic Lyme disease, treatment for 28 days is probably warranted.

14.10.4 Outcome

The above or similar treatment regimens are associated with excellent outcomes in both North America and Europe [10].

14.11 Mycoplasma

Mycoplasma pneumoniae is primarily a respiratory tract pathogen that is an important cause community-acquired pneumonia. CNS complications develop in <0.1 % of children.

M. pneumoniae causes a wide range of CNS complications which can be divided into those that are thought to be a result of the direct invasion of the CNS, i.e., meningitis, encephalitis, Bickerstaff brainstem encephalitis, stroke, and acute bilateral striatal necrosis and those that are postinfectious immunologically mediated disorders, i.e., ADEM, postinfectious hemorrhagic leukoencephalitis, transverse

myelitis, Guillain-Barré syndrome, or acute motor axonal neuropathy. The differentiation is not easy. The meningitis and encephalitis can present with status epilepticus which is difficult to control.

Children usually present with a respiratory prodrome (except in children <5 years of age), with the neurological signs of direct invasion occurring within a week later, while 1–3 weeks in postinfectious immune-mediated complications such as ADEM, transverse myelitis, and Guillain-Barré syndrome.

14.11.1 Recommended Assessments

The diagnosis of *M. pneumoniae* infection is made on serology, culture, and/or PCR. The organism is rarely detected in CSF or brain tissue. The detection of IgM or IgA in acute sera, demonstration of either seroconversion from negative to positive, or a four-fold rise to anti-mycoplasma titer between acute and convalescent sera indicates an acute or recent infection. *M. pneumoniae* is very difficult to culture, so this is rarely used for the diagnosis. PCR assays using primers directed at a variety of genes have been developed and are useful for detection of mycoplasma in respiratory specimens. They are very sensitive and help in diagnosis before the development of specific antibodies.

14.11.2 Recommended Interventions

Antimicrobial therapy of mycoplasma infections of the CNS is unproven. Since some of the CNS manifestations are caused by the direct involvement of the CNS, it seems prudent to treat with antimicrobials. Erythromycin, azithromycin, tetracyclines, fluoroquinolones, ketolides, streptogramins, and chloramphenicol have good activity against mycoplasma. The macrolides have poor CNS penetration and a fluoroquinolone may be better.

Corticosteroids, intravenous immune globulin, and plasma exchange have been used in the postinfectious immunologically mediated disorders, with anecdotal improvement, but no clinical trials have been conducted.

14.11.3 Outcome

The outcome varies by clinical syndrome. Complete recovery occurs in children with aseptic meningitis. Neurological sequelae, such as cognitive impairment, focal neurologic deficits, or epilepsy, occur in up to 60 % following encephalitis or ADEM. Mortality is rare.

14.12 Neurocysticercosis

Taenia solium is endemic in Latin America, India, China, and many parts of sub-Saharan Africa. It occurs in areas with poor conditions where pigs have access to human feces. Cysticerci are ingested from infected pigs or fecal matter, then invade striated muscle and the CNS. Most active cysts are asymptomatic, and they usually die within 2 years without any clinical manifestations. The CNS manifestations usually occur when a cyst is degenerating or as a result of a chronic, calcified lesion.

14.12.1 Presenting Signs and Symptoms

The main clinical features are seizures, symptoms of RICP, alterations of mental status, and focal neurological signs [11]. Seizures may be generalized tonic-clonic seizures, despite the focal lesions. Neurocysticercosis may present with headaches (including migraine) or neurocognitive deficits or myalgia.

The clinical features depend upon the size, number, type, location, and stage of the cysticerci:

- Ventricular cysts may cause seizures or meningeal irritation. Nausea, vomiting, headache, ataxia, and confusion occur, but focal neurological deficits are uncommon. RICP may occur.
- Cysts in the basal cisterns present with meningeal signs, hydrocephalus, vasculitis, and stroke.
- Cysticercal encephalitis caused by multiple parenchymal cysts, associated with diffuse cerebral edema, occurs particularly in young girls, and these patients may develop severe neurological sequelae.
- Spinal cysticercosis presents with radicular pain or paresthesia or progressive cord compression.
- Ophthalmic manifestations include blurred vision, proptosis with restriction of ocular movements, papilledema, atypical optic neuritis, cyst, or nodules in the eye.

