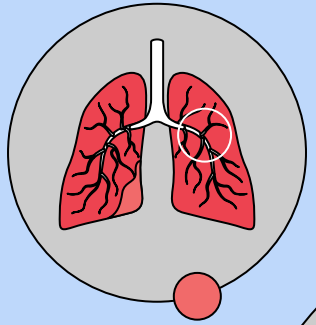
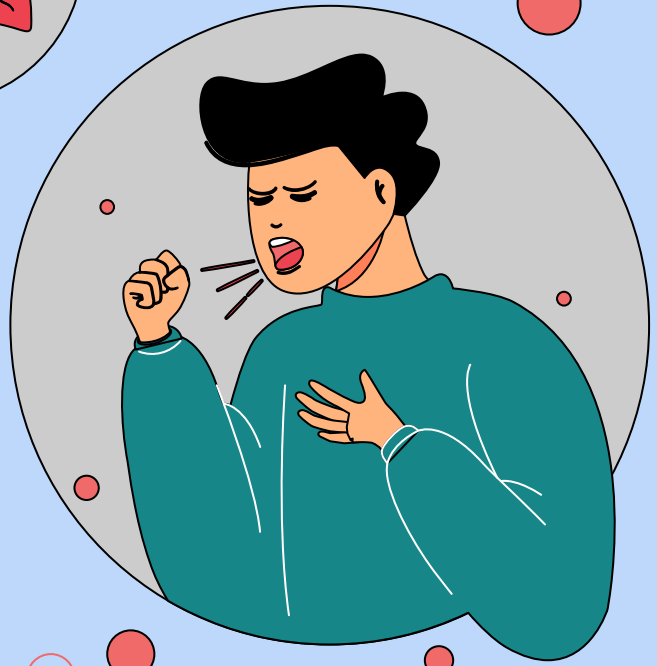
Neurologic Complications of Tuberculosis





Prach Uthayo, MD.
Department of Neurology, Faculty of Medicine
Chulalongkorn University

Scope of Talk

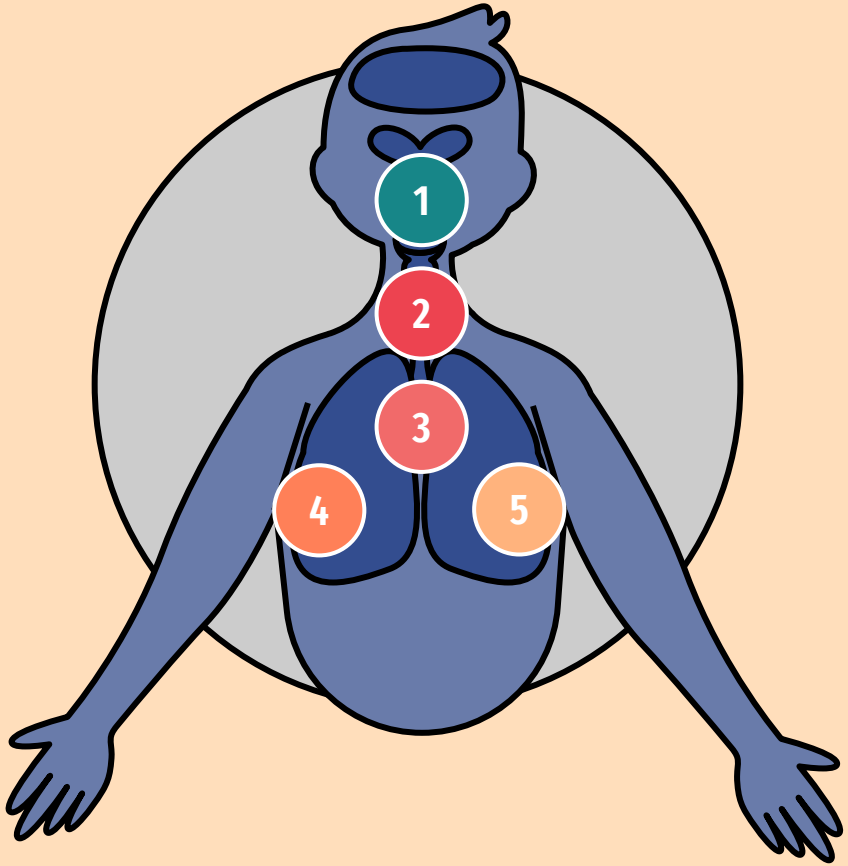
01
Introduction & Epidemiology

02
Pathogenesis & Pathophysiology

03
Clinical Manifestation

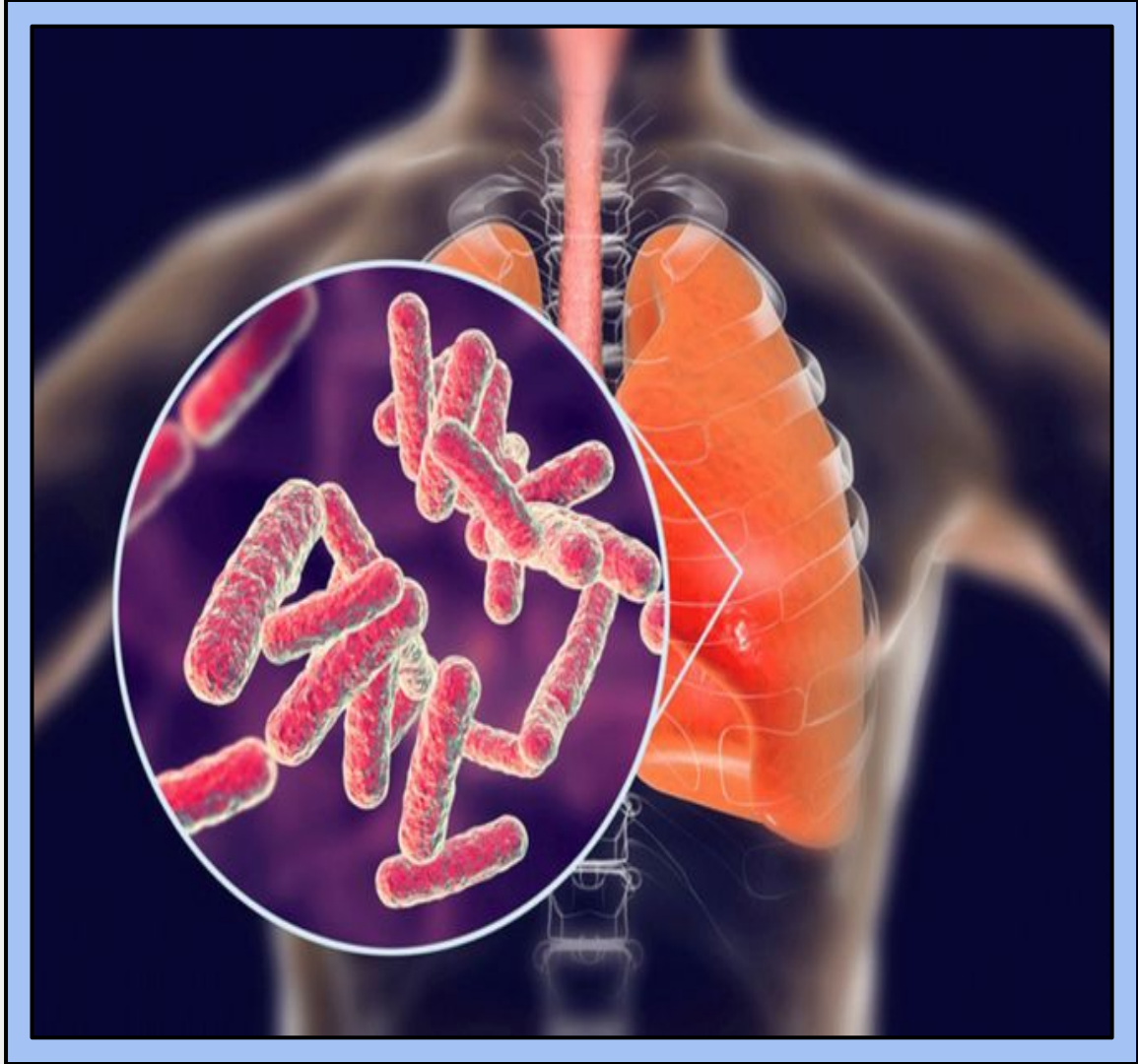
04
Investigation & Diagnosis

05
Treatment & Prognosis



01

Introduction & Epidemiology



What is the Tuberculosis ?

- **Tuberculosis (TB)** is the disease caused by acid-fast bacillus Mycobacterium tuberculosis.
- TB is the leading cause of death from an infectious etiology and remains in the top 10 causes of death globally.
- This bacteria mainly affect the pulmonary system; however, extrapulmonary complications are not uncommon.
- Neurologic complications of TB might be rare yet highly devastating manifestation, which was universally fatal in the era before antituberculosis therapy.
- CNS infection is seen to comprise three categories of illness: tuberculous meningitis, intracranial tuberculoma, and spinal manifestation of tuberculosis.
- HIV is strongly associated with both TB infection overall and central nervous system (CNS) TB in particular.

Global tuberculosis report. World Health Organization, 2020.
Centers for Disease Control and Prevention. GA: Centers for Disease Control and Prevention, 2019.

Epidemiology

- TB accounted for 10 million new symptomatic infections and 1.4 million deaths globally, with a global prevalence estimated at 25% of the world's population.
- 90% of global infections are found in 30 high TB-burden countries.
- Variations in its worldwide prevalence reflect its strong association with poverty, malnutrition, and HIV infection.

