Tuberculosis in Clinical Practice

Onn Min Kon
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Pranabashis Haldar

The Natural History of *M.tuberculosis* Infection

The Pathogen

Mtb is one member of a closely related group of organisms that comprise the *Mycobacterium tuberculosis* complex (MTBC). Other members of this complex include *M.bovis*, *M.africanum* and *M.microti* and are pathogenic to humans. Although clinical disease arising from these infections is well recognised and often similar in presentation to disease caused by Mtb, the latter is by the far the most dominant contributor to the global burden of TB.

Mtb is an obligate aerobic organism with some unusual properties. It has a characteristic lipid laden cell wall that has likely evolved to resist desiccation in air. The biochemical properties of the cell wall have some important clinical consequences that include resistance to gram staining, necessitating special laboratory staining methods for examination, and a greater resistance to antibiotic penetration. Mtb is a slow growing organism, with a doubling time in vitro of approximately 15 h. This prolongs the time to culture detection from clinical samples (typically take 2–4 weeks), presenting a significant limitation to rapid diagnosis. Furthermore, extended courses of bactericidal antibiotics, reliant on active bacterial replication are required for effective treatment.

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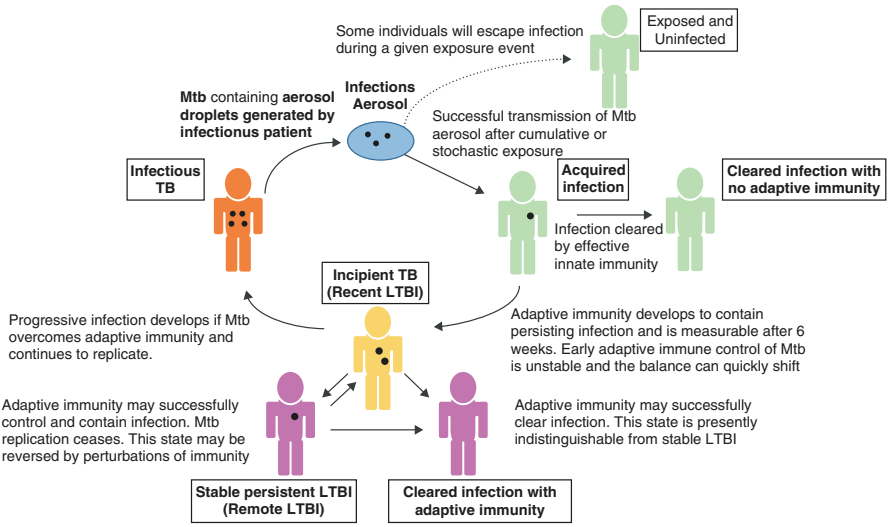

Fig. 1 The Mtb infection cycle and recognised stages of human infection

The Mtb Infection Cycle

Figure 1 summarises the key stages of the Mtb infection cycle, together with the clinical correlates that associate with the different phases of infection.

Transmission

Mtb is reliant on human infection to propagate. The cycle of infection shares characteristics with both major categories of infectious diseases—the more contemporary crowd diseases that are usually highly virulent and dependent on high population density to maximise transmission; and the older human infections that were adapted to exist in conditions of low population density by maintaining a state of chronic infection within the host, often associated with a period of latency followed by reactivation, to improve chances of capturing sporadic opportunities for transmission [1]. The dual properties of Mtb reflect its adaptation to the history of humans over millennia, presenting complex challenges to develop effective strategies for eradication.

In common with most crowd diseases, Mtb is transmitted in aerosol and has flourished as population levels and density have risen across the globe. Evidence supports the view that transmissible aerosol droplets need to be sufficiently small (<5 microns) to be effectively deposited in the lower airways for infection to occur. Larger droplets are trapped in the upper airways and do not contribute to

transmission. It is widely believed that most transmissible aerosols are generated by forced expiratory manoeuvres, typically coughing and sneezing, although some evidence is now emerging to suggest that infectious TB patients may also generate aerosol droplets containing Mtb during normal expiration. One implication of the small droplet size needed for infection is that the Mtb infection dose (the number of organisms required to cause infection) is very low [2]. In this respect, the infection risk presented by an individual with pulmonary TB is determined by their propensity to generate infectious aerosol [3]. Although we recognise advanced, cavitatory pulmonary TB, with high bacillary burden in sputum to be most indicative of infectious TB, this neglects the potential transmission risk associated with milder forms of disease. Early studies reported a dissociation of aerosol generation and bacillary burden in sputum, such that people with more advanced disease, thick tenacious sputum and ineffective cough were less infectious than ambulatory patients with less viscous sputum. Recent studies support the view that cough associates more closely with risk of transmission than sputum bacillary burden, despite the latter being a commonly used surrogate measure in clinical practice.

Infection is acquired by susceptible individuals inhaling infectious aerosol that deposits in the terminal airways. In addition to the size of aerosol droplets already described, environmental factors that include close proximity, prolonged duration of exposure and poor surrounding ventilation all promote the likelihood of successful aerosol transmission. The Wells-Riley equation is a frequently used mathematical model that incorporates each of these parameters to quantify transmission risk in outbreak settings and inform infection control policy.

It is notable that while the Wells-Riley equation can provide an objective guide to dose-dependent transmission risk, many cases of infection may be attributable to very minor periods of exposure—an observation that can now be scientifically verified by whole genome sequencing of the organism between linked cases. This pattern supports the view that a proportion of transmission events will occur stochastically, although little more is presently understood about this phenomenon.

Primary Mtb Infection and Primary TB

An understanding of the early events that occur after Mtb enters the lung are important as there is increasing evidence to suggest that the early interactions of the pathogen with the host immune response have a critical bearing on the fate of the infection [4]. Moreover, an awareness of these processes can aid interpretation of the clinical phenotype of infection with which a patient presents. The early events of Mtb infection are incompletely understood and necessarily derived from a range of different animal infection models. The accepted paradigm is of rapid intracellular habitation of Mtb by infection of resident lung macrophages [5]. This process triggers activation of additional macrophages and other effector cells of the innate immune response, notably neutrophils, to the site of infection. The early activation of macrophages is a hallmark of the innate lung immune response with

pro-inflammatory signalling driving incremental recruitment of both macrophages and neutrophils to the site of infection, promoting phagocytosis of dead cells and driving the formation of primary granulomas. The pro-inflammatory response at this very early stage of infection may be sufficiently robust to induce pulmonary and systemic manifestations that include a transient flu-like illness, erythema nodosum and patchy infiltrates on a chest radiograph. It is likely that a proportion of early infections are effectively cleared at this stage and before an adaptive response is mounted. Recent studies have reported differences in the innate immune responses of recent household contacts of pulmonary TB, depending on whether an adaptive immune response, measured by T-cell reactivity to Mtb antigens, has occurred [6]. Such differences could help inform the constituents of an effective innate immune response to guide prospective vaccine development. In this respect, evidence supports a role for BCG vaccination in enhancing innate immune memory to clear Mtb infection [7].

