Mycobacterial Disease

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Introduction

Tuberculosis (TB) has been affecting humans for thousands of years. Mankind is the only known reservoir for the disease, although animals can get infected. The disease may affect any dense community, will smolder amongst people living in poorly ventilated circumstances, and will flourish in the malnourished and weak.

TB infections decreased in the developed world as a consequence of better hygiene and nutrition; even before the discovery of *Mycobacterium tuberculosis* (MTB) infection in 1882, infection rates dropped. The discovery of streptomycin in the 1940s led to the world's first known randomised controlled trial. The development of para-amino salicylic acid (PAS) and combination therapy shortly after caused a paradigm shift in the treatment of tuberculosis; sanatoria and healthy food were replaced largely by antibiotic treatment. This subsequently caused a further reduction in tuberculosis cases in the UK and other developed countries.

However, despite being greatly reduced in wealthier nations, TB is far from eradicated. In developing countries, active TB is a major cause of death, especially since the global HIV epidemic. Recent estimates state about one in four people in the world have latent TB, [1] just under the 20-year-old WHO estimate of 1 in 3 [2]. In the UK there are around 6500 new TB cases per year, which is still one of the highest rates in Western Europe. The current TB case load in the UK is a reflection of global patterns; more than two-thirds of people diagnosed with active TB originate in high-prevalence countries, and another 10% of cases are people who have risk factors that might make them more vulnerable to falling ill with TB such as malnutrition, homelessness, or imprisonment [3]. The rest may be part of localized epidemics, or people with decreased immunity.

Since the late 1990s treatment-resistant TB strains have become a worldwide problem. Multidrug-resistant TB (MDR-TB) and extensively-drug-resistant TB (XDR-TB) are major public health threats. This chapter intends to give practical guidance on the treatment of TB in adults; for the treatment of MDR-TB it is recommended to seek expert advice.

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Current Thinking on TB Immunology

Immunity to *M. tuberculosis* has largely been thought to be related to the activity of macrophages and cells of the adaptive immune system (CD4+ and CD8+ T lymphocytes) in the control of mycobacteria. Failure of this causes dissemination in the primary stage of disease. In addition to these adaptive mechanisms, innate immune responses are also involved in both the early and late responses to MTB. The concept that granuloma formation is a host-protective structure has changed, and granulomas are now actually seen as dynamic structures that may allow the mycobacteria to replicate and spread to other locations.

There appear to be two phases of immunological activity in the granuloma. The early stages of mycobacterial infection are dominated by the innate immune system, with increased macrophage accumulation (via TNF) as a consequence of mycobacterial replication. The subsequent adaptive phase involves IFN-γ-producing or polyfunctional (IL-2, IFN-γ and TNFα) CD4+ and CD8+ T lymphocytes and leads to the control of MTB replication. This process is also influenced by a number of other cells, including NK (natural killer) cells, regulatory CD4+ T cells (Tregs), and Th1 (T helper 1) CD4+ T cells. The CD4+ and CD8+ T cells produce high levels of TNF, and NK cells produce IFN-γ. Interaction of mycobacteria with TLR2 (toll-like receptor 2) on NK cells may directly affect entry of mycobacteria in the lung tissue.

The transition from latency to post-primary tuberculosis is a poorly understood process, with multiple non-mutually exclusive mechanisms contributing to exit from latency in infected individuals. Among any cohort of latently infected subjects, it is impossible to predict who will fall in the 10% that eventually will experience reactivation, but two clinical scenarios are well known. The first is when there is a depletion of CD4+T cells (e.g. during HIV infection), and the second is represented by impairment of TNF signaling (e.g. biological agents for rheumatoid arthritis). TLR-2 and TLR-9 polymorphisms are also associated with an increased risk of TB in different populations, possibly due to attenuation of NK cell activation.

Diagnostic Testing

Tuberculin Skin Test and Interferon-γ Release Assays

The tuberculin skin test (TST) and Interferon-γ Release Assay (IGRA) tests rely on IFN-γ release from antigen-specific T-lymphocytes when re-exposed to MTB antigens. These tests do not distinguish between active and latent TB infection, and a positive result does not accurately predict progression to active tuberculosis. Moreover, in severely immunocompromised patients, patients with overwhelming tuberculosis infection or smear negative tuberculosis, IGRAs as well as TST may fail in the diagnosis of TB infection. Their use is therefore not recommended as the sole investigation for the diagnosis of active tuberculosis. Diagnosis, if clinically suspected, should be pursued by aggressive sampling, cultures, biopsies, and imaging.

Tuberculin Skin Test

During tuberculin skin testing a small amount of antigenic components of MTB (tuberculin) is injected intradermally. In patients previously exposed to TB, a T-cell mediated delayed-type hypersensitivity reaction will occur at the injection site. Ideally, the size of the resulting skin induration is measured 72 h after injection [4]. A positive TST will also occur in patients who have received BCG vaccination (a live attenuated mycobacterial strain derived from *M. bovis*) in childhood, but TST positivity tends to wane over time. Current UK guidelines thus consider any cutaneous response of 5 mm or more to be positive, regardless of BCG vaccination status [5]. It had been presumed that larger TST results correlated with active disease, but recent data challenge this presumption [6].