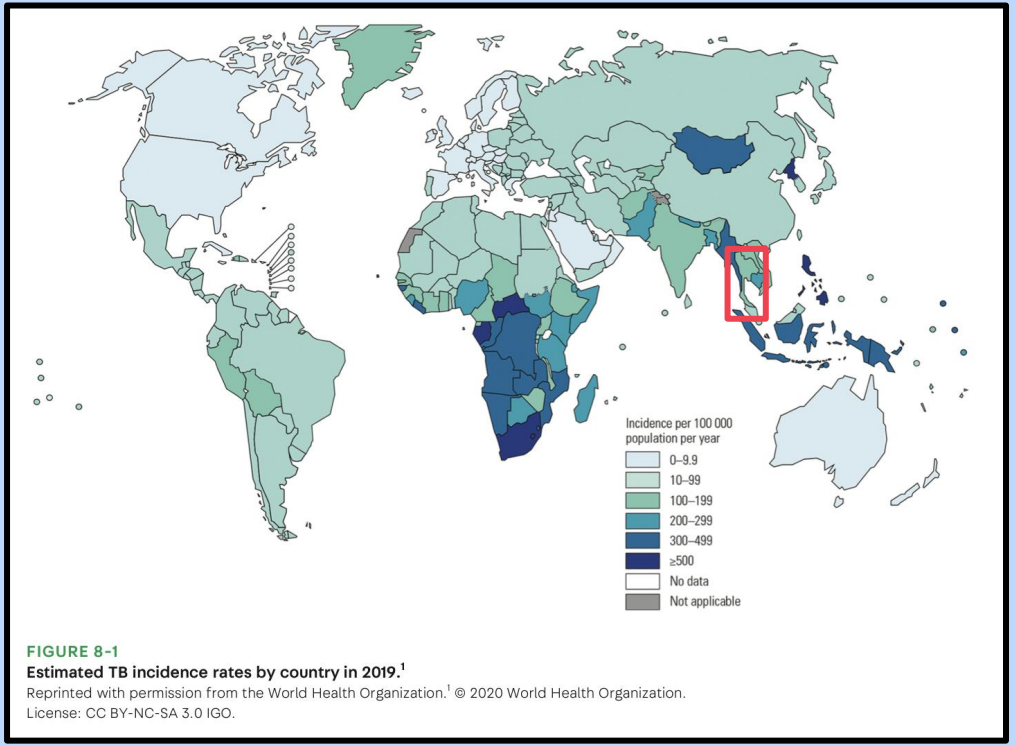
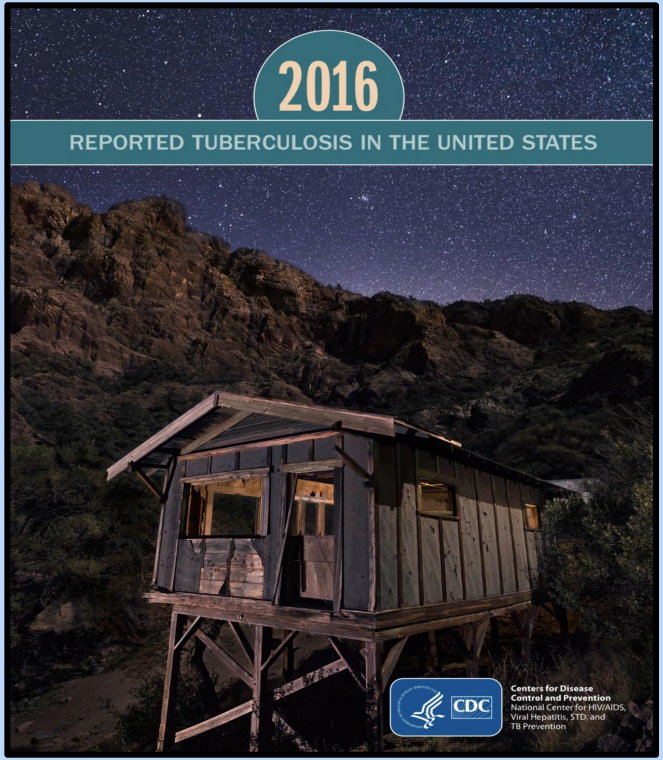


FIGURE 8-1
Estimated TB incidence rates by country in 2019.[1]
Reprinted with permission from the World Health Organization.[1] © 2020 World Health Organization.
License: CC BY-NC-SA 3.0 IGO.

Global tuberculosis report. World Health Organization, 2020.
Centers for Disease Control and Prevention. GA: Centers for Disease Control and Prevention, 2019.

Epidemiology

- The majority of TB infections remain latent throughout an individual's lifetime with only 5% to 10% of infections leading to active disease
- The majority of active infections (approximately 90%) represent reactivation of latent infection rather than symptomatic presentations of primary infection.
- Clinical CNS TB occurs in 1 to 2% of all patients with active TB and accounts for about 8% of all extra- pulmonary cases of the infection reported to occur in immunocompetent individuals.



Global tuberculosis report. World Health Organization, 2020.
Centers for Disease Control and Prevention. GA: Centers for Disease Control and Prevention, 2019.

02

Pathogenesis & Pathophysiology

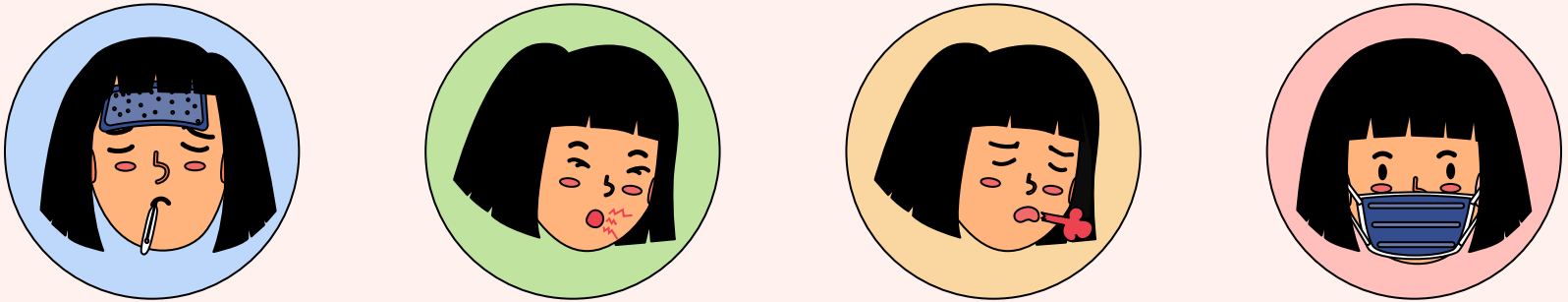
Pathogenesis

- M. tuberculosis is an aerobic, nonmotile, non-spore-forming, acid-fast bacillus (AFB) that infects primarily humans.
- Infection occurs through the inhalation of droplet nuclei containing the bacilli, eventually leading to deposition in the lung alveoli.
- Once in the alveoli, the bacilli interact with alveolar macrophages and the innate immunity was activated.
- Numerous cytokines and chemokines are released, the activation of a type 1 T helper cell-mediated immune response occurs, and, ultimately, a granuloma is formed.
- Bacilli are filtered into draining lymph nodes, and there exists a low-level bacteremia in which M. tuberculosis hematogenously disseminated to distant sites in the body that are highly oxygenated, including the brain.
- Host immune factors and M. tuberculosis virulence factors in the end determines whether or not the infection is contained or produced clinical disease.

Rock RB, Olin M, Baker CA et al. Clin Microbiol Rev. 2008 Apr;21

Pathogenesis

- For **CNS tuberculosis**, the disease begins with the development of small tuberculous foci (Rich foci) in the brain, spinal cord, or meninges.
- The location of these foci and the capacity to control them ultimately determine which form of CNS tuberculosis occurs.
- CNS tuberculosis manifests itself primarily as **tuberculous meningitis (TBM)** and less commonly as **intracranial tuberculoma**, **tuberculous brain abscess**, or a **spinal infection of tuberculosis**.



Rock RB, Olin M, Baker CA et al. Clin Microbiol Rev. 2008 Apr;21
Saylor D. Continuum (Minneap Minn). 2021 Aug 1;27

Pathogenesis

- TNF plays a definitive role in granuloma formation and containment of mycobacterial infections, since it leads to altered blood-brain barrier (BBB) permeability and cerebrospinal fluid (CSF) leukocytosis and has been implicated in fostering the progression of TBM.
- A distinctive characteristic of M. tuberculosis is its capacity to enter and replicate within macrophages.
- Within the CNS, microglial cells are the principal target in the CNS of M. tuberculosis.
- M. tuberculosis-infected microglia also produce robust amounts of several cytokines and chemokines in vitro, including TNF-∝, IL-6, IL-1, CCL2, CCL5, and CXCL10.
- Mycobacterial infection induces immunosuppressive effects on microglial cells, which is more evident with more virulent strains.

Rock RB, Olin M, Baker CA et al. Clin Microbiol Rev. 2008 Apr;21
Saylor D. Continuum (Minneap Minn). 2021 Aug 1;27

03

Clinical Manifestation

Clinical Manifestation

Tuberculous Meningitis

Tuberculoma & Tuberculous Abscess

Spinal Tuberculosis

Clinical Manifestation

1

Tuberculous Meningitis

Clinical Manifestation

- **Common presentation**
  - Subacute progressive fever that passes through three discernible phases
  - **Prodromal phase:** within first 2 weeks
    - Malaise and lassitude
    - Intermittent headache
  - **Meningitis phase:** 2-3 weeks
    - Protracted headache with meningismus
    - Nausea and vomiting
    - Mild confusion
    - Multiple cranial neuropathies
  - **Comatose phase:** > 3 weeks
    - Delirium followed by stupor and coma
    - Seizures
    - Multiple cranial neuropathies
    - Hydrocephalus
    - Stroke

Table 2 The presenting clinical features of tuberculous meningitis in older children and adults as described by recent clinical series.[6,8,11–13]

	Frequency/range
Symptom	
Headache	50–80%
Fever	60–95%
Vomiting	30–60%
Photophobia	5–10%
Anorexia/weight loss	60–80%
Clinical sign	
Neck stiffness	40–80%
Confusion	10–30%
Coma	30–60%
Cranial nerve palsy	30–50%
VI	30–40%
III	5–15%
VII	10–20%
Hemiparesis	10–20%
Paraparesis	5–10%
Seizures – children	50%
Adults	5%
Cerebrospinal fluid	
Clear appearance	80–90%
Opening pressure >25 cm H_2O	50%
Leucocyte count ($\times 10^3$/ml)	5–1000
Neutrophils	10–70%
Lymphocytes	30–90%
Protein (g/L)	0.45–3.0[a]
Lactate (mmol/L)	5.0–10.0
CSF glucose:blood glucose < 0.5	95%

[a] Cerebrospinal protein can be >10 g/l in those with spinal block.

Thwaites G, Fisher M, Hemingway C et al. J Infect. 2009 Sep;59(3):167-87.

