BMJ Best Practice

Pulmonary tuberculosis

Straight to the point of care

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Table of Contents

Summary

Pulmonary tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* .

Key risk factors include exposure to infection, birth in an endemic country, and HIV infection.

Symptoms may include cough, fever, and weight loss.

If pulmonary TB is suspected, the patient should be isolated, a chest x-ray obtained, and three sputum samples collected for acid-fast bacilli smear and culture; nucleic acid amplification test should be performed on at least one respiratory specimen.

Directly observed therapy is highly recommended and is particularly indicated in groups where adherence cannot be assumed.

Early recognition and implementation of effective treatment for infectious TB is crucial in interrupting TB transmission.

Definition

In many patients, *Mycobacterium tuberculosis* becomes dormant before it progresses to active TB. TB most commonly involves the lungs (pulmonary TB) and is communicable in this form, but may affect almost any organ system including the lymph nodes, central nervous system, liver, bones, genitourinary tract, and gastrointestinal tract. See Extrapulmonary tuberculosis .

THEORY

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.[1] 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, in 2021 the number of reported cases increased again, with the WHO estimating that there were 1.6 million TB-related deaths, including 187,000 TB-related deaths among people with HIV.[2] The increase in TB-related deaths between 2019 and 2021 reverses years of decline between 2005 and 2019. The majority of deaths (82% of HIV-negative and HIV-positive TB deaths) were in the WHO African Region and South-East Asia Region.[2] TB is particularly devastating in areas with high prevalence of HIV infection.[3] The Global Burden of Disease Study reports that in 2019, there were 217,000 (153,000-279,000) deaths due to TB among people with HIV and 1.15 million (1.01-1.32) incident cases.[4]

In the US, the Centers for Disease Control and Prevention estimates that up to 13 million people have latent TB infection.[5] In 2021, 7882 cases of TB were reported in the US, with an incidence rate of 2.4 cases per 100,000 people, an increase from the rate in 2020 (2.2 per 100,000) but lower than in 2019 (2.7 per 100,000).[6] The change in reported cases is considered to be due to under-diagnosis during the COVID-19 pandemic. The TB case rate in 2021 was 0.8 per 100,000 for US-born people and 12.5 for non-US-born people, with 71.4% of TB cases occurring among non-US-born persons.[6] According to provisional data for 2022, 8300 cases were reported, with an incidence rate of 2.5 per 100,000; a slight increase indicating a return to pre-pandemic incidence rates.[7]

Aetiology

The development of TB requires infection by *Mycobacterium tuberculosis* and inadequate containment by the immune system. Patients infected with *M tuberculosis* who have no clinical, bacteriological, or radiographic evidence of active TB are said to have latent TB infection. Active TB may occur from re-activation of previously latent infection or from progression of primary infection.

Transmission of TB occurs from individuals infected with pulmonary (and rarely laryngeal) disease. Infection results from the inhalation of aerosolised particles (droplet nuclei) containing the bacterium. The likelihood of transmission depends on the infectivity of the source patient (e.g., smear status and extent of cavitation on chest x-ray), the degree of exposure to the patient (e.g., proximity, ventilation, and the length of exposure), and susceptibility of the person in contact with an infected patient.[8] HIV-infected individuals are at greater risk of reactivation as well as progression to primary TB. Other groups at increased risk for the development of active TB include persons with recent tuberculin skin test conversion, the homeless, injection drug users, cigarette smokers, and immunocompromised individuals (e.g., people with diabetes, prolonged corticosteroid therapy, end-stage renal disease, malnutrition, or haematological malignancies).[9] [10]

Pathophysiology

Infection with TB requires inhalation of aerosolised particles called droplet nuclei. Following deposition in the alveoli, *Mycobacterium tuberculosis* is engulfed by alveolar macrophages, but survives and multiplies within the macrophages. Proliferating bacilli kill macrophages and are released; this event produces a response from the immune system. Exposure may lead to clearance of *M tuberculosis* , 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), *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 non-infectious and have latent TB infection; the majority of these patients will have a normal chest x-ray and be tuberculin skin test-positive.

Active TB typically occurs through a process of re-activation. Approximately 10% of individuals with latent infection will progress to active disease over their lifetime. The risk is greatest within the 2 years following initial acquisition of *M tuberculosis* . A number of conditions can alter this risk, particularly untreated HIV infection, in which the annual risk of developing active TB is 8% to 10%. Immunocompromised conditions and treatment with immunosuppressing medicines, including systemic corticosteroids and tumour necrosis factor-alpha antagonists, also contribute to re-activation.

Case history

Case history #1

A 34-year-old man presents to his primary care physician with a 7-week history of cough that he describes as non-productive. He has had a poor appetite during this time and notes that his clothes are loose on him. He has felt febrile at times, but has not measured his temperature. He denies dyspnoea or haemoptysis. He is originally from the Philippines. He denies any history of TB or TB exposure. Physical examination reveals a thin, tired-appearing man but is otherwise unremarkable.

Other presentations

The presentation of pulmonary TB is varied, as patients may present early or late in the course of the disease, or have different host factors (e.g., HIV, age) that may impact disease presentation. Classic findings, including haemoptysis, night sweats, and weight loss, make the diagnosis obvious, but may be absent. A number of features associated with the misdiagnosis of TB include lack of pulmonary symptoms, a sputum smear that is acid-fast bacilli-negative, negative tuberculin skin test, atypical chest x-ray findings, and the presence of other diseases that may alter immune status. Careful attention to epidemiological risk factors (e.g., residence or work in a congregate setting, birth or long-term living in TB-prevalent counties, history of latent TB infection, or recent exposure to an infectious case) will often lower the threshold to consider TB as part of the differential diagnosis.

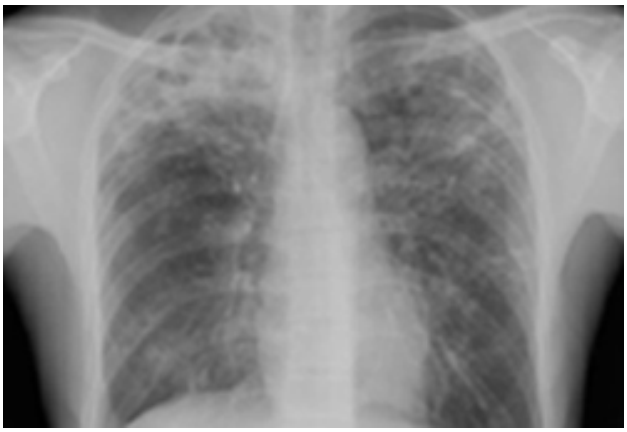
Approach

The diagnosis may be obvious in some cases but is frequently difficult. A high level of suspicion is important in evaluating a patient with risk factors. Diagnosis confirmation requires culturing of *Mycobacterium tuberculosis* . Delays in diagnosis and initiation of therapy are associated with transmission of disease and increased mortality.[12]

If suspicion for disease is high, the patient should be isolated (at home or in a negative-pressure room in a hospital) until 5 days to 2 weeks of therapy has been completed. Active TB, confirmed or highly suspected, is a reportable condition to the local health authorities.

Clinical history and risk factors

The possibility of TB should be considered in any person with risk factors for TB exposure, who has suggestive symptoms (e.g., fever, malaise, pleuritic chest pain, cough longer than 2-3 weeks, night sweats, and weight loss, hemoptysis, psychological symptoms, clubbing, erythema nodosum) or chest x-ray abnormalities. Although the presence of upper lobe infiltrates is characteristic of the disease, atypical chest x-ray presentation is common among children, and among people who are immunocompromised, have HIV infection, or have diabetes.



Pulmonary TB with cavitation

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Diagnostic investigations

Investigations for active infection include chest x-ray, three sputum samples obtained for acid-fast bacilli (AFB), nucleic acid amplification testing (NAAT), full blood count, and electrolytes (e.g., sodium). If the patient is unable to spontaneously produce sputum, it should be induced (with appropriate precautions to prevent transmission) or obtained via bronchoscopy or gastric aspirate.[12] Stained smears should be made from sputum specimens to identify AFB, as this is the first bacteriological evidence of infection and gives an estimate of how infectious the patient is. If AFBs are seen on smear, therapy should be started and the patient maintained in isolation.

Sputum culture supports the diagnosis of TB, is more sensitive and specific than smear staining, facilitates identification of the mycobacterium species by nucleic acid hybridisation or amplification, and evaluates drug sensitivity. Broth culture systems allow for rapid growth and detection in 1 to 3 weeks as opposed to 4 to 8 weeks by a solid medium.[12]

NAAT should be performed on at least one respiratory specimen when a diagnosis of TB is being considered. NAAT may speed the diagnosis in smear-negative cases and may be helpful to differentiate non-tuberculous mycobacteria when sputum is AFB smear positive but NAAT negative.[31] Genotyping might be considered useful in outbreaks of TB to identify recent transmission of TB, especially when contact had not been identified in the course of epidemiological investigations. Several rapid NAATs are available and some are also able to detect genes encoding resistance to TB drugs.[30] [32] [33] [34] [35] [36] [37] A positive NAAT is adequate for initiation of anti-tuberculosis treatment. When the patient has previously been treated for TB, especially within the prior 2 years, a positive NAAT may represent a false-positive result.

Use of stool samples is an alternative to respiratory specimens in diagnosis of pulmonary TB (sputum is swallowed and *M tuberculosis* may pass through the gastrointestinal tract). One systematic review evaluating AFB-smear, culture, and NAAT (polymerase chain reaction [PCR]) testing of stool in pulmonary TB found a pooled sensitivity of one or more of the three tests was 79.1% (95% CI 61.5 to 92.5).[38] The sensitivity of stool microscopy, PCR, and culture was 41.1% (95% CI 24.9 to 58.2), 89.7% (95% CI 81.4 to 95.9), and 38.0% (95% CI 26.2 to 50.6), respectively.[38]

The World Health Organization (WHO) recommends that in children with signs and symptoms of pulmonary TB, the NAAT Xpert Ultra should be used for initial diagnostic testing and detection of rifampicin resistance on sputum, nasopharyngeal aspirate, gastric aspirate, or stool, rather than smear microscopy/culture and phenotypic drug susceptibility testing (DST).[30]

CT of the chest, although not done routinely, may be of use to exclude other pathology: for example, cancer.

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.[39] WHO recommends that LF-LAM can be used to assist in the diagnosis of active TB in HIV-positive adults, adolescents, and children.[30] [32] 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.[40] Culture would still be required for drug susceptibility testing (DST).

It is recommended that all patients who have TB should be tested for HIV within 2 months of diagnosis.

Negative smear or cultures

Around 40% to 50% of cases are AFB smear negative and 15% to 20% have negative cultures. In patients where there is a strong clinical suspicion of TB, especially if the tuberculin skin test is positive (reaction of ≥5 mm induration), empirical TB therapy may be tried before laboratory confirmation of infection. Clinical and radiographic improvement with appropriate anti-tuberculosis treatment supports the diagnosis. NAAT of sputum cultures may also be helpful in this situation. Bronchoscopy can be done to obtain bronchoalveolar lavage samples or transbronchial biopsy, and gastric aspirate can be used in patients unable to provide an adequate sputum sample, such as young children. In patients where suspicion for active TB is low and smears are negative for AFB, it is acceptable to wait for the results of AFB culture or repeat chest x-ray before starting treatment.[9]

Patients with smear-negative disease may be infectious, although the risk of transmission is lower than in smear-positive disease.[41] If the suspicion of TB is high, consideration should be given to starting anti-tuberculous medicines prior to laboratory confirmation.

Susceptibility testing

In adequately resourced settings, culture-based DST is routinely performed on initial *M tuberculosis* isolates. A limitation of culture-based DST is that it can take >2 weeks to grow the isolate for testing. When there is a higher suspicion for drug resistance, then rapid molecular DST may be appropriate to guide treatment. Rapid molecular DST for rifampicin with or without isoniazid using the respiratory specimens of persons who are either AFB smear positive or NAAT positive should be considered in patients who:

- Have been treated for TB in the past, or
- Were born in or have lived for at least 1 year in a foreign country with at least a moderate TB incidence (≥20 per 100,000) or a high primary multidrug-resistant (MDR) TB prevalence (≥2%), or
- Are contacts of patients with MDR TB, or
- Are HIV-positive.