14.12.2 Recommended Assessments

Neuroimaging is the diagnostic test of choice (Table 14.6). The cysts may be single or multiple, scattered throughout the brain, and in different stages. Both CT and MRI are useful for the detecting the stages. Sometimes the invaginated scolexes can be seen as an eccentric mural nodule, which, if multiple, give rise to the "starry night effect," which is pathognomonic of neurocysticercosis. Single-enhancing lesions on CT scans have increased signal intensity on MRI and may be caused by resolution or calcification. They need to be differentiated from tuberculomas,

Table 14.6 Neuroimaging findings in neurocysticercosis

	CT scan	MRI scan
	Better for detecting calcified lesions	Better for detecting intraventricular or subarachnoid cysts demonstrating inflammation around cysts
Active	Rounded, hypodense areas	CSF-like signal
Degenerate	Diffuse hypodense lesion with an irregular border, enhances on contrast	Low signal areas on T2-weighted MRI images
Calcified	Inactive calcified nodule	low intensity on proton-weighted nodule

although abscess, fungal infection, vasculitis, and neoplasia may produce similar appearances.

Immunological tests are not reliable for the diagnosis of neurocysticercosis. Standard enzyme-linked immunosorbent assay techniques are insensitive and non-specific. The enzyme-linked immunoelectrotransfer blot assays on blood or CSF have a higher sensitivity and specificity, but its usefulness varies with region.

Electroencephalography is variable, since it may show focal or generalized abnormalities, but is often normal. CSF may have mild abnormalities such as elevated protein or pleocytosis often with eosinophils.

14.12.3 Recommended Interventions

There is no evidence to support the treatment of asymptomatic lesions. In symptomatic neurocysticercosis, the use of cysticidal agents and steroids for epilepsy is controversial. Cysticidal therapy appears to improve the resolution of cysts but may be associated with an exacerbation of neurological symptoms, with case reports of severe cerebral edema and death in patients with multiple cysts. Praziquantel (20 mg/kg/day) and albendazole (10 mg/kg/day) for at least 8 days are the most commonly used cysticidal agents [12]. Randomized clinical trials of cysticidal drugs have failed to show consistent clinical benefit, and an increase in hydrocephalus and seizure are frequency reported. Corticosteroids are thought to reduce the inflammatory response and prevent the neurological deterioration, but randomized controlled trials have been inconclusive. The seizures in neurocysticercosis are usually easily controlled with AEDs; phenobarbitone and phenytoin induce the metabolism of praziquantel.

14.13 Malaria

Plasmodium falciparum is one of the four species that infects humans and is responsible for most of the CNS complications. The erythrocytic stages of the parasite are responsible for the symptoms, particularly the later erythrocytic stages which

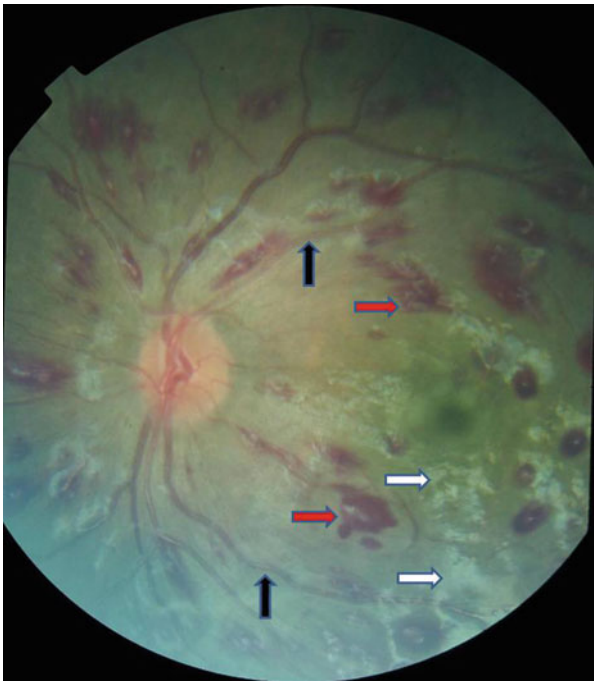

Fig. 14.1 A photograph of the retina of a child with cerebral malaria showing hemorrhages (*red arrows*), exudates (*white arrows*), and discoloration of the retinal vessels (*black arrows*) (Courtesy Nicke Beere)

sequester within postcapillary venules of the deep vascular beds, especially the brain, which is thought to cause the severe manifestations [13]. The direct CNS involvement of *P. falciparum* is difficult to define, since there are no pathognomonic features.

14.13.1 Presenting Signs and Symptoms

Falciparum malaria should be suspected in any child who has visited or even transiently landed at an airport in an endemic area within the last 3 months and develops CNS symptoms. Children usually have a history of fever, headache, irritability, restlessness, or drowsiness. Vomiting and to a lesser extent diarrhea are common. Fever is usually present, although its absence does not exclude the diagnosis. Seizures are common and often precipitate the lapse into coma. Brainstem signs including dysconjugate eye movement and decerebrate posturing occur. Falciparum malaria is associated with a distinctive retinopathy, which includes retinal hemorrhages, retinal whitening, color changes in the vessels, and less frequently papilledema (Fig. 14.1) [14]. These features are associated with sequestration in the brain and may help differentiate cerebral malaria from other causes of encephalopathy.

