BMJ Best Practice

Extrapulmonary tuberculosis

Straight to the point of care

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Summary

Extrapulmonary tuberculosis (EPTB) is an infectious disease caused by *Mycobacterium tuberculosis* that occurs in organ systems other than the lungs.

Epidemiological risk factors include birth in high TB-prevalent countries, exposure at place of residence/work in an institutional setting, and homelessness.

Diagnosis may be delayed as a result of non-specific clinical manifestations that progress slowly and the low sensitivity of acid-fast bacilli (AFB) smear on extrapulmonary specimens.

Microbiological proof is the key to diagnosis and treatment, and tissue biopsy is frequently required. Other supportive findings are granulomas and positive AFB stain on pathology, and chest x-ray findings.

Initial therapy is a 4-drug regimen typically consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol; treatment lasts for at least 6 months.

Definition

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* . In many cases, *M tuberculosis* infection becomes latent before progression to active TB disease. Patients who are infected but who have no clinical, bacteriological, or radiographic evidence of active TB are said to have latent TB infection. When there is progression from latent infection to active disease, it most commonly involves the lungs and is communicable in this form, but it may affect almost any organ system, including the lymph nodes, central nervous system, bones/joints, genitourinary tract, abdomen (intra-abdominal organs, peritoneum), and pericardium. When TB occurs in organ systems other than the lungs, it is referred to as extrapulmonary TB (EPTB).

Epidemiology

According to the World Health Organization (WHO), every year an estimated 10 million people develop TB, and there are an estimated 1.5 million TB-related deaths.[4] In 2020, disruption caused by the coronavirus disease 2019 (COVID-19) pandemic resulted in a large global decrease in the number of reported new cases; however, the number of reported cases has increased again, with WHO estimating that in 2022 there were 1.3 million TB-related deaths, including 167,000 TB-related deaths among people with HIV.[5] The increase in TB-related deaths between 2019 and 2021 reverses years of decline between 2005 and 2019. In England, 4125 people were reported to have TB in 2020 (an incidence of 7.3 in 100,000 population).[6]

Of the 8331 reported cases of active TB in the US in 2021, 18.8% had EPTB only and 10.6% had both pulmonary and extrapulmonary sites of TB.[7] In the 2022 US surveillance report, EPTB included lymphatic (26.1% of EPTB), pleural (22.1%), bone or joint (9.4%), peritoneal (6.3%), meningeal (5.8%), genitourinary (4.2%), laryngeal (1.1%), and 'other' (25.1%).[7] Patients born outside the US accounted for 73.8% of the total cases of TB in 2022.[7] The TB incidence rate was 0.8 in 100,000 for US-born people, and 13 for non-US-born people.[7]

Risk factors for EPTB in the US, in addition to HIV infection, include black ethnicity, female sex, young age, and having cirrhosis.[8] [9]

In 2022, 170,365 cases of TB were reported in the WHO European Region and 17.0% of these had EPTB.[10] In England, there were 4425 TB cases in 2021, and 47.3% of these had EPTB.[11]

TB is particularly devastating in areas with a high prevalence of HIV infection, such as sub-Saharan Africa.[12] The Global Burden of Disease Study reports that in 2019, there were 217,000 (153,000-279,000) deaths due to tuberculosis among people with HIV and 1.15 million (1.01 to 1.32) incident cases.[13]

TB lymphadenitis was historically considered a disease of childhood, but it is now commonly seen in the young to middle-aged adult population. An increased prevalence has been noted in Asian and black women from TB-endemic areas.

Aetiology

At the time of initial infection, it is thought that a small number of *Mycobacterium tuberculosis* organisms are contained in various body organs. The development of active TB requires infection by *M tuberculosis* and inadequate containment by the immune system. Active TB disease may occur from reactivation of previously latent infection or from progression of primary infection.[14] EPTB in immunocompetent adults usually results from reactivation of TB. In children and adults with HIV infection, EPTB may result from recent infection (primary disease). TB enteritis, often seen in the ileocecal region, can also result from ingestion of infected sputum or dairy products.[15] Disseminated TB is due to the haematogenous dissemination of *M tuberculosis* throughout the body.

Pathophysiology

Infection with *Mycobacterium tuberculosis* requires inhalation of aerosolised particles called droplet nuclei. In the course of primary infection, a period of subclinical bacillaemia usually occurs and a small number of *M tuberculosis* organisms are contained in various body organs. Exposure may be followed by clearance, persistent latent infection, or progression to primary disease.

Successful containment of TB is dependent on the cellular immune system, mediated primarily through T-helper cells (TH1 response). T cells and macrophages form a granuloma with a centre that contains necrotic material (caseous centre) and *M tuberculosis* , and peripheral granulation tissue consisting primarily of macrophages and lymphocytes. The granuloma serves to prevent further growth and spread of *M tuberculosis* . These individuals are not infectious and have latent TB infection; the majority of these patients will have a normal chest x-ray and positive tuberculin skin test and positive interferon-gamma release assays.

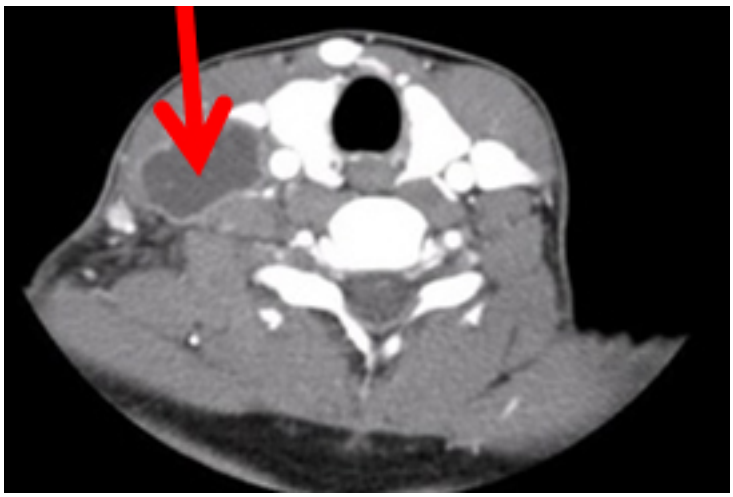
- Pleural TB (particularly primary disease) may occur from a few mycobacteria gaining access to the pleural space with a resultant T-cell response and delayed hypersensitivity reaction. The effusion is due to increased capillary permeability and decreased lymphatic drainage. As TB pleural effusion results from intensive inflammatory response, recovery of *M tuberculosis* from the pleural fluid occurs in about 40% of cases.
- Skeletal TB is an osteomyelitis that starts in the growth plates of bones where the blood supply is the richest, and from there spreads into joint spaces. Vertebral disease usually starts in the subchondral cancellous bone, from where it spreads to the cortex and on to the disc. Bone destruction is more extensive on the ventral aspect leading to anterior wedging. Paraspinous collections may also develop.[16] Spinal or vertebral TB has been known historically as Pott's disease.
- TB meningitis results from haematogenous spread of *M tuberculosis* with the development of submeningeal or intrameningeal foci called Rich foci. With rupture of a Rich focus into the subarachnoid space, meningitis develops. This may result from reactivation (more common in adults) or primary infection (more common in children). BCG vaccination is about 64% effective against TB meningitis in young children.[17] In a population in Vietnam, a polymorphism in leukotriene A4 hydrolase, which regulates the balance of pro- and anti-inflammatory eicosanoids, was associated with protection against TB meningitis, improved survival, and response to corticosteroid therapy.[18] [19]
- Abdominal TB includes disease of the intestines, peritoneum, and mesenteric lymph nodes. In peritoneal TB, the peritoneum becomes studded with tubercles. As protein-rich fluid is exuded, ascites accumulate.
- More than 90% of patients with peritoneal TB will have ascites; the remainder generally have more advanced disease and present with fibroadhesions ('doughy abdomen'). TB enteritis may occur secondary to ingestion of infected sputum or initial haematogenous spread. If the enteric source spreads to the mesenteric lymph nodes, they may rupture into the peritoneum. TB enteritis occurs most frequently in the ileocecal region. Its appearance may be ulcerative or hypertrophic.[15]
- Pericardial TB results from contiguous spread from adjacent mediastinal lymph nodes, or progression of a primary or latent focus within the pericardium. Some patients present with signs of cardiac constriction without an acute phase of pericarditis being noticed.
- Disseminated TB refers to simultaneous involvement of multiple organ sites that may occur with primary infection (particularly in immunocompromised individuals) or with reactivation. Disseminated TB is sometimes called miliary TB; its lesions are yellowish granulomas 1 to 2 mm in diameter that resemble millet seeds on chest x-ray. It is due to haematogenous spread of *M tuberculosis* .

Classification

Extrapulmonary TB categorised by affected organ system

Acquisition of *Mycobacterium tuberculosis* is followed by systemic dissemination and immunological containment in the majority of cases. As such, progression to TB disease can take place in various areas of the body.

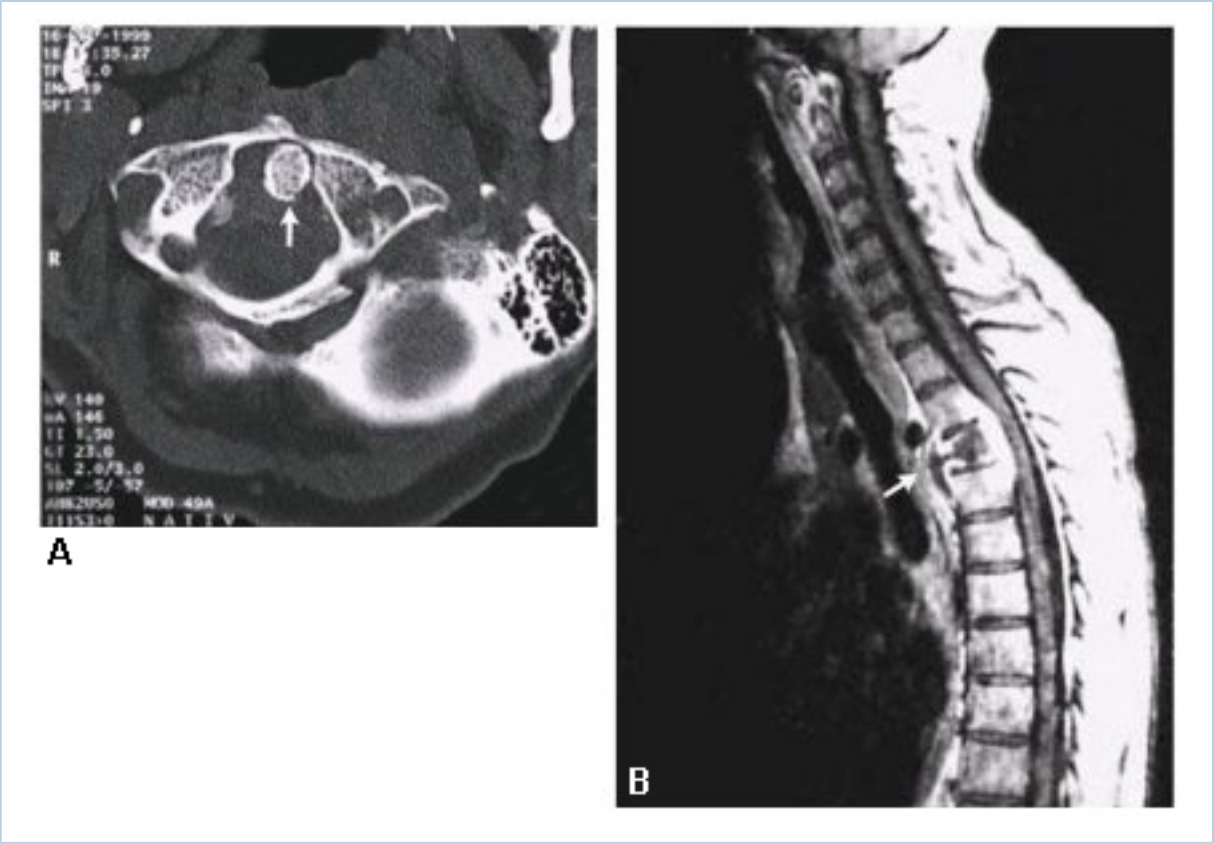
- Lymphatic TB: most commonly found in the cervical or supraclavicular regions, and often seen in Asian and black women from TB-endemic areas.[1]



CT showing necrotic cervical lymph node

From the collection of Dr David J. Horne and Dr Masahiro Narita; used with permission

- Pleural TB: at least 40% of pleural TB is the result of primary TB (occurring shortly after acquisition of tubercle bacilli), rather than due to reactivation of latent foci (post-primary TB).[2] [3] In this regard it differs from other sites of EPTB.
- Skeletal TB: results from haematogenous spread. The most common sites of involvement are the vertebral column (especially the lower thoracic and lumbar regions), hip, and knee. TB involving the spine is also known as Pott's disease. TB in the joints is usually monoarticular.



CT showing spinal TB (Pott's disease)

Massachusetts Medical Society; reproduced with permission from N Engl J Med. 2002;347:1849; used with permission

- Central nervous system TB: includes meningitis and tuberculomas, with meningitis being the most common presentation. TB meningitis typically involves the base of the brain. Meningeal TB is a devastating form of EPTB and early treatment is important to prevent irreversible deficits or death.
- Peritoneal TB: arises from reactivation of *M tuberculosis* foci established in the peritoneum from haematogenous spread or may occur in disseminated TB. Risk factors include cirrhosis, peritoneal dialysis, and diabetes mellitus.
- Genitourinary TB: may involve either the urinary or genital tract or both. Symptoms include dysuria, haematuria, and urinary frequency. Genital TB is a common cause of infertility in endemic settings.
- Pericardial TB: the common findings are related to pericardial fluid (e.g., cardiac tamponade) or pericardial fibrosis (e.g., constriction).
- Disseminated TB: due to the haematogenous dissemination of *M tuberculosis* throughout the body with involvement of multiple organs. When a characteristic chest radiograph pattern (diffuse, bilateral, symmetrical, discrete, 1-2 mm opacities) is present, this condition is also known as miliary TB.

Case history

Case history #1

A 42-year-old woman presents to her primary care physician with a 7-week history of an enlarging mass on the left side of her neck. She denies pain or drainage. The mass failed to respond to antibiotics. She denies cough, fever, night sweats, or anorexia. She is originally from Vietnam but has lived in the US for 4 years. She denies any history of TB or TB exposure. Physical examination reveals a well-appearing

woman. There is a 2 x 4 cm left neck mass consistent with a lymph node in the anterior cervical chain. There is no tenderness; the node is firm and mobile. There are smaller subcentimetre lymph nodes in the left supraclavicular fossa. The physical examination is otherwise unremarkable.

Case history #2

A 66-year-old man presents to the emergency department with a history of fever and weight loss. He reports that he has had little appetite for the last 3 months and has lost 11 kg during that time. He has noted tactile fevers over the last 6 weeks but has not had access to a thermometer. He has been having headaches for the last week but denies cough, haemoptysis, or chest pain. He has been intermittently homeless over the last 2 years and has a history of heavy alcohol use but recently stopped. On examination, he is a thin man with a temperature of 38.8°C (101.9°F) and a respiratory rate of 20 breaths per minute. Physical examination is notable for temporal wasting and hepatomegaly without tenderness.

Other presentations

The spectrum of EPTB is extremely broad and signs and symptoms include those related to the involved organ system and non-specific constitutional symptoms.

Approach

Many forms of EPTB are paucibacillary, and the diagnosis of EPTB is therefore challenging. Acid-fast bacilli (AFB) smear of biological specimens is often negative. Constitutional symptoms associated with EPTB, (such as fever, weakness, and weight loss) may be infrequent and non-specific. In addition, EPTB is less common than pulmonary TB and may be less familiar to clinicians.