False positive results may occur due to prior vaccination with BCG, or due to cross-reaction with non-tuberculous mycobacteria. Because the TST it is cheap and does not require laboratory

facilities, it is still used widely in low- and middle-income settings. Efforts are underway to produce a new TST unaffected by prior BCG vaccination.

Anergy can occur in a number of cases where immunity is compromised, including overwhelming active TB infection [7]. It is estimated that in up to 25% of microbiologically confirmed TB cases, the TST is negative. Those patients appear to be the more severe cases and have a higher likelihood of succumbing to their TB infection.

IGRA Testing

IGRAs measure the amount of interferon released from blood leukocytes when mixed with mycobacterial antigens. IGRAs require a single blood sample and produce a standardized, non-operator dependent result. They appear to be more sensitive than TST in detecting latent TB in most settings [8].

There are currently two types of commercially available IGRA test; Quantiferon-Gold™ and T-SPOT®.*TB*™. Quantiferon-Gold uses a standardized amount of blood and is less labour-intensive. T-SPOT®.*TB* uses a standardized number of peripheral blood mononuclear cells, giving this test a theoretical advantage in immunocompromised patients.

Lateral Flow Lipoarabinomannan Assay

The lateral flow lipoarabinomannan assay (LF-LAM) is a urine test for the presence of lipoarabinomannan, a glycolipid antigen from the MTB cell wall. Urine LAM testing may be a valuable and rapid adjunct to available tuberculosis testing tools in HIV-positive individuals with low CD4 counts who are seriously ill [9]. In other patients, LF-LAM sensitivity and specificity are too low to be used in daily practice; this includes ambulatory patients established in HIV care [10].

Acid-Fast Stains and Cultures

Sputum cultures are the cornerstone of TB diagnostics, but any material can be sent for TB culture. The first step in identifying MTB is conventional microscopy using Ziehl-Nielsen or dark field electron microscopy using Auramine stains. Sensitivity of stains for detecting MTB in sputum in pulmonary TB infection is around 50–65%. Severely ill patients with TB are often unable to self-expectorate sputum, and may need sputum induction, or alternative invasive sampling such as bronchoscopy, to acquire material for diagnostic testing. Sensitivity of staining in other samples, such as CSF, tissue, or ascitic fluid can be much lower, ranging from 10% to 80% depending on sample site.

Definite diagnosis occurs after a positive mycobacterial culture. Because of the relatively slow growth of mycobacteria, it will take at least a week for colonies to form, but it is not unusual for a positive sample to emerge after 4–6 weeks of incubation.

Clear instructions for patients for sputum sample collection procedures are important for accurate TB diagnosis [11]. If not instructed well, saliva rather than sputum may be sampled, leading to false-negative results. In TB high-endemic settings the number of patients needed to screen in an in-patient population to find one case of active TB is less than ten, regardless of a patient's HIV status [12]. In reality, even in high-endemic settings, many more samples are needed to identify a case of TB [11]. Many simple and visual instruction cards are available readily and freely online.

Nucleic Acid Amplification Tests (NAAT)

Molecular methods can detect mycobacteria with high specificity by amplifying target DNA using methods based on polymerase chain reaction (PCR). The most commonly used assay is genXpert™ but there are several others available. The assays detect dead as well as live bacteria. Less than 200 bacilli per mL of sputum are needed for the NAAT to detect acid fast bacilli compared to 10,000 in microscopic examination.

The sensitivity for detecting mycobacterial DNA in smear-positive sputum samples is 95–98% which is close to that of culture, and can yield a result in about 90 min. Smear-negative but culture-positive sputum samples show a lower sensitivity of 68%. The sensitivity of NAAT in sputum samples from patients who

are co-infected with TB and HIV is close to that in sputum samples from HIV-negative patients.

For the detection of spinal TB, NAAT showed a sensitivity of 70–96% and specificity of 96% in CSF samples. The World Health Organization recommends NAAT over conventional stain tests for diagnosis of TB in lymph nodes and other tissues, and as the preferred initial test for diagnosis of TB meningitis [13]. In specimens with a lower bacterial load, such as pleural or pericardial fluid, NAAT sensitivity drops to below 40%.

Chest Imaging

Standard chest-X ray is still a mainstay of TB diagnosis, and computed-tomography (CT) scanning provides additional detail. Upper lobe infiltrates and pulmonary cavities are the classic signs of pulmonary tuberculosis (Fig. 13.1a–d). Although previously deemed to be a sign of reactivation disease, these upper lobe infiltrates can also occur in primary disease. Some patients show a parenchymal infiltrate, making it difficult to distinguish from conven-