Clinical Manifestation

- **Atypical presentation**
  - Acute rapidly progressive meningitis syndrome indistinguishable from pyogenic bacterial infection
  - Slowly progressive dementia over many months, marked by personality change, social withdrawal, and memory deficits
  - At times focal neurologic deficits (CN palsies, hemiparesis, and seizures) or symptoms of hydrocephalus (headache, papilledema, diplopia, and visual disturbance) precede the signs of meningitis.
  - Encephalitis syndrome has been described to occur in children, and occasionally adults, manifesting as stupor, coma, and convulsions with neither meningitis signs nor significant CSF abnormalities.

- Death commonly occurs within 5 to 8 weeks of the onset of illness.
- In children, headache is less common, while irritability, restlessness, anorexia, and protracted vomiting are prominent symptoms.
- Seizure is more common in the children with tuberculous meningitis

Thwaites G, Fisher M, Hemingway C et al. J Infect. 2009 Sep;59(3):167-87.

Clinical Staging

- Overall clinical severity is most often graded by using the **modified British Medical Research Council (MRC) criteria** with higher grades associated with higher mortality

Modified British Medical Research Council Criteria for Grading Severity of Tuberculous Meningitis[a,b]

Grade	Criteria
Grade I	Glasgow Coma Scale (GCS) 15, no focal neurologic deficits
Grade II	GCS 11-14
	GCS 15 and focal neurologic deficit(s)
Grade III	GCS ≤10

[a] Data from Marais BJ, et al, Clin Infect Dis.[8]
[b] Higher Medical Research Council (MRC) stage is correlated with higher mortality rates.

Saylor D. Continuum (Minneap Minn). 2021 Aug 1;27

Complication

- **Stroke**
  - One of the most common complications of tuberculous meningitis
  - Occurring in approximately 30% to 60% of cases.
  - Usually found in the basal ganglia because of involvement of small penetrating arteries that are surrounded by exudates in the basal cisterns, but abnormalities of the large anterior circulation arteries are also common as the result of tuberculous vasculopathy.
  - Endothelial reactions to inflammatory exudates, proliferative and necrotizing arteritis, and hypercoagulable states.
  - **Predictors of stroke** among individuals with tuberculous meningitis:
    - Advanced disease stage, HIV co-infection, presence of basal exudates, optochiasmatic arachnoiditis, focal neurologic deficits, cranial nerve palsy, hydrocephalus, meningeal enhancement, and vision impairment

Saylor D. Continuum (Minneap Minn). 2021 Aug 1;27

Complication

- **Seizure**
  - Also common, occurring in 34% of individuals in a 2018 Indian case series.15
  - 30% of seizures occurred within 1 month of the onset of meningitis, and 70% occurred late (more than 1 month after onset).
  - The majority were focal onset, and nearly one-quarter presented with status epilepticus.
  - **Early seizures** were associated with meningeal irritation, whereas **late seizures** were more common in those with tuberculomas, infarcts, and hyponatremia.
  - Recurrent new-onset seizures and status epilepticus were associated with nearly 3 times higher mortality among individuals with tuberculous meningitis.

Saylor D. Continuum (Minneap Minn). 2021 Aug 1;27

Clinical Manifestation

2

Tuberculoma & Tuberculous Abscess

Tuberculoma & Tuberculous Abscess

- **Tuberculomas** are conglomerate caseous foci in the brain that develop from deep-seated tubercles acquired during a recent or remote disseminated bacillemia.
- Centrally located, active lesions may reach considerable size without producing meningitis.
- Microscopic granulomatous foci, called "**Rich foci**", develop over time, organizing into caseous granulomas with fibrous encapsulation.
- When the host response to infection is poor, this process may result in focal cerebritis and frank abscess formation.

- Approximately 10% of individuals with tuberculous meningitis have concomitant tuberculomas, but tuberculomas can also occur in the absence of meningitis and without evidence of TB infection outside the CNS.
- Tuberculomas are similar to tuberculous abscesses, but abscesses are often larger and have a pus-filled cavitary center.

Leonard JM. Microbiol Spectr. 2017 Mar;5(2).

Clinical Manifestation

- It can develop anywhere within the CNS including the brain parenchyma, spinal cord, or subdural, epidural, subependymal, or subarachnoid spaces.
- Overall, tuberculomas are more common in children, in whom they tend to be infratentorial, but are more commonly supratentorial in adults.
- Lesions are solitary in one-third of cases and multiple, with an average of approximately five, in the remainder.
- Clinical presentation typically consists of focal neurologic deficits corresponding to the site of the lesion, accompanied by headaches, fever, and, often, seizures. Examination frequently reveals papilledema.

- **Paradoxical expansion of tuberculomas**, defined as the development of a new tuberculoma or enlargement of an existing tuberculoma while on appropriate TB treatment, is not uncommon and usually occurs within 3 months of initiating TB treatment.
- This is more common in people with HIV, especially in those initiating antiretroviral therapy for the first time, in which case it is a manifestation of IRIS.
- The development of paradoxical tuberculomas does not seem to be related to outcome, including mortality.

Leonard JM. Microbiol Spectr. 2017 Mar;5(2).

Clinical Manifestation

Spinal Tuberculosis

Spinal Tuberculosis

- TB can involve every compartment of the spine including bony structures, intradural and extradural spaces, the spinal cord, and nerve roots.
- The **thoracic and lumbar regions are most commonly involved**, but cervical involvement occurs in more than one quarter of affected individuals and is associated with more frequent neurologic sequelae than other locations.
- The majority of cases of spinal TB occur in the absence of pulmonary disease.
- The most common manifestations of spinal TB are **spondylitis** and intradural tuberculous spinal infections including radiculomyelitis, **spinal arachnoiditis**, intramedullary tuberculomas, and myelitis.

- Spinal tuberculosis is associated with the breakdown of a rich focus within the cord or meninges, or by extension from an adjacent area of spondylitis.
- The resulting inflammatory reaction is usually confined locally and progresses gradually over weeks to months, producing a partial or complete encasement of the cord by a gelatinous or fibrous mass.

Leonard JM. Microbiol Spectr. 2017 Mar;5(2).

Clinical Manifestation

- **Intradural tuberculous spinal infections**
  - Including radiculomyelitis, spinal arachnoiditis, intramedullary tuberculomas, and myelitis, are seen most commonly in the setting of tuberculous meningitis because of the spread of inflammatory exudates from the cranial to the spinal compartment.
  - These inflammatory exudates often settle in the lumbosacral subarachnoid space and present with a conus medullaris or cauda equina syndrome.
  - Areflexic paraparesis with prominent bladder symptoms and neuropathic pain are common. The subarachnoid space may also become irregularly obstructed because of these exudates, resulting in the formation of CSF loculations
  - **Tuberculous radiculomyelitis** is the most common intradural spinal manifestation of TB, occurring in nearly 40% of individuals with tuberculous meningitis.
  - Intradural spinal infections are most often symptomatic during illness with tuberculous meningitis, but they can occasionally be asymptomatic or present many years after resolution of the meningitis.

Leonard JM. Microbiol Spectr. 2017 Mar;5(2).

Clinical Manifestation

- In addition, paradoxical worsening of spinal tuberculosis during treatment is common and often responds to increased dosages or repeated courses of corticosteroids. Uncommon complications of these infections include spinal cord vasculitis and infarcts.

- **Tuberculous Vasculitis**
  - Presents as a localized vasculitis which may result in thrombosis of the anterior spinal artery and infarction of the cord
- **Spondylitis**
  - Also known as **Pott disease**, is the most common form of spinal TB and accounts for 50% of cases of skeletal TB.
  - It presents with insidiously back pain that is then followed by kyphosis, paraparesis, sensory symptoms, and finally bowel and bladder symptoms.
  - Progression through these stages occurs over the course of months to more than 1 year.
  - Acute presentations of neurologic deficits are not uncommon because of vertebral fracture or abscess formation with subsequent spinal cord compression.

Leonard JM. Microbiol Spectr. 2017 Mar;5(2).

04

Investigation & Diagnosis

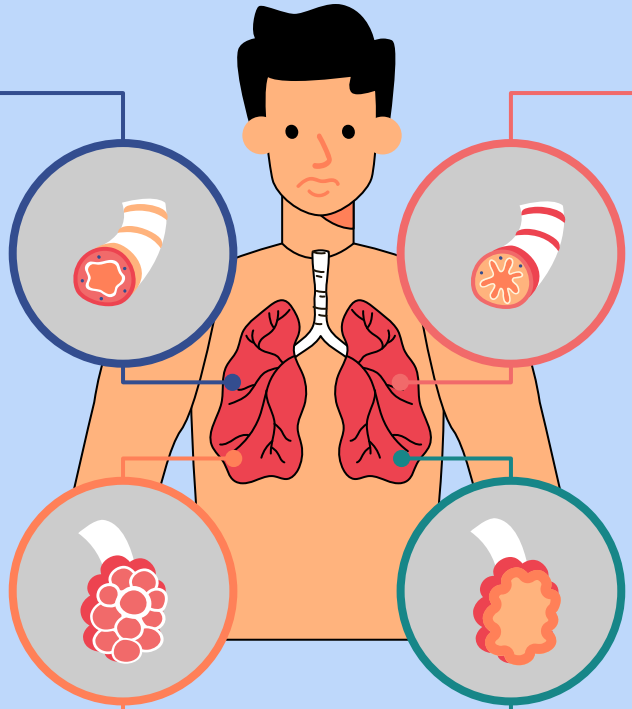
Investigation

CSF Examination & Cultures

- CSF Study
- CSF AFB smear
- CSF Culture for TB

Molecular Diagnosis

- PCR for TB
- Xpert MTB/RIF
- Other assays



- CT Brain
- MRI Brain

Neuroimaging

- Chest X-ray
- Blood samples

Routine Studies

1 CSF Examination & Culture

- **Tuberculous Meningitis**
  - CSF study reveals **lymphocytic pleocytosis (10-1,000 cells/ml)**, **elevated proteins (50-300 g/dl)**, and **CSF hypoglycorrhachia (CSF:serum glucose < 50%)**
  - Atypical CSF findings, particularly in immunosuppressed patients, can be acellular or contain a predominance of neutrophil.
  - **Acid-fast bacilli (AFB)** in CSF is crucial for the rapid diagnosis of TBM and the older literature suggest that they can be seen in up to 80% of adult cases.
  - Positive CSF smear and culture is independently associated with large volumes (>6 ml) of CSF submitted for examination.
  - Repeated lumbar punctures and CSF examination also increase diagnostic yield.