When Xpert MTB/RIF or Xpert Ultra (rapid molecular tests endorsed by the World Health Organization) are used as part of TB diagnosis, rifampicin resistance will be automatically assessed.[12] [32] Cochrane reviews of Xpert MTB/RIF and Xpert Ultra found that they provide accurate results for rifampicin-resistant and multidrug-resistant tuberculosis.[33] [34] [37] Xpert MTB/XDR assesses resistance to isoniazid, fluoroquinolones, injectables (amikacin, kanamycin, capreomycin), and ethionamide. One Cochrane review found Xpert MTB/XDR is accurate for detecting isoniazid and fluoroquinolone resistance.[35]

Tuberculin skin test and interferon gamma release assays

Investigations for latent 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. As false-negative results occur in 20% to 25% of patients with active pulmonary TB, these tests should not be used alone to exclude a diagnosis of active TB.[42] The American Academy of Pediatrics advises that a negative result of either TST or IGRA should be considered especially unreliable in a child younger than 3 months.[43] Interpretation of the TST depends on patient characteristics including immunocompetence and vaccination status. For patients with normal immunity and no additional risk factors, induration of ≥15 mm in diameter is taken to mean a positive result, but a smaller diameter is used as a cut-off in people with additional risk factors and in children.[12] [30] [44] An IGRA may be used in place of a TST in all situations in which TSTs are used to diagnose latent infection, though TST may be preferred in children aged younger than 2 years.[43] [45] An IGRA is preferred in individuals with a history of bacille Calmette-Guérin vaccination due to superior specificity.[44] In addition, IGRA is preferred for testing persons from groups that historically have low rates of returning to have TSTs read.

Targeted testing for latent TB infection is recommended by the US Centers for Disease Control and Prevention/American Thoracic Society as part of strategic control and reduction of TB. High-risk groups include people with HIV, intravenous drug users, healthcare workers who serve high-risk populations, and contacts of individuals with pulmonary TB.[12] Testing for latent TB infection should also be performed in patients prior to tumour necrosis factor-alpha antagonist therapy.[46]

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 TB infection, reporting that the diagnostic accuracy of TBSTs is similar to that of IGRAs and greater than that of the TST.[47]

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include exposure to infection, immunosuppression, silicosis, malignancy, birth in an endemic country, and HIV in appropriate areas.

cough (common)

- Duration over 2 to 3 weeks; initially dry, later productive. Outpatient study found that only 50% of patients had cough over 2 weeks.[48]

fever (common)

- Fever is usually low-grade. Up to 20% of patients may have no fever. Fever is less common in older people.

anorexia (common)

- May be seen in patients with other suggestive symptoms.

weight loss (common)

- May be seen in patients with other suggestive symptoms.

malaise (common)

- May only be noticed in hindsight, after treatment.

Other diagnostic factors

night sweats (common)

- If present; usually drenching.

pleuritic chest pain (uncommon)

- May suggest pleuritic involvement.

haemoptysis (uncommon)

- Present in <10% of patients (typically with advanced disease). May be the result of sequelae (e.g., bronchiectasis) and not represent active disease.

psychological symptoms (uncommon)

- May include depression or hypomania.

abnormal chest auscultation (uncommon)

- Chest examination may be normal in mild/moderate disease. Possible findings include crackles, bronchial breath sounds, or amphoric breath sounds (distant hollow breath sounds heard over cavities).

asymptomatic (uncommon)

- Patient may be asymptomatic and diagnosis made from coincidental findings or screening.

dyspnoea (uncommon)

- A late finding in the setting of extensive lung destruction or effusion.

clubbing (uncommon)

- Only in long-standing disease.

erythema nodosum and erythema induratum (uncommon)

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

Risk factors

Strong

exposure to infection

- This is necessary but not sufficient for development of TB. Among household contacts, approximately one third acquire latent TB infection and 1% to 2% are found to have active TB disease. People with recently acquired infection (e.g., tuberculin skin test conversion within the past 2 years) have a greatly increased risk of developing active TB.[11] [12]

birth in an endemic country

- High-risk regions include Asia, Latin America, and Africa.[13]

HIV infection

- Increases the risk for both progression to primary disease and re-activation of latent disease. The risk for re-activation in an HIV-positive patient with latent infection is up to 10% per year, as opposed to 10% lifetime risk in HIV-negative patients. In addition, active TB has been found to increase HIV viral loads.[14] [15] [16] [17]

immunosuppressive medicines

- Especially systemic corticosteroids and tumour necrosis factor-alpha antagonists. Risk with steroids increases with increasing doses (odds ratio 7.7 for >15 mg/day of prednisone) and varies with underlying condition. The risk with infliximab is greater than with etanercept. Relative risk following organ transplantation is 20- to 74-fold greater.[18] [19]

silicosis

- 30 times increased risk compared with controls.[21]

apical fibrosis

- Patients whose chest x-ray shows upper lobe fibrotic opacities consistent with prior untreated pulmonary TB are at greater risk for developing active disease (estimated risk ≥0.3% per year, depending on the size of radiographic abnormalities).[22]

Weak

malignancy

- Risk is increased in patients with haematological malignancy and head and neck cancer. However, US-born patients with other solid tumours do not appear to be at higher risk of progression to active TB.[20]

end-stage renal disease

- Patients on haemodialysis are at increased risk.

intravenous drug use

- Increases risk, even without HIV infection.[12]

malnutrition

- Includes people with low body weight (<90% of ideal body weight), coeliac disease, and history of gastrectomy. Risk is also greater in patients with jejunoileal bypass.

alcoholism

- Hard to separate from other risk factors.

diabetes

- The estimated global prevalence of diabetes among patients with pulmonary TB in one meta-analysis was 13.73%.[23]

high-risk congregate settings

- Residents or employees of correctional facilities, homeless shelters, or nursing homes are at increased risk.

low socio-economic status or black/Hispanic/Native American ancestry

- Multivariate models suggest at least half the risk attributed to ethnicity (black, Hispanic, Native American) may be the result of low socio-economic status.[24]

age

- Both the very young (age <5 years) and older people are at increased risk for progression to disease.

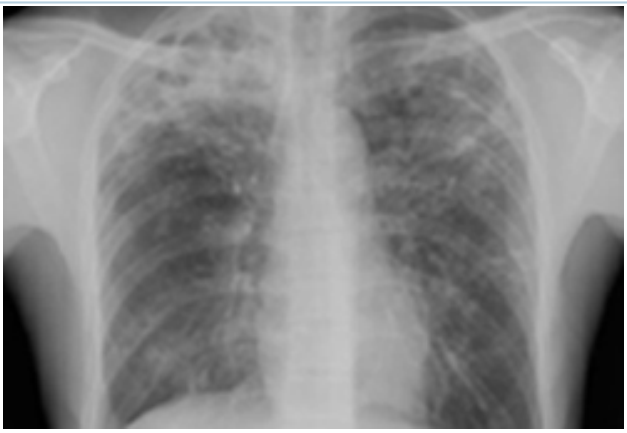
tobacco smoking

- There is an association between passive or active tobacco smoke exposure and latent infection, active TB, and poor outcome following TB treatment.[10] [25]

Investigations

1st test to order

Test	Result
chest x-ray • First-line test. • Is almost always abnormal in immunocompetent individuals. Typically presents as fibronodular opacities in upper lobes with or without cavitation. Atypical pattern includes opacities in middle or lower lobes, hilar or paratracheal lymphadenopathy, and/or pleural effusion.	**abnormal typical for TB; abnormal atypical for TB; or normal**



Pulmonary TB with cavitation
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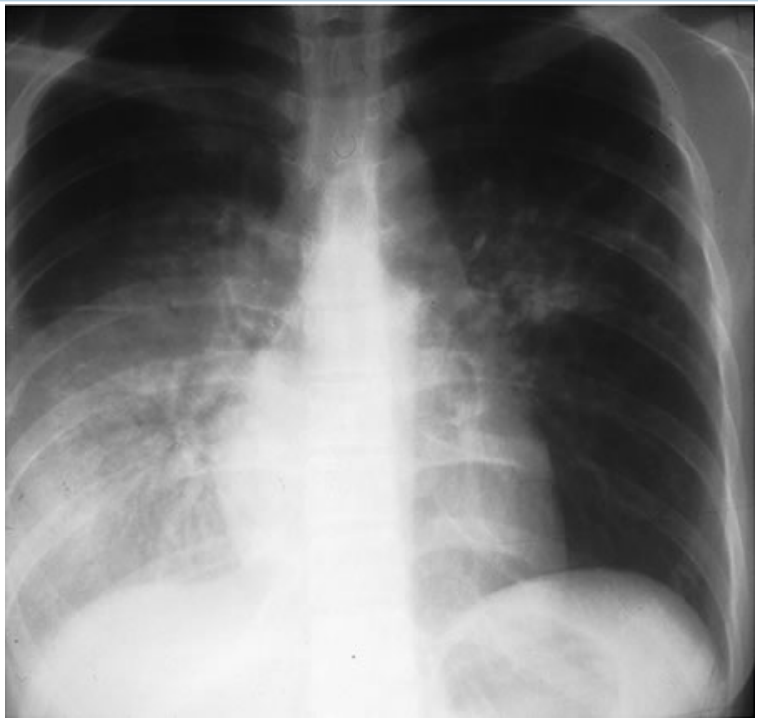
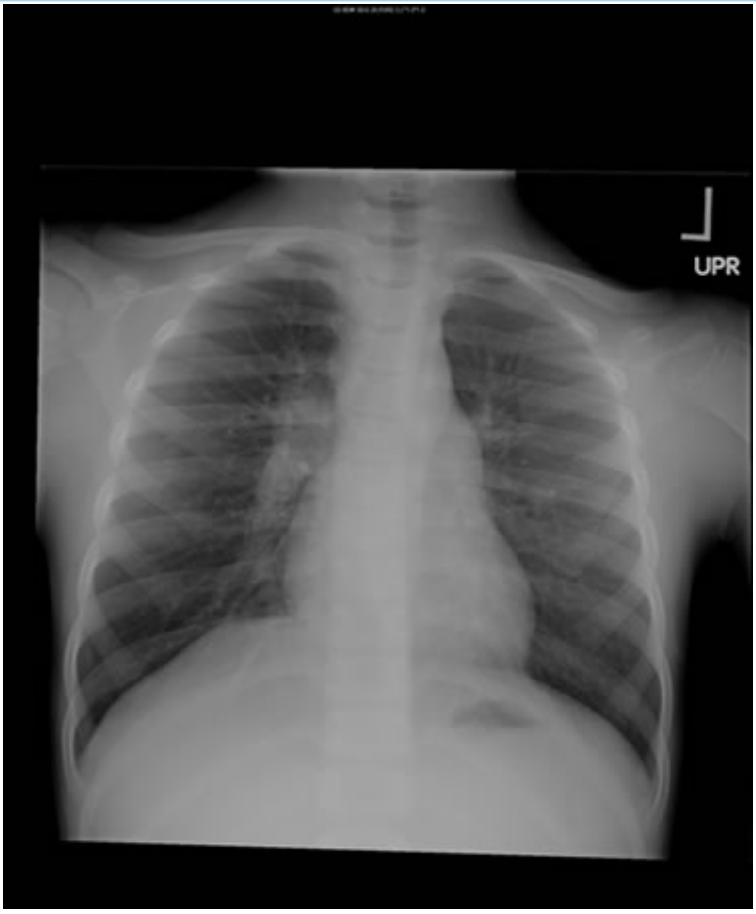
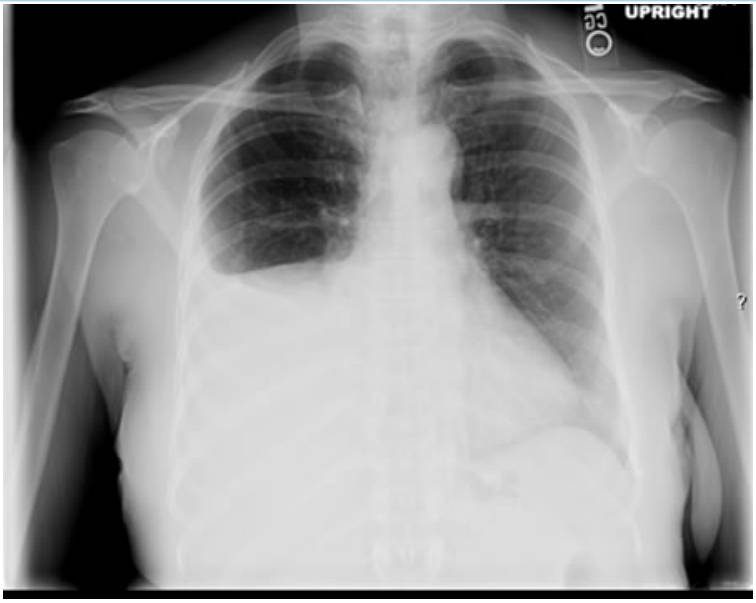
Test	Result



Opacities in right lower lobe in a patient with pulmonary TB and diabetes
From the personal collection of David Horne and Masahiro Narita; used with permission

Test	Result
 *Right hilar adenopathy in a child* *From the personal collection of David Horne and Masahiro Narita; used with permission*	