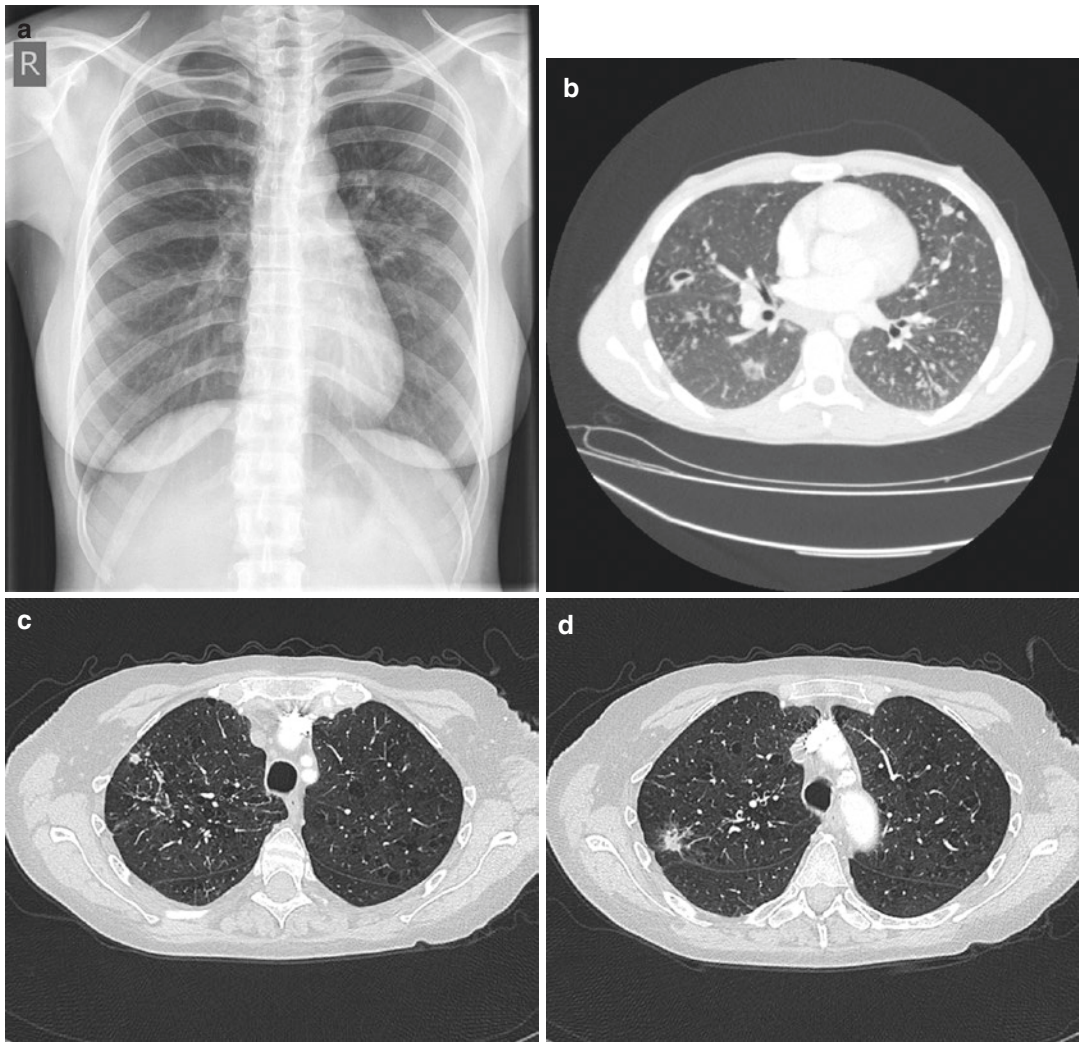

Fig. 13.1 (**a**–**d**) Reactivated TB. Examples of secondary (reactivated) pulmonary TB. (**a**) Focal left upper lobe infiltrate on chest-ray with patchy consolidation without visible cavitation. (**b**) Cavities and endobronchial disease on CT. Cavitation is a characteristic feature of reactivated TB and should immediately arouse suspicion of that diagnosis. A branching tree-in-bud pattern results from bronchiolar inflammation and dilatation, is common in many infections including TB (as in this case). In larger airways, tuberculous granulomatous inflammation may progress to bronchial stricture and distal atelectasis. (**c**, **d**) Multifocal right upper lobe infiltrate on CT with a wide differential diagnosis including lung cancer, and which was confirmed as TB

tional bacterial pneumonia [14]. In patients with impaired immunity for any reason, adenopathy, effusion, or mid lower lung zone infiltrates or a miliary pattern (Fig. 13.2a, b) are more common. Around one-third of patients will develop a radiological scar after primary infection (Fig. 13.3) [14].

In patients with cavitation but without clear infiltrate on the chest X-ray, differentiation between active and old disease can be challenging. CT scan may be helpful in differentiating between the two, since it may detect early bronchogenic spread in active disease. Typical findings include a centrilobular branching linear structure, defined