- Bacteria may be seen in the CSF of up to 80% of adult patients with TBM
- Once anti-tuberculosis medication is commenced, the sensitivity of smear and culture falls rapidly.
- **CSF culture is often used as the gold standard** for definitive diagnosis and may provide critical drug susceptibility information once treatment has started, but it can take up to 6 weeks to grow M. tuberculosis.

Thwaites G, Fisher M, Hemingway C et al. J Infect. 2009 Sep;59(3):167-87.

1 CSF Examination & Culture

- **Tuberculous Meningitis**

Table 3 Published diagnostic rules for the diagnosis of tuberculous meningitis.

Age group	Presenting clinical features predictive of TBM	Suggested use and performance
Children rule (1 month to 12 years)[16]	More than 6 days of symptoms Optic atrophy Abnormal movements Focal neurological deficit Neutrophils forming less than half the total numbers of CSF leucocytes	≥1 variable present (98% sensitive, 44% specific) ≥2 variables present (77% sensitive, 57% specific) ≥3 variables present (55% sensitive, 98% specific)
Children and adults rule (5 months to 56 years)[18]	Duration of symptoms greater than 5 days Clear CSF CSF white cell count $< 1000 \times 10^3$/ml Lymphocytes >30% of total number of CSF white cells CSF protein >100 mg/dl	≥2 variables present (93% sensitive and 77% specific)
Adult rule (>15 years)[17]	Age ≥ 36 years (score +2) or < 36 (score 0) Blood WCC (10^3/ml) ≥15000 (score +4) or <15000 (score 0) History of illness ≥ 6 days (score −5) or < 6 days (score 0) CSF total WCC (10^3/ml) ≥ 750 (score +3) or < 750 (score 0) CSF neutrophils ≥ 90% (score +4) or < 90% (score 0)	Total score ≤ +4 = TBM Total score > +4 = bacterial meningitis (90–99% sensitive, 79–82% specific)

Thwaites G, Fisher M, Hemingway C et al. J Infect. 2009 Sep;59(3):167-87.

1 CSF Examination & Culture

- **Tuberculoma (without Tuberculous Meningitis)**
  - Examination of the CSF reveals an elevated total protein in most patients and a pleocytosis of 10-100 cells/mm^3 in 50%.
  - Tuberculomas cannot be distinguished from other cerebral space-occupying lesions by clinical features alone.
- **Spinal Tuberculosis**
  - Around 10% of cases with TBM have some form of spinal tuberculosis.
  - Spinal tuberculosis without TBM could produces normal CSF study.

- AFB are less commonly found in the CSF of patients with cerebral tuberculoma or spinal tuberculosis compared to those with TBM
- **Tissue examination** is usually required to confirm the diagnosis of tuberculoma or spinal tuberculosis.
- A search for extra-neural disease that may be biopsied safely.
- Further imaging with ultrasound, MRI and computerised tomography (CT) of abdomen, pelvis and chest may reveal evidence of tuberculosis not detected by plain radiography.
- **Stereotactic brain biopsy** should be considered for the diagnosis of tuberculoma if other investigations fail to confirm active extra-neural tuberculosis.

2 Molecular Diagnosis

- **Nucleic Acid-based Amplification Techniques (NAATs)**
  - based on **Polymerase Chain Reaction (PCR)**
  - is an effective method for the rapid detection of specific bacterial DNA by using template DNA and DNA primers to replicate M.tuberculosis DNA.
  - There are variability in sensitivity and specificity across multiple laboratories.
  - The sensitivity varied widely and false-positive rate results ranged from 3 to 20%.
  - In clinical suspicious of TB, CSF specimens negative for AFB should be submitted for the PCR, bearing in mind that a negative result neither excludes the diagnosis nor provides a basis for discontinuing therapy.
  - Most studies conclude that commercial NAA tests can confirm cerebral tuberculosis, but cannot rule it out.
  - The sensitivity of mycobacterial DNA in the CSF remain detectable within the CSF until one month after the start of treatment.

Thwaites G, Fisher M, Hemingway C et al. J Infect. 2009 Sep;59(3):167-87.

2 Molecular Diagnosis

- **Tuberculous Meningitis**
  - Recent meta-analysis calculated that commercial nucleic acid amplification (NAA) assays for the diagnosis of TBM were 56% sensitive (95% CI 46-66%) and 98% specific (95% CI 97-99%).
  - **Xpert MTB/RIF nucleic acid amplification test** in 2010 and, more recently, the second-generation **Xpert MTB/RIF Ultra assay** in 2017 brought hopes of more sensitive CSF assays for CNS TB.
  - CSF Xpert MTB/RIF Ultra has been found to be more sensitive than Xpert MTB/RIF in several cohorts, but the sensitivity of both assays remains suboptimal.
  - CSF MTB/RIF Xpert, Xpert MTB/RIF Ultra, and multiplex PCR all demonstrated 100% specificity but 71%, 28%, and 88% sensitivity, respectively.

Recommendation

- Performing a commercial NAA assay on CSF for all forms of suspected CNS tuberculosis.
- NAA assays that detect the rifampicin resistance genotypes should be requested when the risk of drug resistant tuberculosis is high.

2 Molecular Diagnosis

- **Other promising assays**
  - **Tuberculin skin testing**
    - The diagnostic utility of skin testing for CNS tuberculosis is highly variable: in some studies only 10-20% of patients with CNS tuberculosis have a positive test
    - Individuals from high tuberculosis prevalence areas are more likely to have positive tests with an unrelated illness.
  - **CSF adenosine deaminase activity (CSF ADA)**
    - The activity of adenosine deaminase (ADA) is raised in the CSF of patients with TBM.
    - False positive in patients with lymphomas, malaria, brucellosis and pyogenic meningitis.
    - A recent study in HIV infected adults reported a diagnostic sensitivity of 57% with false positive tests observed in cerebral CMV infection, cryptococcal meningitis, and cerebral lymphomas.

Leonard JM. Microbiol Spectr. 2017 Mar;5(2).

2 Molecular Diagnosis

- **Other promising assays**
  - **Interferon-gamma release assays (IGRA)**
    - Two new commercial assays (QuantiFERON-TB gold and T-SPOT.TB)
    - Based on the detection of interferon-gamma from lymphocytes in response to M. tuberculosis specific antigens
    - The detection of interferon-gamma-producing T-cells in bronchoalveolar lavage fluid has been used successfully to diagnose pulmonary tuberculosis.
    - 50% of patients with culture confirmed TBM had no detectable M. tuberculosis-specific interferon-gamma producing lymphocytes in peripheral blood at presentation.

- CSF ADA is not recommended as a routine diagnostic test for CNS tuberculosis
- The tuberculin skin test and IGRAs using peripheral blood may provide indication of previous tuberculosis infection and are probably most useful in young children, but results are insufficiently to diagnose active disease.

Leonard JM. Microbiol Spectr. 2017 Mar;5(2).

3 Neuroimaging

Tuberculous Meningitis

- The commonest cerebral CT features of TBM are **hydrocephalus** and **basal contrast enhancing exudates**.
- Both features are more common in children (80%) than adults (40%) and may be absent in the elderly with TBM.
- Infarctions as a result of ongoing vasculitis or tuberculoma are found in approximately 20% of patients at presentation.
- Infarctions most commonly involve the basal ganglia and the territories of the medial striate and thalamoperforating arteries.

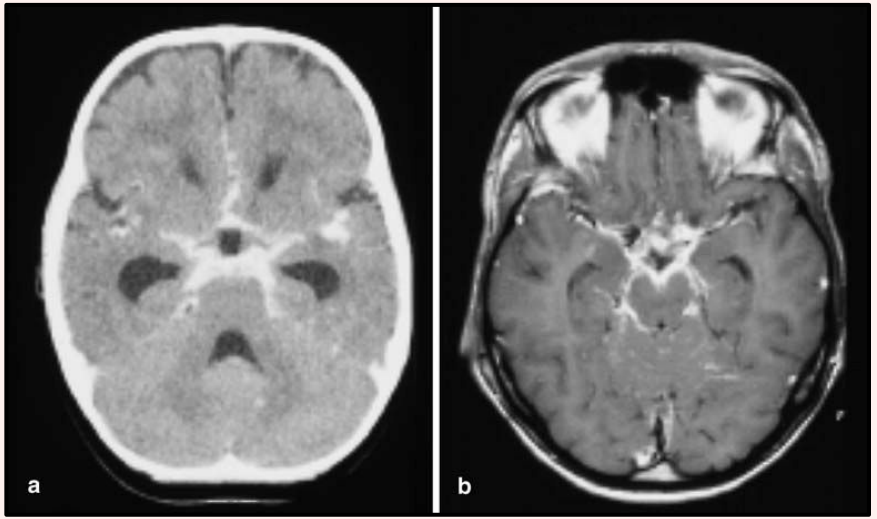


Figure 1 Contrast enhancement at basal cistern in exudative tuberculous meningitis

Leonard JM. Microbiol Spectr. 2017 Mar;5(2).

3 Neuroimaging

Tuberculous Meningitis

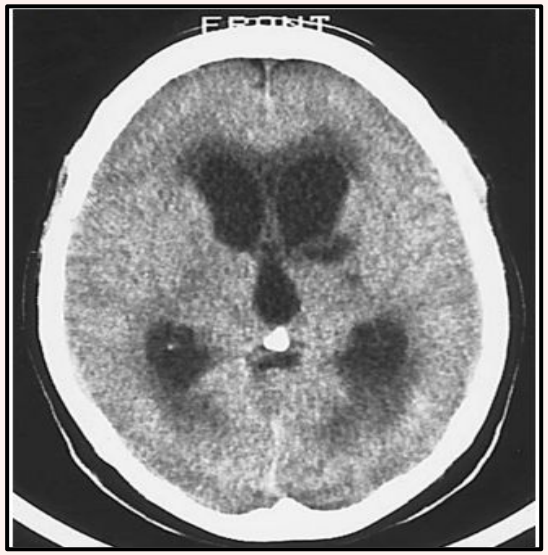


Figure 1 Hydrocephalus in tuberculous meningitis. Note the enlarged ventricles and effacement of sulci, indicating raised intracranial pressure

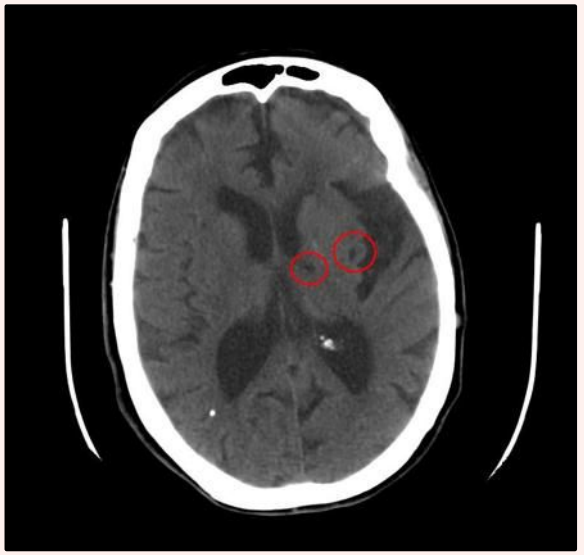


Figure 2 Lacunar infarction at posterior internal capsule and putamen of left basal ganglia in patient with tuberculous meningitis.