Test	Result
 *Right-sided pleural effusion* *From the personal collection of David Horne and Masahiro Narita; used with permission* • Studies indicate that an atypical chest radiograph is a reflection of immunosuppression, rather than primary TB.[49] • HIV status is associated with lymphadenopathy, effusion, lower lung zone involvement, and miliary pattern; cavitary lesions are less often seen. Patients with advanced HIV may have a normal chest x-ray.[49] [50]	
sputum acid-fast bacilli smear • Sputum may be spontaneously expectorated or induced (with appropriate precautions to prevent transmission), and three specimens should be collected (minimum 8 hours apart, including an early morning specimen, which is the best to detect *Mycobacterium tuberculosis*).[12] • The examiner looks for acid-fast bacilli (AFB) (the stained dye remains even after exposure to acidic media) consistent with *M tuberculosis* . Other organisms, especially non-tuberculous mycobacteria (e.g., *Mycobacterium kansasii* and *Mycobacterium avium*), are positive on AFB stain. Thus, a positive AFB smear is not specific in populations with low TB prevalence. • If sputum is positive for AFB, the results will be graded from 1+ to 3+ or 4+ depending on number of organisms seen and grading scale. Smear positivity and its grading may help estimate the degree of infectiousness and burden of TB. In the US, sensitivity is 50% to 60%.[51]	**positive for AFB**

Test	Result
sputum culture • The most sensitive and specific test. Should always be performed as it is required for precise identification and for drug susceptibility testing. • Growth on solid media may take 4 to 8 weeks; growth in liquid media may be detected in 1 to 3 weeks. Growth on solid media if positive is reported on quantitation scale (1+ to 4+). • While on treatment, the patient should have sputum cultures performed at least monthly until two consecutive cultures are negative.[9]	**positive; no growth; or other mycobacteria**
FBC#(full blood count) • Leukocytosis (without left shift) and anaemia each seen in 10%.[52] Other abnormalities include elevated monocyte and eosinophil counts. Pancytopenia may be seen in disseminated disease.	**raised WBC; low Hb**
nucleic acid amplification tests (NAAT) • NAAT should be performed on at least one respiratory specimen when a diagnosis of TB is being considered. NAAT may speed the diagnosis in smear-negative cases and may be helpful to differentiate non-tuberculous mycobacteria when sputum is AFB smear positive but NAAT negative.[31] Genotyping might be considered useful in outbreaks of TB to identify transmission of TB, especially when contact had not been appreciated in the course of epidemiological investigations. Several rapid NAATs are available and some are also able to detect genes encoding resistance to TB drugs.[32] [33] [34]	**positive for *M tuberculosis***

Other tests to consider

Test	Result
gastric aspirate • Used in patients unable to produce sputum (e.g., young children). Based on overnight collection of bronchial secretions in the stomach. In early morning after 8 to 10 hours of fasting, 10 to 20 mL of sterile water infused into stomach through nasogastric tube and 50 mL aspirated. After neutralisation, the aspirate is sent for culture.[12]	**positive for acid-fast bacilli**
bronchoscopy and bronchoalveolar lavage • Many studies demonstrate that sputum induction has better sensitivity for TB diagnosis than bronchoscopy and bronchoalveolar lavage (BAL).[12] BAL may be indicated in patients in whom sputum induction is unsuccessful or in whom smear and nucleic acid amplification tests are negative. Bronchoscopy is useful when other diagnoses strongly considered or in patients in whom pulmonary TB is still suspected after other methods proved non-diagnostic. • Highest yield sputum collection is first expectorated sputum following bronchoscopy. • Transbronchial lung biopsies are useful in the diagnosis of miliary disease as granulomas may be seen and/or *Mycobacterium tuberculosis* may be cultured.	**positive for acid-fast bacilli**
stool testing • Use of stool samples is an alternative to respiratory specimens in diagnosis of pulmonary TB (sputum is swallowed and *M tuberculosis* may pass through the gastrointestinal tract). One systematic review evaluating AFB-smear, culture, and NAAT (polymerase chain reaction [PCR]) testing of stool in pulmonary TB found a pooled sensitivity of one or more of the three tests was 79.1% (95% CI 61.5 to 92.5).[38] The sensitivity of stool microscopy, PCR, and culture was 41.1% (95% CI 24.9 to 58.2), 89.7% (95% CI 81.4 to 95.9), and 38.0% (95% CI 26.2 to 50.6).[38]	**positive for acid-fast bacilli and/or *M tuberculosis***
tuberculin skin testing • A negative tuberculin skin test (TST) does not rule out active TB as false-negative results occur in 20% to 25% of patients with active pulmonary TB.[42] The sensitivity of TST in diagnosing active TB is around 75% to 80% and its inability to distinguish between latent infection and active disease limits its usefulness. • The TST uses 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. • There is diminished immune response in patients with active TB, especially with increased age, poor nutrition, and advanced disease.[53]	**millimetres of induration; 0-4 mm generally considered negative and no treatment indicated, though may be considered positive in child under 5 years of age at high risk of TB infection; ≥5 mm considered positive in situation of HIV infection, contact with infectious TB case within past 2 years, fibrotic opacities on chest x-ray consistent with untreated but healed TB, severely immunosuppressed patients (e.g., organ transplant, tumour necrosis factor-alpha-blocker, prednisolone ≥15 mg/day for 1 month**

Test	Result
	or longer); ≥10 mm considered positive in situation of TST conversion within 2 years, medical or social conditions associated with increased risk of progression to active TB (e.g., diabetes, malnutrition, cigarette smoking, alcohol consumption >3 drinks/ day, intravenous drug users, leukaemia, lymphoma, head and neck cancer, lung cancer, chronic renal failure), recent immigrants from countries with high prevalence of TB, residents and employees of high-risk congregate settings (e.g., nursing homes, prisons), TB laboratory personnel; ≥15 mm considered positive in people with no risk factors for TB
interferon-gamma release assays • Measure the response of T cells to TB antigens in order to diagnose prior exposure. • interferon-gamma release assays, similar to tuberculin skin testing, have low sensitivity in diagnosing active TB, with a false-negative rate of 20% to 25% in patients with active pulmonary TB.[42] They do not distinguish between latent infection and active disease, which limits their usefulness in the diagnosis of active TB. Sensitivity of QuantiFERON®-TB Gold for active TB is 75%.[53] [54]	**positive**
empirical treatment • Diagnosis of active TB may be made based on clinical history including risk factors and radiographic findings. • Other diagnoses and evaluation with bronchoscopy and bronchoscopy and bronchoalveolar lavage should be considered if the suspicion for TB is not high enough or differential diagnoses, including concurrent pathology, affect clinical management. • When clinical suspicion of pulmonary TB is high, empirical TB treatment with standard regimen (isoniazid, rifampicin, pyrazinamide, ethambutol) is generally initiated after collecting optimal sputum samples. • For culture-negative cases who are placed on empirical TB treatment, a clinical and radiographic response should be re-evaluated at 2 months of treatment, and isoniazid and rifampicin continued for at least 2 more months (4 months of treatment in total) if there is a clinical and radiographic response. If there was not a response at 2 months of treatment, TB medicines should be stopped and another diagnosis looked for.[9]	**clinical response**

Test	Result
drug susceptibility testing • Perform on initial isolates.	**drug sensitivities**
genotyping • Useful in the investigation of outbreaks, contacts, and laboratory cross-contamination, as well as epidemiological studies. There is evidence that some strain 'families' of TB may have increased virulence. • Currently, the US Centers for Disease Control and Prevention and other laboratories use spoligotyping (a polymerase chain reaction method for simultaneous detection and typing of strains of *Mycobacterium tuberculosis*) and/or a technique called mycobacterial interspersed repetitive units-variable number tandem repeats (MIRU-VNTR) as initial genotyping techniques.	**genotype of infective agent**
HIV test • It is recommended that all patients with TB have an HIV test within 2 months of diagnosis of TB.[9] In the setting of HIV infection, pulmonary TB is an AIDS-defining diagnosis. • HIV infection may alter the treatment of TB and treatment of HIV infection may lead to more rapid resolution of TB.[9]	**positive or negative**
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.[39] The World Health Organization recommends that LF-LAM can be used to assist in the diagnosis of active TB in HIV-positive adults, adolescents, and children.[30] [32] 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.[40] • Culture would still be required for drug susceptibility testing.	**positive**
CT of chest • Not part of the standard evaluation but may assist in assessing for other diagnoses. May show same patterns of disease as seen with chest x-ray. In addition, there may be a tree-in-bud pattern. Cavities that are seen on CT, but are not noted on chest x-ray, do not place the patient in the category of cavitary disease.	**abnormal**
TB antigen-based skin tests (TBSTs) • 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 TB infection, reporting that the diagnostic accuracy of TBSTs is similar to that of interferon gamma release assays and greater than that of the TST.[47]	**positive**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Coronavirus disease 2019 (COVID-19)	• Residence in/travel to a country/area or territory with local transmission, or close contact with a confirmed or probable case of COVID-19, in the 14 days prior to symptom onset. • The situation is evolving rapidly; see our COVID-19 topic for further information.	• Real-time reverse transcription polymerase chain reaction (RT-PCR): positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA.
Community-acquired pneumonia	• Signs of lobar or atypical pneumonia including crackles and dyspnoea. Generally, shorter duration of symptoms compared with TB. If there is doubt, consider treating for bacterial pneumonia first (without using fluoroquinolones or other antibiotics with significant anti-tuberculous activity) and assess for response.	• Sputum examination with presence of bacteria other than normal flora.
Lung cancer	• TB and lung cancer may co-exist; malignancy may erode granulomas. Despite acid-fast bacilli in sputum, if features suggest cancer (e.g., irregular cavities) or lung abnormalities progress in patients on anti-tuberculous treatment, further evaluation for cancer should be pursued.[52]	• Sputum cytology; CT of the chest; tissue biopsy.
Non-tuberculous mycobacteria	• Nontuberculous mycobacteria, present in soil and water, such as Mycobacterium avium complex and *Mycobacterium kansasii* may present as non-cavitary or cavitary lung disease. Patient risk factors for TB may point to most likely diagnosis.	• If sputum acid-fast bacilli culture is positive, DNA probe may be used for species identification. Similarly a nucleic acid amplification test that is negative for TB on a smear-positive sputum (95% sensitivity) makes *Mycobacterium tuberculosis* less likely after polymerase chain reaction inhibitors have been excluded. Non-tuberculous mycobacteria

Condition	Differentiating signs / symptoms	Differentiating tests
		is more common in patients with underlying lung disease.
Fungal infection	• Potential fungi include histoplasmosis, coccidioidomycosis, and blastomycosis. Travel history may help narrow the differential diagnosis.	• Sputum culture and serum antibody titres positive for fungal infection and negative for *Mycobacterium tuberculosis* .
Sarcoidosis	• Other features of sarcoidosis, such as intrathoracic lymphadenopathy and arthralgias, may be present.	• Sputum culture will be negative in sarcoidosis.
Nocardiosis	• Clinical differentiation is difficult. In immunocompetent patients, cavities are more frequently related to tuberculosis. In immunocompromised patients, particularly patients with AIDS, cavities are less frequently associated with tuberculosis and very common in nocardiosis.[55]	• *Mycobacterium* can be differentiated from *Nocardia* in clinical samples, because mycobacteria do not stain well with Gram stain and modified acid-fast stain. They are also microscopically different from *Nocardia* .[56]

Criteria

Centers for Disease Control and Prevention: 2009 case definition of#TB[57]

Clinical criteria

A case that meets all the following criteria:

- A positive tuberculin skin test or positive interferon gamma release assay for *Mycobacterium tuberculosis*
- Other signs and symptoms compatible with TB (e.g., abnormal chest radiograph, abnormal chest computerised tomography scan or other chest imaging study, or clinical evidence of current TB disease)
- Treatment with two or more anti-tuberculosis medications
- A completed diagnostic evaluation.

Laboratory criteria for diagnosis:

- Isolation of *M tuberculosis* from a clinical specimen, OR
- Demonstration of *M tuberculosis* complex from a clinical specimen by nucleic acid amplification test, OR

- Demonstration of acid-fast bacilli in a clinical specimen when a culture has not been or cannot be obtained or is falsely negative or contaminated.

Confirmed case:

A case that meets the clinical case definition or is laboratory confirmed.

World Health Organization: case definition of TB[58]

Clinically diagnosed TB:

- A case which does not fulfil the criteria for bacteriological confirmation, but has been diagnosed with active TB by a clinician or other medical practitioner, and a full course of TB treatment is given
- This definition includes cases diagnosed on the basis of x-ray abnormalities or suggestive histology, and extrapulmonary cases without laboratory confirmation
- Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Bacteriologically confirmed TB:

- Biological specimen is positive by smear microscopy, culture, or World Health Organization-approved rapid diagnostics (e.g., Xpert MTB/RIF).

Bacteriologically confirmed or clinically diagnosed cases of TB are also classified according to:

- Anatomical site of disease
- History of previous treatment
- Drug resistance
- HIV status.