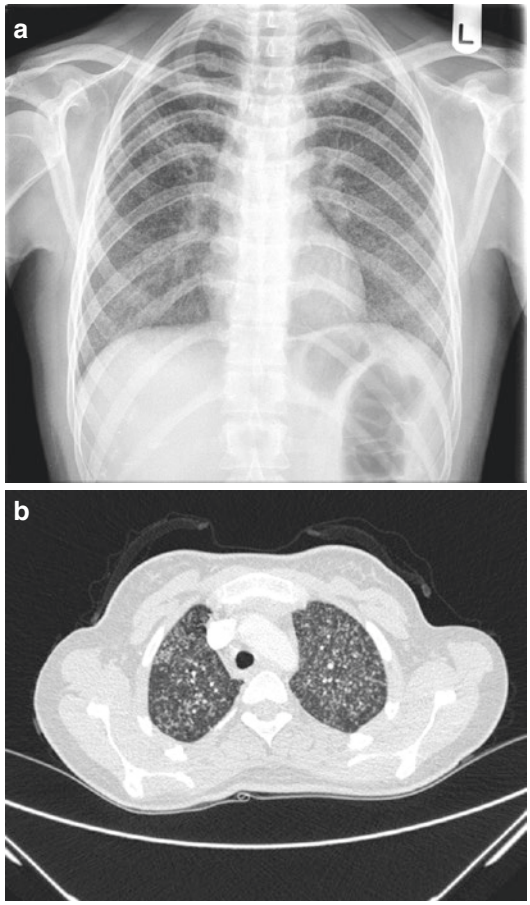

Fig. 13.2 (**a**, **b**) Miliary TB. Miliary pulmonary tuberculosis, appearing on a chest X-ray (panel **a**) and CT scan (**b**) as widespread multiple small (2–3 mm) granulomas. The millet seed radiological pattern only becomes apparent when the granulomas reach a certain size, and some patients with miliary TB will have a normal chest X-ray. Miliary TB may complicate either primary or reactivated disease. Whilst there are other causes of miliary nodulation on X-ray, TB should be the primary concern

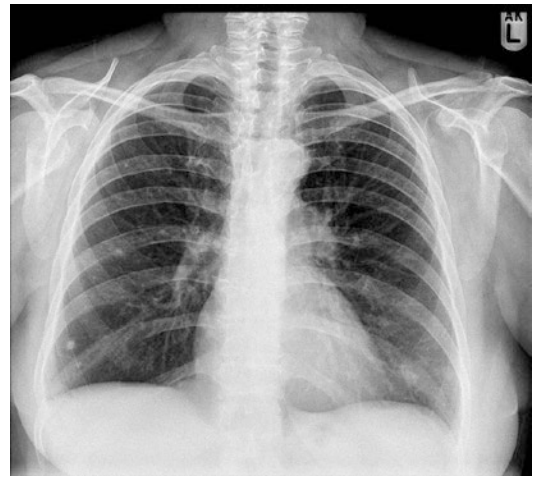

Fig. 13.3 Healed primary focus (Ghon focus). Healed primary tuberculosis, appearing as multifocal calcified scars in the right lung. The focus of primary tuberculosis is often unifocal, and may heal without trace, but calcified nodules or scars occur in about one-fifth of patients. Hilar (and sometimes mediastinal) lymphadenopathy is a very common radiological feature at the time of primary infection, and may resolve or leave hilar node calcification

small centrilobular peribronchiolar nodules, acinar shadows, and lobar consolidation. Patients with thoracic lymphadenopathy may be diagnosed by endobronchial ultrasound examination (EBUS) sampling. Preliminary data suggest that sonographic evidence of central necrosis in the lymph nodes favours tuberculosis over sarcoidosis [15].

In patients presenting with lymphadenopathy, PET-CT may be an additional aid in distinguishing between active disease and latent disease; metabolically active lymph nodes in a TB patient indicate active disease. The limitation of PET in this patient group is the inability to distinguish between infection and malignancy. Because PET-CT is very sensitive in detecting active TB, it may be used as a monitoring tool to assess treatment response, particularly during the treatment of MDR-TB or XDR-TB patients.

Transmission of TB

Transmission of TB has resulted from airborne droplets not only from respiratory infections, but also droplets from drainage of abscesses, from third-space fluids (pleural and peritoneal), and

organisms colonising the mouth. Even solid clinical waste can potentially produce an airborne risk. There is clear evidence that expectorated pathogens from a patient's room can contaminate susceptible individuals outside. Therefore, directional airflow control by negative pressure is recommended (particularly for MDR-TB) so that the airflow is directed from clean zones outwards through 'dirty' zones. This airflow from clean to dirty areas should be sufficient to overcome the escape of air, particularly when enhanced by the presence of ante-rooms. Most negative-pressure clinical areas are designed to provide around 2–15 Pa of negative pressure between neutral and vestibule areas, and 2.5 to 40–45 Pa total difference between neutral areas and patient rooms. Air control of the isolation area is also assisted by adequately engineered ventilation that allows 12–25 air changes per hour in the room.

Pulmonary Tuberculosis

The route of transmission of tuberculosis is in almost all cases through inhalation of aerosols. This can result in primary pulmonary tuberculosis, or in latent infection. Primary pulmonary TB typically presents with upper zone infiltrates on chest X-ray, as seen in Fig. 13.1, but can present as a common bacterial pneumonia, or with a miliary (disseminated) pattern, shown in Fig. 13.2.

Infections that do not cause primary TB often lead to a so-called Ghon complex—a small area of granulomatous inflammation with an associated lymph node that may be detected on a chest X-ray if calcified or large enough (see Fig. 13.3). Typically, these complexes appear in the upper zones of the lungs. They may contain dead or still-viable mycobacteria, and can thus be a source of reactivation later in life, which happens in around 10% of cases.

The presenting symptoms of pulmonary TB, primary or secondary, include cough, weight loss, night sweats, chest pain, increased sputum production, and hemoptysis. Occasionally, patients may present with severe hemoptysis when the infection erodes into a large pulmonary vessel. However, some patients have very few symptoms. Treatment usually improves symptoms rapidly, but may take a few months in those with a very heavy burden of disease.

In general, patients with pulmonary TB are infectious. Current UK guidelines recommend 2 weeks of isolation for those who are producing sputum that is positive for acid–fast bacilli (smear positive). It is generally recommended to repeat sputum testing until two negative samples have been produced, as a measure of treatment success. However, smears may not become negative in some patients with very large cavities, and this does not necessarily mean that treatment needs to be extended. In other patients, the sputum may convert to smear-negative after a few weeks of treatment, but the culture may remain positive. This is usually a sign of early treatment success.