3 Neuroimaging

Tuberculous Meningitis

- **Magnetic resonance imaging (MRI)** provides high definition of infra-tentorial lesions and the early cerebral changes of TBM.
- Data regarding the diagnostic sensitivity and specificity of these features are limited.
- Cryptococcal meningitis, cytomegalovirus encephalitis, toxoplasmosis, sarcoidosis, meningeal metastases, and lymphoma may all produce similar radiographic finding.

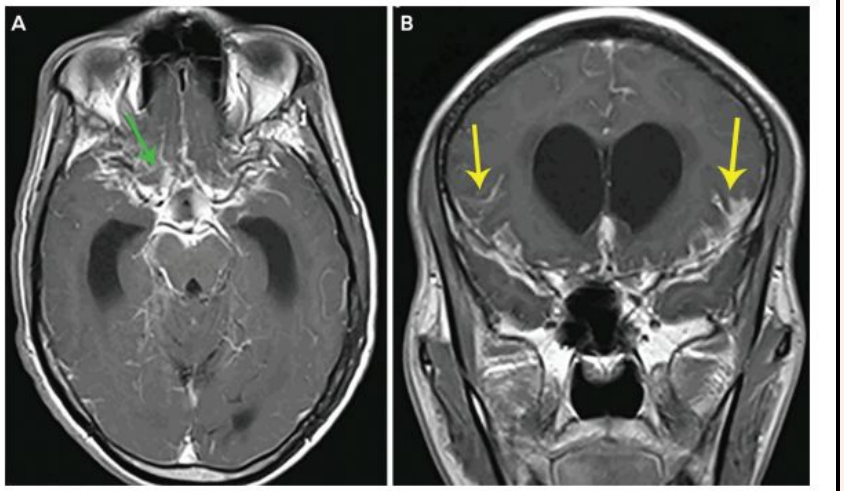


FIGURE 8-2
Axial (*A*) and coronal (*B*) postcontrast T1-weighted MRIs from the patient in CASE 8-1 reveal a thick basal exudate (*A, green arrow*) in the basal cisterns and leptomeningeal enhancement (*B, yellow arrows*) in the frontotemporal regions bilaterally as well as a communicating hydrocephalus.

Leonard JM. Microbiol Spectr. 2017 Mar;5(2).

3 Neuroimaging

Tuberculoma & Tuberculous Abscess

- CT and MRI demonstrate the typical features of contrast enhancing ring lesions with surrounding edema.
- MRI provides better demonstration of lesions in the posterior cranial fossa or brainstem.
- Neither of these imaging modalities is able to reliably distinguish tuberculoma from other causes of ring enhancing lesions, in particular pyogenic bacterial abscess, neurocysticercosis (unless MRI reveals a parasitic scolex within the lesion), toxoplasmosis, or neoplasia.

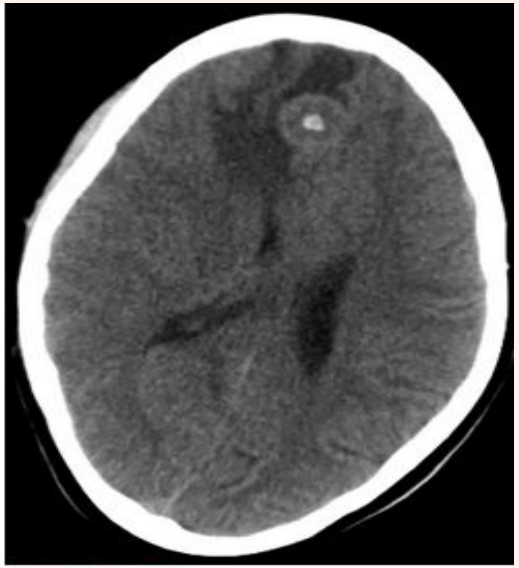


Figure 1 A well-circumscribed lesion with central calcification and surrounding hypodense ring. Marked vasogenic edema is seen with resultant compression of the right lateral ventricle.

Leonard JM. Microbiol Spectr. 2017 Mar;5(2).

3 Neuroimaging

Tuberculoma & Tuberculous Abscess

TABLE 8-3 MRI Features of Tuberculomas by Stage[a]

Tuberculoma stage	T1	T2	Fluid-attenuated inversion recovery (FLAIR)	Diffusion-weighted imaging	T1 + gadolinium
Noncaseous granuloma	Iso/hypointense	Hyperintense	Hyperintense	No restriction	Homogenous enhancement
Caseous granuloma	Iso/hypointense with hyperintense peripheral ring	Hypointense	Hyperintense	No restriction	Homogenous or ringlike enhancement
Noncaseous granuloma with liquefied center	Iso/hypointense with hyperintense peripheral ring	Hyperintense peripheral ring with hyperintense center	Predominantly hyperintense	Heterogenous hyperintensity	Ringlike enhancement
Calcified granuloma	Iso/hypointense	Hypointense	Hypointense	No restriction	No enhancement

MRI = magnetic resonance imaging.

[a] Modified with permission from Salvador GLO, et al, Neuroradiology.[63]

Saylor D. Continuum (Minneap Minn). 2021 Aug 1;27

3 Neuroimaging

Spinal Tuberculosis

- The MRI characteristics of vertebral body tuberculosis have been extensively reported.
- The thoracic spine is most commonly affected
- The radiological features include bone marrow oedema and enhancement, posterior element involvement, canal stenosis, and spinal cord or nerve root compression.
- Intervertebral disc enhancement, vertebral collapse and kyphosis deformity are particularly suggestive of tuberculosis
- Vertebral intraosseous abscess, disc abscess, abnormal paraspinal signal intensity, and involvement of multiple vertebral bodies are common in tuberculosis but rare in pyogenic bacterial disease.

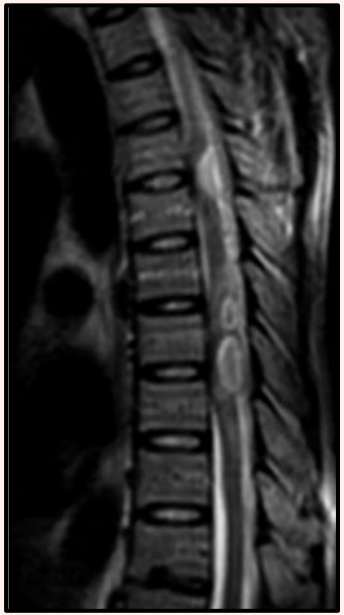


Figure 1 Three thin-walled ring-enhancing lesions in the thoracic subdural region with mass effect on the spinal cord.

Leonard JM. Microbiol Spectr. 2017 Mar;5(2).

3 Neuroimaging

Spinal Tuberculosis

- Tuberculous radiculomyelitis involves more than one spinal region in >80%, with the thoracic and cervical region being most commonly affected.
- The CSF usually shows increased signal intensity on T1-weighted images, which may be associated with complete loss of the CSF lining with irregular cord outline.
- Subarachnoid nodules, clumping of the cauda equina nerve roots, and CSF loculations may also be seen.
- Contrast enhancement may be seen in the meninges (80%), cord (20%), and nerve roots (30%).

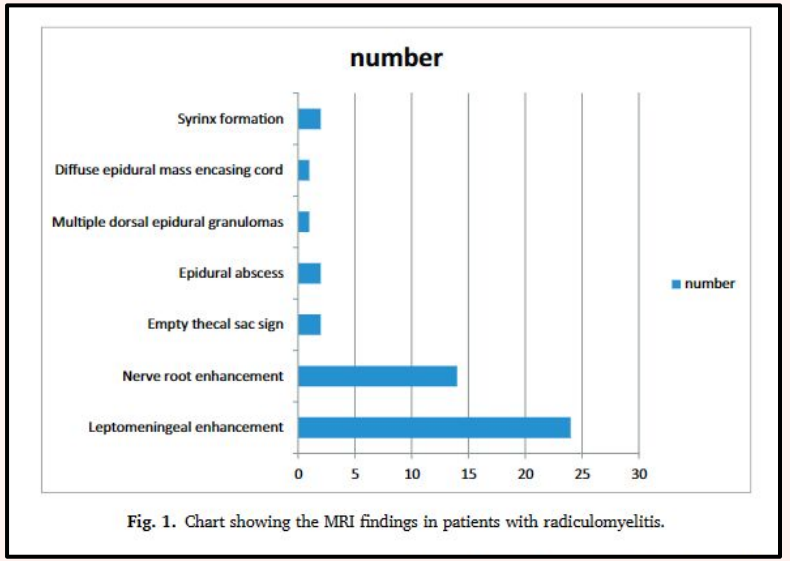


Fig. 1. Chart showing the MRI findings in patients with radiculomyelitis.

Ref: Deepali Saxena et al. NeurologicalSci. 2021

Leonard JM. Microbiol Spectr. 2017 Mar;5(2).