However, the innate immune response to Mtb is in many ways a double-edged sword as Mtb is well adapted to intracellular survival within macrophages and more recent studies suggest that recruitment of macrophages is harnessed and exploited by early virulence factors expressed by the pathogen to promote persistence, replication and provide a vehicle for blood-borne dissemination. Moreover, over exuberant neutrophil activation and influx to the site of infection has been associated with adversely altering the cross-regulatory network of cytokine expression to impair effective adaptive immunity, promoting tissue damage and softening of granuloma structure that favours disseminated infection, culminating in a higher risk of disease progression.

Alongside the innate immune processes described above, local dendritic cells providing lung immune surveillance are rapidly activated by pathogen signals to internalise the organism and transport it to the local draining lymph node, where antigen presentation to naïve T-cells initiates their priming and activation [8]. One implication of this process is the facilitation of Mtb translocation to the local lymph nodes by immune cells. Both animal studies and autopsy studies in humans indicate that Mtb lymph node infection characterised by nodal enlargement and granuloma formation ensues as a consequence [9]. Indeed, utilisation of the immune system by Mtb for its growth and dissemination is a common underlying theme in the pathogenesis of disease. Antigen specific effector T-cells then migrate from the lymph node, in blood, to the site of infection and have a primary role in orchestrating the adaptive immune response to Mtb infection. Studies consistently indicate a rapid decline in bacterial growth after antigen specific T-cells appear, supporting their critical importance in limiting Mtb infection. It is estimated that the time-course of events leading to the development of circulating antigen specific T-cells after Mtb infection in humans is approximately 4–6 weeks. This delay is unusually prolonged and suggests that the pathogen has developed processes to delay the onset of adaptive immunity long enough to establish infection.

Primary infection refers to the pathological events described above and comprises several clinical phenotypes that are summarised in (Table 1).

Table 1 Clinical phenotypes of primary Mtb infection

Clinical phenotype	Underpinning pathological correlates	Comments
Asymptomatic infection		
Infection identified by radiological features Ghon focus: Calcified granulomas in lung parenchyma Ghon complex: Accompanying mediastinal and hilar lymph node enlargement and calcification	Granulomas formed by innate and adaptive immune responses. Calcification indicates granuloma sclerosis and suggests no ongoing active infection	Usually associated with measurable T-cell reactivity in blood Infection may be controlled or cleared in this state. No tests presently discriminate between these two states
Inflammatory response syndromes		
Transient flu-like illness Fever, myalgia and arthralgia that may be associated with lung infiltrates	Manifestation of a systemic inflammatory response during primary Mtb infection	Symptoms are often short-lived and most often either ignored or diagnosed as a viral illness
Erythema nodosum	Non-specific cutaneous hypersensitivity reaction as a manifestation of systemic inflammation	Symptoms are usually self-limiting but should trigger consideration of primary TB as a cause. This is more likely if presenting in children, in a high TB incidence setting
Phlyctenular keratoconjunctivitis	Non-specific nodular inflammation of the cornea and conjunctiva arising as a hypersensitivity response of systemic inflammation	Occurrence is rare but almost always in children. Primary TB should be considered more likely in a high TB incidence setting
Bacteriological disease		
Primary TB	This refers to a state of ongoing bacterial replication progressing to symptomatic disease, after establishment of adaptive immunity	This form of disease is most commonly seen in children. Typical chest radiographic features include significantly enlarged hilar or mediastinal lymph nodes Areas of necrosis may be evident on a CT scan, indicating active inflammation Lobar consolidation when present is more often observed in the lower lobes
Miliary TB	Uncontrolled disseminated Mtb infection arising from a failure of innate and adaptive immune processes to control and contain primary infection	Most often seen in the context of immunodeficiency—usually very young children and people with HIV. Prior BCG vaccination appears to have a significant protective effect in young children to prevent miliary disease

Latent Infection and Post-primary TB

For the majority of Mtb infection events, adaptive immunity is quickly established to effectively contain the pathogen. Active bacterial replication ceases and the infected individual remains completely asymptomatic. This state is referred to as latent TB infection (LTBI), implying that the infection continues to exist but is undetectable or 'hidden'. In the absence of detectable bacteria, LTBI is inferred by tests that reveal T-cell reactivity to Mtb antigens. In clinical practice, two groups of tests are available to measure T-cell reactivity: (1) the tuberculin skin test (TST); and (2) the interferon gamma release assays (IGRAs). A comparative summary of these is provided here (Table 2), with a more detailed account provided in a later chapter.

Modelling studies estimate approximately one-quarter of the global population (1.7 billion people) has LTBI [10]. This is indicative of the extraordinary reach of Mtb across the world, in keeping with the organism's historical relationship with human migration.

That Mtb infection persists and has not been cleared is revealed in a proportion of people with LTBI that subsequently progress to active TB. Early prospective studies carried out in cohorts of recent TB contacts with a positive TST revealed the occurrence of TB in approximately 10%, following a variable period of latent infection. TB occurring following a period of latent infection is nominally referred to as either post-primary or secondary TB and is estimated to account for over 90% of all incident disease. It therefore follows that LTBI represents an important reservoir of future disease.

Prospective studies further indicate the risk of developing TB to be greatest in the first 2 years after acquiring the infection, with recent evidence suggesting 80% of cases arise in this period [11]. On this basis, LTBI is risk stratified and loosely categorised as either recent (identified within 2 years of TB exposure) or remote infection.

Conceptually, recent infection refers to a period when a dynamic and unstable equilibrium exists between the pathogen and host immune response, with an outcome to this 'conflict' usually determined within the 2-year timeframe. It suggests that most cases of post-primary TB are not strictly reactivation events, but rather variably progressive infection. Although most often associated with recently acquired infection, the idea of a distinct phenotype of latent infection that is biologically active and associated with a significantly increased risk of disease progression is gaining broad acceptance and is referred to as incipient TB [12].

Remote infection indicates a conflict outcome in favour of the host. However, it remains unclear whether the infection has been cleared or effectively suppressed. This is an important distinction as cleared infection carries no risk of future TB, unless further infection occurs. In contrast, suppressed infection carries a future risk of becoming reactivated. There is little known about the absolute risk associated