A high level of suspicion is important in evaluating a patient with presence of risk factors (for full details please refer to risk factor section). The firm diagnosis of TB requires culturing of *Mycobacterium tuberculosis* and this is also important for drug-susceptibility testing. Appropriate specimens are obtained and tested microbiologically and histologically.[41] Although culture remains the diagnostic standard, it can take up to 8-10 weeks using a solid media, and in 10% to 15% of patients the diagnosis of TB is based on clinical grounds. Delays in diagnosis and initiation of therapy are associated with increased mortality.[41]

Rapid diagnostic tests (e.g., nucleic acid amplification tests [NAATs]) are available and can be useful in many settings; some are endorsed by the World Health Organization (WHO) and can detect resistance to some TB drugs.[42]

Tests for all suspected EPTB

As the lungs may be involved in patients with EPTB, sputum for AFB smear and culture is indicated for all suspected patients.[43] Culture-positive sputum becomes useful when the specimens from extrapulmonary sites are culture-negative, and it may also add further information on the infectiousness of the patient.[41] Chest x-ray should be part of the basic initial work-up and may show evidence of active or old TB. A positive TST or IGRA are helpful for diagnosis, but a negative TST or IGRA do not rule out active TB disease. A full blood count should be sent and may show abnormalities.[41]

If the suspicion of TB is high or the patient is very ill, consideration can be given to starting antituberculous medicines as soon as diagnostic specimens are obtained.

Several rapid NAATs, for example, polymerase chain reaction (PCR) assays, are available for the diagnosis of TB, and some are also able to detect resistance to some TB drugs. Although NAATs were originally designed and approved for respiratory specimens, they may also be requested on specimens from other sites where involvement of TB is suspected (e.g., cerebrospinal fluid, lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine).[42] In the US, use of NAATs for extrapulmonary specimens is not approved by the US Food and Drug Administration, and use would be off-label.

Xpert MTB/RIF and Xpert Ultra are rapid NAATs recommended by WHO as initial diagnostic tests in adults and children with signs and symptoms of EPTB.[38] [42]

They are also recommended by WHO for detection of rifampicin resistance.[42] Cochrane reviews of Xpert MTB/RIF and Xpert Ultra found that sensitivity of the tests in diagnosing EPTB in patients with presumed infection varied across different site specimens, but the specificity was high.[44] [45] Line probe assays (LPAs) are strip-based tests that can detect TB and determine drug resistance profiles. LPAs are recommended by WHO only for detecting resistance to anti-TB drugs.[42]

Lateral flow tests that detect lipoarabinomannan (LAM) antigen in urine have emerged as potential point-of-care tests. One Cochrane review found the lateral flow urine lipoarabinomannan (LF-LAM) assay to have a sensitivity of 42% in diagnosing TB in HIV-positive individuals with TB symptoms, and 35% in

HIV-positive individuals not assessed for TB symptoms.[46] The WHO recommends that LF-LAM can be used to assist in the diagnosis of active TB in HIV-positive adults, adolescents, and children.[42] This approach is supported by another Cochrane review, which found reductions in mortality and an increase in treatment initiation with use of LF-LAM in inpatient and outpatient settings.[47] Culture would still be required for drug susceptibility testing (DST).

It is recommended that all patients with TB have an HIV test within 2 months of diagnosis. Around 6% of patients with TB are living with HIV.[5]

HIV infection and its treatment may alter the treatment of TB; treatment of HIV may be crucial to the morbidity of HIV-infected TB patients.[48]

TB lymphadenitis

Patients most commonly present with enlarged lymph nodes in the cervical or supraclavicular areas that may be unilateral or bilateral. Scrofula is a term applied to TB adenitis in the neck.

If a patient with superficial lymphadenitis is suspected of having TB, the first diagnostic test is fine-needle aspiration, especially if the lymph node is fluctuant. In addition to AFB smear and culture, aspirate should be submitted for NAAT.[44] If the diagnosis remains in question, a surgical consultation is obtained for lymph node excision.

If the patient has mediastinal lymphadenitis, biopsy is obtained with endobronchial ultrasound (EBUS) bronchoscopy, mediastinoscopy, or thoracoscopy.

Pleural TB

Pleural TB usually presents with symptoms such as pleuritic chest pain, cough, and fever, and a chest x-ray showing a unilateral effusion. The effusion is commonly small to moderate in size; bilateral TB effusions are rare and associated with disseminated disease.

In addition to a chest x-ray, and sputum mycobacterial cultures, a thoracentesis should be performed. Chest x-ray may show no obvious parenchymal disease in 50% of patients with pleural TB. Among those without definite parenchymal involvement, sputum AFB smears are almost always negative and cultures are positive in 20% to 30% of patients. False-negative TST/IGRA are also common.[2]

Pleural fluid analysis is performed on the sample obtained from thoracentesis. Pleural fluid is sent for AFB smear and culture, cell count with differential, protein, LDH, glucose, and pH. AFB smear is rarely positive. Pleural fluid analysis usually shows an exudative effusion that is lymphocyte-predominant and often has low glucose level. The adenosine deaminase (ADA) level may be measured because it is often elevated in pleural TB (sensitivity and specificity approximately 90%), although pneumonia and malignancy, which are frequently differential diagnoses, may also elevate the ADA level.[49] When the ADA level is very low, pleural TB is unlikely. Measurement of pleural fluid free interferon gamma levels is also recommended in diagnosing pleural TB.[41]

Although results of pleural fluid analysis may be helpful, they will seldom confirm a diagnosis of pleural TB. Because a malignancy may also cause a lymphocyte-predominant exudative effusion, the diagnosis of pleural TB is based on microbiology, pathology, identification of granulomas, and negative cytology for malignancy. It is important to obtain a TB isolate for susceptibility testing. Therefore, closed pleural biopsy is indicated when the patient has a lymphocyte-dominant exudative effusion, or even at the same time as thoracentesis if clinical suspicion for TB is very high. The combination of AFB culture and histology

from pleural biopsy is the most sensitive to diagnose pleural TB. If results of biopsy are non-diagnostic, thoracoscopy or thoracotomy may be indicated.[50] [51]

Skeletal TB (bone and joint TB)

Pain of the involved area is the most common complaint in skeletal TB; constitutional symptoms are usually absent. Diagnosis is based on tissue biopsy. Onset of pain is gradual (over weeks to months) and diagnosis is frequently delayed. Local swelling and limitation of movement may be present. Cold abscesses (non-tender) with sinus tracts may form.

If skeletal TB is suspected, magnetic resonance imaging (MRI) (especially in spinal involvement) or computerised tomography (CT) is obtained. One half of cases will have abnormalities on chest x-ray consistent with TB.[52] Microbiological confirmation of TB is also essential. AFB smears are unlikely to be positive due to low bacillary loads. Cold abscesses, if present, may be aspirated for AFB smear and culture. CT-guided biopsy in vertebral TB will have positive microbiological or histological yields in 65% to 90% of patients.

Synovial biopsy should be done to diagnose TB arthritis. Biopsy may yield culture positive in 90% to 95%, and should be performed if the diagnosis of TB arthritis remains in question.[16] In joint involvement, evaluation of synovial fluid is usually not diagnostic; WBC counts in TB arthritis are usually 10,000-20,000/mL but can be much higher. AFB smear is positive in <20% but culture may be positive in up to 80%.

Central nervous system TB

Central nervous system (CNS) TB may present with meningitis or intracranial tuberculomas. Diagnosis of TB meningitis is dependent upon CSF examination, and its rapid diagnosis is essential for improved outcomes. When there is high pre-test probability for CNS TB, empirical TB treatment should be started while awaiting microbiological confirmation.

Signs and symptoms of meningeal TB include headache, neck stiffness, altered mental status, and cranial nerve abnormalities. Only 38% of children with TB meningitis have fever and 9% report photophobia. Seizures are common in children and older people.

In the presence of meningeal signs, the patient undergoes lumbar puncture and the CSF is submitted for cell count with differential, glucose, protein, AFB smear and culture, Gram stain, and bacterial culture. PCR can be added if available. The usual results of analysis include a lymphocyte predominance, elevated protein, and reduced glucose. ADA levels may be useful in the diagnosis of CNS TB.[41] Although smears of spinal fluid are frequently negative, the diagnostic yield is dependent on the volume of CSF submitted and the quality of examination.[53]

In order to maximise the sensitivity of TB diagnosis by spinal fluid analysis, some experts suggest increased CSF volume (≥6 mL of spinal fluid for AFB) and repeated sampling (up to three lumbar punctures on different days).[53] [54]

AFB culture is the definitive standard for diagnosis but treatment must not wait until culture results are available. Treatment is initiated presumptively based on clinical suspicion, risk factors, and CSF results.[16]

Head CT or MRI may show oedema, hydrocephalus, basilar meningeal thickening, or tuberculomas. Tuberculomas present as a slowly growing focal lesion, or, rarely, with signs and symptoms consistent

with increased intracranial pressure. CSF analysis is usually normal and diagnosis is based on CT or MRI findings.

Up to 50% of patients have chest x-ray abnormalities consistent with pulmonary TB.[24]

Abdominal TB

Abdominal TB includes TB peritonitis and TB of the gastrointestinal tract. Chest x-ray may show evidence of old or concurrent pulmonary TB. Definitive diagnosis is based on culture growth of *M tuberculosis* from ascitic fluid or a biopsy of the lesion. Patients may have disease for months before the diagnosis is made. Peritoneal disease is the more common presentation. The presenting symptoms include abdominal swelling, abdominal pain, fever, and change in bowel habits. In TB enteritis (TB of the gastrointestinal tract), common sites of involvement are the ileocecal and anorectal areas. Chronic abdominal pain is the most common symptom in addition to changes in bowel habits and haem-positive stool. Patients may develop small bowel obstruction or a right lower quadrant mass.

CT scan of the abdomen, ascitic fluid analysis, and peritoneal biopsy are done initially.

CT scan may show ascites, bowel-wall thickening, or abdominal lymphadenopathy.

Ascitic fluid analysis is non-specific and rarely AFB smear-positive. Although the sensitivity of culture from peritoneal fluid is high (92%), results require up to 8 weeks and delay in initiating treatment is associated with higher mortality.

Peritoneal biopsy (laparoscopy or laparotomy) is the most effective means for diagnosis. Direct inspection may reveal miliary nodules over the peritoneum and allow a presumptive diagnosis in 80% to 95%. Biopsy demonstrates caseating granulomas (up to 100%) and the presence of AFBs on examination in 67% of samples.[15] [61] Ascitic fluid ADA and free interferon gamma levels may have a role in diagnosing abdominal TB.[41] Abdominal ultrasound may also aid in diagnostic evaluation but should not be used alone for TB diagnosis.[67]

Colonoscopy and biopsy are carried out to diagnose TB enteritis. Colonoscopy will reveal ulcers, pseudopolyps, or nodules. Definitive diagnosis is based on biopsy, which usually shows granulomas and culture positive for TB.[15]

Genitourinary TB

Chest x-ray is abnormal in 40% to 75% of patients with genitourinary (GU) TB.

Diagnosis relies on culturing *M tuberculosis* from morning urine samples (collection of three specimens is recommended) or biopsy of the lesion. The common symptoms are dysuria, haematuria, and urinary frequency. Symptoms may be absent in 20% to 30% of patients. Genital TB in men may present as a scrotal mass, whereas in women it may be asymptomatic or cause pelvic pain, menstrual disorders, or infertility. Constitutional symptoms are rare. Extensive renal destruction may have occurred by the time GU TB is diagnosed.[34] [68]

Urinalysis is done initially. Results commonly show pyuria, haematuria, or proteinuria, although they may be normal. While the pyuria is classically described as 'sterile', superimposed bacterial infections may be present in patients with GU TB. Urine culture for TB may be positive in 80% of patients; three samples for culture improve sensitivity. NAATs of the urine can be helpful adjunctive tools for the rapid diagnosis of GU TB.[44] Definitive diagnosis of genital TB is based on tissue biopsy.[68]

Pericardial TB

Chest x-ray shows cardiomegaly (in 70% to 95% of cases) and pleural effusion (in about 50%). ECG is low voltage (in about 25%) and shows T-wave inversion (in about 90%). Echocardiography, CT, or MRI shows pericardial effusion and thickness across the pericardial space. Diagnosis of pericardial TB requires aspiration of pericardial fluid (by pericardiocentesis) or, usually, pericardial biopsy. Pericardial fluid is exudative with increased leukocytes, predominantly lymphocytes. Pericardial fluid should be sent for AFB smear (sensitivity 0% to 42%), culture (sensitivity 50% to 65%), and ADA. The sensitivity and specificity of an elevated ADA level in pericardial fluid (at a threshold of 40 U/L) are 88% and 83%, respectively. A positive AFB smear and elevated ADA level suggests TB pericarditis; positive culture confirms diagnosis of TB pericarditis.[41] Haemorrhagic effusion is often seen. Pericardial biopsy offers a higher diagnostic yield. Pericardial tissue should be sent for histological examination (sensitivity 73% to 100%) and culture.[41]

Disseminated TB

The diagnosis of disseminated TB concentrates on the organs most likely to be involved. The most commonly involved organs (in order) are lungs, liver, spleen, kidneys, and bone marrow. Patients with disseminated TB will typically have constitutional symptoms including fever (90%), anorexia (78%), and sweats (76%).

If disseminated TB is suspected, chest x-ray (if non-diagnostic, consider a chest CT), sputum for AFB smear and culture, blood culture for mycobacteria, and first-morning-void urine for AFB are obtained; lumbar puncture and biopsy of superficial lymph nodes are also done if applicable. Sputum smear will be positive in one-third of patients with culture positive in about 60%.

As delays in treatment are associated with increased mortality, a rapid diagnostic test (i.e., faster than culture results) is frequently needed. If sputum smears are negative and chest x-ray is abnormal, bronchoscopy with transbronchial biopsies are indicated. If results are non-diagnostic, bone marrow or liver biopsy is also done. Both have similar sensitivities, but bone marrow biopsy may be preferred because of its lower procedure risk. If thrombocytopenia or leukopenia are present, the sensitivity of bone marrow biopsy is increased.[16] [69] [70] [71]

Tests for latent TB infection (LTBI)

Investigations for LTBI (also sometimes referred to as TB infection) in a person exposed to *M tuberculosis* but without signs of active TB are based on the tuberculin skin test (TST) or interferon gamma release assays (IGRAs). The TST and IGRA measure the response of T cells to TB antigens. These tests have limited use in active TB infection and should not be used alone to exclude a diagnosis of active TB.

The TST uses intra-dermal injection of purified protein derivative to evaluate for delayed hypersensitivity response in order to diagnose prior exposure to TB. Different cut-offs in size of induration are used to define a positive test, depending on the patient's risk factors. Response to TST may be diminished in patients with factors such as HIV infection or poor nutrition.[72] IGRAs measure the release of interferon-gamma from T cells reacting to TB antigens.

TB antigen-based skin tests (TBSTs) are a new class of tests that have been developed to measure the cell-mediated immunological response to *M tuberculosis* specific antigens. The WHO recommends that TBSTs may be used to test for LTBI, reporting that the diagnostic accuracy of TBSTs is similar to that of IGRAs and greater than that of the TST.[73]

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include: exposure to TB; born in Asia, Latin America, or Africa; HIV infection; immunosuppressive medicines; haematological or head/neck malignancy; ESRD; apical fibrosis; and very young age.

enlarged lymph node (common)

- Painless and gradual enlargement of unilateral or bilateral cervical or supraclavicular nodes over a period of weeks; nodes are typically firm.
- Other presentations include painful or fluctuant nodes that may have drainage. Nodes may rarely be located in axillary or inguinal regions.[74] [75]
- Concomitant pulmonary TB may also be seen.

pleuritic chest pain (common)

- Present in up to 75% of patients with pleural TB.[75]

skeletal pain (common)

- Pain is common in skeletal TB and its location depends on the site of involvement.
- Pain may evolve over weeks to months.
- In Pott's disease, kyphosis may be present and focal tenderness may be present.
- If the hip or knee is involved, the patient may complain of pain with walking and local swelling may be present.
- If untreated, cold abscesses may form that are not tender or erythematous and are more common in HIV-positive patients. If these rupture, a draining sinus tract forms.[52]

urinary symptoms (common)

- Seen in GU TB. Includes dysuria, haematuria, and urinary frequency.

abdominal swelling (common)

- In peritoneal TB, swelling seen in over 90% of patients.
- The classic doughy abdomen is associated with the chronic fibroadhesive form and is rarely seen.

abdominal pain (common)

- Diffuse pain may be seen in 75% of patients with TB peritonitis.
- In patients with TB enteritis, pain is present in 80% to 90%, most commonly in the right lower quadrant (RLQ). A palpable mass may be present.

headache (uncommon)

- Seen in TB meningitis.