Spinal Tuberculosis

Figure 1 Para-sagittal fat-suppressed contrast-enhanced T1 MRI shows thick enhancing meninges and nerve roots. Diffuse leptomeningitis is noted

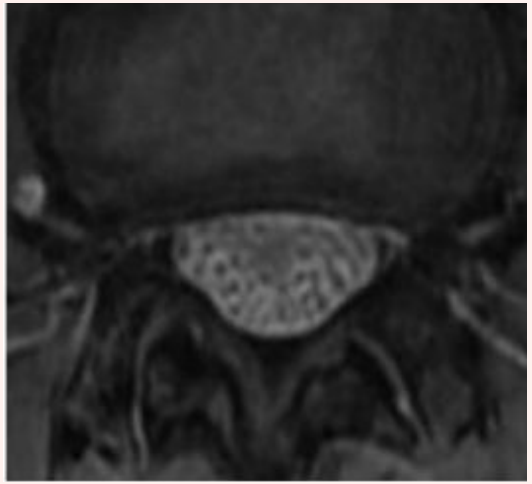


Figure 2 Axial fat-suppressed contrast-enhanced T1 MRI shows arachnoiditis, with thick enhancing nerve roots.

4 Routine Studies

- **Chest X-ray**
  - About 50% of patients with TBM have chest X-rays suggesting active or previous pulmonary tuberculosis
  - 10% have miliary disease, which strongly suggests CNS involvement.
  - Search for hilar adenopathy, interstitial miliary pattern, and parenchymal infiltrate or apical scarring
  - Chest CT may reveal abnormalities missed by conventional X-ray
- **Routine Blood Counts and Blood Chemistries**
  - Mild anemia and leukocytosis are common.
  - Hyponatremia of inappropriate secretion of antidiuretic hormone has been described in a minority of cases with miliary TB complicated by meningitis.

Leonard JM. Microbiol Spectr. 2017 Mar;5(2).
Saylor D. Continuum (Minneap Minn). 2021 Aug 1;27

Diagnosis

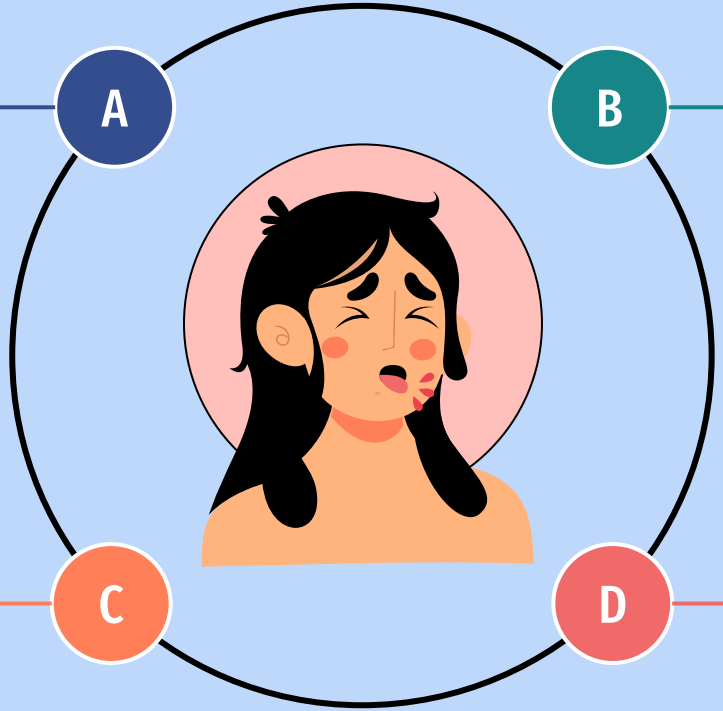
Overview

Clinical presentation

A

B

CSF parameters



Neuroimaging

C

D

Pathology

Diagnosis

Uniform Case Definition for Tuberculous Meningitis[a,b]

Criteria	Score
Clinical criteria	
Symptom duration >5 days	4
Systemic symptoms suggestive of tuberculosis (TB), including weight loss, night sweats, or cough lasting >2 weeks	2
Close contact with someone with TB in the past year	2
Focal neurologic deficits (excluding cranial nerve palsies)	1
Cranial nerve palsy	1
Altered consciousness	1
Maximum score	6
CSF criteria	
Clear appearance	1
10-500 cells/mm^3	1
Lymphocytic predominance	1
Protein >1 g/L	1
CSF to plasma glucose ratio <50% or absolute CSF glucose <40 mg/dL	1
Maximum score	4
Neuroimaging criteria	
Hydrocephalus	1
Basal meningeal enhancement	2
Tuberculoma	2
Infarct	1
Precontrast basal hyperdensity	2
Maximum score	6
Evidence of TB elsewhere	
Chest x-ray suggestive of active TB	
Signs of TB	2
Miliary TB	4
Imaging evidence of TB outside of the central nervous system	2
Acid-fast bacilli identified or *Mycobacterium tuberculosis* cultured from another source (eg, sputum, lymph node)	4
Positive TB nucleic acid amplification test from a source outside of the central nervous system	4
Maximum score	4

CSF = cerebrospinal fluid.
[a] Data from Marais S, et al, Lancet Infect Dis.[18]
[b] To apply this score, individuals must have symptoms and signs of meningitis, including one or more of the following: headache, irritability, vomiting, fever, meningismus, seizures, focal neurologic deficits, lethargy, and/or altered consciousness. In addition, alternative diagnoses, including bacterial, viral, fungal, and parasitic meningitides, should be excluded. If these criteria are met, the case definition can be applied to the individual as follows: Definite tuberculous meningitis requires microbiological confirmation of *M.*

Marais S, Thwaites G et al. Lancet Infect Dis 2010;10(11)

Definite TBM: Microbiological confirmed M.tuberculosis
Probable TBM: Score ≥ 10 (neuroimaging unavailable) **or**
Score ≥ 12 (with support evidence from imaging)
Possible TBM: Score 6-9 (neuroimaging unavailable) **or**
Score 6-11 (with available imaging)

Journal of Infection (2009) 59, 167–187

ELSEVIER

BRITISH INFECTION SOCIETY

www.elsevierhealth.com/journals/jinf

BRITISH INFECTION SOCIETY GUIDELINES

British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children

Guy Thwaites [a,*,h], Martin Fisher [b,i], Cheryl Hemingway [c,j], Geoff Scott [d,k], Tom Solomon [e,l], John Innes [f,g,m]

[a] Centre for Molecular Microbiology and Infection, Imperial College, Exhibition Road, South Kensington, London, UK
[b] Department of HIV/Genitourinary medicine, Brighton and Sussex University Hospitals NHS Trust, Eastern Road, Brighton BN2 5BE, UK
[c] Great Ormond Street Hospital for Children, Great Ormond Street, London WC1N 3JH, UK
[d] Clinical Microbiology, University College London Hospitals, Windeyer Institute, 46 Cleveland St, London W1T 4 JF, UK
[e] Brain Infections Group, Divisions of Neurological Science and Medical Microbiology, University of Liverpool L69 3GA, UK
[f] Department of Infection and Tropical Medicine, Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK
[g] Department of Respiratory Disease, Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK

Accepted 26 June 2009
Available online 4 July 2009

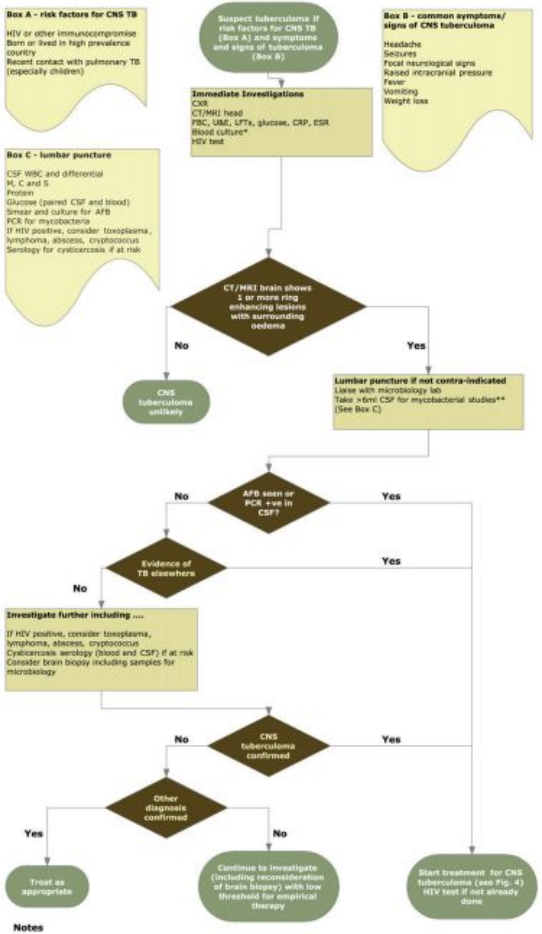


Figure 2 Diagnosis of CNS tuberculoma in adults and children.

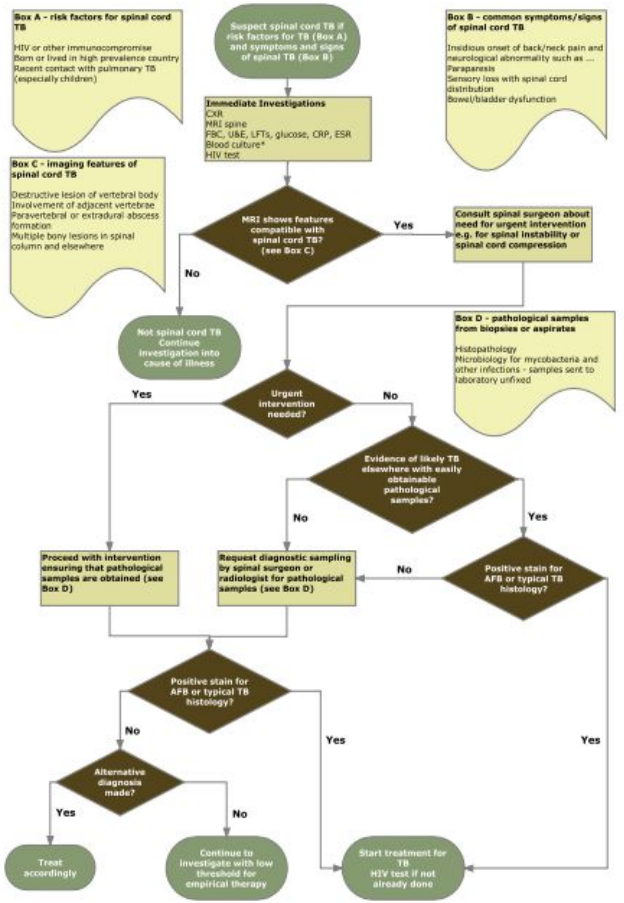


Figure 3 Diagnosis of spinal cord TB in adults and children.