Table 2 Comparison of clinical assays for measuring T-cell reactivity to Mtb

Tuberculin skin test (TST)	Interferon gamma release assays (IGRA)
Description of test	
Intradermal injection of a standardised volume[a] of Purified protein derivative (PPD)—a sterile protein extract derived from the filtrate of Mtb cultures. This induces a cell mediated delayed type hypersensitivity response at the injection site in individuals with exiting antigen specific T-cells Results of testing are based on the size of the inflammatory response (diameter of skin induration) measured after 48–72 h	A standardised preparation of peripheral blood mononuclear cells derived from collected whole blood is incubated with two Mtb antigens: CFP-10 and ESAT-6 The specific interferon gamma (IFNγ) response generated from this is measured using an ELISA Two commercial assays exist 1. QuantiFERON-TB (QFT) by QIAGEN Inc. 2. T.SPOT-*TB* by Oxford Immunotech Ltd. Results of testing are based on the amount (QFT) or number of cells (T-SPOT) producing IFNγ
Immunological specificity	
Induration represents a T-cell response to both specific and non-specific antigenic proteins within PPD	Improved specificity is achieved by choice of antigens for assays. Both CFP-10 and ESAT-6 expression is limited to mycobacterial species of the MTBC and a very limited number of NTMs[b]
There is cross-reactivity with prior exposure to both Mtb and non-tuberculous mycobacteria (NTMs), most importantly prior BCG vaccination	Importantly, there is no cross-reactivity with prior BCG vaccination
Size of the induration provides a guide to the intensity of the response and improves specificity for both Mtb infection and the state of infection (stable vs. active infection) Raising the threshold for a positive response lowers sensitivity for detecting underlying Mtb infection	Results are routinely provided as positive and negative, depending upon whether a threshold IFNγ response has been reached. An 'Indeterminate' result with QFT indicates the test is uninterpretable due to control wells not meeting eligibility criteria. For T-SPOT, a 'Borderline' result is given when the number of spot forming cells lies within a range between a clear positive or negative result Although the magnitude of the measured IFNγ response cannot distinguish between TB and LTBI, there is some emerging evidence that it may be useful for stratifying TB risk in LTBI
Implementation in practice	
No requirement for laboratory facilities The test can be conducted in a field environment	Methodology requires availability of specific laboratory tools and trained personnel
Low-cost and globally licenced	Higher cost and restricted licencing
The conduct of the test and measurement of induration are operator dependent, with between operator variability reported	Blood sampling is largely operator independent with objective and repeatable assay results
Requires two visits to the examining facility by the individual being tested	Results of testing can be made with the tested individual attending on one occasion only

(continued)

Table 2 (continued)

Tuberculin skin test (TST)	Interferon gamma release assays (IGRA)
Test results area available within 72 h	Test results are theoretically available within 36 h, although will be limited by the speed of laboratory reporting pathways
In vivo assay—repeated or serial testing may induce a boosted response	Ex vivo assay—serial testing will be unbiased

[a]UK standard of RT23 is 2TU and 0.1 ml
[b]*M. kansasii, M.szulgai, M.marinum and M.gordonae* also express CFP-10 and ESAT-6 and may give cross-reactivity with IGRAs

with remote infection or the factors that may precipitate reactivation TB in healthy immunocompetent individuals. However, significant TB risk is recognised in cohorts with cell-mediated immune deficiency, most notably with HIV co-infection and in those receiving biological treatment with TNFα blocking agents (Table 3). Studies in HIV cohorts with LTBI report an annual TB risk of 8–10%. While this figure does not take into account the proportion with recent infection, the markedly increased TB rate in HIV populations indicates the relevance of remote infection to the global burden of TB. One final noteworthy caveat is the suggestion that remote LTBI may confer some protection from future TB. This possibility has been raised in studies that have shown a significantly lower TB incidence and disease severity among young adults with prior LTBI, compared with those that were infection naïve [13]. The postulation here is that remote LTBI may provide low grade and persistent immune stimulation to enhance responses to further Mtb exposure.

The Epidemiological Cycle of TB

The first part of this chapter has looked at the natural history of a human Mtb infection and defined the different infection states that may be observed. At population level, the cycle of infection informs key break points at which interventions may effectively interrupt disease propagation (Fig. 2). The WHO End TB Strategy (2015) sets the target of a 90% reduction in global TB incidence by 2035 [14]. To achieve this will principally require highly effective intervention against the two major states of human Mtb infection (Fig. 2):

1. Active pulmonary TB: Early diagnosis and effective treatment of infectious TB to limit onward infection transmission.
2. LTBI: Screening to identify and provide targeted treatment in LTBI groups, at risk of progressing to active TB.

Table 3 Common factors associated with LTBI progression to active TB

TB progression risk factor	Comments
Strong risk (relative risk of TB > 5, with good supporting evidence)	
Recently acquired Mtb infection <2 years	
Infants and young children <5 years	TB progression is frequently associated with disseminated disease. Prior BCG vaccination has a significant protective effect for both progression and dissemination
HIV positive	Risk increases with immunosuppression (falling CD4+ T-cell number in peripheral blood)
TNFα receptor blockade	Studies suggest more potent newer biologics carry a significantly higher risk for TB progression
Silicosis	Confined to areas of the world with an ongoing mining industry. An important risk factor among south African gold miners
Low to moderate risk (relative risk of TB estimated 2–4)	
Evidence of previously healed but untreated active TB	Self-healed TB indicates success of immune processes in overcoming progressive infection. A significant proportion of this group will be maintaining a state of incipient infection
Malnutrition and low BMI (<18 kg/m^2)	
Diabetes mellitus	Diabetes is associated with impairment in both innate and adaptive immune function. Although relative risk with diabetes is modest, the vast population with co-existing LTBI and diabetes poses a significant threat for future TB
End stage renal failure (stage 5 CKD)	A sharp rise in TB risk is seen in chronic kidney disease at the time of requiring dialysis
Excess alcohol consumption	
Smoking and inhalation of biomass fuels	
Maintenance treatment with oral corticosteroids (>15 mg/day)	
Other risk factors (relative risk uncertain, but likely to be significant)	
Older age (>60 years)	Increasing age is associated with a higher rate of TB reactivation among people with remote LTBI that may reflect age-related immune senescence
Male gender	An association with TB progression appears to exist that is independent of the higher presumed Mtb exposure risk of greater gender related social mixing in males

(continued)

Table 3 (continued)

TB progression risk factor	Comments
Inhaled recreational drug use	Smoking of cannabis, cocaine and heroin have been associated with TB outbreaks in low TB incidence settings Shisha smoking has been reported to cause outbreaks in some higher TB incidence settings, where the practice is more common Inhaled substances of misuse increase both Mtb transmission within drug sharing groups and may increase the likelihood of disease progression in those acquiring the infection by drug induced impairment of effective lung defences
Prolonged exposure (>5 h per day for >2 weeks) to highly infectious TB	There is some data to support the view that higher Mtb dose exposure associates with increased risk of progressive infection
Poor ventilation and overcrowding	
Long term residence in detention or prison facilities (>6 months)	
Migrant from high TB incidence country	TB in migrants comprises a large proportion of the incident cases in low incidence, high income Western countries. Over half of such cases occur within 5 years of arrival suggesting reactivation of LTBI remotely acquired from their country of origin. However, it is not clear whether progression risk is actually increased, compared with comparable cohorts resident in the country of origin
Health care workers	Repeated occupational exposure to Mtb increases risk of disease. However, it is not clear whether progression risk in health workers with LTBI is actually increased

Of these two strategic objectives, the early treatment of active TB must be prioritised as it is of immediate relevance to lowering present TB related morbidity and mortality. Furthermore, preventative strategies aimed at LTBI are futile in settings with a high TB burden, where a high lifetime risk of Mtb reinfection exists, unless complementary strategies that prevent reinfection are developed and implemented in parallel. This is a key focus of the developmental pipeline for new vaccines and as discussed earlier, could also include a role for BCG revaccination. In the absence of an effective strategy to prevent Mtb reinfection, the WHO presently recommends LTBI screening as an integral component of the TB control strategy for countries with a TB incidence of less than 100 cases per 100,000 population. In practice, systematic LTBI screening programmes are delivered predominantly in high income, low TB incidence countries of the Western world that have sufficient resources available to deliver such programmes. One consequence of the increased efforts invested toward the WHO strategic objectives has been the growing recognition of additional phenotypes of Mtb infection that challenge the accepted paradigm of the Mtb infection cycle. These are discussed further in the next section.