DIAGNOSIS

Screening

The US Centers for Disease Control and Prevention and the US Preventive Services Task Force recommend that asymptomatic adults at increased risk of infection in the US are screened for latent infection, including residents who were born in high-incidence countries, HIV patients, intravenous drug users, and contacts of individuals with pulmonary TB.[31] [59] Healthcare workers should be tested for latent infection if a TB exposure has occurred.[60] A tuberculin skin test or interferon gamma release assay are the standard method for identifying persons infected with the mycobacterium.[31] Screening persons other than high-risk population places a burden on resources and is therefore not recommended. Cochrane reviews of screening in children and in adults found that screening tests using symptoms or chest x-ray may be useful; however, better screening tests for tuberculosis are needed.[61] [62]

Screening is only one aspect of controlling the disease; it is recommended that priority should be given to completion of treatment of active disease and investigating contacts.

The World Health Organization (WHO) guidelines on systematic screening for TB outline key populations who should be prioritised for TB screening.[63] 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.[63]

Approach

The main goals are to cure the patient and to prevent further transmission of TB to others. The treating physician acts in a public health role as well and thus is responsible for ensuring that the patient successfully adheres to and completes treatment.

Treatment is initiated when TB is confirmed or strongly suspected and consists of an initial intensive phase and a subsequent continuation phase.

While infectious, patients should remain isolated (at home or in an appropriate room in the hospital). The treating physician should discuss the case with the local public health department to learn specific local requirements and to initiate a contact investigation in a timely fashion. Refer to guidelines for latest recommendations.

Contacts of a patient with infectious TB

People who have had significant exposure in the previous 1-2 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.[9]

For patients with LTBI that is presumed to be susceptible to isoniazid or rifampicin, World Health Organization (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).[64] One month of daily rifapentine plus isoniazid (age 13 years and over) or 4 months of daily rifampicin (all ages) are alternative regimens.[64] Isoniazid and rifampicin are options for use in pregnant women with or without HIV who are eligible for preventive treatment.[64] Rifamycins should only be used if there are no significant interactions with other medications (e.g., antiretroviral therapy).

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 for those in whom neuropathy is common (e.g., diabetes, uraemia, alcoholism, malnutrition, HIV infection), for pregnant women, or for patients with seizure disorders.[21]

For patients with LTBI presumed to be due to contact with an infectious patient with multidrug-resistant (MDR) TB, the US guidelines recommend treatment with 6-12 months of a fluoroquinolone (e.g., levofloxacin or moxifloxacin) alone or in combination with a second agent based on susceptibility testing of the source isolate.[65] Expert consultation should be sought, particularly for the management of pregnant patients. WHO guidelines recommend that, in selected high-risk household contacts of patients with multidrug resistant TB, preventative treatment may be considered based on individualised risk assessment and a sound clinical justification.[64]

Mode of administration: active TB

To reduce non-adherence rates, therapy can be given by a healthcare professional in conjunction with a local public health authority as directly observed therapy (DOT). DOT should be given daily, whenever

this is feasible.[66] Although one systematic review has concluded that DOT does not provide a solution to poor adherence in TB treatment, the US and WHO guidelines recommend its use for all patients, especially in certain populations, such as drug-resistant disease; HIV co-infection; substance abuse; psychiatric illness; children and adolescents; and others who, in the physician's opinion, might not comply with self-administered therapy (SAT).[9] [66] [67] [68] [Evidence B] 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 recommend the use of vDOT as equivalent to in-person DOT for patients undergoing tuberculosis treatment.[69] In the 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.[70] Intermittent therapy should be supervised. Non-supervised therapy (SAT) should be daily, 7 days a week. Other regimens may be used; consult guidelines for details.[9] [66]

Intensive phase

WHO guidelines for the treatment of drug-susceptible active pulmonary TB include regimens that are given for a total duration of 4 or 6 months.[66]

The standard 6-month regimen is recommended by the WHO for new patients with pulmonary TB. The initial intensive phase treatment for the 6-month regimen includes the preferred drugs of isoniazid, rifampicin, pyrazinamide, and ethambutol, and lasts 2 months.[66] Patients aged between 3 months and 16 years with non-severe TB (defined as 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.[30] [66] Ethambutol should be included in areas of high prevalence of HIV or isoniazid resistance.[30] [66] Children and adolescents who do not meet the criteria for non-severe TB should receive the standard 6-month treatment regimen (including ethambutol).[30] [66]

Patients aged 12 years and over may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin, and pyrazinamide. The intensive phase of this regimen includes daily administration of isoniazid, rifapentine, moxifloxacin, and pyrazinamide and also lasts 2 months.[66] [71] This regimen is not currently recommended for young children, persons who are pregnant, and patients with HIV infection and CD4 count of <100 cells/microlitre.[66]

Pyridoxine should be administered with isoniazid to help prevent isoniazid-associated neuropathy.

It is unlikely that adjunctive corticosteroid treatment provides major benefits for people with pulmonary TB, and thus its routine use is not recommended.[72]

Continuation phase

WHO guidelines recommend that patients completing the initial intensive standard regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol continue to receive isoniazid and rifampicin in the continuation phase for 4 months (a total of 6 months treatment). Children aged 3 months to 16 years with non-severe pulmonary TB should receive 2 months of continuation phase therapy (4 months total). Those with severe TB, and also children aged less than 3 months, should receive the standard 6-month treatment regimen.[30] [66]

In the continuation phase of the 4-month isoniazid, rifapentine, moxifloxacin, and pyrazinamide regimen, isoniazid, rifapentine, and moxifloxacin are given for another 2 months (total of 4 months).[66] [71]

Interruptions in treatment

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.[9]

Patients with HIV co-infection

Treatment of HIV-positive patients is similar to that of non-HIV-positive patients.[66] Therapy may be DOT or SAT, although DOT is highly recommended for HIV-positive patients.[9] Treatment should be administered daily.

Patients with HIV can be maintained on standard therapy, but rifabutin may be considered in place of rifampicin, depending on the antiretroviral therapy (ART) regimen the patient is on.

Rifabutin has less effect on the serum concentrations of protease inhibitors than rifampicin. Patients on protease-inhibitor-based ART regimens should receive rifabutin instead of rifampicin in their TB-treatment regimen. Specialist consultation is recommended when considering use of rifabutin while the patient is on a protease-inhibitor.

WHO guidelines recommend initiation of ART as soon as possible within 2 weeks after starting treatment for TB, regardless of CD4 count.[66] Survival is improved in co-infected individuals with CD4+ counts of <50 cells/microliter if ART is initiated within 2 weeks of starting TB treatment.[73] [74] [75] Management of patients with additional comorbidities is complex, and will require consultant advice.

Impaired renal function

Patients who have reduced renal function but have a creatinine clearance >30 mL/minute should receive medications in the standard doses. However, monitoring serum drug levels should be considered.[9]
In patients with a creatinine clearance of <30 mL/minute, ethambutol and pyrazinamide are given three times a week (dose given after haemodialysis if the patient is on dialysis; expert consultation recommended).[9]

Drug-induced hepatitis or pre-existing liver disease

Tests for hepatitis A, B, and C should be ordered if the patient has no pre-existing liver disease but has abnormal liver function test results. Patients should be asked about other hepatotoxins, including alcohol use. Liver function (aminotransferases, bilirubin, alkaline phosphatase) should be checked at baseline. Monthly liver function tests (LFTs) should be obtained in patients with abnormal baseline liver function, underlying liver disease, HIV co-infection, and other risk factors for hepatitis.

Isoniazid, rifampicin, and pyrazinamide can all cause or exacerbate liver disease. The decision about whether it is safe to continue one, two, or all three of these drugs depends on severity of liver disease. An asymptomatic increase in alanine aminotransferase (ALT) occurs in 20% of patients treated with regimens containing these drugs. If this is under five times upper limit of normal (ULN) with no symptoms, or less than three times ULN with symptoms, first-line regimens can be continued, but LFTs and symptoms should be monitored.

Where ALT increase is more than five times ULN, or more than three times ULN with symptoms, hepatotoxic drugs should be stopped and treatment initiated with at least three drugs without hepatotoxic effects (e.g., ethambutol, fluoroquinolone, and linezolid) especially if the burden of TB is more than minimal. It may be possible to continue with one or two of the more effective drugs, isoniazid and/or rifampicin, with careful monitoring of liver function, especially when ALT becomes less than two times ULN. These can be serially re-introduced, one by one, waiting 4-7 days before adding the next drug. Before introducing each new drug, LFTs should be checked. If an increase in ALT occurs, the most recently introduced drug is likely responsible for the hepatitis.[9] [76]

When using fluoroquinolones, clinicians should be aware that they have been associated with disabling and potentially irreversible musculoskeletal and nervous system adverse events.[77] In addition, the US Food and Drug Administration has issued warnings about the increased risk of aortic dissection, significant hypoglycaemia, and mental health adverse effects in patients taking fluoroquinolones.[78] However, considering the benefit-risk ratio in selected situations (e.g., drug-induced hepatitis, isoniazid-resistant TB), levofloxacin and moxifloxacin may play a key role in TB treatment.

Although rifabutin may cause hepatic injury (mainly a cholestatic pattern like rifampicin), it has been found to be less hepatotoxic compared with rifampicin and may be substituted for rifampicin in order to achieve short-course TB regimen. For example, if liver injury recurs with the re-introduction of rifampicin, rifabutin may be considered as a replacement.

Management of patients with additional comorbidities is complex, and will require consultant advice.

Pregnancy and breastfeeding

Pregnant women who are suspected of having active TB should be treated as there is a risk of TB transmission to the fetus. Initial treatment is normally with isoniazid, rifampicin, and ethambutol. Pyrazinamide is probably safe and can be considered in addition to triple therapy, especially for patients with HIV infection or high bacillary burden. The minimum total duration of treatment is 9 months for women who did not receive pyrazinamide as part of the initial regimen.[9]

Women taking anti-tuberculosis treatment can breastfeed because only low levels of drugs are passed into the milk. However, levels are not high enough to provide effective treatment for the baby.[9]

Management of patients with additional comorbidities is complex, and will require consultant advice.

Isoniazid-resistant TB

Isoniazid-resistant TB is defined as resistance to isoniazid and susceptibility to rifampicin that has been confirmed in vitro. The WHO estimates that globally, 13.1% of patients with new TB and 17.4% of patients with previously treated TB have rifampicin-susceptible, isoniazid-resistant infection.[2] In patients with confirmed rifampicin-susceptible and isoniazid-resistant TB, WHO recommends treatment with rifampicin, ethambutol, pyrazinamide, and levofloxacin for a duration of 6 months.[79] If levofloxacin cannot be used (because of toxicity or resistance) WHO recommends that the patient is treated with rifampicin, ethambutol, and pyrazinamide for 6 months.[79]

Resistance to rifampicin must be excluded before starting the regimen, and preferably, resistance to fluoroquinolones and pyrazinamide should also be excluded. If isoniazid resistance is identified after a patient has started a regimen for drug-susceptible TB, rapid molecular testing for rifampicin resistance should be done, and if rifampicin resistance is excluded, the patient should begin a full 6-month course

of rifampicin, ethambutol, pyrazinamide, and levofloxacin. If rifampicin resistance is detected, the patient should begin an appropriate treatment regimen for multidrug-resistant TB.[79]

In contrast to regimens for drug-susceptible and multidrug-resistant TB, the recommended treatment regimens for isoniazid-resistant TB do not have initial intensive and continuation phases.

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 TB is defined as resistance to at least isoniazid and rifampicin, as well as any fluoroquinolone, and either bedaquiline or linezolid (or both).[80] Pre-XDR-TB is resistance to isoniazid, rifampicin, and any fluoroquinolone.

Drug resistance may be suspected on the basis of historical or epidemiological information. Management requires expert consultation.

Patients with rifampicin-resistant (RR) TB are also eligible for treatment with MDR TB regimens.[79] 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.[79] 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).[79] [81] [82] The WHO suggests that this regimen is used where appropriate rather than the 9-month or longer MDR/RR-TB regimens.[79] The WHO advises that if the patient has documented resistance to fluoroquinolones, then the regimen should continue without moxifloxacin (BPaL); although initiation of BPaLM should not be delayed while waiting for results of drug susceptibility testing. The WHO recommends the use of this 6-month regimen for adults and adolescents aged 14 and over, regardless of HIV status, who have less than 1 month exposure to bedaquiline, linezolid, pretomanid, or delamanid.[79]

The 9-month all-oral regimen is recommended by the WHO 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.[79] 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 TB disease, regardless of HIV status, and who have less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid, and clofazimine.[79]

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.[79] This longer term regimen is recommended for all patients who do not fulfil the criteria for the shorter term regimens.[79] 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.[79]

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.