Other diagnostic factors

cough (uncommon)

- Active pulmonary TB is found in 15% to 20% of patients with EPTB. Higher rates of pulmonary involvement along with EPTB are seen in children, patients with disseminated disease, and those with pleural TB (up to 55%); patients with pleural TB often have a non-productive cough (70%).[76] [77] [78]

altered mental status (uncommon)

- Seen in TB meningitis.

neurological symptoms (uncommon)

- Cranial nerve involvement results from TB meningitis, as the process is located primarily at the base of the brain.
- Peripheral nerve symptoms may result from vertebral involvement with cord compression. May include numbness, weakness, or paralysis. Vertebrae in thoracolumbar region most commonly involved.

hepatomegaly (uncommon)

- May be seen in up to one-third of patients with disseminated TB. May also have splenomegaly.[16]

abnormal chest examination (uncommon)

- Chest examination may be abnormal if pulmonary TB also present or if pleural disease.
- Possible findings include a friction rub, crackles, decreased breath sounds, or dullness to percussion.

fever (uncommon)

- May be seen in one third of patients with EPTB, although fever may be more common in HIV-positive patients and peritoneal TB.
- Fever is very common in disseminated TB (up to 95% of patients). EPTB can be considered in patients with fever of unknown origin (FUO).[77] [78]

weight loss of more than 10% body weight (uncommon)

- Common in disseminated TB (60%) and in HIV-positive patients.[77] [78]

anorexia (uncommon)

- Common in disseminated TB and in HIV-positive patients.[77] [78]

malaise (uncommon)

- May be seen in 15% to 30% of patients.[77] [78]

night sweats (uncommon)

- If present, usually drenching. Common in disseminated TB.[78]

dyspnoea (uncommon)

- May be seen in disseminated TB.

asymptomatic (uncommon)

- Particularly patients with GU TB, who may be suspected on routine urinalysis.

erythema nodosum and erythema induratum (uncommon)

- Painful raised erythematous nodules over pretibial region or on the calves.

Risk factors

Strong

exposure to TB

- Exposure to an infectious case (i.e., pulmonary or laryngeal TB) is necessary but not sufficient for development of TB. Among household contacts, about one third will acquire latent TB infection and 1% to 2% will have active TB disease. Persons with recently acquired infection (e.g., new TB skin test conversion) have an increased risk of developing active TB, although this relationship holds less strong for EPTB compared with pulmonary TB.[20] [21]

born in Asia, Latin America, or Africa

- These are high-risk regions, particularly if immigration occurred within the prior 5 years. People from Southeast Asia and India are at higher risk for TB lymphadenitis.[22] [23]

HIV infection

- HIV infection increases the risk for both progression to primary disease and reactivation of latent disease. The risk for reactivation in an HIV-positive patient with latent TB infection is up to 10% per year, as opposed to a 10% lifetime risk in HIV-negative people. Extrapulmonary manifestations of TB are more common in HIV, and patients are at a higher risk for central nervous system TB.[3] [24] [25] [26] [27]

immunosuppressive medicines

- Especially systemic corticosteroids and tumour necrosis factor (TNF) antagonists. Risk with corticosteroids increases with increasing doses (odds ratio 7.7 for >5 mg per day of prednisolone) and varies with underlying condition. Patients receiving TNF antagonists are at 2-20 times higher risk for TB; more than 50% of TNF antagonist-related TB cases will be extrapulmonary.[28] The risk for TB with infliximab is greater than etanercept. Relative risk following organ transplantation is 20- to 74-fold higher.[29] [30]

haematological or head/neck malignancy

- Patients with haematological malignancy and head-and-neck cancer have a higher risk than people without malignancies.[31] The risk with other types of cancer has not been determined.

end stage renal disease

- Patients on haemodialysis are at increased risk of EPTB. Patients on peritoneal dialysis are at increased risk for peritoneal TB.[15]

apical fibrosis

- Patients whose chest x-ray shows fibrotic changes consistent with prior pulmonary TB are at higher risk for developing active disease again (estimated risk 0.3% per year).[32]

very young age

- The very young (<5 years) are at increased risk for progression to disease. EPTB is more common in younger patients. Disseminated TB is seen in higher rates in patients <14 years.[3] [34]

Weak

intravenous drug use

- Even without HIV infection.[33]

female sex

- Odds ratio for development of EPTB compared with pulmonary TB is 3.69.[20]

Asian, black, and Native American ethnicity

- EPTB is more likely in Asian, black, and Native American people than in white people.[34]

malnutrition

- Includes people with low body weight (<90% of ideal body weight), coeliac disease, and history of gastrectomy. Risk higher in patients who have undergone jejunoileal bypass.

alcoholism

- Hard to separate from other risk factors.

diabetes

- A relative risk of 2 to 4 if uncontrolled.

cirrhosis

- Increased risk for peritoneal TB.[15]

high-risk congregate settings

- Resident or employee of correctional facility, homeless shelter, or nursing home.

low socioeconomic status

- Multivariate models suggest at least half the risk attributed to ethnicity (black, Hispanic, Native Americans) may be due to low socioeconomic status.[35]

Investigations

1st test to order

Test	Result
chest x-ray • Evidence of unrecognised pulmonary TB or evidence of old healed TB (e.g., upper lobe fibrosis) may be present; such abnormalities should prompt sputum collection for smear, culture, and nucleic acid amplification testing. • Abnormalities may be seen in about one-quarter of adults with TB lymphadenitis. Over 80% of children with TB lymphadenitis may have an abnormal chest x-ray.[74] [79] • Patients with pleural TB will usually have a small to moderate unilateral pleural effusion; up to 20% of patients can have parenchymal abnormalities. • In skeletal TB and central nervous system TB, over 50% of patients may have chest x-ray findings compatible with prior TB. • Disseminated TB is known as miliary TB because of the chest x-ray appearance, which shows multiple 1-2 mm nodules throughout the lung fields (resembling millet seeds) that are small granulomas. While an abnormal chest x-ray may be seen in up to 85% of patients with disseminated TB, only 30% will have a miliary pattern.[69]	**abnormal typical for TB; abnormal atypical for TB; normal**
sputum smear • Except for children and patients with miliary disease, active pulmonary TB is seen in 15% to 20% of EPTB.[74] [77] [78] • Sputum is submitted in patients with EPTB to evaluate for infectiousness. Sputum may be spontaneously expectorated or induced.[41]	**positive for acid-fast bacilli**
sputum culture • Sputum culture is performed to evaluate for pulmonary TB (and potential infectiousness). May be spontaneous or induced. • Almost 5% of HIV-negative patients with EPTB and normal chest x-ray have sputum cultures that grow out *Mycobacterium tuberculosis* .[43] Sputum culture may be positive in 20% to 30% of cases of pleural TB without parenchymal involvement on chest x-ray; patients with parenchymal involvement may have a positive sputum culture 50% to 95% of the time.[16] [70] [71]	**positive; no growth; other mycobacteria**
FBC (full blood count) • Leukocytosis (without left shift) and anaemia each seen in 10%. Other abnormalities include elevated monocyte and eosinophil counts. Lymphopenia or pancytopenia may be seen in disseminated disease.	**normal or low haemoglobin and leukocytosis**
lymph node fine-needle aspiration • Overall sensitivity exceeds 80% when specimens are sent for cytological and microbiological evaluation. • May be higher in HIV-positive patients. • Considered as initial test if fluctuant.[80] [81] [82] • Fine-needle aspiration may be performed with a 21- or 23-gauge needle and sent for smear, culture, and cytology.	**culture positive**

Test	Result
pleural fluid analysis • Pleural fluid is obtained by thoracentesis. Usually clear/straw-coloured. • Analysis will display an exudative effusion that is lymphocyte-predominant (early in the course of effusion, neutrophils may predominate). • Mesothelial cells >5% are almost never present except for HIV-infected.[76] • Usual results include a pH 7.3 to 7.4, elevated LDH, glucose <60 mg/dL. • Acid-fast bacilli (AFB) smear has very low yield while culture may be positive in about 30%. Culture sensitivity improved by bedside inoculation of a radiometric mycobacteria diagnostic system (e.g., BACTEC brand). • Adenosine deaminase (ADA) levels are frequently elevated in pleural TB (sensitivity and specificity approximately 90%).[49] • Free interferon gamma levels are frequently elevated in pleural TB. The sensitivity and specificity of free interferon gamma measurements are ≥89% and ≥97%, respectively, for detecting TB in pleural fluid.[41]	**clear/straw-coloured exudate; AFB smear and culture positive; elevated ADA level; elevated free interferon gamma level**
ascitic fluid analysis • Ascitic fluid analysis is non-specific and reveals exudate and low serum-ascitic albumin gradient (SAAG). However, in cirrhotics with TB peritonitis, low-protein ascites is seen. • A lymphocytosis (>30% lymphocytes) may be seen about half the time. Especially in cirrhotics, a polymorphonuclear count >250/mL may be seen and thus mimics spontaneous bacterial peritonitis. Ascites will rarely be acid-fast bacilli (AFB) positive (0% to 6%) and estimated sensitivity of culture ranges from 10% to 92%.[15] [83] • Adenosine deaminase (ADA) levels are frequently elevated in peritoneal TB. The sensitivity and specificity of ADA are ≥79% and ≥83%, respectively, for detecting TB in peritoneal fluid.[41] • Free interferon gamma levels are frequently elevated in peritoneal TB. A meta-analysis of six studies estimated the sensitivity and specificity of elevated free interferon gamma levels in peritoneal fluid as 93% and 99%, respectively.[41]	**SAAG; cell count with differential; AFB smear and culture positive; elevated ADA levels; elevated free interferon gamma level**
bone films • Skeletal TB causes lytic destruction without sclerotic reactions. • In vertebral involvement, calcifications within paraspinous collections or anterior wedging of vertebral bodies. • If the hip or knee is involved, plain films may show subchondral erosions and joint space narrowing.	**normal; abnormal (including lytic areas, anterior wedging of vertebrae, joint space narrowing)**
cerebrospinal fluid analysis • Patients undergo lumbar puncture if central nervous system (CNS) TB is suspected or in disseminated disease to evaluate for CNS involvement. • Typical cerebrospinal fluid (CSF) profile in TB meningitis includes low cell count with a lymphocyte predominance (100-500 cells/microlitre), low glucose (40-50 mg/dL), and elevated protein (100-800 mg/dL). In the first 10 days of infection, polymorphonuclear cells may predominate.[24] • Detection of acid-fast bacilli (AFB) in CSF is improved by sending more fluid (e.g., at least 6 mL), and repeating the lumbar puncture.	**low cell count with a lymphocyte predominance (100-500 cells/microlitre), low glucose (40-50 mg/dL), and elevated protein (100-800 mg/dL); AFB smear and culture positive; elevated ADA levels**

Test	Result
There are reports of the sensitivity of AFBs being 58% to 87% in TB meningitis if three or more lumbar punctures are performed. AFB culture has 70% sensitivity.[24] [54] [68] • Following initiation of treatment, CSF changes will be evident for 10-14 days and AFB smear may remain positive for at least 1 week.[54] • Adenosine deaminase (ADA) levels are frequently elevated in CSF.[41]	
urinalysis • Urinalysis abnormal in more than 90% of patients with genitourinary TB including haematuria and pyuria. Pyuria without bacteriuria suggestive of TB. • Urine is sent for acid-fast bacilli (AFB) smear and culture. Nucleic acid amplification tests of the urine, where available, can be helpful adjunctive tools.[44] • Urinalysis may also be smear/culture positive in disseminated TB.	**white blood cell; red blood cell; AFB smear and culture positive; protein**
nucleic acid amplification test (NAAT) • Several rapid NAATs are available for the diagnosis of TB, and some are also able to detect resistance to some TB drugs. Although NAATs were originally designed and approved for respiratory specimens, they may also be requested on specimens from other sites where involvement of TB is suspected (e.g., cerebrospinal fluid, lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine).[42] In the US, use of NAATs for extrapulmonary specimens is not approved by the US Food and Drug Administration, and use would be off-label. • Xpert MTB/RIF and Xpert Ultra are rapid NAATs recommended by WHO as initial diagnostic tests in adults and children with signs and symptoms of EPTB.[42] They are also recommended by WHO for detection of rifampicin resistance.[42] Cochrane reviews of Xpert MTB/RIF and Xpert Ultra found that sensitivity of the tests in diagnosing EPTB varied across different site specimens, but the specificity was high.[44] [45] Line probe assays (LPAs) are strip-based tests that can detect TB and determine drug resistance profiles. LPAs are recommended by WHO only for detecting resistance to anti-TB drugs.[42]	**positive for *Mycobacterium tuberculosis* ; negative**

Other tests to consider

Test	Result
lymph node biopsy • Total excisional biopsy can be done because there is a high risk for ulceration or sinus tract formation with incomplete biopsy. • Drains are not to be left in place. • Tissues are sent for acid-fast bacilli (AFB) smear, culture, sensitivity, and histology. • Histology cannot differentiate between TB and non-tuberculous mycobacteria.	**granulomas; smear or culture AFB positive**
pleural biopsy • Percutaneous biopsy performed with Abrams or Cope needle. • Sensitivity improves with greater number of samples (6 or more). • Acid-fast bacilli (AFB) culture (60% sensitivity) and histology (80% sensitivity) are done with combined sensitivity 87%.[76] [84]	**granulomas; AFB smear or culture positive**
synovial biopsy • Synovial biopsy should be done to diagnose TB arthritis. • Biopsy may yield culture positive in 90% to 95%, and should be performed if the diagnosis of TB arthritis remains in question.[16]	**acid-fast bacilli smear or culture positive**
liver biopsy • May be useful in diagnosing disseminated TB. • May be culture positive in 40% and granulomas seen in 88% of biopsies.[71]	**granulomas; smear or culture acid-fast bacilli positive**
bone marrow biopsy • Done if less invasive means are non-diagnostic in disseminated TB. • May be culture positive in 54% of patients with disseminated TB. • Granulomas may be seen in 35% to 67%, which support a diagnosis of TB.[70] [71]	**granulomas; smear or culture acid-fast bacilli positive**
blood culture • Positive in disseminated disease in 58% of patients.[70]	**positive; negative**
peritoneal biopsy • Performed with laparotomy or laparoscopy. Good for rapid diagnosis of peritoneal TB as caseating granulomas may be seen in up to 100% and acid-fast bacilli (AFB) in 67%. Samples are submitted for culture. • Visual appearance may be highly suggestive of TB and may demonstrate yellow-white nodules, erythematous patches, or adhesions. • Blind peritoneal biopsies are not performed.[15]	**caseating granulomas; AFB positive**
gastric aspirate • Used in patients unable to produce sputum (e.g., young children). Based on overnight collection of swallowed respiratory secretions in the stomach. In early morning after 8-10 hours of fasting, 10-20 mL sterile water infused into stomach through nasogastric tube, and 50 mL aspirated. After neutralisation, the aspirate is sent for same studies as sputum.	**positive for acid-fast bacilli**

Test	Result
bronchoscopy • May be useful in patients who have evidence of pulmonary TB in addition to EPTB and where the diagnosis remains uncertain. • Also useful in patients with miliary TB for expedited diagnosis (smear positive or granulomas on transbronchial lung biopsies) in up to 80%.[85]	**positive for acid-fast bacilli**
thoracoscopy • Reserved for when pleural biopsy is non-diagnostic. • Thoracoscopy may show tubercles on the parietal pleura. • May be most sensitive tool for diagnosis of pleural TB and useful in assessing for malignant aetiology.[76]	**visual appearance; pathology results; acid-fast bacilli smear and culture results**
drug susceptibility testing • Performed on all initial isolates. • Susceptibility testing is to the first-line drugs (isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin) and results reported as fully sensitive, partial resistance, or full resistance depending on minimum inhibitory concentration. • If there is documented resistance to any first-line medicines, or if there is suspicion that patient has resistant strain, or if TB cultures remain positive after 3 months of treatment, susceptibility test against second-line drugs are performed. In the US, 10% to 15% of isolates are isoniazid-resistant and 1% are multidrug-resistant.	**drug sensitivities**
genotyping • Genotyping or DNA fingerprinting is useful in outbreak investigation and laboratory cross-contamination. There is evidence that some families of TB may have increased virulence. Most states offer genotyping of isolates.	**match with other strain**
HIV test • It is recommended that all patients with TB have an HIV test within 2 months of diagnosis. • HIV infection and its treatment alter the management of active TB. Treatment of HIV is crucial to the mortality and morbidity of HIV-infected TB patients.[48] •	**positive**
lateral flow urine lipoarabinomannan (LF-LAM) assay • Lateral flow tests that detect lipoarabinomannan (LAM) antigen in urine have emerged as potential point-of-care tests. One Cochrane review found the lateral flow urine lipoarabinomannan (LF-LAM) assay to have a sensitivity of 42% in diagnosing TB in HIV-positive individuals with TB symptoms, and 35% in HIV-positive individuals not assessed for TB symptoms.[46] WHO recommends that LF-LAM can be used to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children.[42] This approach is supported by another Cochrane review, which found reductions in mortality and an increase in treatment initiation with use of LF-LAM in inpatient and outpatient settings.[47] Culture would still be required for drug susceptibility testing (DST).	**positive**