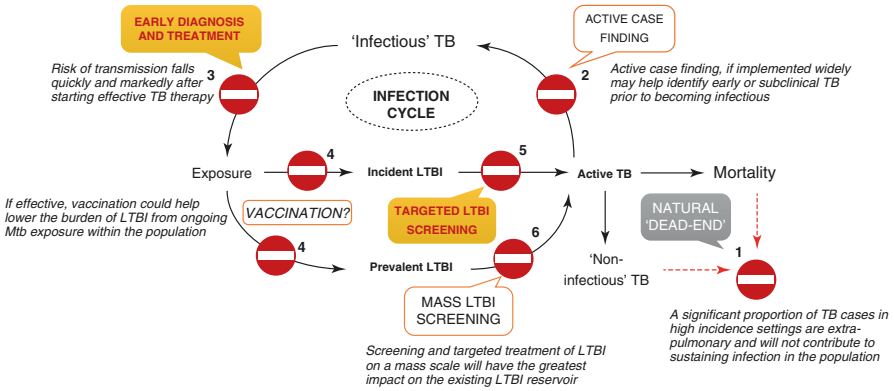

Fig. 2 Epidemiological cycle of TB and potential breakpoints for control. Shaded callout boxes represent strategies that are currently in use and encompass the strategic pillars for TB control advocated by the WHO End-TB strategy. Unshaded callout boxes are aspirational targets that are presently the focus of intensive research

Early Diagnosis of Infectious TB and Outcomes of Active Case Finding

Active case finding (ACF) refers to a systematic programme of investigation to identify cases of TB before they present to healthcare. Studies that have evaluated the outcome of ACF programmes consistently report identification of early active TB, both in household contacts and more generally in the absence of a history of recent contact in areas of high TB incidence. Strikingly, disease is frequently identified in the absence of clinical symptoms and may be associated with positive Mtb culture from respiratory tract sampling [15]. This state of Mtb infection is termed subclinical disease and is characterised by few or no symptoms [16]. Where symptoms exist, they are relatively non-specific and insufficient to raise a concern of TB in either the affected individual or a clinician. Chest radiographic abnormalities are often absent, although more high sensitivity imaging with CT, and more recently combined positron emission tomography with CT (PET-CT) reveal subtle abnormalities, including early 'tree-in-bud' change that is a feature of terminal bronchiolitis, active nodules and metabolically active parenchymal granulomas and intra-thoracic lymph nodes, in the absence of significant nodal enlargement [17]. In the evolving framework of Mtb infection, subclinical TB represents a phenotype of transition from incipient TB to active TB.

The observation that this very early stage of disease is associated with microbiologically detectable infection suggests that unrecognised transmission may be a significant contributor to the persistence of Mtb within the population. This presents a significant challenge to disease control, both in respect of identifying prevalent TB and having diagnostic tools that are fit for this purpose. Currently, the diagnosis of pulmonary TB relies on the detection of Mtb from samples of the respiratory tract,

notably sputum. However, individuals with subclinical disease may not be able to expectorate sputum and new diagnostic tools that are not reliant on sputum are needed. In addition to this, effective strategies are needed to provide targeted testing of groups or whole communities at high risk of TB.

LTBI Screening and TB Prevention

Modelling studies indicate mass LTBI screening and treatment has the largest impact on future TB incidence and necessarily requires adoption to approach the targets of the WHO End-TB strategy. Critical to the successful implementation of this approach is the availability of reliable screening tools to identify the subset of the global LTBI population at sufficient future risk of TB to warrant preventative treatment [18].

LTBI is presently defined by evidence of T-cell reactivity to Mtb antigens, in the absence of any clinical, radiological or microbiological features of active TB. However, this definition is too broad to be meaningful in practice and fails to discriminate between the multiple phenotypes of infection that have been described here. The optimisation of screening will require biomarkers that empirically distinguish between three asymptomatic states, which correspond to these phenotypes of LTBI:

1. Cleared state: The absence of viable or potentially viable Mtb infection.
2. Stable state: Persistent latent Mtb infection that exhibits no significant biological activity and is well controlled by a competent immune system
3. Active state: Biologically active infection that is under containment (incipient TB) or is no longer contained (subclinical TB)

An example of how knowledge of these states could enhance the efficiency and effectiveness of screening is provided in a comparison with current screening practice (Fig. 3).

Summary

This chapter has reviewed our present understanding of the complex natural history of human Mtb infection and the challenges thereof to develop effective interventions for control.

With advances in scientific methodology, sophisticated animal models of infection and the availability of highly sensitive diagnostic tools, the recognised spectrum of infective states has grown, with a growing appreciation that infection likely

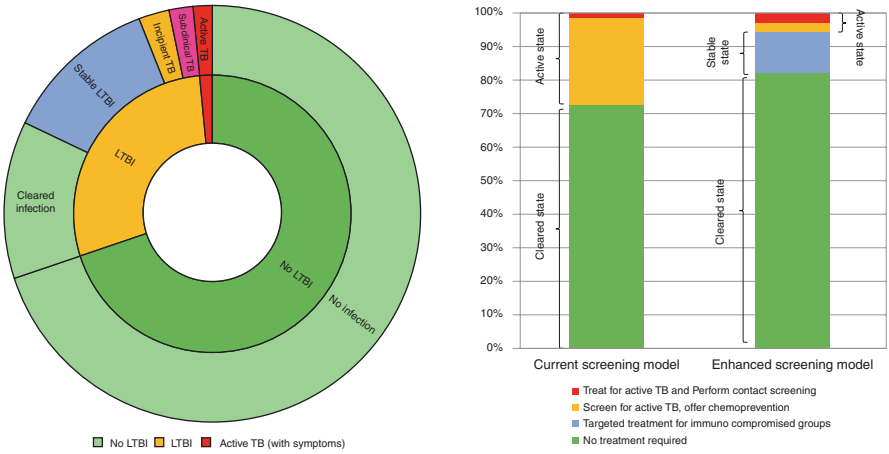

Fig. 3 Phenotypes of LTBI and their relevance to enhanced programmatic screening. The figure provides a representative breakdown of the different phenotypes of Mtb infection and their approximate proportion. The impact of improved characterisation of Mtb infection phenotype on screening practice is clear. A significantly smaller proportion of the population with T-cell reactivity and no symptoms (present day LTBI) would require preventative therapy and better screening tools would also improve identification of more previously unrecognised active TB, in the form of subclinical disease. Current screening is limited to high risk populations due to the numbers that would require treatment and investigation. An enhanced model could enable large scale screening, with better targeted treatment

exists on a continuum, determined by the dynamic relationship of the pathogen to its host.

Specifically, phenotypic distinction of the different states of latent infection provides a framework for the targeted development of discriminatory biomarkers that will improve our capacity to provide effective strategies for future disease prevention.