Specific regimens should be selected by a specialist in the treatment of MDR TB.[79] The total number of TB medicines to include in the regimen needs to balance expected benefit with risk of side effects and non-adherence when the pill burden is high.

In patients with RR TB or MDR TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR TB regimen.[79]

Management of patients with additional comorbidities is complex, and requires specialist advice.

Treatment failure and TB recurrence

WHO defines treatment failure as a positive sputum smear or culture at 5 months or later during TB treatment.[58] When either the sputum smear or culture remains positive beyond 2-3 months into TB treatment, adherence with TB medications must be verified. Emerging drug-resistant TB during treatment and gastrointestinal malabsorption of TB medications should also be evaluated.

Recurrence of TB occurs in a case previously considered to have been successfully treated for TB. Recurrent cases include relapses due to the same *M tuberculosis* strain as that responsible for the previous episode, as well as new episodes of TB due to re-exposure resulting in reinfection. In the US, recurrence is generally a result of recrudescence of the original organism (i.e., relapse), whereas in TB-endemic countries, it may be the result of exogenous reinfection. Most relapse events occur in the first 6-12 months following completion of treatment and occur in 2% to 5% of appropriately treated patients.[83]

If the patient initially had drug-susceptible isolates and treatment was directly observed, recurrence will likely be the result of the same susceptible organisms and prior therapy can be used. However, if the patient initially received SAT, there is a greater possibility of the development of a drug-resistant organism.

In this situation, or if drug susceptibility has not previously been tested, an expanded MDR TB regimen with addition of at least two new drugs not previously used should be considered.

If exogenous reinfection is suspected, TB treatment should be based on the drug susceptibility profile of the index case, if known.[9]

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	**specialty consultation**

Acute (summary)

active TB HIV-negative non-pregnant: no hepatic dysfunction		
▪ drug resistance not suspected	1st	intensive phase therapy
	plus	continuation phase therapy
▪ isoniazid resistance	1st	anti-tuberculosis treatment
▪ multidrug resistance	1st	standardised 6-month regimen
	adjunct	surgery
	1st	standardised 9-month regimen (intensive phase)
	plus	standardised 9-month term regimen (continuation phase)
	adjunct	surgery
	1st	standardised or individualised longer term regimen
	adjunct	surgery
active TB HIV-positive non-pregnant: no hepatic dysfunction		
▪ drug resistance not suspected	1st	intensive phase therapy
	plus	continuation phase therapy
▪ isoniazid resistance	1st	anti-tuberculosis treatment
▪ multidrug resistance	1st	standardised 6-month regimen
	adjunct	surgery
	1st	standardised 9-month regimen (intensive phase)
	plus	standardised 9-month term regimen (continuation phase)
	adjunct	surgery
	1st	standardised or individualised longer term regimen
	adjunct	surgery
active TB pregnant		
	1st	speciality consultation

Acute			(summary)
active TB non-pregnant: pre-existing or drug-induced hepatic dysfunction			
	1st	**speciality consultation**	

Ongoing			(summary)
recurrent TB			
	1st	**speciality consultation**	

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

Initial

-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.

» Treatment for latent infection can be considered prior to this, and in people with a positive skin test (usually taken to be induration ≥5 mm in this patient group) but no clinical or bacteriological sign of active infection.

» The decision whether to treat depends on the duration, proximity, and environment of exposure, as well as the immune status of the exposed contacts.[9]

» For patients with LTBI that is presumed to be susceptible to isoniazid or rifampicin, World Health Organization (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).[64] One month of daily rifapentine plus isoniazid (age 13 years and over) or 4 months of daily rifampicin (all ages) are alternative regimens.[64]

Initial

Rifamycins should only be used if there are no significant interactions with other medications (e.g., antiretroviral therapy).

» 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.[21] [64] [84]

» Ideally, all medications within a given regimen should be administered at the same time of day if possible. 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.[9]

» 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 multidrug-resistant (MDR) TB, the US guidelines recommend treatment 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.[65] Specific regimens are not detailed here and expert consultation should be sought. 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.[64]

latent TB infection: pregnant

1st **specialty consultation**

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

Initial

increased incidence of serious drug-induced hepatitis during perinatal period.

» Specialist consultation is recommended in pregnancy.

Acute

active TB HIV-negative non-pregnant: no hepatic dysfunction

drug resistance not suspected

1st

intensive phase therapy

Primary options

4- or 6-month regimen

» isoniazid: 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
-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.

OR

4-month regimen

» isoniazid: children ≥12 years of age and ≥40 kg body weight and adults: 300 mg orally once daily
Pyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.
-and-
» rifapentine: children ≥12 years of age and ≥40 kg body weight and adults: 1200 mg orally once daily
-and-
» moxifloxacin: children ≥12 years of age and ≥40 kg body weight and adults: 400 mg orally once daily
-and-
» pyrazinamide: children ≥12 years of age and ≥40 kg body weight and adults: consult specialist for guidance on dose (dose is based on lean body weight and available tablet formulation)

» World Health Organization (WHO) guidelines for the treatment of drug-susceptible active

Acute

pulmonary TB include regimens that are given for a total duration of 4 or 6 months.[66]

» The standard 6-month regimen is recommended by the WHO for new patients with pulmonary TB. The initial intensive phase treatment for the 6-month regimen includes the preferred drugs of isoniazid, rifampicin, pyrazinamide, and ethambutol, and lasts 2 months.[66] Patients aged between 3 months and 16 years with non-severe TB (defined as 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.[30] [66] Ethambutol should be included in areas of high prevalence of HIV or isoniazid resistance.[30] [66] Children and adolescents who do not meet the criteria for non-severe TB should receive the standard 6-month treatment regimen (including ethambutol).[30] [66]

» Patients aged 12 years and over may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin, and pyrazinamide. The intensive phase of this regimen includes daily administration of isoniazid, rifapentine, moxifloxacin, and pyrazinamide and also lasts 2 months.[66] [71] This regimen is not currently recommended for young children, persons who are pregnant, and patients with HIV infection and CD4 count of <100 cells/microlitre.[66]

» Pyridoxine should be administered with isoniazid to help prevent isoniazid-associated neuropathy, and is recommended in all cases of active TB.

» Pyrazinamide is used during the initial phase only. It is not recommended for patients with acute gouty arthritis (but can be used in patients with past history of gout) because of little information about the safety data.

» Expert consultation should be sought in patients with a creatinine clearance of <30 mL/minute.

plus **continuation phase therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

4- or 6-month regimen

MANAGEMENT

Acute

» 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-
» 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

4-month regimen

» isoniazid: children ≥12 years of age and ≥40 kg body weight and adults: 300 mg orally once daily
Pyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.
-and-
» rifapentine: children ≥12 years of age and ≥40 kg body weight and adults: 1200 mg orally once daily
-and-
» moxifloxacin: children ≥12 years of age and ≥40 kg body weight and adults: 400 mg orally once daily

» World Health Organization (WHO) guidelines recommend that patients completing the initial intensive standard regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol continue to receive isoniazid and rifampicin in the continuation phase for 4 months (a total of 6 months treatment). Children aged 3 months to 16 years with non-severe pulmonary TB should receive 2 months of continuation phase therapy (4 months total). Those with severe TB, and also children aged less than 3 months, should receive the standard 6-month treatment regimen.[30] [66]

» In the continuation phase of the 4-month isoniazid, rifapentine, moxifloxacin, and pyrazinamide regimen, isoniazid, rifapentine, and moxifloxacin are given for another 2 months (total of 4 months).[66] [71]

» Ideally, all medications within a given regimen should be administered at the same time of day if possible. 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. Daily therapy is preferred throughout the continuation phase.

Acute

» Pyridoxine should be administered with isoniazid to help prevent isoniazid-associated neuropathy, and is recommended in all cases of active TB.

isoniazid resistance | **1st** | **anti-tuberculosis treatment**

Primary options

» rifampicin
-and-
» ethambutol
-and-
» pyrazinamide
-and-
» levofloxacin

Secondary options

» rifampicin
-and-
» ethambutol
-and-
» pyrazinamide

» Isoniazid-resistant TB is defined as resistance to isoniazid and susceptibility to rifampicin that has been confirmed in vitro.[2]

» In patients with confirmed rifampicin-susceptible and isoniazid-resistant TB, the World Health Organization (WHO) recommends treatment with rifampicin, ethambutol, pyrazinamide, and levofloxacin for a duration of 6 months.[79] If levofloxacin cannot be used (because of toxicity or resistance) WHO recommends that the patient is treated with rifampicin, ethambutol, and pyrazinamide for 6 months.[79]

» Resistance to rifampicin must be excluded before starting the regimen, and preferably, resistance to fluoroquinolones and pyrazinamide would also be excluded. If isoniazid resistance is identified after a patient has started a regimen for drug-susceptible TB, rapid molecular testing for rifampicin resistance should be done, and if rifampicin resistance is excluded, the patient should begin a full 6-month course of rifampicin, ethambutol, pyrazinamide, and levofloxacin. If rifampicin resistance is detected, the patient should begin an appropriate treatment regimen for multidrug-resistant (MDR) TB.[79]

» In contrast to regimens for drug-susceptible and MDR TB, the WHO recommended treatment regimen for isoniazid-resistant TB does not have initial intensive and continuation phases.

Acute

multidrug resistance

1st **standardised 6-month regimen**

Primary options

» bedaquiline
-and-
» pretomanid
-and-
» linezolid
-and-
» moxifloxacin

» The 6-month all-oral regimen recommended by the World Health Organization (WHO) is composed of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM).[79] [81] [82] The WHO advises that if the patient has documented resistance to fluoroquinolones, then the regimen should continue without moxifloxacin (BPaL); although initiation of BPaLM should not be delayed while waiting for results of drug susceptibility testing.

» The WHO recommends the use of this 6-month regimen over the 9-month or longer multidrug-resistant (MDR)/rifampicin-resistant-TB regimens for adults and adolescents aged 14 and over, regardless of HIV status, who have less than 1 month exposure to bedaquiline, linezolid, pretomanid, or delamanid.[79]

» Specific regimens should be selected by a specialist in the treatment of MDR TB. Consult specialist for guidance on doses.

adjunct **surgery**

Treatment recommended for SOME patients in selected patient group

» In patients with rifampicin-resistant TB or multidrug-resistant (MDR) TB, elective partial lung resection (i.e., lobectomy or wedge resection) may be used alongside a recommended MDR TB regimen.[79]

1st **standardised 9-month regimen (intensive phase)**

Primary options

» bedaquiline
--AND--
» levofloxacin
-or-
» moxifloxacin
--AND--
» ethionamide
-or-

MANAGEMENT

Acute

» linezolid

--AND--

» clofazimine

--AND--

» isoniazid

--AND--

» pyrazinamide

--AND--

» ethambutol

» The 9-month all-oral regimen is recommended by the World Health Organization (WHO) over the longer multidrug-resistant (MDR)/rifampicin-resistant-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 intensive phase of 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). Two months of linezolid may be used in place of the 4 months of ethionamide.[79]

» The WHO recommends the use of the 9-month regimen for adults and children without extensive TB disease, regardless of HIV status, and who have less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid, and clofazimine.[79]

» Specific regimens should be selected by a specialist in the treatment of MDR TB. Consult specialist for guidance on doses.

plus **standardised 9-month term regimen (continuation phase)**

Treatment recommended for ALL patients in selected patient group

Primary options

» levofloxacin
-or-
» moxifloxacin

--AND--

» clofazimine

--AND--

» pyrazinamide

--AND--

» ethambutol

MANAGEMENT

Acute

» The continuation phase of the 9-month regimen consists of 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol, and pyrazinamide.[79]

» Management of patients with additional comorbidities is complex and will require specialist advice.

» Specific regimens should be selected by a specialist in the treatment of multidrug-resistant TB. Consult specialist for guidance on doses.

adjunct **surgery**

Treatment recommended for SOME patients in selected patient group

» In patients with rifampicin-resistant TB or multidrug-resistant (MDR) TB, elective partial lung resection (i.e., lobectomy or wedge resection) may be used alongside a recommended MDR TB regimen.[79]

1st **standardised or individualised longer term regimen**

Primary options

Group A (include all#3 drugs)

» levofloxacin
-or-
» moxifloxacin
--AND--
» bedaquiline
--AND--
» linezolid

OR

Group B (add 1 or both drugs)

» clofazimine
--AND/OR--
» cycloserine
-or-
» terizidone

OR

Group C (add to complete the regimen and when drugs from#groups A and B#cannot be used)

» ethambutol

OR

» delamanid

Acute

OR

» pyrazinamide

OR

» imipenem/cilastatin
-or-
» meropenem

OR

» amikacin
-or-
» streptomycin

OR

» ethionamide
-or-
» prothionamide

OR

» aminosalicylic acid

» The longer term regimen is recommended for all patients who do not fulfill the criteria for the shorter term regimens.[79]

» The longer term regimen, previously referred to as conventional treatment, refers to regimens for rifampicin-resistant (RR) TB or multidrug-resistant (MDR) TB, which last 18 months or more and which may be standardised or individualised. The World Health Organization 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. [79]

» A treatment duration of 15-17 months after culture conversion is suggested for most patients; however, the duration may be modified according to the patient's response to therapy. In longer regimens containing amikacin or streptomycin, an intensive phase of 6-7 months is suggested for most patients, but again, the

Acute

duration may be modified according to the patient's response to therapy.