Test	Result
empiric treatment • Many patients with EPTB will be started on empiric antituberculous therapy prior to a confirmation of positive TB culture, as it takes TB culture several weeks to be positive. • In a patient whose diagnosis has not been confirmed but TB suspicion remains high, an empiric initiation of TB treatment is reasonable after adequate sampling is completed (e.g., AFB smear is positive, TB PCR is positive, or pathology shows caseating granulomas but the TB culture is pending).[16] • At 2 months of treatment if there is a clinical or radiographic response and no other aetiology is present, the presumptive diagnosis of TB is made. If there is no response at 2 months of treatment, another diagnosis is sought.	**clinical response**
CT scan chest or abdomen • In peritoneal TB, CT may show ascites (wet type), bulky mesenteric thickening and lymphadenitis (dry type), or omental thickening. • In gastrointestinal TB, CT may show bowel wall thickening.	**abnormal**
abdominal ultrasound • Abdominal ultrasound may aid in diagnostic evaluation but should not be used alone for TB diagnosis.[67]	**abnormal**
colonoscopy • Used to diagnose TB enteritis with biopsy. • Common sites of involvement are the ileocecal and anorectal areas. • Findings on colonoscopy include ulcers, strictures, pseudopolyps, and fistulas.	**visual appearance; biopsy results**
pericardial fluid analysis • Pericardial fluid is obtained by pericardiocentesis. Pericardial fluid should be sent for acid-fast bacilli (AFB) smear (sensitivity 0% to 42%), culture (sensitivity 50% to 65%), and adenosine deaminase (ADA). Using a threshold to define an elevated ADA level of 40 U/L, the sensitivity and specificity of an elevated ADA level in pericardial fluid are 88% and 83%, respectively.[41]	**positive AFB smear and elevated ADA level suggests TB pericarditis; positive culture confirms diagnosis of TB pericarditis**
pericardial biopsy • Pericardial tissue should be sent for histological examination (sensitivity 73% to 100%) and culture.[41]	**presence of granuloma and/or positive acid-fast bacilli suggests TB pericarditis; positive culture confirms diagnosis of TB pericarditis**
tuberculin skin testing • Used for investigation for latent TB infection. A negative tuberculin skin testing (TST) does not rule out active TB. • The TST uses intra-dermal injection of purified protein derivative to evaluate for delayed hypersensitivity response in order to diagnose prior exposure to TB. Different cut-offs in size of induration are used to define a positive test, depending on the patient's risk factors. • Response to TST may be diminished in patients with factors such as HIV infection or poor nutrition.[72]	**millimetres of induration**

Test	Result
interferon-gamma release assays • Used for investigation for latent TB infection. A negative Interferon-gamma release assay (IGRA) does not rule out active TB. • IGRAs measure the release of interferon-gamma from T cells reacting to TB antigens.	**positive, negative, indeterminate**
TB antigen-based skin tests (TBST) • TBSTs are a new class of tests that have been developed to measure the cell-mediated immunological response to *M tuberculosis* specific antigens. The World Health Organization recommends that TBSTs may be used to test for latent TB infection, reporting that the diagnostic accuracy of TBSTs is similar to that of IGRAs and greater than that of the TST.[73]	**positive**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Lymphoma	• There may be no difference in signs and symptoms. • Constitutional symptoms and widespread lymphadenitis are more common in lymphoma. • TB lymphadenitis is most commonly found in the cervical or supraclavicular regions.	• Chest x-ray may show abnormalities consistent with prior pulmonary TB in about 25% of patients with TB lymphadenitis. • Fine needle aspiration will usually be able to diagnose TB lymphadenitis; if this is non-diagnostic, excisional biopsy must be performed.
Non-tuberculous mycobacteria lymphadenitis	• There may be no difference in signs and symptoms. • TB lymphadenitis predominates in patients older than 12 years and non-tuberculous mycobacteria (NTM) is more common in children younger than 12 years of age. • TB lymphadenitis predominates in women of Asian background from TB-endemic areas.[1]	• Chest x-ray may show abnormalities consistent with prior pulmonary TB in about 25% of patients with TB lymphadenitis. • In an adult with acid-fast bacilli or caseating granulomas on fine needle aspiration, empiric therapy for TB can be started. This is also true if a child has epidemiological risk factors for TB, pending results of culture. • In a child with presumed NTM, the diagnosis must be proved with culture results.[16] [86]
Sarcoidosis	• Features of sarcoidosis, such as intrathoracic lymphadenopathy and arthralgias, may be present. A careful review of epidemiological risk factors for TB can be performed.	• Tuberculin skin testing will usually be negative with sarcoidosis and chest x-ray may have findings more consistent with TB or sarcoidosis. • Granulomas are non-caseating in sarcoidosis, although it is not diagnostic. • Acid-fast bacilli (AFB) may be seen on fine-needle aspiration in TB lymphadenitis. Culture for AFB is negative in sarcoidosis.
Malignant pleural effusion	• There may be no difference in signs and symptoms.	• CT scan of the chest may show findings more consistent with malignancy (particularly if primary bronchogenic) or with pulmonary TB. A search

Condition	Differentiating signs / symptoms	Differentiating tests
		for a primary in metastatic disease may also diagnose the aetiology (e.g., in an effusion due to metastatic breast or ovarian cancer). Cytological evaluation of the pleural effusion may diagnose a malignant effusion. • Pleural biopsy may reveal granulomas, acid-fast bacilli, or malignant pathology. • Video-assisted thoracic surgery differentiates between an effusion-caused TB and those caused by malignancy.
Cryptococcal meningitis, other fungal central nervous system infections, neurosyphilis	• The differential diagnosis of TB meningitis includes disease processes that cause a subacute to chronic meningitis and a lymphocyte-predominant pleocytosis. • Cranial nerve abnormalities are more common in TB.	• Cerebrospinal fluid (CSF) analysis is the key to making the diagnosis. • Acid-fast bacilli and fungal stain and cultures are usually diagnostic. • Nucleic acid amplification test of CSF may also help in diagnosis. • An elevated adenosine deaminase may support the diagnosis of TB.[87] • Tuberculin skin tests has poor sensitivity with central nervous system TB (approximately 50%).[53]
Inflammatory bowel disease	• There may be no difference in signs and symptoms. • The presence of epidemiological risk factors for TB, a positive tuberculin skin test, or chest x-ray findings consistent with TB all support TB as the aetiology. • The presence of ascites is more consistent with a diagnosis of TB enteritis.	• Colonoscopy with biopsy is the best method for diagnosis, with a sensitivity of up to 80%. • The presence of mesenteric lymphadenopathy with central necrosis is suggestive of TB.[83]
Peritoneal carcinomatosis	• Epidemiological risk factors may be present in patients with TB.	• Cytological analysis of ascites identifies patients with malignant ascites. • CT scan may identify a primary neoplasm.

Condition	Differentiating signs / symptoms	Differentiating tests
Spontaneous bacterial peritonitis	• In patients with a history of cirrhosis and epidemiological risk factors for TB, a high index of suspicion must be maintained for TB peritonitis. • Symptoms are more chronic in those with TB enteritis.	• Patients with TB peritonitis usually have ascites with a low serum-ascitic albumin gradient and lymphocytes >30%. However, cirrhotics may have peritoneal TB with a low protein and polymorphonuclear leukocytes >250/mL, mimicking spontaneous bacterial peritonitis. • In TB peritonitis, CT scan may reveal abdominal lymphadenopathy. • Differentiating tests include nucleic-acid amplification test, adenosine deaminase, acid-fast bacilli culture, and peritoneal biopsy.
Fever of unknown origin	• There may be no difference in signs and symptoms. • The presence of epidemiological risk factors for TB or co-existence of pulmonary TB may help diagnosis.	• EPTB, especially disseminated disease, may be responsible for fever of unknown origin. Tuberculin skin tests will usually be negative. Diagnosis may require transbronchial, liver, or bone marrow biopsies.

Screening

It is recommended that asymptomatic adults at increased risk of infection are screened.[88] These include persons born in or former residents of countries with high TB prevalence, current or former residents of high-risk congregate settings, people living with HIV, recent immigrants from moderate- and high-incidence countries, patients starting immunosuppressive medications, intravenous drug users, healthcare workers who serve high-risk populations, and contacts of infectious TB cases. Tuberculin skin testing (TST) and interferon-gamma release assays (IGRAs) are the standard methods for identifying people with latent TB infection (LTBI).

Targeted screening and treatment of LTBI is only one aspect of controlling TB in a community; it is recommended that priority is given to early detection and completion of treatment of active TB cases and investigating close contacts of infectious TB cases.

Screening persons other than those in high-risk populations is not recommended. It places a burden on resources and can give rise to false-positive results (both TST and IGRA).

The World Health Organization (WHO) guidelines on systematic screening for TB outline key populations who should be prioritised for TB screening.[89] Systematic screening is strongly recommended in the following populations:

- People living with HIV
- Household contacts and other close contacts of individuals with TB
- People in prisons and penitentiary institutions

- Current and former workers in workplaces with silica exposure.

Systematic screening is also conditionally recommended in the following populations:

- Areas with an estimated TB prevalence of 0.5% or higher
- Sub-populations with structural risk factors for TB, including urban poor communities, homeless communities, communities in remote or isolated areas, indigenous populations, migrants, refugees, internally displaced persons and other vulnerable or marginalised groups with limited access to health care
- People with a risk factor for TB who are either seeking health care or who are already in care and TB prevalence is 0.1% or higher
- People with an untreated fibrotic lesion seen on chest x-ray.

Screening tools recommended by WHO include symptom screen, chest x-ray, molecular rapid diagnostic tests, and C-reactive protein. Computer-aided detection is also recommended in some cases as an alternative to human interpretation of digital chest x-ray for screening and triage for TB.[89]

Approach

The goals of TB treatment are to cure the patient clinically, minimise the chance of relapse, and prevent further transmission of TB to others.

The treating physician acts in a public health role and is responsible for ensuring that the patient successfully completes treatment. Therefore, many physicians share that responsibility with a local public health department.

Empirical treatment may be initiated before confirmatory tests and drug-susceptibility results are available when TB is strongly suspected and after appropriate specimens are collected.

Latent TB infection

People who have had significant exposure in the previous 2 years should be evaluated for active TB disease and latent TB infection (LTBI) (also sometimes referred to as TB infection). A repeat test for LTBI (TB skin test or interferon-gamma release assay) is recommended 8-10 weeks after the last exposure, if the initial evaluation was performed prior to this and the initial test result was negative. The decision whether to treat depends on the duration, proximity, and environment of exposure, as well as the immune status of the exposed contacts.[41]

For patients with LTBI that is presumed to be susceptible to isoniazid or rifampicin, WHO guidelines recommend the following regimens regardless of HIV status: 6 or 9 months of daily isoniazid (all ages), 3 months of weekly rifapentine plus isoniazid (age 2 years and over), or 3 months of daily isoniazid plus rifampicin (all ages).[38] [90] One month of daily rifapentine plus isoniazid (age 13 years and over) or 4 months of daily rifampicin (all ages) are alternative regimens.[38] [90] Isoniazid and rifampicin are options for use in pregnant women with or without HIV who are eligible for preventive treatment.[90] Rifamycins should only be used if there are no significant interactions with other medications (e.g., antiretroviral therapy [ART]).

Peripheral neuropathy is a common adverse effect of isoniazid due to pyridoxine antagonism. Pyridoxine supplementation should, therefore, be considered for prevention of peripheral neuropathy in patients with latent infection taking isoniazid, particularly in those in whom neuropathy is common (e.g., diabetes, uraemia, alcoholism, malnutrition, HIV infection), pregnant women, or patients with seizure disorders.[33]

For patients with LTBI presumed to be due to contact with an infectious patient with drug-resistant TB, expert consultation should be sought.[91] [90] [92] [93] For patients exposed to isoniazid-resistant TB, 4 months of daily rifampicin may be an option.[90] [93] US guidelines recommend that patients with multidrug-resistant (MDR) TB are treated with 6-12 months of a fluoroquinolone (i.e., levofloxacin or moxifloxacin) alone or in combination with a second agent based on susceptibility testing of the source isolate.[91] WHO guidelines recommend that, in selected high-risk household contacts of patients with MDR TB, preventive treatment may be considered based on individualised risk assessment and a sound clinical justification.[90]

Active TB: intensive phase therapy (drug resistance not suspected)

Microbiological confirmation of EPTB can take several weeks and this delay in treatment initiation may increase mortality in some forms (central nervous system [CNS], disseminated, peritoneal). Therefore, antituberculous therapy is initiated based on clinical suspicion after optimal diagnostic samplings.

Initial intensive-phase treatment involves the first-line drugs of isoniazid, rifampicin, pyrazinamide, and ethambutol, for 2 months with drug-susceptibility testing for those agents.[48] [94]

WHO guidelines for the treatment of drug-susceptible EPTB advise that regimens are given for a total duration of 6 months, except TB of the central nervous system, bone, or joint, for which a longer duration of therapy is recommended.[94]

WHO guidelines recommend that children aged between 3 months and 16 years with non-severe TB (defined as peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern) may receive a 4-month version of this regimen. The intensive phase of this regimen includes daily administration of isoniazid, rifampicin, and pyrazinamide, with or without ethambutol, for 2 months.[38] [94] Ethambutol should be included in areas of high prevalence of HIV or isoniazid resistance.[38] [94] Children and adolescents who do not meet the criteria for non-severe TB should receive the standard 6-month treatment regimen (including ethambutol) or extended treatment regimens for severe forms of extrapulmonary TB.[38] [94]

An alternative option for children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis is an intensive treatment regimen composed of 6 months of isoniazid, rifampicin, pyrazinamide, and ethionamide. The WHO recommends that this shorter intensive regimen is suitable for children and adolescents who have a low likelihood of drug resistant TB. Due to a lack of data, this shorter intensive regimen should not be used in children and adolescents living with HIV.[38]

Patients can receive treatment through direct observation of therapy (DOT) whereby the patient is provided with the tablets and is observed swallowing them. This is often done in conjunction with a local public health department. Video DOT (vDOT) is the use of video calls to view patients ingesting their medications remotely. In the US, the Centers for Disease Control and Prevention recommends the use of vDOT as equivalent to in-person DOT for patients undergoing tuberculosis treatment.[95] Note that in World Health Organization (WHO) guidelines, the term 'directly-observed therapy (DOT)' has been replaced with 'treatment support', which refers to any person (not necessarily a healthcare worker) observing the patient taking medication in real time, including via video.[96]

The decision on the use of DOT as opposed to daily self-administered therapy (SAT) depends on the resources available to local public health, collaboration with community partners, and prioritisation of cases. Centers for Disease Control and Prevention (CDC) guidelines suggest that the high priority should be given to situations such as treatment failure, drug resistance, relapse, HIV co-infection, current or prior substance abuse, psychiatric illnesses, memory impairment, and cases in children/adolescents.

Active TB: continuation phase therapy (drug resistance not suspected)

After 2 months of intensive phase treatment in patients with drug-susceptible EPTB, pyrazinamide and ethambutol are discontinued, and isoniazid and rifampicin are given for the continuation phase. Duration of the continuation phase depends on the site of infection and severity of disease. Generally, for EPTB that does not involve CNS or bones and joints, continuation phase therapy is given for 4 months (i.e., 6 months of total treatment).