Some patients may present with a large TB pleural effusion only, and this is considered to be a form of extrapulmonary TB. Immunocompromised patients or patients with advanced TB infection may present atypically, or with a miliary pattern on their chest X-ray. This is considered a sign of disseminated TB.

Extra-Pulmonary TB

Around one-fifth to one-half of TB in developed countries is extra-pulmonary. Although the overall incidence of tuberculosis in high-income countries is declining, the annual incidence of extra pulmonary TB is remarkably stable, with a notification level rate around 4/100,000 in Europe [16]. Since most cases originate from haematogeneous spread, tuberculosis can reactivate in any organ. The most common sites of extra-pulmonary disease are pleural (36%), lymph nodes (20%), bone, central nervous system, and gastro-intestinal tract. Although occasional transmission through aerosolisation of pus or needle stick incidents have been described, in general, patients with extra-pulmonary TB are not contagious. However, pulmonary involvement always needs to be ruled out, and each TB patient needs a full workup including a chest-X-ray and sputum cultures.

Lymph Node TB

Virtually all lymph nodes can be affected in TB infection. When biopsying a lymph node, enough tissue should be taken to provide a histological as well as a microbiological sample, and if lymphoma is in the differential diagnosis, a whole lymph node should be removed for diagnostic purposes. If this is not the case, fine-needle aspirates are a less-invasive and effective alternative.

Lymph nodes biopsies or aspirates may show a granulomatous pattern or acute inflammation. Stains for acid fast bacilli are not very sensitive in lymph node samples (perhaps only 30%). Diagnosis of TB lymphadenitis is often made on a combination of a positive screening test, histological pattern, and either culture or NAAT. The sensitivity of NAAT is around 70% in FNA aspirates and 43% in histological biopsies. NAAT can be performed on paraffinised tissue using special techniques; sensitivity is around 90% in tissue that is smear positive; it is much lower in smear-negative samples.

TB Meningitis/Tuberculoma

Lumbar puncture in the case of tuberculous meningitis will typically show a clear CSF with a raised protein count, with a normal to raised white cell count and a normal or decreased glucose concentration. Typically there is a predominance of lymphocytes, however, neutrophils can predominate, especially early in the course of CNS infection, and the CSF/serum glucose ratio can be normal. NAAT of CSF has a high sensitivity and is now recommended by WHO over the use of stains for the diagnosis of tuberculous meningitis [17]. However, despite a higher sensitivity, it is not 100%, and negative NAAT does not exclude tuberculous meningitis. MRI of the brain can aid in diagnosing TB meningitis; visibility of the meninges pre-contrast is highly suggestive of TB. Parenchymal lesions may appear as plaques—homogeneous, uniformly enhancing, dural-based masses.

Non-tuberculous Mycobacteria

Non-tuberculosis mycobacteria (NTM) is a term reserved for mycobacterial species other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*. NTM are ubiquitous organisms found in water and soil, and can cause infections in lung, sinus, lymph node, joint, CNS, and disseminated infection. NTM, when infecting the lung, can cause lung disease or sometimes be asymptomatic. Pulmonary disease (NTM-PD) may be fibro-cavitary or nodular. NTM are divided into slow-growing and rapid-growing species. The most common species causing lung infection are the slow-growing *M. avium* complex (MAC; consisting of *M. avium*, *M. intracellulare*, and *M. chimaera*), *M. kansasii*, *M. malmoense*, and *M. xenopi*, and the rapid-growing *M. abscessus*, *M. chelonae*, and *M. fortuitum*. Currently there is an increasing incidence of NTM infections worldwide, but more so in the resource-rich settings. This may be due to a number of reasons including reduced incidence of MTB, more contact with shower aerosols, and increased use of antibiotics and immunosuppressive treatments. Host susceptibility factors seem to be primarily associated, including impaired mucociliary clearance in patients with chronic lung diseases. Other risk factors include co-morbidities such as gastro-oesophageal reflux, rheumatoid arthritis, and immunodeficiency states.

The mechanism of transmission remains unclear, but there is growing evidence through whole genome sequencing that although person-to-person spread is unlikely, spread may be possible through fomites and long-lived infected aerosols.

The diagnosis is based on ATS/IDSA criteria for NTM-PD. A patient must have characteristic symptoms, compatible radiology, and two or more positive sputum samples of the same NTM species, or one positive bronchial wash/lavage, or compatible histopathological findings with one positive culture. Other potential causes of pulmonary disease must also be excluded. Although culture remains the gold standard of diagnosis, direct molecular detection by PCR is now available, though less sensitive. Culture itself can be difficult, but a combination of liquid

Table 13.1 Treatment of *M. avium* complex pulmonary disease

M. avium complex pulmonary disease	Antibiotic regimen
Non-severe	Rifampicin 600 mg 3× per week Plus ethambutol 25 mg/kg 3× per week Plus azithromycin 500 mg 3× per week Or clarithromycin 500 mg BD 3× per week Continue for at least 12 months after culture conversion
Severe	Rifampicin 600 mg daily Plus ethambutol 15 mg/kg daily Plus azithromycin 250 mg daily or clarithromycin 500 mg twice daily Consider intravenous or nebulized amikacin Continue for at least 12 months after culture conversion
Clarithromycin-resistant	Rifampicin 600 mg daily Plus ethambutol 15 mg/kg daily Plus isoniazid 300 mg daily (+pyridoxine) Or moxifloxacin 400 mg daily Continue for at least 12 months after culture conversion

systems (mycobacteria growth indicator tube) and solid systems tend to give the best positive yields. Currently many laboratories have Matrix-assisted laser desorption ionisation-time of flight (MALDI-TOF) mass spectrometry which provides early speciation of the NTM.