» Management of drug-resistant TB requires expert consultation.

adjunct **surgery**

Treatment recommended for SOME patients in selected patient group

» In patients with rifampicin-resistant TB or multidrug-resistant (MDR) TB, elective partial lung resection (i.e., lobectomy or wedge resection) may be used alongside a recommended MDR TB regimen.[79]

active TB HIV-positive non-pregnant: no hepatic dysfunction

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
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
-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.

OR

4-month regimen

» isoniazid: children ≥12 years of age and ≥40 kg body weight and adults: 300 mg orally once daily
Pyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.
-and-

Acute

» rifapentine: children ≥12 years of age and ≥40 kg body weight and adults: 1200 mg orally once daily
-and-
» moxifloxacin: children ≥12 years of age and ≥40 kg body weight and adults: 400 mg orally once daily
-and-
» pyrazinamide: children ≥12 years of age and ≥40 kg body weight and adults: consult specialist for guidance on dose (dose is based on lean body weight and available tablet formulation)

Secondary 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
Pyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.
-and-
» 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 HIV-positive patients is similar to that of non-HIV-positive patients.[66]

» World Health Organization (WHO) guidelines for the treatment of drug-susceptible active pulmonary TB include regimens that are given for a total duration of 4 or 6 months.[66]

» The standard 6-month regimen is recommended by the WHO for new patients with pulmonary TB. The initial intensive phase treatment for the 6-month regimen includes the preferred drugs of isoniazid, rifampicin, pyrazinamide, and ethambutol, and lasts 2 months.[66] Patients aged between 3 months and 16 years with non-severe TB (defined

Acute

as 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.[30] [66] Ethambutol should be included in areas of high prevalence of HIV or isoniazid resistance.[30] [66] Children and adolescents who do not meet the criteria for non-severe TB should receive the standard 6-month treatment regimen (including ethambutol).[30] [66]

» Patients aged 12 years and over may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin, and pyrazinamide. The intensive phase of this regimen includes daily administration of isoniazid, rifapentine, moxifloxacin, and pyrazinamide and also lasts 2 months.[66] [71] This regimen is not currently recommended for young children, persons who are pregnant, and patients with HIV infection and CD4 count of <100 cells/microlitre.[66]

» Pyridoxine should be administered with isoniazid to help prevent isoniazid-associated neuropathy, and is recommended in all cases of active TB.

» Pyrazinamide is used during the initial phase only. It is not recommended for patients with acute gouty arthritis (but can be used in patients with past history of gout) because of little information about the safety data.

» Expert consultation should be sought in patients with a creatinine clearance of <30 mL/minute.

» If the patient is on antiretroviral therapy, there are some additional considerations including the potential for drug interactions, especially between rifampicin and non-nucleoside reverse-transcriptase inhibitors or protease-inhibitors. For this reason, rifabutin may be considered as an alternative to rifampicin. Specialist consultation is recommended when considering use of rifabutin.

plus **continuation phase therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

4- or 6-month regimen

MANAGEMENT

Acute

» 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-
» 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

4-month regimen

» isoniazid: children ≥12 years of age and ≥40 kg body weight and adults: 300 mg orally once daily
Pyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.
-and-
» rifapentine: children ≥12 years of age and ≥40 kg body weight and adults: 1200 mg orally once daily
-and-
» moxifloxacin: children ≥12 years of age and ≥40 kg body weight and adults: 400 mg orally once daily

Secondary 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
Pyridoxine (vitamin B6) is given with isoniazid to all people at risk of neuropathy.
-and-
» 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 HIV-positive patients is similar to that of non-HIV-positive patients.[66]

» The World Health Organization guidelines recommend that patients completing the initial intensive standard regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol continue to receive isoniazid and rifampicin in the continuation phase for 4 months (a total of 6 months treatment). Children aged 3 months to 16 years with non-severe pulmonary TB should receive 2 months of continuation phase therapy (4 months total). Those with severe TB, and also

Acute

children aged less than 3 months, should receive the standard 6-month treatment regimen.[30] [66]

» In the continuation phase of the 4-month isoniazid, rifapentine, moxifloxacin, and pyrazinamide regimen, isoniazid, rifapentine, and moxifloxacin are given for another 2 months (total of 4 months).[66] [71] This regimen is not currently recommended for young children, persons who are pregnant, and patients with HIV infection and CD4 count of <100 cells/microlitre.[66]

» Ideally, all medications within a given regimen should be administered at the same time of day if possible. 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. Daily therapy is preferred throughout the continuation phase.

» Pyridoxine should be administered with isoniazid to help prevent isoniazid-associated neuropathy, and is recommended in all cases of active TB.

» If the patient is on antiretroviral therapy, there are some additional considerations including the potential for drug interactions, especially between rifampicin and non-nucleoside reverse-transcriptase inhibitors or protease-inhibitors. For this reason, rifabutin may be considered as an alternative to rifampicin. Specialist consultation is recommended when considering use of rifabutin.

isoniazid resistance — **1st** — **anti-tuberculosis treatment**

Primary options

» rifampicin
-and-
» ethambutol
-and-
» pyrazinamide
-and-
» levofloxacin

Secondary options

» rifampicin
-and-
» ethambutol
-and-
» pyrazinamide

MANAGEMENT

Acute

» Isoniazid-resistant TB is defined as resistance to isoniazid and susceptibility to rifampicin that has been confirmed in vitro.[2]

» In patients with confirmed rifampicin-susceptible and isoniazid-resistant TB, the World Health Organization (WHO) recommends treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin or a duration of 6 months.[79] If levofloxacin cannot be used (because of toxicity or resistance) WHO recommends that the patient is treated with rifampicin, ethambutol, and pyrazinamide for 6 months.[79]

» Resistance to rifampicin must be excluded before starting the regimen, and preferably, resistance to fluoroquinolones and pyrazinamide would also be excluded. If isoniazid resistance is identified after a patient has started a regimen for drug-susceptible TB, rapid molecular testing for rifampicin resistance should be done, and if rifampicin resistance is excluded, the patient should begin a full 6-month course of rifampicin, ethambutol, pyrazinamide, and levofloxacin. If rifampicin resistance is detected the patient should begin an appropriate treatment regimen for multidrug-resistant (MDR) TB.[79]

» In contrast to regimens for drug-susceptible and MDR TB, the WHO recommended treatment regimens for isoniazid-resistant TB does not have initial intensive and continuation phases.

multidrug resistance **1st** **standardised 6-month regimen**

Primary options

» bedaquiline
-and-
» pretomanid
-and-
» linezolid
-and-
» moxifloxacin

» The 6-month all-oral regimen recommended by the World Health Organization (WHO) is composed of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM).[79] [81] [82] The WHO advises that if the patient has documented resistance to fluoroquinolones, then the regimen should continue without moxifloxacin (BPaL); although initiation of BPaLM should not be delayed while waiting for results of drug susceptibility testing.

» The WHO recommends the use of this 6-month regimen over the 9-month or longer

Acute

multidrug-resistant (MDR)/rifampicin-resistant-TB regimens for adults and adolescents aged 14 and over, regardless of HIV status, who have less than 1 month exposure to bedaquiline, linezolid, pretomanid, or delamanid.[79]

» Specific regimens should be selected by a specialist in the treatment of MDR TB. Consult specialist for guidance on doses.

adjunct **surgery**

Treatment recommended for SOME patients in selected patient group

» In patients with rifampicin-resistant TB or multidrug-resistant (MDR) TB, elective partial lung resection (i.e., lobectomy or wedge resection) may be used alongside a recommended MDR TB regimen.[79]

1st **standardised 9-month regimen (intensive phase)**

Primary options

» bedaquiline
--AND--
» levofloxacin
-or-
» moxifloxacin
--AND--
» ethionamide
-or-
» linezolid
--AND--
» clofazimine
--AND--
» isoniazid
--AND--
» pyrazinamide
--AND--
» ethambutol

» The 9-month all-oral regimen is recommended by the World Health Organization (WHO) over the longer multidrug-resistant (MDR)/rifampicin-resistant-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 intensive phase of 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

Acute

of extending to 6 months if the patient remains sputum smear positive at the end of 4 months). Two months of linezolid may be used in place of the 4 months of ethionamide.[79]

» The WHO recommends the use of the 9-month regimen for adults and children without extensive TB disease, regardless of HIV status, and who have less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid, and clofazimine.[79]

» Specific regimens should be selected by a specialist in the treatment of MDR TB. Consult specialist for guidance on doses.

plus **standardised 9-month term regimen (continuation phase)**

Treatment recommended for ALL patients in selected patient group

Primary options

» levofloxacin
-or-
» moxifloxacin
--AND--
» clofazimine
--AND--
» pyrazinamide
--AND--
» ethambutol

» The continuation phase of the 9-month regimen consists of 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol, and pyrazinamide.[79]

» Management of patients with additional comorbidities is complex and will require specialist advice.

» Specific regimens should be selected by a specialist in the treatment of multidrug-resistant TB. Consult specialist for guidance on doses.

adjunct **surgery**

Treatment recommended for SOME patients in selected patient group

» In patients with rifampicin-resistant TB or multidrug-resistant (MDR) TB, elective partial lung resection (i.e., lobectomy or wedge resection) may be used alongside a recommended MDR TB regimen.[79]

Acute

1st **standardised or individualised longer term regimen**

Primary options

Group A (include all 3 drugs)

» levofloxacin
-or-
» moxifloxacin
--AND--
» bedaquiline
--AND--
» linezolid

OR

Group B (add 1 or both drugs)

» clofazimine
--AND/OR--
» cycloserine
-or-
» terizidone

OR

Group C (add to complete the regimen and when drugs from groups A and B cannot be used)

» ethambutol

OR

» delamanid

OR

» pyrazinamide

OR

» imipenem/cilastatin
-or-
» meropenem

OR

» amikacin
-or-
» streptomycin

OR

» ethionamide

Acute

-or-
» prothionamide

OR

» aminosalicylic acid

» The longer term regimen is recommended for all patients who do not fulfill the criteria for the shorter term regimens.[79]

» The longer term regimen, previously referred to as conventional treatment, refers to regimens for rifampicin-resistant (RR) TB or multidrug-resistant (MDR) TB, which last 18 months or more and which may be standardised or individualised. The 2020 World Health Organization 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.[79]

» A treatment duration of 15-17 months after culture conversion is suggested for most patients; however, the duration may be modified according to the patient's response to therapy. In longer regimens containing amikacin or streptomycin, an intensive phase of 6-7 months is suggested for most patients, but again, the duration may be modified according to the patient's response to therapy.

» Management of drug-resistant TB requires expert consultation.

adjunct **surgery**

Treatment recommended for SOME patients in selected patient group

» In patients with rifampicin-resistant TB or multidrug-resistant (MDR) TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR TB regimen.[79]

active TB pregnant

1st **speciality consultation**

MANAGEMENT

Acute

		» Specialist consultation is recommended in the treatment of TB in pregnancy.
active TB non-pregnant: pre-existing or drug-induced hepatic dysfunction		
	1st	**speciality consultation** » Specialist consultation is recommended in the setting of drug-induced hepatic dysfunction for less hepatotoxic treatment options.

Ongoing

recurrent TB

1st **speciality consultation**

» Treatment failure is defined as a positive sputum smear or culture at 5 months or later during treatment.[58] When either the sputum smear or culture remains positive beyond 2-3 months into treatment, adherence with medications must be verified; emerging drug-resistant TB strains and gastrointestinal malabsorption of TB medications should also be evaluated.

» Recurrence occurs in a case considered to have completed successful treatment. Recurrent cases include relapses due to the same *Mycobacterium tuberculosis* strain as that responsible for the previous episode, as well as new episodes of TB due to re-exposure resulting in reinfection. In non-endemic countries, recurrence is generally a result of relapse with the original organism, whereas in TB-endemic countries, it may be the result of exogenous reinfection. Relapse usually occurs in the first 6-12 months following completion of treatment and occurs in 2% to 5% of appropriately treated patients.[83]

» If the patient initially had drug-susceptible isolates and treatment was directly observed, recurrence will likely result from the same susceptible organisms and prior therapy can be used. If the patient initially received self-administered therapy, there is a greater possibility of the development of a drug-resistant organism. In this situation, or if drug susceptibility has not previously been tested, an expanded multidrug-resistant regimen with addition of at least two drugs not previously used should be considered.[9]

» If exogenous reinfection is suspected, treatment should be based on the drug susceptibility profile of the index case, if known.