Total therapy for 9 months is considered for patients with extensive skeletal TB, especially when large joints are involved with slow clinical response. Patients with CNS TB receive 7-10 months of continuation phase therapy (9-12 months total).[48] [94]

Children aged 3 months to 16 years with non-severe TB (defined as peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern) should receive 2 months of continuation phase therapy (4 months total). Those with severe TB, other than TB meningitis or osteoarticular TB, and also children aged less than 3 months, should receive the standard 6-month treatment regimen.[38] [94] Children with osteoarticular TB or TB meningitis should receive 10 months of continuation phase therapy (12 months total).[38]

Interruptions in treatment of active TB

Interruptions in therapy are common in the treatment of TB. The decision is then whether to restart a complete course of treatment or simply to continue. As a general guide, the earlier in the course of treatment and the greater the length of the lapse, the more likely the need to return to the beginning of the intensive phase of treatment.[48]

Isoniazid-resistant TB

Drug-resistance may be suspected on the basis of historical or epidemiological information. Isoniazid-resistant TB is defined as resistance to isoniazid and susceptibility to rifampicin that has been confirmed in vitro.

In patients with confirmed rifampicin-susceptible and isoniazid-resistant pulmonary TB, US and World Health Organization (WHO) guidelines recommend treatment with a 6-month regimen of rifampicin, ethambutol, pyrazinamide, and a later-generation fluoroquinolone.[91] [97] The WHO guidelines note that this regimen is likely to be effective in patients with extrapulmonary TB, but that no data are available for patients with exclusive extrapulmonary isoniazid-resistant TB.[97]

Consultation with an appropriate specialist is recommended to determine the most appropriate antituberculous therapy and supportive care.

Multidrug-resistant TB

Multidrug-resistant (MDR) TB is defined as resistance to isoniazid and rifampicin, with or without resistance to other first-line drugs. Extensively drug-resistant (XDR) TB is defined as resistance to at least isoniazid and rifampicin, as well as any fluoroquinolone and either bedaquiline or linezolid (or both).[98] Pre-XDR-TB is resistance to isoniazid, rifampicin, and any fluoroquinolone.

The treatment regimen should be based on the results of drug susceptibility testing. Specific regimens should be selected by a specialist in the treatment of MDR TB.[97] The total number of TB medicines to include in the regimen needs to balance expected benefit with risk of adverse effects and non-adherence when the pill burden is high. Treatment of MDR-TB and rifampicin-resistant (RR) TB/RR-TB meningitis should be guided by knowledge of TB medicines that cross the blood-brain barrier.[97]

Patients with rifampicin-resistant (RR) TB are also eligible for treatment with MDR TB regimens.[97] Short (6 or 9 months) and longer (18 months or more) regimens are included in the WHO guidelines for the treatment of people with drug-resistant TB.[97] The WHO short-course regimens are a major step forward for low- and middle-income settings where access to second-line drug susceptibility testing may not be available. In places with the ability to check second-line drug sensitivities, creation of an appropriate regimen would be based on drug susceptibilities. The short-course regimens may expose patients to drugs that are not indicated.

The 6-month all-oral regimen is composed of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM).[97] [99] [100] The WHO recommends the use of this 6-month regimen for adults and adolescents aged 14 and over with confirmed pulmonary TB and all forms of extrapulmonary TB (except for TB involving the CNS, osteoarticular and disseminated [miliary] TB), regardless of HIV status, who have less than 1 month exposure to bedaquiline, linezolid, pretomanid, or delamanid. The WHO suggests that this regimen is used where appropriate rather than the 9-month or longer MDR/RR-TB regimens.[97] If the patient has documented resistance to fluoroquinolones, the WHO advises that the regimen should continue without moxifloxacin (BPaL); although initiation of BPaLM should not be delayed while waiting for results of drug susceptibility testing.

The 9-month all-oral regimen is recommended by the WHO for patients who have extrapulmonary TB that is not severe, where severe disease is defined as miliary TB or TB meningitis, or in children aged less than 15 years defined as extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression).[97] It is recommended over the longer MDR/RR-TB regimens (18 months or more) when resistance to fluoroquinolones has been excluded and can be used when patients are not eligible for the 6-month regimen. In the 9-month regimen, bedaquiline is used for 6 months in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide, and clofazimine for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months), and this is followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol, and pyrazinamide.[97] Two months of linezolid may be used in place of the 4 months of ethionamide. The WHO recommends the use of the 9-month regimen for adults and children without extensive pulmonary TB disease, regardless of HIV status, and who have less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid, and clofazimine.[97]

Longer MDR TB regimens last 18 months or more and may be standardised or individualised; regimens are designed to include a minimum number of medicines considered to be effective based on patient history or drug-resistance patterns.[97] This longer -term regimen is recommended for all patients with extrapulmonary TB who do not fulfil the criteria for the shorter-term regimens; however, adjustments may be required, depending on the specific location of the disease.[97] The WHO guidelines recommend that patients with RR TB or MDR TB on longer regimens receive treatment with at least four TB agents likely to be effective, including all three Group A agents and at least one Group B agent, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents should be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.[97]

Group A (include all three medicines):

- Levofloxacin or moxifloxacin
- Bedaquiline
- Linezolid

Group B (add one or both medicines):

- Clofazimine
- Cycloserine or terizidone

Group C (add to complete the regimen and when medicines from Groups A and B cannot be used):

- Ethambutol
- Delamanid
- Pyrazinamide

- Imipenem/cilastatin or meropenem
- Amikacin or streptomycin
- Ethionamide or prothionamide
- Aminosalicylic acid

Adjunctive corticosteroids

Adjunctive corticosteroid therapy has been shown to attenuate the inflammatory response in TB meningitis and result in improved survival.[101] [102]

The American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC)/Infectious Diseases Society of America (IDSA) and WHO guidelines recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks for patients with tuberculous meningitis.[48] [94] US guidelines for the prevention and treatment of opportunistic infections in those with HIV recommend adjunctive treatment with dexamethasone for adults with TB involving the CNS, though notes that studies involving those with HIV are limited.[92] One subsequent randomised controlled trial in adults with HIV infection and TB meningitis found that adjunctive dexamethasone did not reduce mortality over 12 months (death from any cause) compared with placebo.[103] US guidelines for the prevention and treatment of opportunistic infections in children with HIV recommend considering adjunctive corticosteroid treatment for those with TB meningitis.[93] The British Infection Society recommends that, in children, the initial dose of dexamethasone should be given for 4 weeks, then tapered over 4-8 weeks.[53]

One Cochrane review assessing treatments for tuberculous pericarditis found moderate certainty evidence that corticosteroids probably reduce death from pericarditis in people without HIV infection.[104] Low certainty evidence found that in people living with HIV infection (but not on ART) use of corticosteroids had little or no effect on deaths. [Evidence C] The ATS/CDC/IDSA guideline suggests that adjunctive corticosteroid therapy should not be routinely used in patients with TB pericarditis but may be appropriate for selected patients who are at the highest risk for inflammatory complications, including those with large pericardial effusions, high levels of inflammatory markers, or signs of constriction.[48] Guidelines for the prevention and treatment of opportunistic infections in those with HIV state that adjunctive corticosteroid therapy is not recommended in the treatment of adults and adolescents with TB pericarditis; however, it may be considered in children.[93] The WHO recommends that adjunctive corticosteroid therapy may be used in tuberculous pericarditis.[94]

Situations in which the use of pyrazinamide is not recommended

Pyrazinamide is not recommended for patients experiencing acute gout as it further elevates uric acid levels. Its use in pregnant women is controversial due to lack of detailed teratogenicity data, but it should be considered in patients with EPTB, particularly when HIV co-infection is present. Older patients (age >75 years) may not tolerate pyrazinamide and providers may consider leaving it out of treatment regimens.[48] Those patients who do not receive pyrazinamide during the intensive phase should receive 7 months of continuation phase therapy (9 months total).

Liver injury

Several TB medicines (e.g., isoniazid, rifampicin, and pyrazinamide) are metabolised by the liver and may potentially cause or exacerbate hepatic injury. Mild hepatitis may require only closer monitoring without changes in the standard regimen. However, severe hepatitis while on TB treatment may make it

necessary to hold medicines and use an alternate liver-sparing regimen. A specialist should be consulted for guidance on choice of regimen and appropriate doses.

If drug-induced liver injury (DILI) occurs, potentially hepatotoxic drugs should be stopped and alcohol should be avoided (alcohol should ideally be avoided in all patients who start TB therapy [either latent or active]).

An asymptomatic, mild increase in aspartate aminotransferase (AST) occurs in 20% of patients; if this is <5 times upper limit of normal (ULN) with no symptoms, or <3 times ULN with symptoms, TB medicines can be continued but liver function tests (LFTs) and symptoms are monitored closely.

While LFTs are normalising and symptoms are improving, at least 3 drugs without hepatotoxic effects may be given, especially if the burden of TB disease is more than minimal. When AST becomes <2 times ULN, first-line drugs are serially reintroduced one by one, waiting 4-7 days before adding next drug. Before introducing each new drug LFTs are checked. If an increase in AST occurs, the most recently introduced drug is likely responsible for hepatitis.[48] Expert opinion should be sought.

Renal insufficiency

Renal insufficiency complicates treatment as some medicines and their metabolites (e.g., ethambutol, streptomycin, pyrazinamide, aminoglycosides, capreomycin, levofloxacin) are cleared by the kidneys. Dose adjustments may be required in patients with renal insufficiency or end-stage renal disease.[48] A specialist should be consulted for guidance on choice of regimen and appropriate doses.

As there is increased risk of retrobulbar neuritis resulting from ethambutol toxicity in patients with renal failure, particular attention to testing of visual acuity/colour discrimination and counselling of patients is also required in this population.

HIV infection

Although there are many TB patients co-infected with HIV globally, expert advice should be sought if the clinician is not familiar with management of TB patients co-infected with HIV.

Patients with TB and HIV infection should receive antiretroviral therapy during antituberculosis treatment. WHO guidelines recommend that ART is started as soon as possible within 2 weeks of starting TB treatment, regardless of CD4 cell count, unless the patient has TB meningitis (when ART is delayed for 4-8 weeks).[94]

TB medications should be administered daily. Intermittent twice-weekly administration is not recommended for HIV-infected patients.[105]

A rifamycin (rifampicin or rifabutin) should be included in TB regimens for patients receiving antiretroviral therapy; however, consideration should be given to drug interactions when building the regimen.[92] Dosage should be adjusted as necessary.

Safety of fluoroquinolones

Systemic fluoroquinolone antibiotics are a key part of some TB treatment regimens, but it is important to note that they may cause serious, disabling, and potentially long-lasting or irreversible adverse events. This includes, but is not limited to: tendinopathy/tendon rupture; peripheral neuropathy; arthropathy/arthralgia; aortic aneurysm and dissection; heart valve regurgitation; dysglycaemia; and central nervous system effects including seizures, depression, psychosis, and suicidal thoughts and behaviour.[106]

- Prescribing restrictions apply to the use of fluoroquinolones, and these restrictions may vary between countries. In general, fluoroquinolones should be restricted for use in serious, life-threatening bacterial infections only. Some regulatory agencies may also recommend that they must only be used in situations where other antibiotics, that are commonly recommended for the infection, are inappropriate (e.g., resistance, contraindications, treatment failure, unavailability).
- Consult your local guidelines and drug formulary for more information on suitability, contraindications, and precautions.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial		(summary)
latent TB infection: non-pregnant		
	1st	**treatment for latent TB infection**
latent TB infection: pregnant		
	1st	**referral to specialist**

Acute (summary)

active TB: non-pregnant, HIV-negative		
drug resistance not suspected	**1st**	**intensive phase therapy**
	plus	**continuation phase therapy**
	adjunct	**corticosteroid**
isoniazid resistance	**1st**	**antituberculous therapy**
multidrug resistance	**1st**	**antituberculous therapy**
active TB: non-pregnant, HIV-positive		
drug resistance not suspected	**1st**	**intensive phase therapy**
	plus	**continuation phase therapy**
	adjunct	**corticosteroid**
isoniazid resistance	**1st**	**antituberculous therapy**
multidrug resistance	**1st**	**antituberculous therapy**
active TB: pregnant		
	1st	**referral to specialist**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Initial

latent TB infection: non-pregnant

1st **treatment for latent TB infection**

Primary options

» isoniazid: children <10 years of age: 7-15 mg/kg orally once daily for 6 or 9 months, maximum 300 mg/dose; children ≥10 years of age and adults: 5 mg/kg orally once daily for 6 or 9 months, maximum 300 mg/dose
Pyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.

OR

» isoniazid: children 2-14 years of age and body weight 10-15 kg: 300 mg orally once weekly for 3 months; children 2-14 years of age and body weight 16-23 kg: 500 mg orally once weekly for 3 months; children 2-14 years of age and body weight 24-30 kg: 600 mg orally once weekly for 3 months; children 2-14 years of age and body weight >30 kg: 700 mg orally once weekly for 3 months; children >14 years of age and adults: 900 mg orally once weekly for 3 months
Pyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.

-and-
» rifapentine: children 2-14 years of age and body weight 10-15 kg: 300 mg orally once weekly for 3 months; children 2-14 years of age and body weight 16-23 kg: 450 mg orally once weekly for 3 months; children 2-14 years of age and body weight 24-30 kg: 600 mg orally once weekly for 3 months; children 2-14 years of age and body weight >30 kg: 750 mg orally once weekly for 3 months; children >14 years of age and adults: 900 mg orally once weekly for 3 months

OR

» isoniazid: children <10 years of age: 7-15 mg/kg orally once daily for 3 months, maximum 300 mg/dose; children ≥10 years of age and adults: 5 mg/kg orally once daily for 3 months, maximum 300 mg/dose

Initial

Pyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.

-and-

» rifampicin: children <10 years of age: 10-20 mg/kg orally once daily for 3 months, maximum 600 mg/dose; children ≥10 years of age and adults:10 mg/kg orally once daily for 3 months, maximum 600 mg/dose

Secondary options

» isoniazid: children ≥13 years of age and adults: 300 mg orally once daily for 1 month
Pyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.

-and-

» rifapentine: children ≥13 years of age and adults: 600 mg orally once daily for 1 month

OR

» rifampicin: children <10 years of age: 10-20 mg/kg orally once daily for 4 months, maximum 600 mg/dose; children ≥10 years of age and adults: 10 mg/kg orally once daily for 4 months, maximum 600 mg/dose

» People who have had significant exposure to an active infectious TB case in the previous 1-2 years should be evaluated for active TB disease and latent TB infection (LTBI). A repeat test for LTBI (TB skin test or interferon-gamma release assay) is recommended 8-10 weeks after the last exposure, if the initial evaluation was performed prior to this and the initial test result was negative.

» The decision whether to treat depends on the duration, proximity, and environment of exposure, as well as the immune status of the exposed contacts.[41]

» For patients with LTBI that is presumed to be susceptible to isoniazid or rifampicin, WHO guidelines recommend the following regimens regardless of HIV status: 6 or 9 months of daily isoniazid (all ages), 3 months of weekly rifapentine plus isoniazid (age 2 years and over), or 3 months of daily isoniazid plus rifampicin (all ages).[38] [90] One month of daily rifapentine plus isoniazid (age 13 years and over) or 4 months of daily rifampicin (all ages) are alternative regimens.[38] [90] Rifamycins should only be used if there are no significant interactions with other medications (e.g.,

Initial

antiretroviral therapy). World Health Organization (WHO) guidelines recommend that 3 months of daily isoniazid plus rifampicin is the preferred option for children without HIV and 6 months of daily isoniazid is the preferred regimen for children living with HIV.[38]

» Peripheral neuropathy is a common adverse effect of isoniazid due to pyridoxine antagonism. Pyridoxine supplementation should therefore be considered for the prevention of peripheral neuropathy in patients with latent infection taking isoniazid, particularly in those in whom neuropathy is common (e.g., diabetes, uraemia, alcoholism, malnutrition, HIV infection), pregnant women, or patients with seizure disorders.[33] [90] [92]

» Ideally, all medications within a given regimen should be administered at the same time. If the patient cannot tolerate the pill burden, different medications can be administered separately, but the dose of each individual medication should not be split up. Consult guidelines for dosing information.[48]

» Rifapentine may not be available in some countries.

» Patients with complex comorbidity, or for whom treatment is contraindicated, should be managed after expert consultation.