Treatment and the clinical value of *in vitro* drug susceptibility testing remains uncertain. Currently the best approach may be to determine the exact MICs to determine susceptibility. There are no RCTs to help guide when treatment should be commenced. Current NICE guidelines suggest that treatment should be started after taking into consideration both the patient's characteristics and the severity of the clinical syndrome (rate of progression, severity, radiological change, underlying lung disease) and mycobacterial factors (bacterial load, time to positivity of culture, smear positivity). The patient's views should also be taken into consideration, as their disease can remain stable without antibiotic treatment and "no treatment" may be a reasonable option. Antibiotic treatments are summarized in Table 13.1.

Treatment

Latent Tuberculosis

Treating latent tuberculosis decreases the risk of developing active TB by 60–80%. Commonly used treatment strategies for latent tuberculosis include a 3-month course of a combination of rifampicin and isoniazid, or a 6–9 month course of isoniazid monotherapy. However, other strategies such as rifampicin monotherapy for 3–4 months, or weekly rifapentin plus daily isoniazid for 3 months, may offer similar efficacy and lower toxicity. The optimum strategy for targeting patients for latent TB screening and offering chemoprophylaxis is controversial, and depends on the balance between perceived risks of active TB versus therapy-induced toxicity. Recent NICE guidance advises offering treatment to all patients up to 65 years of age who have a positive screening test. However, the risk of therapy-related toxicity increases significantly with age, and a careful judgement on a case-by-case basis is warranted. A pragmatic approach to offering therapy for latent TB is shown below.

Patients Who should Be Offered Therapy for Latent TB (Once Active TB Has Been Excluded)

- Significant past TB exposure
- TST >5 mm in patients regardless of prior BCG vaccination
- Positive IGRA

Latent TB in Immunocompromised Patients

Patients with latent TB undergoing treatment with TNF-blocking biologic agents have an approximately fivefold increased risk of progression to active TB. This risk can be substantially reduced by treatment for latent TB prior to starting anti-TNF therapy. The risk of progressing to active TB for patients with latent TB taking other immunosuppressive agents is not exactly known, but in general the risk increases with the degree of immunosuppression. Patients in this severely immunocompromised category could be (but are not limited to) those with HIV and CD4 counts of fewer than 200 cells/mm^3, or after solid organ or allogeneic stem cell transplant, those on dual or more immunosuppressive agents, or those after severely immunosuppressive chemotherapy for cancer.

In severely immunocompromised patients, TST as well as IGRA may not be sensitive enough to detect latent TB. It would be pragmatic in those patients to offer both IGRA and TST *alongside* the clinical risk-assessment. In case of extensive exposure to TB, chemoprophylaxis can still be offered despite negative screening tests. If active TB develops during anti-TNF therapy, therapy should be stopped until TB treatment is well established. In other cases, a risk-benefit assessment of stopping immunosuppressive medication against treating TB should be made.

In the case of exposure to MDR-TB, there currently are no clear guidelines regarding chemoprophylaxis. Although a few case series suggest efficacy of pyrazinamide and a quinolone, randomised trials are needed to confirm this effect. Since the highest risk of converting to active disease is during the first 2 years after inoculation, a practical approach may be to regularly assess the patient clinically, and to repeat chest X-rays on a serial basis during the first 24 months.

First Line-TB Treatment

Before the widespread availability of anti-mycobacterial chemotherapy in the 1950s, the mainstays of treatment of pulmonary TB were collapse therapy and bed rest. Cavitatory disease was likely to become widespread with aspiration to previously unaffected lung, and carried a poor prognosis. Strict and prolonged bed rest in a dependent position was sometimes able to close cavities, but to prevent them from reopening when the patient became ambulant required some other procedure, such as a phrenic crush combined with a pneumoperitoneum, regular artificial pneumothoraces, two-stage thoracoplasty, or extra periosteal plombage with foreign material such as lucite balls.

Anti-mycobacterial therapy should be used as follows:

- For people with active TB without central nervous system involvement, offer:
  1. Isoniazid (with pyridoxine), rifampicin, pyrazinamide, and ethambutol for 2 months, then
  2. Isoniazid (with pyridoxine) and rifampicin for a further 4 months.
  3. Modify the treatment regime according to drug susceptibility testing.

Rifampicin and Isoniazid are dependent on gastric acid for absorption, so they should thus be taken at least 30 min before a meal or 2 h after a meal.

- For people with active TB of the central nervous system, offer:
  1. Isoniazid (with pyridoxine), rifampicin, pyrazinamide and ethambutol for 2 months, then
  2. Isoniazid (with pyridoxine) and rifampicin for a further 10 months.
  3. Modify the treatment regimen according to drug susceptibility testing.