» Consult specialist for guidance on appropriate combinations of agents and doses.

Emerging

Oral bedaquiline/levofloxacin/linezolid-containing regimens (for MDR-TB)

In one multicentre randomised controlled trial in adults with multidrug-resistant (MDR)/rifampicin-resistant (RR)-TB (NExT trial), an all-oral 6-month levofloxacin, bedaquiline, and linezolid-containing MDR/RR-TB regimen was associated with a significantly improved 24-month World Health Organization-defined treatment outcome compared with traditional injectable-containing regimens.[85] However, drug toxicity occurred frequently in both intervention arms.

8-week regimens

In the TRUNCATE-TB trial, patients with rifampicin-susceptible pulmonary TB were randomised to either standard treatment (rifampicin and isoniazid for 24 weeks with pyrazinamide and ethambutol for the first 8 weeks) or to a strategy involving initial treatment with an 8-week regimen containing bedaquiline and linezolid, extended treatment for persistent clinical disease, monitoring after treatment, and re-treatment for relapse.[86] The study found that an 8-week regimen containing bedaquiline and linezolid was non-inferior to standard treatment with respect to the risk of a composite clinical outcome (death, ongoing treatment, or active disease) at week 96.[86]

Novel vaccine candidates

The M72/AS01E candidate vaccine contains an immunogenic fusion protein (M72) derived from two *Mycobacterium tuberculosis* antigens (Mtb32A and Mtb39A), combined with the AS01E adjuvant system. In a phase 2b double-blind randomised placebo-controlled trial, M72/AS01E provided approximately 50% protection against progression to active pulmonary tuberculosis for 3 years in *M tuberculosis* -infected, HIV-negative adults.[87] [88]

Primary prevention

The bacille Calmette-Guérin (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.[26] BCG may offer protection against latent TB infection and pulmonary TB.[27] [28] It is no longer routinely offered. 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.[29] The World Health Organization 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.[30]

Active TB, confirmed or highly suspected, is a reportable condition to the local health authorities in order to interrupt further TB transmission in the community.

Secondary prevention

Because of the infectious nature of the condition, patients should avoid new encounters with people who are not household members while they are infectious. Household members should be promptly evaluated and treated if appropriate. The patient may need to be isolated in the short term. After approximately 2 weeks of effective TB treatment, the patient is less infectious to others

Patient discussions

Patients should be informed about the condition; in particular, the following should be discussed:

- The importance of completing the recommended course of treatment. If side effects occur, medical attention should be sought
- The need for routine monitoring of kidney and liver function
- The need for regular sputum samples to be provided and technique for providing sample.

Because of the infectious nature of the condition, the patient may need to be isolated in the short term. After approximately 2 weeks, the patient is less infectious to close contacts.

Physicians should inform all infectious and potentially infectious TB patients that they must not travel by air, on any commercial flight of any duration, until they are sputum smear-negative on at least two occasions.

Physicians should inform all multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB patients that they must not travel by any commercial flight until they are shown to be non-infectious (i.e., two consecutive negative sputum-culture results).[97] MDR TB is defined as resistance to isoniazid and rifampicin, with or without resistance to other first-line drugs, and XDR TB is defined as resistance to at least isoniazid and rifampicin, and to any fluoroquinolone, and either bedaquiline or linezolid (or both).[79] [80] Pre-XDR-TB is resistance to isoniazid, rifampicin, and any fluoroquinolone.

Physicians should immediately inform the relevant public health authority when they are aware that an infectious or potentially infectious TB patient intends to travel against medical advice or may have exceptional circumstances requiring commercial air travel.

Physicians should immediately inform the public health authority when an infectious or potentially infectious TB patient has a history of commercial air travel within the previous 3 months.[98] [CDC: tuberculosis] (http://www.cdc.gov/TB)

Monitoring

Monitoring

Liver function (aminotransferases, bilirubin, alkaline phosphatase) should be checked at baseline prior to starting therapy. Monthly liver function tests should be obtained in patients with abnormal baseline liver function, underlying liver disease, HIV co-infection, pregnancy, and other risk factors for hepatitis.

Patients on ethambutol are monitored for visual disturbance and, if treated for more than 2 months, will need monthly vision checks. Routine monitoring of renal and liver function may be necessary.

In general, patients should have a chest x-ray at the completion of treatment for pulmonary TB to serve as a new baseline. Otherwise, no routine monitoring after completion of treatment is indicated. In patients with multidrug-resistant TB, close follow-up for 2 years after completion of treatment is recommended (e.g., chest x-ray and sputum collection every 4-6 months).

Complications

Complications	Timeframe	Likelihood
transmission of TB	**short term**	**high**
Patients may transmit infection to close contacts. As soon as TB is suspected, the treating physician must take steps to prevent further transmission. These include isolating the patient at home or in a negative-pressure room (if hospitalised). If isolated at home, the patient must not have new contacts or come into contact with small children or immunocompromised individuals. The conservative approach dictates that patients are considered infectious until 3 consecutive sputum acid-fast bacilli smears are negative, they have been on standard therapy for at least 2 weeks, and they show clinical improvement on TB therapy.[92]		
immune reconstitution inflammatory syndrome (IRIS)	**short term**	**medium**
Also known as a paradoxical response. This syndrome involves transient worsening of TB symptoms and lesions following initiation of anti-tuberculosis therapy. This is much more common in HIV-positive patients with severe immunosuppression who are placed on antiretroviral therapy (ART).[75] Up to 20% to 30% of HIV-infected TB patients may develop IRIS after initiation of ART (median onset 2 weeks). IRIS is also described in HIV-negative patients, where median onset of paradoxical symptoms is 8 weeks after initiation of therapy. In both groups, IRIS appears to be more common in extrapulmonary TB. Presentation may include fever, worsening of chest x-ray, lymphadenopathy, or an increase in pleural effusions. Other aetiologies, such as bacterial pneumonia and *Pneumocystis jirovecii* pneumonia, should be eliminated, as well as TB treatment failures because of undetected non-adherence to TB therapy or drug-resistant TB.[76] [93] [94] Paradoxical responses are transient, and generally anti-tuberculosis or ART therapy does not need to be discontinued. If there are significant symptoms, consider steroids (e.g., prednisone 1-2 mg/kg once daily for a few weeks then taper gradually over several weeks) while maintaining anti-tuberculosis and ART. For severe and occasionally life-threatening IRIS, some or all therapy might need to be discontinued.		
ARDS	**short term**	**low**
TB is an uncommon cause of respiratory failure requiring mechanical ventilation (MV). There is a stronger association between respiratory failure and miliary TB than with tuberculous pneumonia (20-fold greater risk). Mortality rate in TB requiring MV is up to 69%.[91] Treatment is directed at respiratory support with MV and anti-tuberculosis therapy. In these critically ill patients malabsorption may be present with resulting inadequate drug concentrations, and treatment may require use of parenteral anti-tuberculosis medicines (e.g., isoniazid, rifampicin, levofloxacin, and amikacin).		
pneumothorax	**short term**	**low**
Results from rupture into the pleural space of a peripheral cavity or of a subpleural caseous focus that has liquefied. The associated bronchopleural fistula (BPF) may seal off or persist. Large BPF may lead to		

Complications	Timeframe	Likelihood
empyema formation.[52] Management is with chest tube (tube thoracostomy). Persistent BPF may require surgical repair.		
empyema	**short term**	**low**
May be seen in primary disease but usual presentation is in the setting of extensive parenchymal disease. Management is with chest tube (tube thoracostomy). May require surgical intervention.		
bronchiectasis	**long term**	**low**
May result from primary TB, distal to the site of obstruction if adenopathy causes bronchial compression. If re-activation causes parenchymal destruction, bronchiectasis may develop in the area of involvement. Symptoms are similar to those associated with other causes of bronchiectasis, but may be minimal (dry bronchiectasis). Diagnosis is best made with high-resolution computed tomography.		
extensive lung destruction	**long term**	**low**
Extensive pulmonary parenchymal destruction may occur in primary or re-activation TB. Pulmonary destruction is usually the result of chronic, progressive, untreated pulmonary TB. Radiological studies may show a fibrotic, contracted lung; hilar elevation, lower lobe emphysema, and bronchiectasis may also be present. An uncommon, rapidly progressive process of pulmonary destruction is known as pulmonary gangrene. Diffuse vascular thrombosis leads to infarction and necrosis.		
right middle lobe (RML) syndrome	**long term**	**low**
Intermittent or persistent collapse of the RML due to compression of the RML bronchus by adjacent enlarged lymph nodes. May be seen as a result of TB or other aetiologies. May predispose to recurrent RML pneumonias. Diagnosed by bronchoscopy. Severe cases may require lobectomy.		
haemoptysis	**variable**	**low**
TB accounts for <10% of cases of haemoptysis.[95] [96] It may be seen in active or treated disease and is usually small in volume. Cases of massive haemoptysis because of TB may result from a Rasmussen aneurysm resulting from erosion of a TB cavity into a vessel wall. TB-related aetiologies of haemoptysis include bronchiectasis, aspergilloma, or scar carcinoma. Evaluation for haemoptysis may include sputum studies (for TB recurrence), bronchoscopy, and chest computed tomography. In active TB, sedation, bed rest, and anti-tuberculosis therapy may be adequate. For more severe haemoptysis, pulmonary consultation should be obtained and treatment may involve interventional radiology (for embolisation) or thoracic surgery for resection.[52]		

Prognosis

Without treatment the mortality rate of TB exceeds 50%; however, TB is a treatable disease. In the US in 2009 there were 529 deaths because of TB out of 11,528 reported cases, a case fatality rate of 4.6%. Risk factors for death include increased age, delay in diagnosis of TB, extent of radiographic involvement, the need for mechanical ventilation, end-stage renal disease, diabetes, and immunosuppression.[89] [90]

In general, patients with treated TB can expect to do well with minimal or no sequelae.

Diagnostic guidelines

United Kingdom

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

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

Published by: National Institute for Health and Care Excellence **Last published:** 2019

International

WHO consolidated guidelines on tuberculosis: module 3: diagnosis: tests for tuberculosis infection (https://www.who.int/publications/i/item/9789240056084)

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/item/9789240046764)

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/i/item/9789240022676)

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

WHO consolidated guidelines on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection (https://www.who.int/publications/i/item/9789240029415)

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

WHO consolidated guidelines on tuberculosis: module 1: prevention: tuberculosis preventive treatment (https://www.who.int/publications/i/item/9789240001503)

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

North America

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

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

Cough due to TB and other chronic infections (https://journal.chestnet.org/guidelines)

Published by: American College of Chest Physicians **Last published:** 2018

Diagnosis of tuberculosis in adults and children (https://www.thoracic.org/statements/tuberculosis-pneumonia.php)

Published by: American Thoracic Society; Infectious Diseases Society of America; Centers for Disease Control and Prevention **Last published:** 2016

Asia

Prevention, diagnosis and management of tuberculosis (https://www.moh.gov.sg/hpp/doctors/guidelines)

Published by: Singapore Ministry of Health **Last published:** 2016

Treatment guidelines

United Kingdom

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

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

Published by: National Institute for Health and Care Excellence **Last published:** 2019

Standards of care for people living with HIV in 2018 (https://www.bhiva.org/ClinicalStandards)

Published by: British HIV Association **Last published:** 2018

International

WHO consolidated guidelines on tuberculosis: module 5: management of tuberculosis in children and adolescents (https://www.who.int/publications/i/item/9789240046764)

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/item/9789240047716)

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

WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-susceptible tuberculosis (https://www.who.int/publications/i/item/9789240047716)

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/publications/i/item/9789240063129)

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

WHO consolidated guidelines on tuberculosis: module 1: prevention: tuberculosis preventive treatment (https://www.who.int/publications/i/item/9789240001503)

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

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; Centers for Disease Control and Prevention; European Respiratory Society; Infectious Diseases Society of America **Last published:** 2019

GUIDELINES

North America

Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: mycobacterium tuberculosis infection and disease (https://clinicalinfo.hiv.gov/en/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: 2022

Canadian tuberculosis standards, 8th edition (https://cts-sct.ca/guideline-library)

Published by: Canadian Thoracic Society

Last published: 2022

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

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

Published by: National Tuberculosis Controllers Association

Last published: 2021

Treatment of drug-susceptible tuberculosis (https://www.thoracic.org/statements/tuberculosis-pneumonia.php)

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

Last published: 2016

Asia

Prevention, diagnosis and management of tuberculosis (https://www.moh.gov.sg/hpp/doctors/guidelines)

Published by: Singapore Ministry of Health

Last published: 2016

Online resources

1. CDC: tuberculosis (http://www.cdc.gov/TB) *(external link)*

EVIDENCE TABLES

Evidence tables

How does directly observed therapy affect outcomes in people being treated for tuberculosis?