05

Treatment & Prognosis

Journal of Infection (2009) 59, 167–187

ELSEVIER

BRITISH INFECTION SOCIETY

www.elsevierhealth.com/journals/jinf

BRITISH INFECTION SOCIETY GUIDELINES

British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children

Guy Thwaites [a,*,h], Martin Fisher [b,i], Cheryl Hemingway [c,j], Geoff Scott [d,k], Tom Solomon [e,l], John Innes [f,g,m]

[a] Centre for Molecular Microbiology and Infection, Imperial College, Exhibition Road, South Kensington, London, UK
[b] Department of HIV/Genitourinary medicine, Brighton and Sussex University Hospitals NHS Trust, Eastern Road, Brighton BN2 5BE, UK
[c] Great Ormond Street Hospital for Children, Great Ormond Street, London WC1N 3JH, UK
[d] Clinical Microbiology, University College London Hospitals, Windeyer Institute, 46 Cleveland St, London W1T 4 JF, UK
[e] Brain Infections Group, Divisions of Neurological Science and Medical Microbiology, University of Liverpool L69 3GA, UK
[f] Department of Infection and Tropical Medicine, Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK
[g] Department of Respiratory Disease, Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK

Accepted 26 June 2009
Available online 4 July 2009

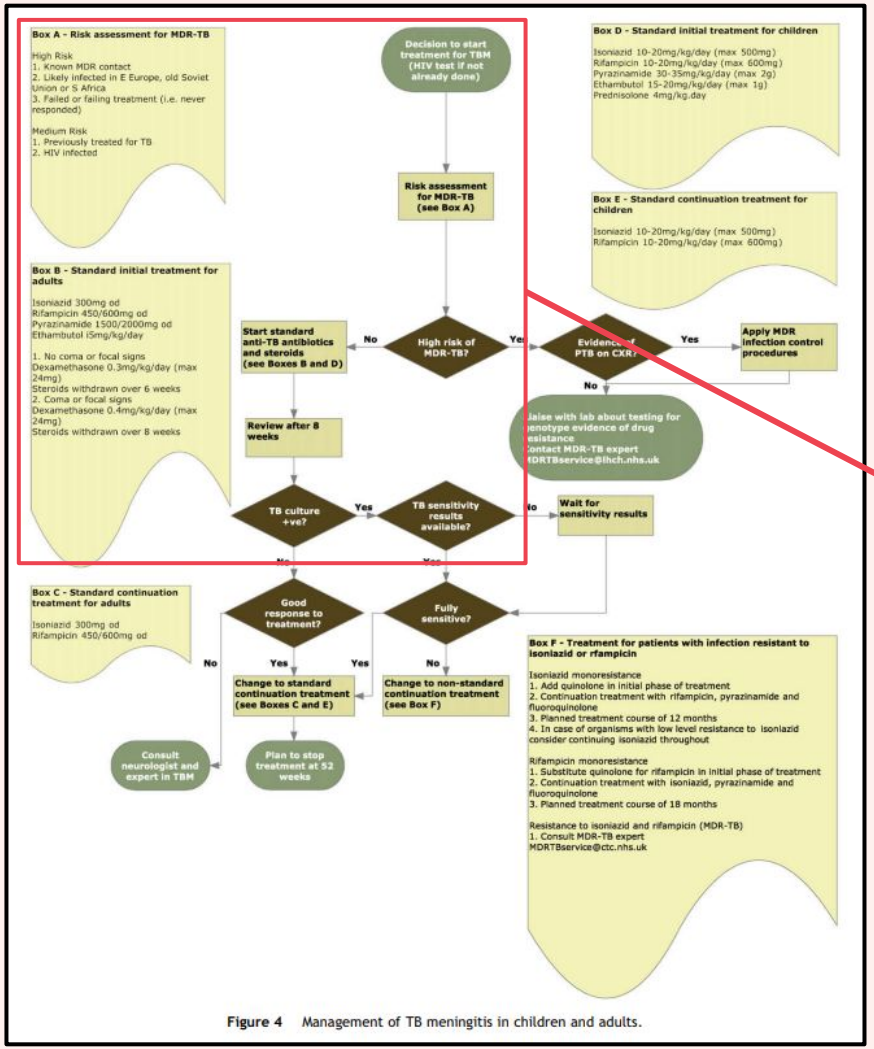
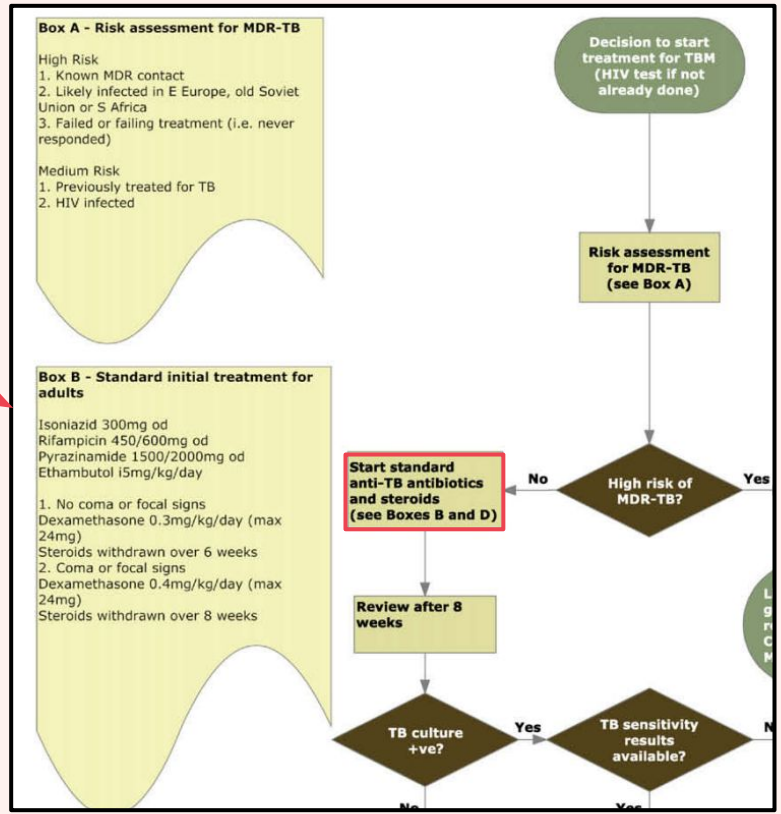


Figure 4 Management of TB meningitis in children and adults.



Thwaites G, Fisher M, Hemingway C et al. J Infect. 2009 Sep;59(3):167-87.

Treatment

1 Anti-tuberculosis Regimen

- There are 2 phases of treatment; **induction phase** and **maintenance (continuation) phase**
- The doses of anti-tuberculosis drugs for the treatment of CNS tuberculosis have conventionally followed those used for pulmonary tuberculosis.

- Isoniazid, rifampicin and pyrazinamide are considered mandatory at the beginning of TBM treatment
- Isoniazid penetrates the CSF freely and has potent early bactericidal activity.
- Rifampicin penetrates the CSF less well (maximum concentrations around 30% of plasma), but the high mortality from rifampicin resistant TBM has confirmed its central role in the treatment of CNS disease.
- Pyrazinamide is controversy in improvement of CNS tuberculosis, although it is well absorbed orally and achieves high concentrations in the CSF.
- There are no data from controlled trials to guide choice of the fourth drug.
- Most authorities recommend either streptomycin or ethambutol, although neither penetrates the CSF well in the absence of inflammation.

Thwaites G, Fisher M, Hemingway C et al. J Infect. 2009 Sep;59(3):167-87.

Treatment

1 Anti-tuberculosis Regimen

Table 5 Recommended treatment regimen for CNS tuberculosis caused by fully susceptible *M. tuberculosis*.

Drug	Daily dose		Route	Duration
	Children	Adults		
Isoniazid	10–20 mg/kg (max 500 mg)	300 mg	Oral	12 Months
Rifampicin	10–20 mg/kg (max 600 mg)	450 mg (<50 kg) 600 mg (≥50 kg)	Oral	12 Months
Pyrazinamide	30–35 mg/kg (max 2 g)	1.5 g (<50 kg) 2.0 g (≥50 kg)	Oral	2 Months
Ethambutol	15–20 mg/kg (max 1 g)	15 mg/kg	Oral	2 Months

Recommendation

- The first-line treatment regimen for all forms of CNS tuberculosis is given in the table below.
- **Induction phase (IRZE)** for first 2 months then **Continuation phase (IR)** for next 10 months.
- Patients should be treated for a minimum of 12 months.

Treatment

2 Adjunctive Corticosteroid

Tuberculous Meningitis

- Adjunctive corticosteroid treatment of TBM has been recommended for more than 50 years, but there has been long-standing concern that corticosteroids reduce the penetration of anti-tuberculosis drugs into the CNS, cause gastrointestinal bleeding, and might save lives but increase the number of disabled survivors.
- A recent Cochrane systematic review and meta-analysis of 7 randomised controlled trials involving 1140 participants (with 411 deaths) concluded that corticosteroids improved outcome in HIV-negative children and adults with TBM, but the benefit in HIV infected individuals remains uncertain.
- There are no data from controlled trials comparing different corticosteroid regimens; therefore choice of regimen should be based on those found to be effective in the published trials.

Thwaites G, Fisher M, Hemingway C et al. J Infect. 2009 Sep;59(3):167-87.

Treatment

2 Adjunctive Corticosteroid

Tuberculous Meningitis

Table 6 Corticosteroid regimens used in controlled trials associated with significant improvements in outcome.