Key Learning Points

- The infection cycle of Mtb in humans is complex and associated with several possible outcomes that are determined by host innate and adaptive immune responses. In broad terms, immune mechanisms designed to combat infection are frequently exploited by the pathogen to promote its survival.
- Human Mtb infection has traditionally been categorised as latent TB infection (LTBI) or active TB, on the basis of whether T-cell reactivity is associated with clinical, microbiological or radiological features of disease exist.
- We recognise the current definition of LTBI comprises multiple underlying clinical relevant infection phenotypes that are determined by the nature of the interaction between the pathogen and host immune response.
- There is increasingly a move toward developing biomarkers that stratify LTBI into low risk, stable infection, high risk incipient infection and subclinical active TB.

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Bacillus Calmette–Guérin (BCG) Vaccine

Elizabeth Whittaker and Surinder K. Tamne

History of BCG Vaccine

BCG is the collective term applied to a family of live, attenuated vaccines derived from the passage of *Mycobacterium bovis* by Albert Calmette and Camille Guérin. In 1900, they started work on developing an anti-tuberculosis (TB) vaccine at the Pasteur Institute in Lille. They began with cultivating a bovine strain of tubercle bacilli on a glycerin and potato medium but found it difficult to produce a homogeneous suspension of the bacilli. In an attempt to stop the tendency of the bacilli to cluster they added ox bile to the medium and noted that subculture led to a lowering of the virulence of the organism. Over a period of 13 years they went on to produce increasingly less virulent subcultures of the bovine strain of the tubercle bacillus. By 1921 they believed the bacillus they had produced was harmless to humans however retained its ability to stimulate antibody formation; the BCG vaccine was born.

The BCG vaccine was first used in 1922 to vaccinate a newborn infant whose mother's death in childbirth was attributed to TB, and whose primary caregiver was a grandmother also infected with TB. The infant was followed up for 6 months and as she remained well this new method of vaccination was extended to all newborn infants at the Charite hospital of Paris. BCG vaccine was initially given orally however the intradermal route was introduced in 1927 because of better induction of delayed type hypersensitivity (DTH) response to the tuberculin skin test [1].

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By 1928, 114,000 infants were vaccinated without serious complications [2]. The vaccine was largely used in Europe during the 1920s until a serious incident occurred in Lübeck, Germany in 1929, where due to laboratory error, a BCG vaccine batch accidentally contaminated with the distinct virulent human strain caused 72 deaths among 251 vaccinated children, creating a negative impact on BCG vaccination. Although the BCG vaccine itself was eventually exonerated as the cause of the Lübeck disaster, confidence in the vaccine had been undermined and its use declined for several years afterwards.

Further evidence for the effectiveness of BCG in the prevention of tuberculosis were later accumulated, though it was not until the 1930s when the first formal trial of BCG vaccination was carried out, in Native Americans [3]. By the 1940s, BCG vaccination, administered percutaneously or intradermally, had been shown to be efficacious in several studies [3–5]. In the 1950s, two major trials were started in the UK and the USA, by the Medical Research Council (MRC) and the United States Public Health Service [6, 7]. The results of these trials differed, with the study in the UK showing that BCG vaccination (Dutch strain) was highly efficacious against tuberculosis, whereas the US study (Tice strain) concluded that it provided very little protection. Based on this, the UK implemented a policy of universal vaccination of all school-age children who were tuberculin skin test negative; the US based on their findings decided not to use BCG vaccination routinely other than for select high-risk populations.

Following the lead of Europe and the WHO, the use of BCG vaccination increased globally as the majority of countries introduced routine BCG according to various schedules; at birth, school entry and leaving school.

Subsequent strains have undergone further development through repeated subculturing in many laboratories around the world. These strains are not bacteriologically identical, due to the biological variability of the strains, with different genotypic and phenotypic characteristics. As a result, depending on the strain, they have different viability, immunogenicity, reactogenicity, and residual virulence. The Pasteur strain of BCG serves as the reference strain of the vaccine, and its complete genome sequence has been determined [6]. Currently, the main sub-strains used for vaccine production are Brazilian (Moreau/Rio de Janeiro), Danish (Copenhagen—1331), Japanese (Tokyo—172-1), Russian (Moscow—368) and Bulgarian (Sofia—SL222). In terms of efficacy, no BCG strain is demonstrably better than another, and there is no global consensus as to which strain of BCG is optimal for general use [8]. However, there are significant differences in the immune responses induced by BCG vaccine strains in newborn infants, with BCG-Denmark and Japan having greater Th1 and polyfunctional T cell responses that BCG-Russia [9, 10].

Efficacy of the BCG Vaccine

The protective efficacy of a vaccine is measured in terms of the reduction of the risk of infection or disease in vaccinated individuals when compared with similarly exposed unvaccinated individuals. Regardless of the debate regarding its role in

tuberculosis control globally, BCG vaccination is widely used, with over 100 million doses given annually. Randomised controlled trials (RCTs) and case–control studies have shown consistently high efficacy of infant vaccination in preventing severe forms of primary tuberculosis, which usually present as meningitis and miliary disease, but also as pulmonary disease in childhood [11]. Trunz et al. using the data from the same trials included in previous reviews [12], estimated the efficacy of BCG vaccination against meningitis and miliary tuberculosis to be 70% and 80%, respectively. Randomised controlled trials (RCTs) of BCG have shown varying efficacy in different populations [13]. A number of hypotheses have been postulated for this observed variation, but no firm consensus has been reached.

One hypothesis is that individual BCG strains induce different levels of protection. However, several large systematic reviews, which included 18 RCTs with active TB as endpoint and 6 RCTs with TB meningitis or miliary TB as endpoint concluded that there was no evidence that efficacy was associated with BCG strain [14, 15]. There appears to be a strong association between vaccine efficacy and latitude at which the study was conducted [16], and the variable geographic prevalence of non-tuberculous mycobacteria (NTM) or helminth infection has been implicated.

More recently, the meta-analysis of 14 studies involving 3855 participants found that BCG vaccinated children were less likely than unvaccinated children to have evidence of TB infection after exposure, upholding the recommendation that BCG should be given as soon as possible after birth to prevent children from getting infected [17]. BCG is less effective in preventing pulmonary disease, and it does not prevent reactivation of latent pulmonary infection, the principal source of bacillary spread in the community. Its role in preventing transmission of tuberculosis is therefore limited.

Protection has been shown to last for at least 15 years [18], with more recent studies suggesting protection may last up to 60 years [19], but protective efficacy is likely to wane with time [20–22].

Policy and Delivery of BCG Immunisation in the UK

The UK BCG immunisation programme has undergone several changes since its introduction in 1953 when the highest rates of tuberculosis were in older teenagers and young adults. It was targeted at young people of school-leaving age (then 14 years) with the aim of protecting them before they left school. In the 1960s, the programme was extended to include selective immunisation of neonates born to recent entrants to the UK from countries with high rates of TB. This was due to the increased risk that these babies had of developing the disease. Cases of tuberculosis TB in the UK fell from 50,000 per year in the 1950s to a low of 5745 cases in 1987. In 2005, following a continued decline in TB rates in the indigenous UK population, the Joint Committee on Vaccination and Immunisation (JCVI), (the expert committee that advises the UK Government on vaccination and immunisation), recommended that the national schools routine BCG immunisation programme be replaced by a risk-based vaccination programme in the UK.