» For patients with LTBI presumed to be due to contact with an infectious patient with drug-resistant TB, expert consultation should be sought.[91] [90] [92] [93] For patients exposed to isoniazid-resistant TB, 4 months of daily rifampicin may be an option.[90] [93] US guidelines recommend that patients with multidrug-resistant (MDR) TB are treated with 6-12 months of a fluoroquinolone (i.e., levofloxacin or moxifloxacin) alone or in combination with a second agent based on susceptibility testing of the source isolate.[91] Specific regimens are not detailed here. WHO guidelines recommend that in selected high-risk household contacts of patients with MDR TB, preventive treatment may be considered based on individualised risk assessment and a sound clinical justification.[90]

latent TB infection: pregnant

1st **referral to specialist**

» Pregnancy has minimal influence on progression of latent TB infection to active

Initial

disease, and pregnant women should be tested based on the presence of risk factors. If there is a high risk for progression to TB (e.g., recent TB infection, HIV infected), immediate treatment is indicated. Otherwise treatment may be deferred until at least 3 months postnatal because of increased incidence of serious drug-induced hepatitis during peripartum period.

» Specialist consultation is recommended in pregnancy.

Acute

active TB: non-pregnant, HIV-negative

drug resistance not suspected

1st

intensive phase therapy

Primary options

4- or 6-month regimen

» isoniazid: children: 7-15 mg/kg orally once daily, maximum 300 mg/dose; adults: 5 mg/kg orally once daily, maximum 300 mg/dosePyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.
-and-
» rifampicin: children: 10-20 mg/kg orally once daily, maximum 600 mg/dose; adults: 10 mg/kg orally once daily, maximum 600 mg/dose
-and-
» pyrazinamide: children: 30-40 mg/kg orally once daily; adults: consult specialist for guidance on dose (dose is based on lean body weight and available tablet formulation)
-and-
» ethambutol: children: 15-25 mg/kg orally once daily; adults: consult specialist for guidance on dose (dose is based on lean body weight and available tablet formulation)The 4-month regimen may be given with or without ethambutol.
-and-

OR

6-month TB meningitis regimen

» isoniazid: children and adolescents: 20 mg/kg orally once daily, maximum 400 mg/dose Pyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.

-and-
» rifampicin: children and adolescents: 20 mg/kg orally once daily, maximum 600 mg/dose
-and-
» pyrazinamide: children and adolescents: 40 mg/kg orally once daily, maximum 2000 mg/dose
-and-
» ethionamide: children and adolescents: 20 mg/kg orally once daily, maximum 750 mg/dose

» Antituberculous therapy is initiated based on clinical suspicion after optimal diagnostic samplings.

Acute

» While awaiting that information, an empiric regimen may be used. The final regimen will be based on the results of drug-susceptibility testing.

» All medications should be administered together.

» Initial intensive-phase treatment involves the first-line drugs of isoniazid, rifampicin, pyrazinamide, and ethambutol, for 2 months with drug-susceptibility testing for those agents.[48] [94] After 2 months, the continuation phase is started.

» WHO guidelines recommend that children aged between 3 months and 16 years with non-severe TB (defined as peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern) may receive a 4-month version of this regimen. The intensive phase of this regimen includes daily administration of isoniazid, rifampicin, and pyrazinamide, with or without ethambutol, for 2 months.[38] [94] Ethambutol should be included in areas of high prevalence of HIV or isoniazid resistance.[38] [94] Children and adolescents who do not meet the criteria for non-severe TB should receive the standard 6-month treatment regimen (including ethambutol) or extended treatment regimens for severe forms of extrapulmonary TB.[38] [94]

» An alternative option for children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis is an intensive treatment regimen composed of 6 months of isoniazid, rifampicin, pyrazinamide, and ethionamide. The World Health Organization (WHO) recommends that this shorter intensive regimen is suitable for children and adolescents who have a low likelihood of drug resistant TB. Due to a lack of data, this regimen should not be used in children and adolescents living with HIV.[38]

» Pyrazinamide is not recommended for patients experiencing acute gout as it further elevates uric acid levels. Older patients (age >75 years) may not tolerate pyrazinamide and providers may consider leaving it out of treatment regimens.[48] Patients who do not receive pyrazinamide during the intensive phase should receive 7 months of continuation phase (to give 9 months of total treatment).

Acute

» Regimens may need to be modified in patients with hepatic injury or renal insufficiency; a specialist should be consulted for guidance on choice of regimen and appropriate doses. Several TB medications are metabolised by the liver and may potentially cause or exacerbate hepatic injury. Mild hepatitis may require only closer monitoring without changes in the standard regimen. However, severe hepatitis while on TB treatment may make it necessary to hold medications and use an alternate liver-sparing regimen. Dose adjustments may be required in patients with renal insufficiency or end-stage renal disease.[48]

» As there is increased risk of retrobulbar neuritis resulting from ethambutol toxicity in patients with renal failure, particular attention to testing of visual acuity/colour discrimination and counselling of patients is also required in this population.

plus **continuation phase therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» isoniazid: children: children: 7-15 mg/kg orally once daily, maximum 300 mg/dose; adults: 5 mg/kg orally once daily, maximum 300 mg/dose
Pyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.

-and-
» rifampicin: children: 10-20 mg/kg orally once daily, maximum 600 mg/dose; adults: 10 mg/kg orally once daily, maximum 600 mg/dose

» After 2 months of intensive phase treatment in patients with drug-susceptible EPTB, pyrazinamide and ethambutol are discontinued, and isoniazid and rifampicin are given for the continuation phase. Duration of the continuation phase depends on the site of infection and severity of disease. Generally, for EPTB that does not involve CNS or bones and joints, continuation phase therapy is given for 4 months (i.e., 6 months of total treatment).

» Total therapy for 9 months is considered for patients with extensive skeletal TB, especially when large joints are involved with slow clinical response. Patients with central nervous system (CNS) TB receive 7-10 months of continuation phase therapy (9-12 months total).[48] [94]

Acute

» Children aged 3 months to 16 years with non-severe TB should receive 2 months of continuation phase therapy (4 months total). Those with severe TB, other than TB meningitis or osteoarticular TB, and also children aged less than 3 months, should receive the standard 6-month treatment regimen.[38] [94]

» Children with osteoarticular TB or TB meningitis should receive 10 months of continuation phase therapy (12 months total).[38]

» Note that children and adolescents who received the shorter 6-month intensive regimen for TB meningitis do not receive continuation phase treatment.[38]

» Patients with MDR-TB should have their final regimen based on the results of drug-susceptibility testing, in consultation with a specialist.

adjunct **corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

» dexamethasone: children and adults: consult specialist for guidance on dose
-and-
» prednisolone: children and adults: consult specialist for guidance on dose

» Corticosteroids may be used in limited situations. Adjunctive corticosteroid therapy has been shown to attenuate the inflammatory response in TB meningitis and result in improved survival.[101] [102]

» The American Thoracic Society (ATS)/ Centers for Disease Control and Prevention (CDC)/Infectious Diseases Society of America (IDSA) and WHO guidelines recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks for patients with tuberculous meningitis.[48] [94] The British Infection Society recommends that, in children, the initial dose of dexamethasone should be given for 4 weeks, then tapered over 4-8 weeks.[53]

» Limited evidence suggests there may be a mortality benefit for use of corticosteroids in TB pericarditis without HIV infection.[104] Currently, the ATS/CDC/IDSA guideline suggests that adjunctive corticosteroid therapy should not be routinely used in patients with

Acute

TB pericarditis but may be appropriate for selected patients who are at the highest risk for inflammatory complications, including those with large pericardial effusions, high levels of inflammatory markers, or signs of constriction.[48] The WHO recommends that adjunctive corticosteroid therapy may be used in tuberculous pericarditis.[94]

» Consult local guidelines for dosing information as dose regimens vary.

isoniazid resistance **1st** **antituberculous therapy**

» Drug-resistance may be suspected on the basis of historical or epidemiological information. Isoniazid-resistant TB is defined as resistance to isoniazid and susceptibility to rifampicin that has been confirmed in vitro.

» In patients with confirmed rifampicin-susceptible and isoniazid-resistant pulmonary TB, US and World Health Organization (WHO) guidelines recommend treatment with a 6-month regimen of rifampicin, ethambutol, pyrazinamide, and a later-generation fluoroquinolone.[91] [97] The WHO guidelines note that this regimen is likely to be effective in patients with extrapulmonary TB, but that no data are available for patients with exclusive extrapulmonary isoniazid-resistant TB.[97]

» Consultation with an appropriate specialist is recommended to determine the most appropriate antituberculous therapy and supportive care.

multidrug resistance **1st** **antituberculous therapy**

» Multidrug-resistant (MDR) TB is defined as resistance to isoniazid and rifampicin, with or without resistance to other first-line drugs. Extensively drug-resistant (XDR) TB is defined as resistance to at least isoniazid and rifampicin, as well as any fluoroquinolone and either bedaquiline or linezolid (or both).[98] Pre-XDR-TB is resistance to isoniazid, rifampicin, and any fluoroquinolone.

» The treatment regimen should be based on the results of drug susceptibility testing. Specific regimens should be selected by a specialist in the treatment of MDR TB.[97] The total number of TB medicines to include in the regimen needs to balance expected benefit with risk of adverse effects and non-adherence when the pill burden is high. Treatment of MDR-TB and rifampicin-resistant (RR) TB/RR-TB meningitis should be guided by knowledge of TB medicines that cross the blood-brain barrier.[97]

Acute

» Patients with rifampicin-resistant (RR) TB are also eligible for treatment with MDR TB regimens.[97] Short (6 or 9 months) and longer (18 months or more) regimens are included in the WHO guidelines for the treatment of people with drug-resistant TB.[97] The WHO short-course regimens are a major step forward for low- and middle-income settings where access to second-line drug susceptibility testing may not be available. In places with the ability to check second-line drug sensitivities, creation of an appropriate regimen would be based on drug susceptibilities. The short-course regimens may expose patients to drugs that are not indicated.

» The 6-month all-oral regimen is composed of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM).[97] [99] [100] The WHO recommends the use of this 6-month regimen for adults and adolescents aged 14 and over with confirmed pulmonary TB and all forms of extrapulmonary TB (except for TB involving the CNS, osteoarticular and disseminated [miliary] TB), regardless of HIV status, who have less than 1 month exposure to bedaquiline, linezolid, pretomanid, or delamanid. The WHO suggests that this regimen is used where appropriate rather than the 9-month or longer MDR/RR-TB regimens.[97] If the patient has documented resistance to fluoroquinolones, the WHO advises that the regimen should continue without moxifloxacin (BPaL); although initiation of BPaLM should not be delayed while waiting for results of drug susceptibility testing.

» The 9-month all-oral regimen is recommended by the WHO for patients who have extrapulmonary TB that is not severe, where severe disease is defined as miliary TB or TB meningitis, or in children aged less than 15 years defined as extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression).[97] It is recommended over the longer MDR/RR-TB regimens (18 months or more) when resistance to fluoroquinolones has been excluded and can be used when patients are not eligible for the 6-month regimen. In the 9-month regimen, bedaquiline is used for 6 months in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide, and clofazimine for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months), and this is followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol, and

Acute

pyrazinamide.[97] Two months of linezolid may be used in place of the 4 months of ethionamide. The WHO recommends the use of the 9-month regimen for adults and children without extensive pulmonary TB disease, regardless of HIV status, and who have less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid, and clofazimine.[97]

» Longer MDR TB regimens last 18 months or more and may be standardised or individualised; regimens are designed to include a minimum number of medicines considered to be effective based on patient history or drug-resistance patterns.[97] This longer-term regimen is recommended for all patients with extrapulmonary TB who do not fulfil the criteria for the shorter-term regimens; however, adjustments may be required, depending on the specific location of the disease.[97] The WHO guidelines recommend that patients with RR TB or MDR TB on longer regimens receive treatment with at least four TB agents likely to be effective, including all three Group A agents and at least one Group B agent, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents should be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.[97]

» Group A (include all three medicines): levofloxacin or moxifloxacin; bedaquiline; linezolid.

» Group B (add one or both medicines): clofazimine; cycloserine or terizidone.

» Group C (add to complete the regimen and when medicines from Groups A and B cannot be used): ethambutol; delamanid; pyrazinamide; imipenem/cilastatin or meropenem; amikacin or streptomycin; ethionamide or prothionamide; aminosalicylic acid.

active TB: non-pregnant, HIV-positive

drug resistance not suspected

1st

intensive phase therapy

Primary options

4- or 6-month regimen

» isoniazid: children: 7-15 mg/kg orally once daily, maximum 300 mg/dose; adults: 5 mg/kg orally once daily, maximum 300 mg/dose

Acute

Pyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.

--AND--

» rifampicin: children: 10-20 mg/kg orally once daily, maximum 600 mg/dose; adults: 10 mg/kg orally once daily, maximum 600 mg/dose

-or-

» rifabutin: children and adults: consult specialist for guidance on dose

A dose adjustment may be required in patients on concomitant protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

--AND--

» pyrazinamide: children: 30-40 mg/kg orally once daily; adults: consult specialist for guidance on dose (dose is based on lean body weight and available tablet formulation)

--AND--

» ethambutol: children: 15-25 mg/kg orally once daily; adults: consult specialist for guidance on dose (dose is based on lean body weight and available tablet formulation)

The 4-month regimen may be given with or without ethambutol.

» Treatment of TB in HIV-positive patients follows the same general principles as in other patients with TB. However, there are some additional considerations, including the potential for drug interactions, especially between rifampicin and antiretrovirals (non-nucleoside reverse-transcriptase inhibitors and protease-inhibitors). For this reason, rifabutin may be considered as an alternative to rifampicin.[48] Dosage should be adjusted as necessary.

» Patients with TB and HIV infection should receive antiretroviral therapy (ART) during antituberculosis treatment. World Health Organization (WHO) guidelines recommend that ART is started as soon as possible within 2 weeks of starting TB treatment, regardless of CD4 cell count, unless the patient has TB meningitis (when ART is delayed for 4-8 weeks).[94]

» The antituberculous therapy is given once-daily on 5 days per week by directly observed therapy (DOT) during the intensive phase with the weekend/holiday doses self-administered.[48] All medications are administered together.

Acute

» Initial intensive-phase treatment involves the first-line drugs of isoniazid, rifampicin, pyrazinamide, and ethambutol, for 2 months with drug-susceptibility testing for those agents.[48] [94] After 2 months, the continuation phase is started.

» WHO guidelines recommend that children aged between 3 months and 16 years with non-severe TB (defined as peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern) may receive a 4-month version of this regimen. The intensive phase of this regimen includes daily administration of isoniazid, rifampicin, and pyrazinamide, with or without ethambutol, for 2 months.[38] [94] Ethambutol should be included in areas of high prevalence of HIV or isoniazid resistance.[38] [94] Children and adolescents who do not meet the criteria for non-severe TB should receive the standard 6-month treatment regimen (including ethambutol) or extended treatment regimens for severe forms of extrapulmonary TB.[38] [94]

» TB medications should be administered daily; intermittent twice-weekly administration is not recommended for HIV-infected patients. The preferred method for HIV patients is daily DOT.[48]

» Pyrazinamide is not recommended for patients experiencing acute gout as it further elevates uric acid levels. Older patients (age >75 years) may not tolerate pyrazinamide and providers may consider leaving it out of treatment regimens.[48] Patients who do not receive pyrazinamide during the intensive phase should receive 7 months of continuation phase (to give 9 months of total treatment).

» Regimens may need to be modified in patients with hepatic injury or renal insufficiency; a specialist should be consulted for guidance on choice of regimen and appropriate doses. Several TB medications are metabolised by the liver and may potentially cause or exacerbate hepatic injury. Mild hepatitis may require only closer monitoring without changes in the standard regimen. However, severe hepatitis while on TB treatment may make it necessary to hold medications and use an alternate liver-sparing regimen. Dose adjustments may be required in patients with renal insufficiency or end-stage renal disease.[48]

Acute

» As there is increased risk of retrobulbar neuritis resulting from ethambutol toxicity in patients with renal failure, particular attention to testing of visual acuity/colour discrimination and counselling of patients is also required in this population.

plus **continuation phase therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» isoniazid: children: 7-15 mg/kg orally once daily, maximum 300 mg/dose; adults: 5 mg/kg orally once daily, maximum 300 mg/dose
Pyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.

--AND--

OR

» rifampicin: children: 10-20 mg/kg orally once daily, maximum 600 mg/dose; adults: 10 mg/kg orally once daily, maximum 600 mg/dose
-or-
» rifabutin: children and adults: consult specialist for guidance on dose
A dose adjustment may be required in patients on concomitant protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

» Treatment of TB in HIV-positive patients follows the same general principles as in other patients with TB. However, there are some additional considerations, including the potential for drug interactions, especially antiretrovirals. For this reason, rifabutin may be considered as an alternative to rifampicin. Dosage should be adjusted as necessary.