Trial	Girgis et al.[193]	Schoeman et al.[194]	Thwaites et al.[111]	
Age of subjects	60% <14 years (median 8 years)	<14 years	>14 years	
MRC Grade	All grades	Grade II and III	Grade I	Grade II and III
Drug	Dexamethasone	Prednisolone	Dexamethasone	Dexamethasone
Time	Dose/route	Dose/route	Dose/route	Dose/route
Week 1	12 mg/day im (8 mg/day if <25 kg)	4 mg/kg/day[b]	0.3 mg/kg/day iv	0.4 mg/kg/day iv
Week 2	12 mg/day im (8 mg/day if <25 kg)	4 mg/kg/day	0.2 mg/kg/day iv	0.3 mg/kg/day iv
Week 3	12 mg/day im(8 mg/day if < 25 kg)	4 mg/kg/day	0.1 mg/kg/day oral	0.2 mg/kg/day iv
Week 4	Reducing over 3 weeks to stop[a]	4 mg/kg/day	3 mg total/day oral	0.1 mg/kg/day iv
Week 5		Reducing dose to stop[c]	Reducing by 1 mg each week over 2 weeks	4 mg total/day oral
Week 6				Reducing by 1 mg each week over 3 weeks

[a] Dexamethasone tapered to stop over 3 weeks: exact regimen not published.
[b] Route of administration not published.
[c] Prednisolone tapered to stop over unspecified time: regimen not published.

Thwaites G, Fisher M, Hemingway C et al. J Infect. 2009 Sep;59(3):167-87.

Treatment

2 Adjunctive Corticosteroid

Tuberculoma & Spinal Tuberculosis

- No published controlled trials have examined whether patients with intracranial tuberculomas without meningitis or spinal cord tuberculosis benefit from adjunctive corticosteroids, although they are widely advocated.
- Corticosteroid might improves symptom and seizure control and reduce tuberculoma size and perilesional edema.
- Duration of therapy varies depending on response; it is common for symptoms to return once the dose is reduced.

Recommendation

- All patients with TBM receive adjunctive corticosteroids regardless of disease severity at presentation.
- There is insufficient evidence to recommend routine adjunctive corticosteroids for all patients with tuberculomas without meningitis, or with spinal cord tuberculosis.
- However, they may be helpful in those patients whose symptoms are not controlled, or are worsening, on anti-tuberculosis therapy, or who have acute spinal cord compression secondary to vertebral tuberculosis

Afghani B, Leiberman JM.. Clin Infect Dis 1994

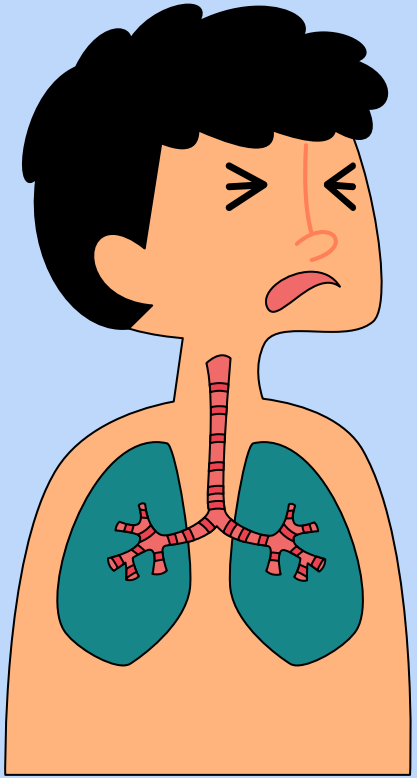
Treatment

3 Surgical Intervention

- Hydrocephalus, tuberculous cerebral abscess, and vertebral tuberculosis with paraparesis are all indications for neurosurgical referral.
- **Early ventriculoperitoneal shunting** should be considered in those with noncommunicating hydrocephalus and in those with communicating hydrocephalus failing medical management.
- **Communicating hydrocephalus** may be treated initially with furosemide (40 mg/24 h adults; 1 mg/kg children) and acetazolamide (10-20 mg/kg adults; 30-50 mg/kg children) **or** repeated lumbar punctures.
- **Urgent surgical decompression** should be considered in all those with extradural lesions causing paraparesis.

Afghani B, Leiberman JM.. Clin Infect Dis 1994

Treatment



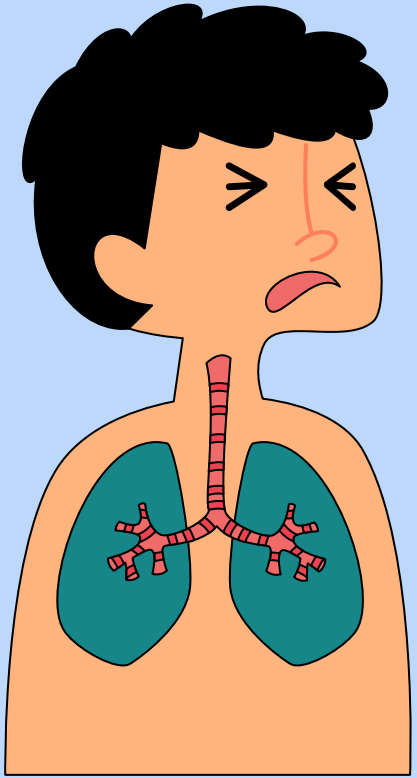
Special Consideration: HIV Patient

- HIV is strongly associated with both TB infection overall and central nervous system (CNS) TB in particular.
- People with HIV are at significantly increased risk of acquiring TB infection and progressing from having latent infection to active disease.
- CNS TB is up to 5 times more common in people with HIV, which may account for the higher mortality rates seen with HIV and TB co-infection
- The clinical, laboratory, and radiological features of CNS tuberculosis are slightly unsimilar in HIV infected and uninfected individuals.
- The diagnostic yield of CSF mycobacterial smear and culture is probably higher in patients with HIV infection.
- Higher mortality associated with HIV infection

Thwaites G, Fisher M, Hemingway C et al. J Infect. 2009 Sep;59(3):167-87.

Treatment

Special Consideration: HIV Patient



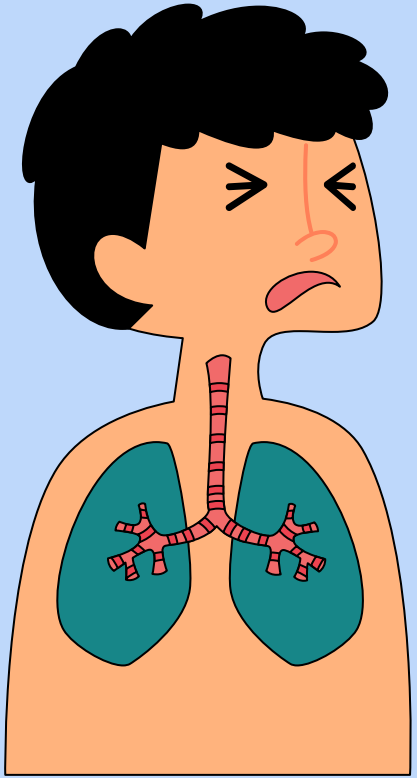
Recommendations

- All patients with suspected CNS TB should be tested for HIV (A,II).
- CSF microscopy, culture, and antigen tests for cryptococcal infection should be performed in addition to mycobacterial tests in all HIV infected patients with suspected CNS infection (A,II).
- The diagnosis of intra-cerebral mass lesions is difficult. Response to toxoplasmosis empirical therapy may be helpful in those at low demographic risk for tuberculosis and with no evidence of previous or current extra-neural tuberculosis (B,II).
- In all others, tissue biopsy should be strongly considered (B,III).
- Other sites of tuberculosis infection should be sought from which tissue specimens might be easily and safely taken (B,III)

Thwaites G, Fisher M, Hemingway C et al. J Infect. 2009 Sep;59(3):167-87.

Treatment

Special Consideration: HIV Patient



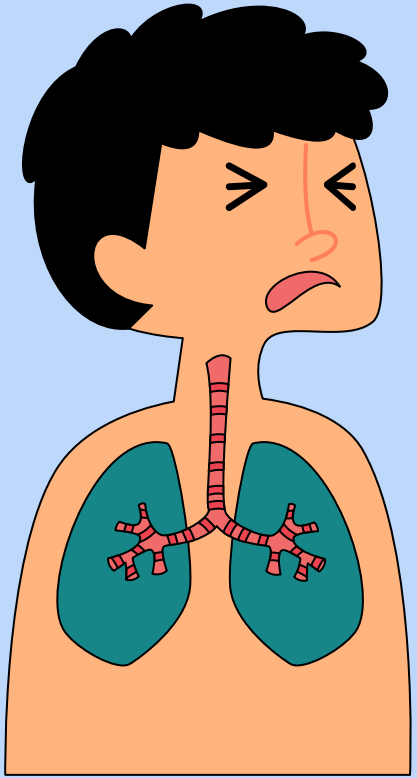
Recommendations

- Anti-tuberculosis drug regimen should be the same as that recommended for HIV uninfected individuals; whenever possible the regimen should include rifampicin (B,II).
- Adjunctive corticosteroids are recommended for those with TBM and HIV infection (B,I)

Table 7 Recommendation for when to start anti-retroviral drugs in relation to anti-tuberculosis treatment for CNS tuberculosis in adults (B,II).

Peripheral blood total CD4 lymphocyte count	Recommended action
>200 Cells/μl	Defer HIV treatment as long as possible, ideally until end of tuberculosis treatment. Start anti-retroviral treatment if the CD4 count falls below 200 cells/μl during tuberculosis treatment.
100–200 Cells/μl	Start HIV treatment after approximately 2 months of anti-tuberculosis treatment.
<100 Cells/μl	Start HIV treatment within the first 2 weeks of anti-tuberculosis treatment

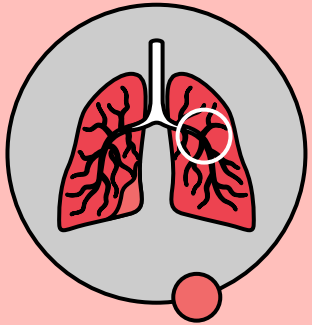
Treatment



Special Consideration: HIV Patient

- HIV is strongly associated with both TB infection overall and central nervous system (CNS) TB in particular.
- People with HIV are at significantly increased risk of acquiring TB infection and progressing from having latent infection to active disease.
- CNS TB is up to 5 times more common in people with HIV, which may account for the higher mortality rates seen with HIV and TB co-infection
- The clinical, laboratory, and radiological features of CNS tuberculosis are slightly unsimilar in HIV infected and uninfected individuals.
- The diagnostic yield of CSF mycobacterial smear and culture is probably higher in patients with HIV infection.
- Higher mortality associated with HIV infection

Thwaites G, Fisher M, Hemingway C et al. J Infect. 2009 Sep;59(3):167-87.



Thank You