For this reason the UK BCG immunisation programme is now a risk-based, predominately neonatal programme, targeting babies in areas in the UK with high rates of TB (incidence >40 cases per 100,000 population) or babies whose parents or grandparents were born in a country with a high rate of TB and children [23]. Children up to 16 years may also be vaccinated following an assessment of individual risk factors (see Fig. 1). This includes travel to TB endemic countries and tuberculin-negative household or equivalent close contact of cases of infectious TB.

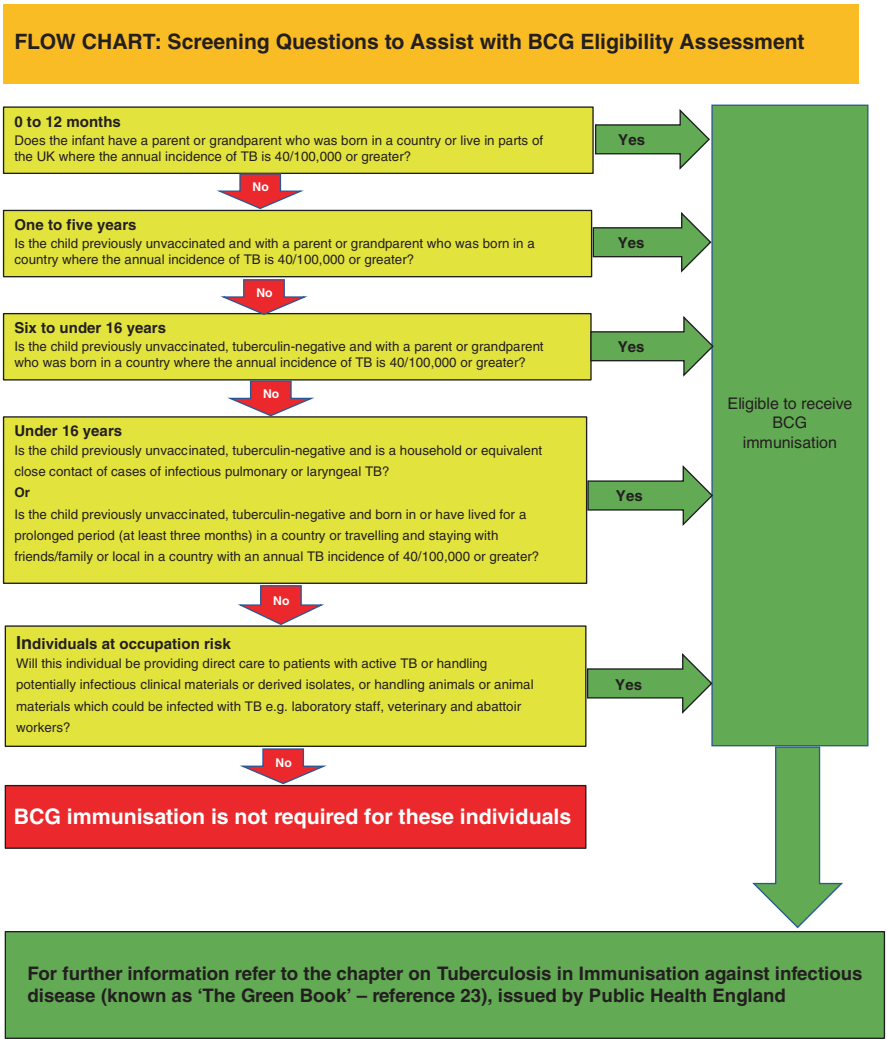

Fig. 1 Assessment for eligibility for BCG vaccine. Determining which individuals meet the criteria for BCG vaccination in the community. Further details available here https://assets.publishing.ervice.gov.uk/government/uploads/system/uploads/attachment_data/file/731848/_Greenbook_chapter_32_Tuberculosis_pdf

There are few data on the protection afforded by BCG vaccine when it is given to people aged 16 years or over and virtually no data for people aged 35 years or over. BCG is therefore not usually routinely recommended for people aged over 16 years, unless the risk of exposure is great (e.g. healthcare or laboratory workers at occupational risk through direct clinical contact with people diagnosed with TB or contact with infectious TB materials).

The existing programme provides a platform on which local services can build on to ensure that the needs of their local population are met and promote a consistent and equitable approach improving BCG uptake. This includes better identification of those eligible for vaccination, provision of neonatal immunisation prior to discharge from hospital and training and education of staff and communities with robust local pathways for delivery of BCG vaccination as part of infant and risk group immunisation, with clear lines of accountability for commissioning, delivery and monitoring.

The UK BCG immunisation programme is subject to revisions in response to epidemiological changes, emerging best practice and scientific evidence. Immunisation against infectious disease (known as 'The Green Book'), issued by Public Health England provides guidance and is the main evidence base for all immunisation programmes.

Immunology of BCG

In recent years, BCG has been extensively studied to elucidate a protective immune response against TB. In brief, following delivery of BCG vaccine by intradermal vaccination, components of the mycobacterial cell wall such as peptidoglycans and mycolic acids interact with pattern recognition receptors (PRR) including toll-like receptors (TLR). This immediate response is characterised by inflammatory cytokines (TNFα, IL-8) followed by a cellular infiltrate of neutrophils, antigen presenting cells and then lymphocytes [24], and live BCG can be detected for up to 4 weeks in previously unvaccinated adults [25]. Dendritic cells then travel to local lymph nodes and present live BCG to activate CD4+ T cells. These Th1 or IFNγ producing T cells have long been thought to represent BCG mediated protection against TB. Other T cells, including CD8+, γδ and regulatory T cells have also been implicated in protection.

Much of what we understand about mycobacterial immune responses comes from studying the impact of BCG vaccine in patients with immunodeficiency, congenital and acquired. The risk groups affected by disseminated BCG disease include severe combined immunodeficiency (SCID), human immunodeficiency virus (HIV), chronic granulomatous disease (CGD) and mendelian susceptibility to mycobacterial disease (MSMD). In 1995, Casanova et al. reviewed 121 published cases of disseminated BCG infections [26], identifying 61 cases of definitive immunodeficiency disease: 45 cases were (SCID), 11 cases were chronic granulomatous disease (CGD), 4 cases were acquired immunodeficiency syndrome and 1 case had

complete DiGeorge syndrome (CDGS). Norouzi et al. reported that out of 158 patients with BCGosis, 120 patients had immunodeficiency disease [27].

SCID is a group of inherited disorders that cause severe abnormalities of the immune system by affecting numbers and function of T- and B-lymphocytes. A diagnosis of SCID is often first considered if an infant vaccinated with BCG at birth presents with multi-system disease and dissemination of BCG. This is a serious and often fatal condition, unless anti-mycobacterial treatment and bone marrow transplantation can be provided swiftly. Patients with SCID and BCG have greater morbidity and mortality peri-transplant and longer admissions post transplant, with the associated increased health costs [28, 29].