Therapy Duration

Therapy should be given for 6 months for fully sensitive pulmonary tuberculosis and most cases of extra-pulmonary tuberculosis, including abdominal. In tuberculous meningitis, treatment

duration should be extended to 12 months. In a small review, spinal TB treatment for 6 months was non-inferior to a treatment of longer than 6 months However, if there is CNS involvement of spinal TB, treatment duration has to be extended to 12 months. Fluoroquinolones add anti-tuberculosis activity to the standard treatment regimen, but to improve outcomes of TB meningitis, they must be started early, before the onset of coma.

There can be other factors that favour longer treatment duration, such as a very long duration of sputum to become culture-negative, patients receiving chemotherapy for malignancy as well as antituberculous drugs, and a very high burden of disease.

Despite a faster sputum culture conversion time by the addition of moxifloxacin to the standard four-drug combination, attempts to shorten the total duration of treatment to 4 months by adding moxifloxacin have not been successful [18].

Side Effect Profiles of Antituberculous Drugs

Main Drugs

Rifampicin: Hepatitis, skin reactions, gastrointestinal, thrombocytopenia, flu-like symptoms. Rarely haemolytic anaemia, acute renal failure, shock.

Isoniazid: Hepatitis, skin reactions, peripheral neuropathy. Neurological symptoms including seizure, optic neuritis, giddiness, mental symptoms. Pyridoxine now routinely co-prescribed.

Ethambutol: Retrobulbar neuritis, arthralgia. Rarely hepatitis, skin reactions, neuropathy, renal failure.

Pyrazinamide: Anorexia, nausea, photosensitivity, hepatitis, arthralgia. Rarely gout, vomiting.

Reserve Drugs

Streptomycin: Skin reactions, numbness, giddiness, tinnitus. Rarely vertigo, deafness, renal damage, ataxia.

Thiacetazone: Gastrointestinal, skin reactions, vertigo, conjunctivitis. Rarely hepatitis.

Significant Drug Interactions Requiring Dose Adjustment or Alternatives

Rifampicin: potent inducer of cytochrome P450 and so may reduce the levels of many drugs including: antiretrovirals[1], oral anticoagulants, oral contraceptive, ciclosporin, digoxin, glucocorticoids, itraconazole, methadone, midazolam, phenytoin, quinidine, theophylline, verapamil.

Isoniazid: inhibits cytochrome P450 and may increase levels of some drugs including: benzodiazepines, anticonvulsants.

Treatment in Special Circumstances and Management of Complications

Rifampicin, isoniazid, ethambutol, and pyrazinamide are safe in pregnancy, but streptomycin should be avoided because of foetal ototoxicity. Only small subtherapeutic amounts of first-line antituberculous drugs are secreted in breast milk, so breastfeeding is regarded as safe. Pregnant patients with MDR-TB will need a specialist-selected regime where toxicity for the foetus and survival of the mother are carefully weighed.

In patients co-infected with hepatitis B or C, usually treatment can be commenced without any problem; however it is advised to seek hepatology

[1]Depending on drug. Rifabutin may be preferred. Advise to seek HIV specialist opinion.

specialist advice if there is liver cirrhosis or severe fibrosis. There is no dose adjustment in this patient group.

In renal failure, isoniazid and rifampicin are used in normal doses. Ethambutol and aminoglycosides require monitoring of drug levels. For stage four or five CKD, or patients on haemodialysis, dosing intervals should be increased to three times weekly for ethambutol, pyrazinamide, and aminoglycosides, and the medication given after haemodialysis.

Mild gastrointestinal symptoms are common, lessen with time, and can be managed symptomatically. Hepatitis with enzymes 5× normal or jaundice occurs in 3%. Pyrazinamide, rifampicin, and isoniazid, in descending order, are the most likely culprits. If it is possible to interrupt treatment, then one approach is to wait until ALT has fallen to <2× normal then reintroduce two drugs (ethambutol and rifampicin or isoniazid) over 10 days. If the patient is too ill or infectious to stop treatment, continue two low risk drugs (ethambutol, streptomycin, quinolone). A similar strategy can be used for severe cutaneous hypersensitivity.

Ethambutol oculotoxicity in patients with normal renal function is rare when using a dosing regimen of 15 mg/kg. Any eye symptoms should be reported and referred to ophthalmology urgently. Formal visual assessment prior to starting treatment is not usually required in patients with no visual impairment, although an informal check is advisable. Ethambutol should be stopped if there is likely to be a delay and, if appropriate, substituted with another drug.

Compliance and Directly Observed Therapy (DOT)

If there are no concerns about compliance and the treatment response is satisfactory, then regular medication checks and opportunistic urine screening for orange (rifampicin-induced) discolouration is usually sufficient. Rifampicin levels can confirm the drug is being taken and may help tailor dose adjustments when the response to treatment is suboptimal or the pharmacokinetics might have altered (e.g. in pregnancy).

DOT is considered when assessment suggests adherence is likely to be poor (see box below). Treatment (isoniazid 15 mg/kg, rifampicin 600–900 mg, pyrazinamide 2.0–2.5 g, ethambutol 30 mg/kg) is given thrice weekly under direct observation. This regime is for 2 months, then rifampicin and isoniazid thrice weekly for a further 4 months. The toxicity profile includes flu-like symptoms, dyspnoea, abdominal symptoms, renal failure, haemolytic anaemia, thrombocytopenic purpura, and anaphylactic shock.