Seizures are common in falciparum malaria, but the cause is unclear. They are not simply febrile seizures; since many occur when the child is apyrexial, they are

often complicated in that they are repetitive (more than one during the acute illness), focal, or prolonged. They do not appear to be related to electrolyte abnormalities, hypoglycemia, or antimalarial drugs.

14.13.2 Recommended Assessments

The diagnosis of malaria can be made by detecting asexual parasites on a peripheral blood film. The lack of a detectable parasitemia does not exclude the diagnosis of cerebral malaria, since the parasites may be sequestered within the deep vascular beds, or chemoprophylaxis may have suppressed the parasitemia. Thus, blood films need to be examined every 6 h for 48 h to exclude this infection.

Rapid diagnostic tests such as the immunochromatographic test for *P. falciparum* histidine-rich protein 2 and lactate dehydrogenase may be helpful, particularly in the absence of a positive blood smear. Parasite messenger RNA or DNA PCR testing is more sensitive than microscopy, but is expensive, more laborious, and does not estimate parasite load.

The following blood investigations should be done:

- CBC
  - Anemia, usually with evidence of hemolysis (raised unconjugated bilirubinemia, low haptoglobin concentration), is a consequence of the infection.
  - Thrombocytopenia is common, but rarely severe enough to cause bleeding.
- Coagulation screen
  - Fibrin degradation products are raised, but laboratory features of frank disseminated intravascular coagulation are uncommon.
- Glucose
  - Hypoglycemia is common and needs to be treated.
- Blood gas status
  - Hypoxemia is associated with pulmonary edema in nonimmune individuals and chest infections.
  - Metabolic acidosis is common, particularly associated with a high lactate and low PCO_2, in children with tachypnoea to compensate for the acidosis.
- Renal function since impairment is common
- Electrolytes
  - Hyponatremia is mainly caused by salt depletion, but some cases may be caused by inappropriate ADH secretion or cerebral salt wasting syndrome.
  - Hypophosphatemia is a feature of severe malaria and may be exacerbated by glucose therapy.

The CSF is usually acellular, and other diagnoses such as encephalitis should be considered if a pleocytosis is found, but cerebral malaria cannot be excluded. CSF lactate concentrations are raised, but total protein and glucose concentrations are usually normal.

Blood cultures may detect bacteremia, particularly caused by gram-negative organisms. Concurrent urinary tract infections can occur.

14.13.3 Recommended Interventions

Treatment of severe falciparum malaria is complicated by the emergence of parasites that are resistant to antimalarial drugs and the difficulty of obtaining specific antimalarial drugs locally. A combination of antimalarials with different actions should be used, in order to prevent the emergence of resistant parasites. This should include a first-line parenteral drug, either the cinchinoid alkaloids (quinine and its diastereomer quinidine) or the artemisinin compounds (http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html). The artemisinin compounds are more parasiticidal, but less available in North America.

The cinchinoid alkaloids are effective against the latter erythrocytic stages. Most authorities recommend a loading dose to rapidly achieve high therapeutic levels. Side effects are common, particularly cinchonism (tinnitus, hearing loss, nausea, restlessness, and blurred vision) and cardiovascular side effects (hypotension).

The artemisinin compounds (artesunate, artemether, and arteether) are fast acting and act against all blood stages, reducing the time to parasite clearance and fever resolution in comparison to the cinchinoid alkaloids. Artesunate is the favored drug, since it can be administered intravenously or intramuscularly, is associated with less neurotoxicity in animal models, and has reduced mortality in adults with severe malaria.

14.13.3.1 Other Antimalarial Drugs

Currently, other antimalarial drugs should be combined with parenteral antimalarials to prevent the emergence of resistant parasites. Atovaquone-proguanil (Malarone™) and mefloquine are the most commonly used.

14.13.3.2 Supportive Treatment

Supportive treatment is important in children with severe malaria, since most children die within 24 h, before the antimalarials have had time to work. Children with severe falciparum malaria should be monitored closely. Blood glucose and fluid balance should be measured every 6 h, parasitemia and hematocrit every 12 h.

Electrolytes, tests of renal function, albumin, calcium, phosphate, and blood gasses should be performed at least daily during the acute stages.

14.13.4 Outcome

The mortality of cerebral malaria in nonimmune individuals ranges from 15 to 26 %, with patients usually dying within the first 4 days of the illness, often from renal failure or pulmonary edema, acidosis, or brainstem herniation.

Neurological sequelae occur in about 5 % of nonimmune individuals and include cranial nerve lesions, extrapyramidal tremor, polyneuropathy, epilepsy, or psychiatric manifestations. In African children living in endemic areas, hemiparesis, ataxia, and cortical blindness are the most common sequelae, but some children are left in a vegetative state. Impairment of a wide range of cognitive functions has been documented, particularly in memory, executive functions, and language.