The consequences of an acquired T cell defect such as HIV are evidenced in perinatally HIV-infected children vaccinated with BCG at birth; data from South Africa show that the incidence of disseminated BCG infection (BCGosis) in these children can be as high as 999/100,000 [30]. HIV infection leads to CD4+ T cell depletion, contributing to TB susceptibility, and an inability to contain BCG. Mycobacteria specific CD4+ T cells primarily produce Th1 cytokines, which include IFNγ, IL-2 and TNFα and it was thought that the ability of T cells to produce several cytokines at once would be an indicator for increased potential to protect an individual from TB. Polyfunctional cells such as these are seen at high frequency in tuberculosis patients and also in people living in high incidence areas and in BCG vaccinated infants [31–33]. However, recent studies do not support a role in protection against disease in response to either BCG or the novel anti-TB vaccine candidate MVA85A, as recently tested in a large Phase IIb vaccine trial [34, 35]. Mycobacterial specific CD8 T cells are also important for protection; in addition to secreting IFNγ and TNFα alongside CD4 T cells, they have direct cytotoxic effects, expressing perforins and granulysins which can kill mycobacteria [36, 37].

In the early 1990s, several investigators reported patients and case series of individuals with unusual manifestations of disseminated mycobacterial infections attributable to non-typical mycobacteria [38], but also included disseminated BCG-infections and some cases of *Mycobacteria tuberculosis* (MTb) [39]. Through the identification of significant mutations within the IFNγ/IFNγ receptor (IFNγR) pathways it became clear that both the cytokine and the receptors play a central role in containment of mycobacteria [40]. The term mendelian susceptibility to mycobacterial disease (MSMD) evolved, as more and more defects also including the IL12 receptor, IL12 genes and signalling pathways were described. To date, more than ten inherited defects have been described [41].

The occurrence of BCG vaccine complications in children diagnosed with chronic granulomatous disease (CGD) confirms a role of neutrophils in containment of mycobacteria [42]. CGD is caused by a defect in the burst of oxygen consumption that normally accompanies phagocytosis in myeloid cells (i.e. neutrophils, eosinophils, monocytes, and macrophages); neutrophils are the cells primarily affected. It is estimated that between 6 and 57% of CGD patients will develop BCG complications if vaccinated. In the majority of CGD patients, BCG will present as a local or regional complication such as swelling, fistula formation or lymphadenitis. Medical treatment often leads to an apparent full clinical recovery, however

recurrence is often observed. Although disseminated BCG disease is less commonly seen in CGD than SCID or MSMD (15% vs. 67 or 33% respectively), it has substantial morbidity. IFNγ treatment has been used with some success in this cohort [43].

Other innate cells have been investigated as part of the research into protective mycobacterial immunity. BCG vaccine elicits both expansion of and IFNγ production by γδ T cells, however similarly to CD4 T cells, the relationship between γδ T cells and protection is uncertain [44, 45]. In infants immunized with BCG at birth, the frequency of IFNγ-producing γδ T cells after immunization did not correlate with protection against TB [34]. NK cells are a further source of IFNγ following vaccination with BCG and infection with TB and in addition, produce IFNγ, perforin and granzyme-A when stimulated with BCG in vitro [37, 45]. Like γδ T cells, NK cells link the innate and adaptive immune systems. They are an important source of early IFNγ which is critical for activating macrophages and may directly present mycobacterial antigens to T cells promoting expansion of an effector Th1 response. There is strong evidence that regulatory T cells are involved in the immune response against MTB, although whether this is protective or pathogenic remains a topic of debate. Regulatory T cells with the CD4 + CD25 + FOXP3+ phenotype actively suppress Th1 T cells and have been reported to down regulate BCG induced IFNγ production. Regulatory T cells are induced by NTM and BCG [46–48] and it is hypothesised that this is a mechanism by which high levels of environmental NTM may contribute to decreased BCG efficacy in some regions [49], however this has not been proven in human models [50, 51].

Severe infection caused by BCG has occasionally been reported in individuals without identified primary immune defects with a reported incidence of approximately 1:10,000–1:1,000,000 [52]. It is likely that children with complications of BCG vaccination such as large ipsilateral lymphadenopathy or continuously discharging BCG vaccine site have some form of immune dysregulation, however most do not have a currently identifiable immune defect either. Although a strong Th1 response to BCG is expected in adults, as neonates and young infants often have a Th2 or regulatory T cell predominance, it was anticipated they would have an equivocal specific immune response to BCG. In fact, infants produce robust IFNγ responses to BCG [20, 53, 54] and this may represent a mechanism by which BCG protects young infants from disseminated TB and TB meningitis.

Due to these described risks of BCGosis, BCG vaccination is not recommended in hosts known to be immunocompromised, such as in HIV infected children or those with SCID. Whilst screening mothers antenatally for HIV allows the identification of the those with majority of infants at risk of HIV, currently in the UK and many European settings, only siblings of those affected by SCID are identified by screening. However, population based newborn screening (NBS) for SCID is possible and is standard of care in many US states [28, 55]. Early identification of cases of SCID would allow the avoidance of harm from live vaccines such as BCG and rotavirus and identify those infants who could benefit from early haematopoietic stem cell transplantation.

Although the immune response to BCG has been extensively described as above, a true mechanism of protection is still not understood.

BCG Protection Beyond TB

Recently, a non-TB benefit or 'non-specific' benefit of neonatal BCG vaccine has been proposed. A series of observational studies in West Africa reported a decrease in all-cause mortality of up to 50% in infants who received a birth dose of BCG vaccine [56]. This was further demonstrated by studies in Uganda, India and Spain [57–59], and more recently these findings have been supported by small randomised controlled trials [60, 61]. Recent work by Netea and others support a novel immunological concept which may underly this phenomenon, now known as 'trained immunity' [62], and murine models demonstrate BCG induction of protection against unrelated infectious agents including a variety of viruses, *Staphylococcus aureus* and *Candida albicans* amongst others [63, 64]. Human studies of BCG vaccinated adults demonstrate a BCG induced higher expression of PRRs and greater reactivity to stimuli such as TLR agonists, resulting in cytokine induction and phagocyte recruitment [65]. This innate immune enhancement is protective against bacterial sepsis in a neonatal model [66], and early life BCG vaccination may train the developing immune system to protect infants from a variety of pathogens [67]. Furthermore, association studies suggest that early immunization with BCG-containing regimens may protect against leukaemia [68], possibly via a similar mechanism of 'trained immunity'. Interestingly, the potential non-specific benefit of other live vaccines such as oral polio vaccine, rotavirus vaccine and measles is currently under consideration [69–72].

The benefit of BCG protection extends beyond TB to other mycobacterial infections, with one study of non-tuberculous mycobacterial infections in children in Finland demonstrating an increase in incidence from 0.2 to 3.9 per 100,000 person years following the withdrawal of universal vaccination [73]. There is extensive evidence that BCG protects against leprosy, but the efficacy varies between 41 and 60% and meta-analyses have been difficult due to heterogeneity in studies [74]. BCG vaccination has been recommended as part of leprosy control programmes, particularly showing benefit when given to household contacts alongside rifampicin prophylaxis, increasing the protective benefit from 58 to 80% [75]. However, BCG may also have unwanted effects. In a human challenge model of malaria infection, BCG vaccinated volunteers had more severe adverse events than unvaccinated volunteers, associated with monocyte activation. Furthermore, BCG vaccination has been demonstrated to impact the antibody response to routine immunisations administered as part of EPI in one study [76], with implications for design and development of future immunisation schedules.