» Patients with TB and HIV infection should receive antiretroviral therapy (ART) during antituberculosis treatment. World Health Organization guidelines recommend that ART is started as soon as possible within 2 weeks of starting TB treatment, regardless of CD4 cell count, unless the patient has TB meningitis (when ART is delayed for 4-8 weeks).[94]

» After 2 months of intensive phase treatment in patients with drug-susceptible EPTB, pyrazinamide and ethambutol are discontinued, and isoniazid and rifampicin are given for the

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continuation phase. Duration of the continuation phase depends on the site of infection and severity of disease. Generally, for EPTB that does not involve CNS or bones and joints, continuation phase therapy is given for 4 months (i.e., 6 months of total treatment). Total therapy for 9 months is considered for patients with extensive skeletal TB, especially when large joints are involved with slow clinical response. Patients with central nervous system (CNS) TB receive 7-10 months of continuation phase therapy (9-12 months total).[94]

» Children aged 3 months to 16 years with non-severe TB should receive 2 months of continuation phase therapy (4 months total). Those with severe TB, other than TB meningitis or osteoarticular TB, and also children aged less than 3 months, should receive the standard 6-month treatment regimen.[94]

» Children with osteoarticular TB or TB meningitis should receive 10 months of continuation phase therapy (12 months total).[38]

» Patients with MDR-TB should have their final regimen based on the results of drug-susceptibility testing, in consultation with a specialist.

adjunct **corticosteroid**

Treatment recommended for SOME patients in selected patient group

Primary options

» dexamethasone: children and adults: consult specialist for guidance on dose

OR

» prednisolone: children and adults: consult specialist for guidance on dose

» Corticosteroids may be used in limited situations. Adjunctive corticosteroid therapy has been shown to attenuate the inflammatory response in TB meningitis and result in improved survival.[101] [102]

» The American Thoracic Society (ATS)/ Centers for Disease Control and Prevention (CDC)/Infectious Diseases Society of America (IDSA) and WHO guidelines recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks for patients with tuberculous meningitis.[48] [94] US guidelines for the

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prevention and treatment of opportunistic infections in those with HIV recommend adjunctive treatment with dexamethasone for adults with TB involving the CNS, though notes that studies involving those with HIV are limited.[92] One subsequent randomised controlled trial in adults with HIV infection and TB meningitis found that adjunctive dexamethasone did not reduce mortality over 12 months (death from any cause) compared with placebo.[103] US guidelines for the prevention and treatment of opportunistic infections in children with HIV recommend considering adjunctive corticosteroid treatment for those with TB meningitis.[93] The British Infection Society recommends that, in children, the initial dose of dexamethasone should be given for 4 weeks, then tapered over 4-8 weeks.[53]

» Limited evidence suggests there may be a benefit for use of corticosteroids in TB pericarditis.[104] Currently, the ATS/CDC/IDSA guideline suggests that adjunctive corticosteroid therapy should not be routinely used in patients with TB pericarditis but may be appropriate for selected patients who are at the highest risk for inflammatory complications, including those with large pericardial effusions, high levels of inflammatory markers, or signs of constriction.[48] US guidelines for the prevention and treatment of opportunistic infections in those with HIV state that adjunctive corticosteroid therapy is not recommended in the treatment of adults and adolescents with TB pericarditis; however, it may be considered in children.[92] [93] The WHO recommends that adjunctive corticosteroid therapy may be used in tuberculous pericarditis.[94]

» Consult local guidelines for dosing information as dose regimens vary.

isoniazid resistance **1st** **antituberculous therapy**

» Drug-resistance may be suspected on the basis of historical or epidemiological information. Isoniazid-resistant TB is defined as resistance to isoniazid and susceptibility to rifampicin that has been confirmed in vitro.

» In patients with confirmed rifampicin-susceptible and isoniazid-resistant pulmonary TB, US and World Health Organization (WHO) guidelines recommend treatment with a 6-month regimen of rifampicin, ethambutol, pyrazinamide, and a later-generation fluoroquinolone.[91] [97] The WHO guidelines note that this regimen is likely to be effective in patients

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with extrapulmonary TB, but that no data are available for patients with exclusive extrapulmonary isoniazid-resistant TB.[97]

» Consultation with an appropriate specialist is recommended to determine the most appropriate antituberculous therapy and supportive care.

multidrug resistance **1st** **antituberculous therapy**

» Multidrug-resistant (MDR) TB is defined as resistance to isoniazid and rifampicin, with or without resistance to other first-line drugs. Extensively drug-resistant (XDR) TB is defined as resistance to at least isoniazid and rifampicin, as well as any fluoroquinolone and either bedaquiline or linezolid (or both).[98] Pre-XDR-TB is resistance to isoniazid, rifampicin, and any fluoroquinolone.

» The treatment regimen should be based on the results of drug susceptibility testing. Specific regimens should be selected by a specialist in the treatment of MDR TB.[97] The total number of TB medicines to include in the regimen needs to balance expected benefit with risk of adverse effects and non-adherence when the pill burden is high. Treatment of MDR-TB and rifampicin-resistant (RR) TB/RR-TB meningitis should be guided by knowledge of TB medicines that cross the blood-brain barrier.[97]

» Patients with rifampicin-resistant (RR) TB are also eligible for treatment with MDR TB regimens.[97] Short (6 or 9 months) and longer (18 months or more) regimens are included in the WHO guidelines for the treatment of people with drug-resistant TB.[97] The WHO short-course regimens are a major step forward for low- and middle-income settings where access to second-line drug susceptibility testing may not be available. In places with the ability to check second-line drug sensitivities, creation of an appropriate regimen would be based on drug susceptibilities. The short-course regimens may expose patients to drugs that are not indicated.

» The 6-month all-oral regimen is composed of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM).[97] [99] [100] The WHO recommends the use of this 6-month regimen for adults and adolescents aged 14 and over with confirmed pulmonary TB and all forms of extrapulmonary TB (except for TB involving the CNS, osteoarticular and disseminated [miliary] TB), regardless of HIV status, who have less than 1 month exposure to bedaquiline, linezolid, pretomanid, or delamanid. The WHO

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suggests that this regimen is used where appropriate rather than the 9-month or longer MDR/RR-TB regimens.[97] If the patient has documented resistance to fluoroquinolones, the WHO advises that the regimen should continue without moxifloxacin (BPaL); although initiation of BPaLM should not be delayed while waiting for results of drug susceptibility testing.

» The 9-month all-oral regimen is recommended by the WHO for patients who have extrapulmonary TB that is not severe, where severe disease is defined as miliary TB or TB meningitis, or in children aged less than 15 years defined as extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression).[97] It is recommended over the longer MDR/RR-TB regimens (18 months or more) when resistance to fluoroquinolones has been excluded and can be used when patients are not eligible for the 6-month regimen. In the 9-month regimen, bedaquiline is used for 6 months in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide, and clofazimine for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months), and this is followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol, and pyrazinamide.[97] Two months of linezolid may be used in place of the 4 months of ethionamide. The WHO recommends the use of the 9-month regimen for adults and children without extensive pulmonary TB disease, regardless of HIV status, and who have less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid, and clofazimine.[97]

» Longer MDR TB regimens last 18 months or more and may be standardised or individualised; regimens are designed to include a minimum number of medicines considered to be effective based on patient history or drug-resistance patterns.[97] This longer-term regimen is recommended for all patients with extrapulmonary TB who do not fulfil the criteria for the shorter-term regimens; however, adjustments may be required, depending on the specific location of the disease.[97] The WHO guidelines recommend that patients with RR TB or MDR TB on longer regimens receive treatment with at least four TB agents likely to be effective, including all three group A agents and at least one Group B agent, and that at least three agents are included for the rest of

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		treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents should be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.[97] » Group A (include all three medicines): levofloxacin or moxifloxacin, bedaquiline, linezolid. » Group B (add one or both medicines): clofazimine; cycloserine or terizidone. » Group C (add to complete the regimen and when medicines from Groups A and B cannot be used): ethambutol; delamanid; pyrazinamide; imipenem/cilastatin or meropenem; amikacin or streptomycin; ethionamide or prothionamide; aminosalicylic acid.
active TB: pregnant		
	1st	**referral to specialist** » Expert consultation is obtained. Antituberculous therapy is initiated based on clinical suspicion after optimal diagnostic samplings. » While awaiting that information, an expanded empiric regimen may be used. The final regimen will be based on the results of drug-susceptibility testing. » Use of pyrazinamide in pregnant women is controversial due to lack of detailed teratogenicity data, but it should be considered in patients with EPTB, particularly when HIV co-infection is present. Patients who do not receive pyrazinamide during the intensive phase should receive 7 months of continuation phase (to give 9 months of total treatment). » All medications should be administered together. » Intensive phase should continue for 2 months, with the ultimate duration to be determined on the basis of eventual drug susceptibilities and expert consultation.[48] » Treatment of drug-resistant TB, especially multidrug-resistant (MDR) TB, should be attempted only with expert advice. » Drug-resistance may be suspected on the basis of historical or epidemiological information.

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MDR isolates are resistant to at least both isoniazid and rifampicin.[91] [97]

» Consult a specialist for guidance on choice of regimen and doses.

Emerging

Rifapentine and moxifloxacin (4-month regimen)

An international, randomised, controlled, open-label phase 3 non-inferiority clinical trial (study 31/A5349) found that a four-month daily treatment regimen containing high-dose (optimised) rifapentine with moxifloxacin is as effective as the standard daily 6-month regimen in the treatment of drug-susceptible pulmonary TB.[107] The US Centers for Disease Control and Prevention and the World Health Organization both now recommend the 4-month regimen (8 weeks of daily treatment with rifapentine, isoniazid, pyrazinamide, and moxifloxacin, followed by 9-weeks of daily treatment with rifapentine, isoniazid, and moxifloxacin) as a treatment option for patients aged ≥12 years with drug-susceptible pulmonary tuberculosis.[94] [108] This regimen is not currently recommended for most types of EPTB but could be an acceptable option for patients with EPTB that is likely to be paucibacillary, does not pose a substantial risk for death or disability, and does not require prolonged treatment (i.e., pleural or lymph node TB).[94] [108] Additional studies are recommended for patients with EPTB.[94] [108]

Primary prevention

Prevention of active TB includes appropriate testing for latent TB infection (LTBI) and treatment of individuals with LTBI who are at increased risk for reactivation (targeted TB testing and treatment). Strategies for prevention of TB include preventing HIV infection and intravenous drug use. BCG vaccine is a live attenuated strain of *Mycobacterium bovis* that is used in many parts of the world. BCG vaccination is effective in prevention of TB meningitis and disseminated TB in infants and young children, although its efficacy in older patients is uncertain and under investigation.[17] [36] In the UK, BCG vaccination is offered to newborn babies who have a parent or grandparent who was born in a country where the yearly incidence of TB is 40 per 100,000 or greater; and/or newborn babies living in areas of the UK where the yearly incidence of TB is 40 per 100,000 or greater.[37] The WHO recommends that a single dose of BCG vaccine should be given to neonates at birth, or as soon as possible afterwards, in countries or settings with a high incidence of TB and/or leprosy.[38] The US Centers for Disease Control and Prevention recommends that travellers from the US who anticipate prolonged exposure to TB or are planning prolonged stays in TB-endemic countries should have pre- and post-travel testing.[39] [40]

Secondary prevention

Active TB, confirmed or highly suspected, is a reportable condition to the local health authorities.

Patient discussions

Patients with TB will need education and support during treatment. Treatment courses are long, which can make adherence to regimens challenging, and patients often face psychosocial issues as a result of stigma.

Adherence to treatment: patients should be aware of the importance of taking all medicines as prescribed, including those receiving treatment for latent TB infection. Potential barriers to adherence should be identified and addressed and patients should be involved in decision-making as much as possible. Use of video rather than in-person directly observed therapy for monitoring treatment may improve adherence.[95]

TB-related stigma: stigma is a global public health challenge that is associated with psychosocial issues, such as depression and reduced quality of life, and can delay health-seeking behaviour and negatively impact treatment outcomes.[125] [126] Tackling TB-stigma is a wide issue that involves educating healthcare professionals, patients, and the general public. Patients benefit from psychosocial support during management.

FOLLOW UP

Monitoring

Monitoring

During treatment, patients should be monitored monthly to assess symptoms, adherence to medications, and weight (with dose changes as needed). Monthly liver function tests (LFTs) may be recommended for those with abnormal baseline LFTs, chronic alcohol consumption, potential hepatotoxicity, other liver disease or injury (e.g., viral hepatitis), or HIV infection.[48] Patients on ethambutol are monitored for visual disturbance and will need monthly vision checks. In patients with TB meningitis, repeated lumbar punctures are done to monitor changes in cell count, glucose, and protein.

At the completion of treatment, patients may have a follow-up imaging study to serve as a new baseline.

In patients with multidrug-resistant TB, close follow up for 2 years after completion of treatment is recommended.

Complications

Complications	Timeframe	Likelihood
immune reconstitution inflammatory syndrome	**short term**	**medium**
Also known as a paradoxical response. This syndrome involves transient worsening of TB symptoms and lesions despite TB treatment, and is often observed among HIV-infected TB patients soon after initiation of antiretroviral therapy. Paradoxical responses may also be seen in up to 23% of HIV-negative patients with TB lymphadenitis and presents with worsening of existing lesions or appearance of new lymphadenopathies while on TB therapy. It occurs most frequently 1 to 2 months after therapy initiation and lasts up to 2 months. Drainage may occur.[113] Up to 20% to 30% of HIV-infected TB patients may develop immune reconstitution inflammatory syndrome (IRIS) after initiation of antiretroviral therapy (ART). IRIS appears to be more common in EPTB. Studies support initiation of ART during the intensive phase of TB therapy to improve survival.[114] [115] Manifestations may include reappearance of fever, worsening of chest x-ray results, lymphadenopathy, or an increase in pleural effusions. It is a diagnosis of exclusion and must rule out other aetiologies, such as *Pneumocystis jiroveci* pneumonia. Does not appear to impact mortality unless IRIS affects the central nervous system.[113] [116] [117] [118] Paradoxical responses are transient and antituberculous or ART does not need to be discontinued. Paradoxical worsening in TB lymphadenitis may require prolongation of the treatment course. Repeat culture can be performed to rule out development of drug-resistant TB or concomitant pathology. Non-steroidal anti-inflammatory drugs may provide relief. If there are significant symptoms, corticosteroids may be considered (e.g., prednisolone 1 to 2 mg/kg once daily for a few weeks then tapered gradually over several weeks) while maintaining antituberculous and ART. For painful or draining lesions, surgical excision may be considered.		
paraspinal abscess, neurological deficits	**short term**	**medium**
Paraspinal abscess can be seen in vertebral TB (Pott's disease), occurring in 90% of cases. Abscess may extend anteriorly to ligaments or posteriorly to the epidural space. A severe complication is spinal cord compression by an adjacent abscess, sequestrum formation or direct invasion that may cause paraplegia. Surgical therapy may be indicated if the patient has neurological deficits or progression while on medical therapy. Disabling neurological deficits may occur in 10% to 30% of TB meningitis survivors.[101] [119]		
septic shock, multi-organ failure	**short term**	**low**
Seen in disseminated TB due to primary infection.[120]		
empyema	**short term**	**low**
Rarely seen in primary TB pleuritis; usual presentation is in the setting of extensive parenchymal disease. Chest tube (tube thoracostomy) is required. May require surgical intervention.		

FOLLOW UP

Complications	Timeframe	Likelihood
recurrence of TB	**long term**	**low**

Relapse occurs when a patient becomes and remains culture-negative while on therapy, but at some point after completion becomes culture-positive again or develops clinical syndrome consistent with active TB. In the US this is generally due to recrudescence of the original organism, whereas in TB-endemic countries it may be due to exogenous reinfection. Most relapse events occur in the first 6 to 12 months following completion of treatment and in 2% to 5% of appropriately treated patients.[123] [124]

If patients initially had drug-susceptible isolates and treatment was directly observed, relapse is likely due to the original susceptible organisms and prior therapy can be used. However, if the patient received self-administered therapy, there is a higher possibility of resistant organism. In this situation, or if drug susceptibility was not previously performed, an expanded regimen can be used while culture and susceptibility results are pending.