14.14 Tetanus

Tetanus is caused by toxins produced by *Clostridium tetani* and is characterized by increased muscular tone and spasms. It occurs in two different clinical situations, neonates (neonatal tetanus) and older children and adults (non-neonatal tetanus). The route of entry in neonatal tetanus is the umbilical cord while, in non-neonatal tetanus, wounds on the lower limbs, compound fractures, and non-sterile intramuscular injections, dental procedures, or infections, e.g., otitis media. Often the route of entry is not identified. Tetanus toxoid vaccination has eliminated tetanus from many countries, although it is still seen in many parts of the developing world.

14.14.1 Presenting Signs and Symptoms

Tetanus is a clinical diagnosis that is made easily in areas where it is seen frequently [15]. It is characterized by increased tone and spasms, which occur spontaneously or are provoked by touching the body, sound, or light.

14.14.1.1 Neonatal Tetanus

Neonates with tetanus present a median 6 (range 3–10) days after birth with refusal to feed, mainly due to difficulty in opening the mouth. Thereafter, sucking stops and "risus sardonicus" may develop. Increased tone, progressing to rigidity, and opisthotonus occur. Spasms of the limbs develop early, but become generalized.

14.14.1.2 Non-neonatal Tetanus

The incubation period is usually 4 days to 3 weeks after the insult. The first symptom is often inability to open the mouth fully owing to rigidity of the masseters (trismus or lockjaw). Pain, headache, stiffness, rigidity, opisthotonus, laryngeal obstruction, and spasms may follow. The spasms are most prominent in the first 2 weeks and are very painful. Dysphagia can occur. Autonomic dysfunction (labile blood pressure especially hypertension, tachyarrhythmias, hyperpyrexia, and hypersalivation) usually starts some days after the spasms. The condition tends to improve thereafter, but the rigidity may last beyond the duration of both spasms and autonomic disturbance, for up to 6 weeks. Tetanus can be localized at the site of injury causing local rigidity and pain.

14.14.2 Recommended Assessments

Tetanus is a clinical diagnosis; since *C. tetani* is difficult to culture, a positive result does not indicate if the organism contains the toxin-producing plasmids, and *C. tetani* may be present without disease in patients with protective immunity.

14.14.3 Recommended Interventions

The main aims of management are to support the patient during the time it takes for new vesicles to replace those that the toxin is bound. This includes good-quality nursing to reduce stimuli that may precipitate spasms, neutralizing the toxin with tetanus immunoglobulin, treating the infection (preferably with metronidazole), reducing spasms and respiratory complications with paralysis and ventilation, treating the cardiovascular complications (autonomic dysfunction), and providing sufficient fluids and calories.

14.14.4 Outcome

In neonates mortality is high, with 65 % neonates dying in hospitals that lack facilities for ventilation, but if ventilation and intensive care are available, the mortality decreases to 22 %. In neonates who survive, microcephaly, mild neurological, developmental, and behavioral problems have been reported.

In older children, mortality varies from 20 to 50 %, with the lowest mortalities in hospitals that can perform tracheostomies and/or provide ventilation. The commonest cause of death is respiratory failure (secondary to uncontrolled spasms), autonomic dysfunction, and septicemia.

14.15 Neurobrucellosis

Brucellosis is still endemic in many parts of the world and is often acquired by contact with infected animals (mainly cattle, sheep, goats, dogs, or pigs) or ingestion of unpasteurized milk.

14.15.1 Presenting Signs and Symptoms

It usually causes a nonspecific febrile illness, which waxes and wanes (undulant fever), often with arthralgia. It affects many organs of the body, but CNS involvement is rare in children [10]. *Brucella* sp. can cause meningoencephalitis, brain abscess, cranial nerve palsies (particularly VIII nerve), myelitis, radiculitis, and a polyneuropathy. It is associated with poor concentration, depression, and chronic fatigue.

14.15.2 Recommended Assessments

The CSF often has a pleocytosis with raised protein, but normal glucose. *Brucella* sp. are difficult to culture, but cultures of blood or bone marrow may isolate the organism. The diagnosis is usually made on a rising titer in serological tests, particular the brucella microagglutination test or brucella-specific ELISA. Brucella antibodies may also be found in the CSF.

14.15.3 Recommended Interventions

The treatment of brucellosis varies with age and country. In general, children younger than 10 years should be treated with trimethoprim/sulfamethoxazole (10 mg/day of trimethoprim iv or po) and rifampicin (20 mg/kg per day divided in two doses) for at least 4 weeks. Tetracyclines may be used in older children instead of the trimethoprim/sulfamethoxazole and streptomycin or gentamicin can be used instead of rifampicin.

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