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.1530/full)

Evidence B *

Confidence in the evidence is moderate or low to moderate where GRADE has been performed and there may be no difference in effectiveness between the intervention and comparison for key outcomes.

Population: People receiving treatment for tuberculosis
Intervention: Direct observation therapy (DOT) [a]
Comparison: Self-administed tuberculosis therapy [a]

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Cure (follow-up: up to 6 months)	No statistically significant difference	Moderate
Completion of treatment (follow-up: 2 to 8 months)	No statistically significant difference	Moderate

Note

[a] This evidence table summarises the findings for the comparison DOT versus self-administered tuberculosis therapy, which is the main comparison as stated in the Cochrane review Summary of Findings table. The reviewers also found no statistically significant difference between community-based DOT versus clinic-based DOT or community-based DOT versus family-based DOT for cure up to 6 months and treatment completion at 2 to 6 months. See the full Cochrane Clinical Answer (CCA) for more information.

The Cochrane systematic review authors noted that the lack of effectiveness of DOT was surprising but was probably due to the complex issues associated with adherence. They recommended further health systems research to explore enhancements or other strategies.

* 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/)

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Images

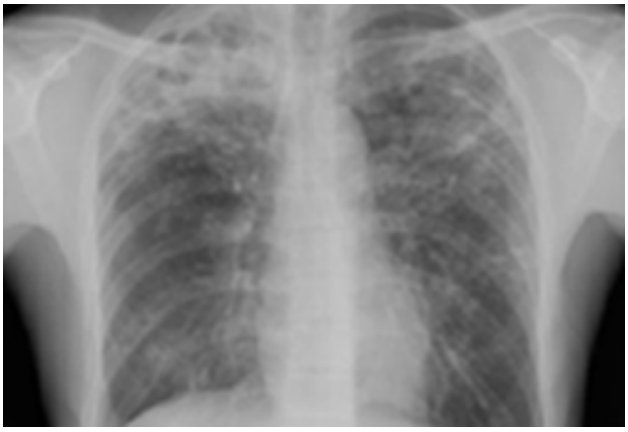

Figure 1: Pulmonary TB with cavitation

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IMAGES

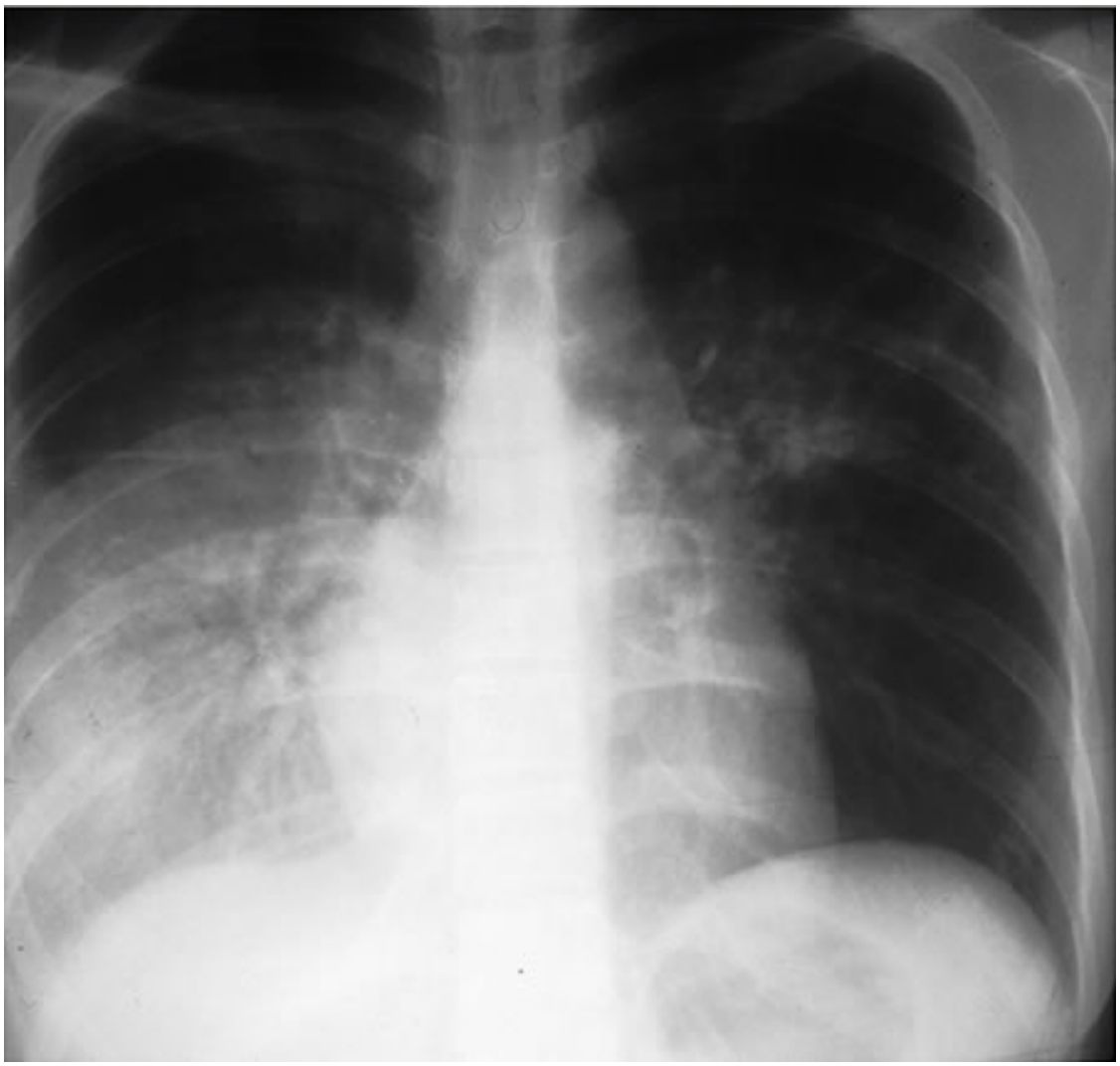

Figure 2: Opacities in right lower lobe in a patient with pulmonary TB and diabetes

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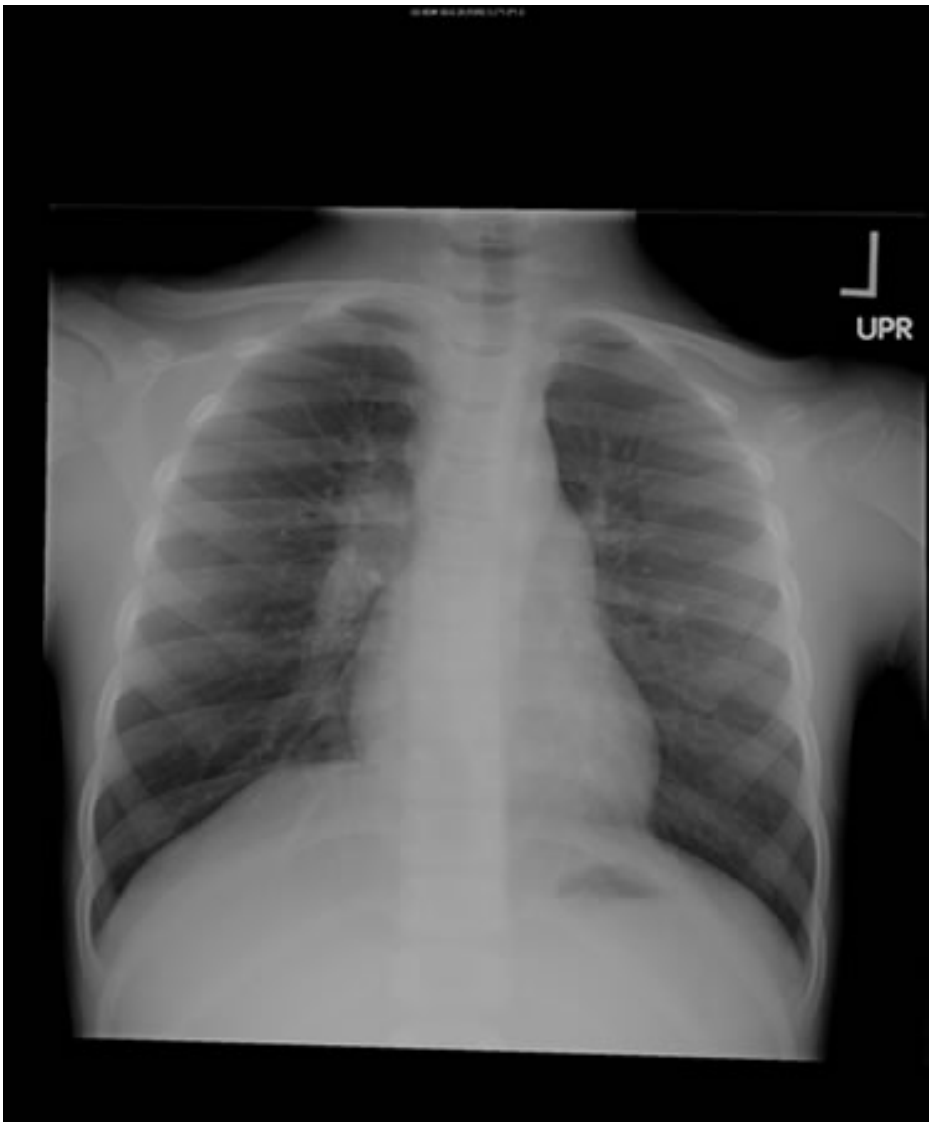

Figure 3: Right hilar adenopathy in a child

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IMAGES

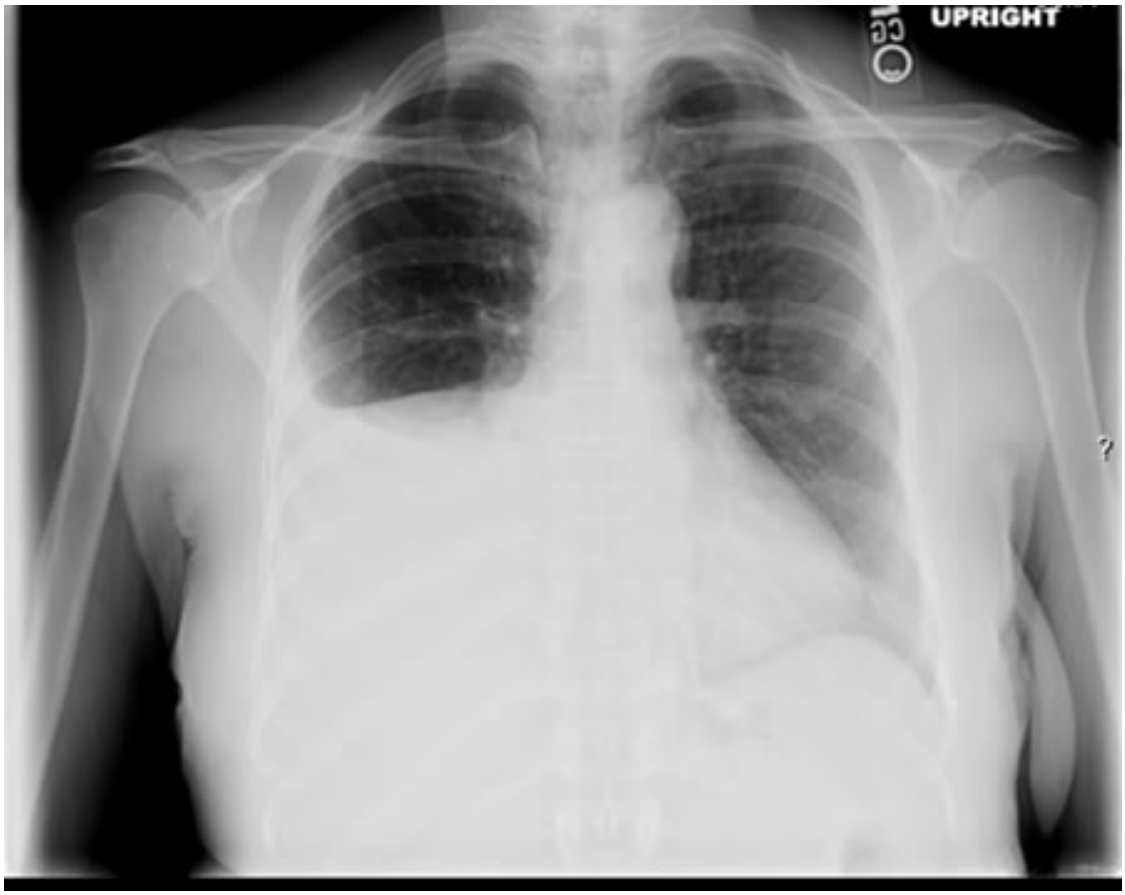

Figure 4: Right-sided pleural effusion

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Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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