Indications for Directly Observed Therapy (DOT) for TB

- Current or previous non-adherence to treatment
- Previous treatment for TB
- Homeless or drug/alcohol misuse
- Prison within the previous 5 years
- Major psychiatric, memory or cognitive disorder
- In denial of diagnosis
- Multidrug-resistant TB
- Requests directly observed therapy
- Too ill to self-administer treatment

Use of Steroids and Paradoxical Reactions

The occurrence of paradoxical reactions in HIV-negative patients is well recognized. In up to 20% of patients with tuberculous lymphadenitis, a worsening of symptoms can occur paradoxically during the first 2–3 months of treatment, or even after completion of treatment. Predictive factors seem to be a swelling >3 cm and simultaneous extra-lymph node TB [19]. If the lymph node swelling occurs after completion of treatment,

paradoxical (sterile) reaction is much more likely than recurrence of infection. Hence follow-up rather than re-treatment is routinely recommended. Other sites of paradoxical reactions in HIV-negative patients can be the pericardium, pleura, bone, muscle, and brain.

Despite a more frequent occurrence of immune reconstitution syndrome (IRIS) after initiating antiretroviral therapy in TB co-infected HIV patients, starting antiretroviral therapy as soon as 2 weeks after initiation of TB treatment rather than later has shown to improve survival in this group.

In some patients, the addition of corticosteroids can be beneficial; in HIV patients with IRIS and in patients with TB meningitis, steroids can reduce mortality [20]. In patients with tuberculous pericarditis there is conflicting evidence, but in clinical practice the use of steroids is usually recommended [5].

Drug-Resistant TB

The classification of drug resistant TB includes four major types:

- Isoniazid-resistant
- Rifampicin-resistant (RR-TB)
- Multidrug-resistant (MDR-TB)
- Extensively drug-resistant (XDR-TB)

The drugs used in the management of resistant TB are also now regrouped based on the current evidence of their effectiveness and safety (Table 13.2). Combination treatment with these drugs depends on the groups. Clofazimine and linezolid are now recommended as core second-line medicines in the MDR-TB regimen, while para-aminosalicylic acid is an add-on agent. Clarithromycin and other macrolides are no longer included among the medicines to be used for the treatment of MDR/RR-TB. MDR-TB treatment is recommended for all patients with RR-TB.

The current WHO recommendations are that shorter MDR-TB treatment is now preferred. These shorter MDR-TB treatment regimens are standardized in content and duration and split into two distinct parts. First, an intensive phase of 4 months (extended up to a maximum of 6 months in case of lack of sputum smear conversion) includes the following drugs: gatifloxacin (or moxifloxacin), kanamycin, prothionamide, clofazimine, high-dose isoniazid, pyrazinamide, and ethambutol. This is followed by a continuation phase of 5 months with the following drugs: gatifloxacin (or moxifloxacin), clofazimine, pyrazinamide, and ethambutol. These guidelines also recommend partial lung resection as the surgical procedure of choice in appropriate situations.

Table 13.2 Grouping to guide longer treatment regimens for rifampicin-resistant TB and MDR-TB[a]

Group A Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin
Group B Second line injectable agents	Amikacin Capreomycin Kanamycin (streptomycin)
Group C Other core second line agents	Ethionamide/prothionamide Cycloserine/terizidone Linezolid Clofazimine
Group D Add-on agents	Pyrazinamide Ethambutol Isoniazid (high dose)
D2	Bedaquiline Delamanid
D3	Para-aminosalicylic acid Imipenem-cilastatin Meropenem Amoxicillin-clavulinic acid Carriage return - (thioacetazone)

[a]Medicines in Groups A and C are shown by decreasing order of usual preference for use (subject to other considerations). In patients with RR-TB or MDR-TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second line TB medicines—one chosen from Group A, one from Group B, and at least two from Group C. If the minimum number of effective TB medicines cannot be composed as given above, an agent from Group D2 and other agents from Group D3 may be added to bring the total to five. In patients with RR-TB or MDR-TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol. (Adapted from WHO treatment guidelines for drug-resistant TB, 2016 update)

Vaccination

The only currently registered vaccine against TB is the BCG vaccination. The BCG is derived from a live attenuated strain of *M. bovis* and contains a mix of over 4000 antigens [21]. Despite variability over the years, it has been shown to be effective in preventing the most severe cases of TB in children, such as TB meningitis and disseminated TB. Little is known about its efficacy in those over age 16. The vaccine does not prevent primary infection or pulmonary tuberculosis, which is the main route of infection in adults, and it does not prevent reactivation of latent tuberculosis. The effect on the spread of tuberculosis in endemic settings is thus dubious.

Caution is warranted when using the vaccine in immunocompromised patients; cases of reactivation of *M. bovis* after vaccination have been described.

Health care workers who are frequently exposed to TB (laboratory workers, employees in a chest clinic) should be given the opportunity to be vaccinated against TB; however they should be aware that there is little evidence for the effectiveness of the vaccine in persons aged 35 and over.

Several trials are currently running with the aim to induce a more sustained immune response in adults by using adjuvant vaccines targeting various antigens, modifying the current BCG vaccine, or by using attenuated MTB strains. These are phase 1, 2, and 3 trials, some of which are promising in HIV-infected as well as HIV-uninfected patients. Alternative routes of vaccination such as inhalation are being explored, but are in a very preliminary phase of development.

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