If exogenous reinfection is suspected, treatment ought to be based on the drug susceptibility profile of the index case.

Prognosis

In the pre-antibiotic era, the mortality rate of TB exceeded 50%, but TB became a treatable disease with the advent of antibiotics. In the US in 2020 (the most recent data available), there were 602 deaths out of 7870 reported cases (a case fatality rate of 7.6%). Risk factors for death include increased age, delay in diagnosis of TB, extent of TB involvement, the need for mechanical ventilation, and concomitant diagnosis of end-stage renal disease, diabetes, and immunosuppression, particularly HIV infection.[109] [110] One meta-analysis found that 3.5% of HIV-uninfected and 18.8% of HIV-infected individuals died during TB treatment.[111]

TB meningitis has a mortality rate of 35% and potentially permanent neurological sequelae. Children with advanced disease and neurological complications have particularly poor outcomes.[24]

In the setting of delayed therapy (more than 6 weeks), mortality from TB peritonitis approaches 60%.[15]

In disseminated TB the mortality rate has been reported as high as 38%. Delay in diagnosis and treatment is associated with higher mortality.[112]

Diagnostic guidelines

United Kingdom

Tuberculosis (https://www.nice.org.uk/guidance/ng33)

Published by: National Institute for Health and Care Excellence **Last published:** 2024

British HIV Association guidelines for the management of tuberculosis in adults living with HIV 2018 (2023 interim update) (https://www.bhiva.org/TB-guidelines)

Published by: British HIV Association **Last published:** 2023

BTS clinical statement for the diagnosis and management of ocular TB (https://www.brit-thoracic.org.uk/quality-improvement/clinical-statements/ocular-tb/)

Published by: British Thoracic Society **Last published:** 2022

Guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children (http://www.britishinfection.org/guidelines-resources/published-guidelines)

Published by: British Infection Society **Last published:** 2009

International

WHO consolidated guidelines on tuberculosis: module 6: tuberculosis and comorbidities (https://www.who.int/publications/i/item/9789240087002)

Published by: World Health Organization **Last published:** 2024

WHO consolidated guidelines on tuberculosis. Module 3: diagnosis - rapid diagnostics for tuberculosis detection, 3rd ed (https://www.who.int/publications/i/item/9789240089488)

Published by: World Health Organization **Last published:** 2024

WHO consolidated guidelines on tuberculosis. Module 3: diagnosis - tests for tuberculosis infection (https://www.who.int/publications/i)

Published by: World Health Organization **Last published:** 2022

WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents (https://www.who.int/publications/i)

Published by: World Health Organization **Last published:** 2022

WHO consolidated guidelines on tuberculosis. Module 2: screening - systematic screening for tuberculosis disease (https://www.who.int/publications)

Published by: World Health Organization **Last published:** 2021

North America

Guidelines for prevention and treatment of opportunistic infections in adults and adolescents with HIV: Mycobacterium tuberculosis infection and disease (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new)

Published by: Centers for Disease Control and Prevention; National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America

Last published: 2024

Guidelines for the prevention and treatment of opportunistic infections in children with and exposed to HIV: Mycobacterium tuberculosis (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-pediatric-opportunistic-infections/whats-new)

Published by: Centers for Disease Control and Prevention; HIV Medicine Association of the Infectious Diseases Society of America; Pediatric Infectious Diseases Society; HHS Panel on Opportunistic Infections in Children with and Exposed to HIV

Last published: 2023

Testing and treatment of latent tuberculosis infection in the United States: clinical recommendations (https://www.tbcontrollers.org/resources/tb-infection/clinical-recommendations)

Published by: National Tuberculosis Controllers Association

Last published: 2021

Tuberculosis infection in children and adolescents: testing and treatment (https://publications.aap.org/pediatrics/article/148/6/e2021054663/183445/Tuberculosis-Infection-in-Children-and-Adolescents)

Published by: American Academy of Pediatrics

Last published: 2021

ACR appropriateness criteria: hemoptysis (https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria)

Published by: American College of Radiology

Last published: 2019

Chronic cough due to TB and other chronic infections (https://www.chestnet.org/Guidelines-and-Resources)

Published by: American College of Chest Physicians

Last published: 2018

Diagnosis of tuberculosis in adults and children (https://www.cdc.gov/tb/publications/guidelines/testing.htm)

Published by: American Thoracic Society; Centers for Disease Control and Prevention; Infectious Diseases Society of America

Last published: 2017

Treatment guidelines

United Kingdom

Tuberculosis (https://www.nice.org.uk/guidance/ng33)

Published by: National Institute for Health and Care Excellence **Last published:** 2024

British HIV Association guidelines for the management of tuberculosis in adults living with HIV 2018 (2023 interim update) (https://www.bhiva.org/Guidelines)

Published by: British HIV Association **Last published:** 2023

BTS clinical statement for the diagnosis and management of ocular TB (https://www.brit-thoracic.org.uk/quality-improvement/clinical-statements/ocular-tb/)

Published by: British Thoracic Society **Last published:** 2022

Guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children (http://www.britishinfection.org/guidelines-resources/published-guidelines)

Published by: British Infection Society **Last published:** 2009

Europe

Immunisation guidelines for Ireland (https://www.rcpi.ie/Healthcare-Leadership/NIAC/Immunisation-Guidelines-for-Ireland)

Published by: Royal College of Physicians of Ireland **Last published:** 2023

International

WHO consolidated guidelines on tuberculosis: module 6: tuberculosis and comorbidities (https://www.who.int/publications/i/item/9789240087002)

Published by: World Health Organization **Last published:** 2024

WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents (https://www.who.int/publications/i)

Published by: World Health Organization **Last published:** 2022

WHO consolidated guidelines on tuberculosis. Module 4: treatment - tuberculosis care and support (https://www.who.int/publications/i)

Published by: World Health Organization **Last published:** 2022

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-susceptible tuberculosis treatment (https://www.who.int/publications/i)

Published by: World Health Organization **Last published:** 2022

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update (https://www.who.int/health-topics/tuberculosis#tab=tab_1)

Published by: World Health Organization **Last published:** 2022

Digestive tract tuberculosis (https://www.worldgastroenterology.org/guidelines/global-guidelines)

Published by: World Gastroenterology Organisation Global Guidelines **Last published:** 2021

WHO consolidated guidelines on tuberculosis. Module 1: Prevention. Tuberculosis preventive treatment (https://www.who.int/health-topics/tuberculosis#tab=tab_1)

Published by: World Health Organization **Last published:** 2020

Tuberculosis and air travel: guidelines for prevention and control (https://apps.who.int/iris/)

Published by: World Health Organization **Last published:** 2008

North America

Guidelines for prevention and treatment of opportunistic infections in adults and adolescents with HIV: Mycobacterium tuberculosis infection and disease (https://aidsinfo.nih.gov/guidelines)

Published by: Centers for Disease Control and Prevention; National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America

Last published: 2024

Guidelines for the prevention and treatment of opportunistic infections in children with and exposed to HIV: Mycobacterium tuberculosis (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-pediatric-opportunistic-infections/whats-new)

Published by: Centers for Disease Control and Prevention; HIV Medicine Association of the Infectious Diseases Society of America; Pediatric Infectious Diseases Society; HHS Panel on Opportunistic Infections in Children with and Exposed to HIV

Last published: 2023

Testing and treatment of latent tuberculosis infection in the United States: clinical recommendations (https://www.tbcontrollers.org/resources/tb-infection/clinical-recommendations)

Published by: National Tuberculosis Controllers Association

Last published: 2021

Tuberculosis infection in children and adolescents: testing and treatment (https://publications.aap.org/pediatrics/article/148/6/e2021054663/183445/Tuberculosis-Infection-in-Children-and-Adolescents)

Published by: American Academy of Pediatrics

Last published: 2021

Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline (https://www.cdc.gov/tb/publications/guidelines/mdr_tb.htm)

Published by: American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America

Last published: 2019

Treatment of drug-susceptible tuberculosis (https://www.cdc.gov/tb/publications/guidelines/treatment.htm)

Published by: American Thoracic Society; Centers for Disease Control and Prevention; Infectious Diseases Society of America

Last published: 2016

EVIDENCE TABLES

Evidence tables

What are the benefits and harms of corticosteroids for people with tuberculous pericarditis?

This table is a summary of the analysis reported in a Cochrane Clinical Answer that focuses on the above important clinical question.

Cochrane Clinical Answers

View the full source Cochrane Clinical Answer (https://www.cochranelibrary.com/cca/doi/10.1002/cca.1937/full)

Evidence C *

Confidence in the evidence is very low or low where GRADE has been performed and there may be no difference in effectiveness between the intervention and comparison for key outcomes. However, this is uncertain and new evidence could change this in the future.

Population: People with tuberculous pericarditis [a]
Intervention: Corticosteroids
Comparison: Placebo or no treatment

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
All-cause mortality: HIV-negative people	No statistically significant difference	Low
All-cause mortality: HIV-positive people	No statistically significant difference	Very Low
Pericarditis-related mortality: HIV-negative people	Favours intervention	Moderate
Pericarditis-related mortality: HIV-positive people	No statistically significant difference	Very Low
Constrictive pericarditis: HIV-negative people	No statistically significant difference	Very Low
Constrictive pericarditis: HIV-positive people	No statistically significant difference	Low
Repeat pericardiocentesis: HIV-negative and HIV-positive people	No statistically significant difference	Low
Cancer: HIV-negative and HIV-positive people	No statistically significant difference	Very Low

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Hospitalisation: HIV-negative people	No statistically significant difference	Very Low
Hospitalisation: HIV-positive people	No statistically significant difference	Low
Pericardiectomy: HIV-negative and HIV-positive people	No statistically significant difference	Very Low
Opportunistic infections: HIV-negative and HIV-positive people	No statistically significant difference	Very Low

Note

[a] Six studies were identified all from sub-Saharan Africa including 1926 people (aged 5 to 66 years). All patients were receiving anti-tuberculous therapy. Tuberculous pericarditis was described as suspected in two trials, and active in one trial. 53% of participants were HIV-positive.

* Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit (https://bestpractice.bmj.com/info/evidence-tables/) for details.

Confidence in evidence

A - High or moderate to high

B - Moderate or low to moderate

C - Very low or low

† Effectiveness (BMJ rating)

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

‡ Grade certainty ratings

High	The authors are very confident that the true effect is similar to the estimated effect.
Moderate	The authors are moderately confident that the true effect is likely to be close to the estimated effect.
Low	The authors have limited confidence in the effect estimate and the true effect may be substantially different.
Very Low	The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different.

BMJ Best Practice EBM Toolkit: What is GRADE? (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/)

Key articles

- World Health Organization. WHO consolidated guidelines on tuberculosis: module 5: management of tuberculosis in children and adolescents. Sep 2022 [internet publication]. Full text (https://www.who.int/publications/i/item/9789240046764)
- Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infect Dis. 2017 Jan 15;64(2):e1-33. Full text (https://www.thoracic.org/statements/resources/tb-opi/diagnosis-of-tuberculosis-in-adults-and-children.PDF) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27932390?tool=bestpractice.bmj.com)
- Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016 Oct 1;63(7):e147-95. Full text (https://cid.oxfordjournals.org/content/early/2016/07/20/cid.ciw376.full.pdf+html) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27516382?tool=bestpractice.bmj.com)
- World Health Organization. WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment. Module 1: prevention. 2020 [internet publication]. Full text (https://www.who.int/publications-detail/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment)
- Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. Am J Respir Crit Care Med. 2019 Nov 15;200(10):e93-142. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6857485) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31729908?tool=bestpractice.bmj.com)
- National Institutes of Health, Centers for Disease Control and Prevention, HIV Medicine Association, and Infectious Diseases Society of America. Panel on guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. Mycobacterium tuberculosis infection and disease. May 2024 [internet publication]. Full text (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/mycobacterium-0?view=full)
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- British HIV Association. British HIV Association guidelines for the management of tuberculosis in adults living with HIV 2018 (2023 interim update). 2023 [internet publication]. Full text (https://www.bhiva.org/file/5c485f3dc7c17/BHIVA-TB-guidelines.pdf)

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Images

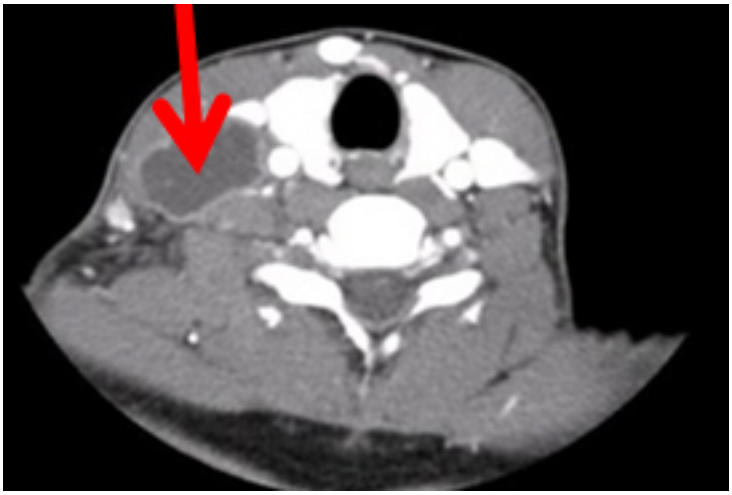

Figure 1: CT showing necrotic cervical lymph node

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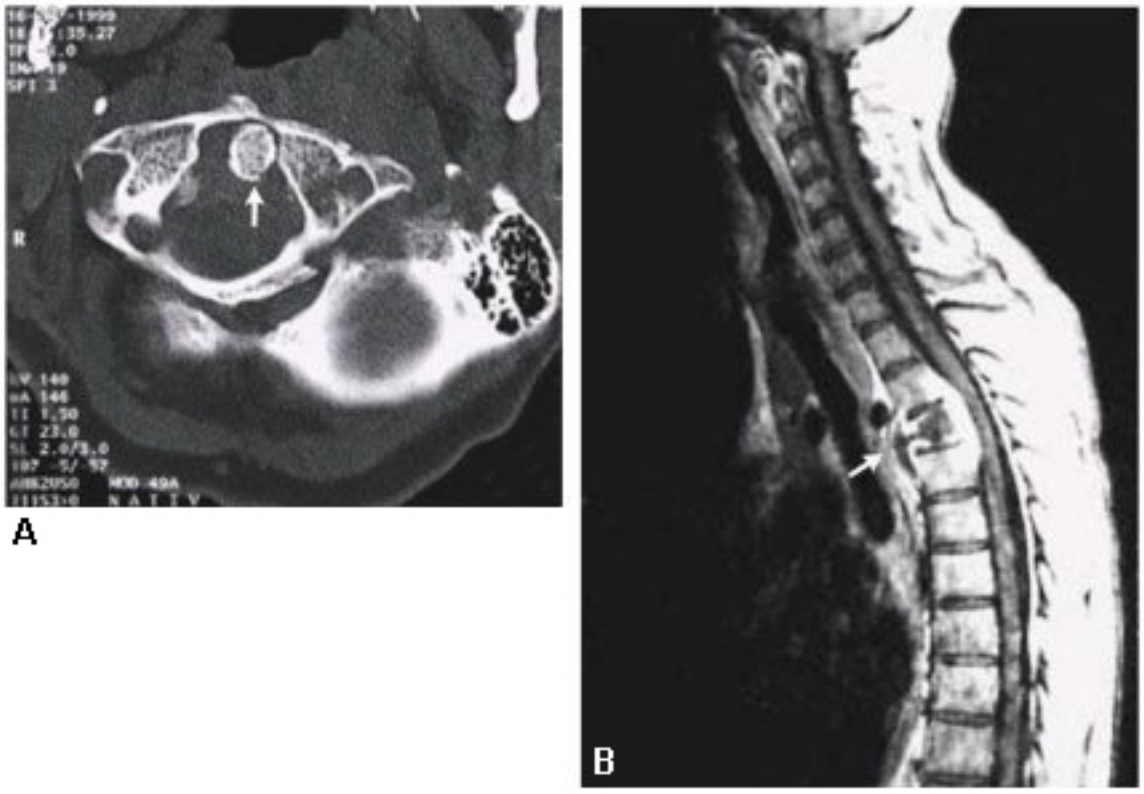

Figure 2: CT showing spinal TB (Pott's disease)

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Figure 1 – BMJ Best Practice Numeral Style

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