Adverse Events due to BCG

A typical reaction to BCG vaccination includes an erythematous indurated area at the injection site which may ulcerate then form a crust, before healing with scar formation. More than 90% of infants produce a scar [77] and although there is no universal recommendation for revaccination in the absence of a scar, a number of

studies have suggested increased protection in infants with scars [78, 79]. Axillary lymphadenopathy of <1 cm is also described within normal range. The global incidence of adverse events is estimated at between 1 and 10%, however they are rarely recorded and are likely to vary with vaccine strain [1]. One Australian study reported an adverse event rate of 87/100,000 doses associated with a Sanofi Pasteur product in 2009 and 201/100,000 doses with an unregistered Danish Statens Serum Institute product in 2014 [80], however total dose administration was unconfirmed. Adverse events related to BCG vaccine include abscess, vaccine site reactions, lymphadenopathy, lymphadenitis and disseminated disease. In one UK study of 60 children presenting with adverse events, 65% had lymphadenitis, 30% injection site complications and 1 child had disseminated BCG disease [81]. The majority of adverse events were managed conservatively with good outcomes, the optimal antibiotic regimen for the management of disseminated disease is unclear. Suggested regimens might include a combination of rifampicin, isoniazid and ethambutol. Other agents including a quinolone or clofazimine may be considered for severe cases [9 82]. The role of phage therapy shows promise, but is yet to be confirmed [83].

In patients with primary immunodeficiencies who had any vaccine adverse event, adverse events due to BCG were the most common, accounting for a third of all events in one study [83]. In a South African setting, 88% of children with adverse events due to BCG had a local event (vaccine site or lymphadenitis), 76% of children were immunocompromised (90% due to HIV) and the mortality rate of disseminated disease was 75% [84]. A later surveillance study of disseminated BCG disease reported a rate of 992/100,000 in HIV infected infants [85, 86]. BCG vaccination is contra-indicated in patients known to have SCID, CGD, or MSMD disorders [29]. The design and implementation of neonatal screening strategies for primary immunodeficiency need to consider BCG vaccine timing to avoid serious complications associated with a birth dose of BCG vaccine in this cohort. WHO recommends that in high-incidence TB countries, infants born to HIV infected mothers or mothers with unknown HIV status who appear well should be given BCG vaccination, as the benefits outweigh the risks of vaccination. For neonates with HIV confirmed on early virological testing, BCG vaccination should be delayed until ART is started and CD4 count in >25% [87].

There is limited data on the safety of BCG vaccination at birth in preterm and low birthweight infants, but a systematic review reported that BCG vaccination is safe and effective in healthy preterm infants born after 32 weeks gestation and weighing more than 1500 g, however there is insufficient data to assess safety and efficacy in very low birthweight or extremely premature infants [88].

BCG Vaccine: Revaccination Strategies

As described above, the role of BCG vaccine in protection from TB is variable and unfortunately far from complete. Novel TB vaccine trials are largely based on a prime boost strategy on a neonatal BCG vaccine dose. The protective efficacy of the

BCG vaccine appears to wane by the age of 10 in the majority of studies. Boosting these immune responses by revaccination is an attractive prospect from a cost-effectiveness and safety perspective, and modelling studies have suggested revaccinating TST negative adolescents in high TB endemic settings may be beneficial [14, 18, 20, 89]. A second dose of BCG given to 19 month olds in Guinea-Bissau however showed no decrease in TB related or all-cause mortality [90]. Revaccination of 7–14 year olds in Brazil in a variety of settings (urban and rural) reported no significant protection on initial analysis [91], but was suggestive of improved vaccine efficacy in an urban setting at 5 years post vaccine (19% (3–33) in Salvador vs. 1% (−27–27) in Manaus) [92]. More recently, secondary analyses of a subunit vaccine (H4:IC31) clinical trial, comparing BCG revaccination vs. placebo vs. the H4:IC31 candidate, demonstrated that BCG revaccination reduced the proportion of sustained conversion of in vitro markers of LTBI by 45%, with unknown clinical significance [93]. The risk of disseminated BCG disease in immunocompromised subjects is the greatest obstacle to large-scale BCG revaccination strategies in HIV and TB co-infection areas, however, further clinical trials are planned.

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Pulmonary, Pleural and Mediastinal TB: Clinical Aspects and Diagnosis

Mirae Park, Clare Ross, and Onn Min Kon

Pulmonary Tuberculosis

Pulmonary tuberculosis (TB) is defined as TB of the lung parenchyma and the tracheobronchial tree. As *Mycobacterium tuberculosis* (MTB) is an aerobic organism, it predominantly affects the lungs but can cause disease throughout the body as extrapulmonary tuberculosis (EPTB).

Clinical Presentation of Pulmonary TB

Symptoms and signs of TB can be non-specific and protracted over many weeks. Constitutional symptoms include weight loss, anorexia, fevers, night sweats, malaise as well as those associated with the specific disease sites.

Typical symptoms of pulmonary TB include cough, sputum and haemoptysis (Fig. 1). Cough is the commonest symptom, often non-productive in the first

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Fig. 1 Symptoms of pulmonary TB

Classic Symptoms for Active TB	
Chest symptoms	Constitutional
• Cough • Sputum • Haemoptysis • Chest pain • Breathlessness	• Fevers • Night sweats • Weight loss • Lack of appetite • Malaise

instance. As disease progresses with inflammation and tissue necrosis, patients become productive of sputum. Haemoptysis can occur with endobronchial erosions or by rupturing of a dilated vessel in a cavity wall described as a Rasmussen's aneurysm. Haemoptysis is often the sequelae of previous disease [1]. Patients may report chest pain with accompanying pleural inflammation and breathlessness in extensive pulmonary disease [2].

However up to 50% of patients with culture positive disease do not have a productive cough, and in early cases up to a quarter of patients with pulmonary TB are asymptomatic [3].

Physical signs of TB are non-specific. In advanced disease, patient can often look unwell and cachectic. Clubbing of the fingernails can occur from bronchiectasis, secondary to previous TB.

Auscultation is often normal or may reveal some crackles, wheeze or bronchial breathing. Amphoric breath sounds are used to describe the movement of air across cavities [2]. Endobronchial TB can cause collapse of the lungs by airway occlusion. Clinical findings should be used to complement diagnostic investigations.

Diagnostic Approach

Diagnosis of TB is either by microbiological confirmation of MTB or a clinical diagnosis in culture negative cases. Any clinical suspicion of TB should be fully investigated.

Several techniques are available to acquire a range of specimens including spontaneous sputum, induced sputum, bronchoalveolar lavage (BAL) and gastric lavage fluid (primarily utilised in the paediatric population) all of which can all be microbiologically tested to confirm MTB. Culture remains the gold standard for TB confirmation.

In the absence of microbiological confirmation, clinical information including medical history, exposure history and risk factors should be considered in combination with diagnostic tools such as imaging which can help support the diagnosis of culture negative clinically defined TB. This still poses a challenge to TB treatment as full drug sensitivities are not available without MTB isolation, hence all available attempts should be made to microbiologically confirm the diagnosis. An example of a diagnostic pathway is shown below (Fig. 2).

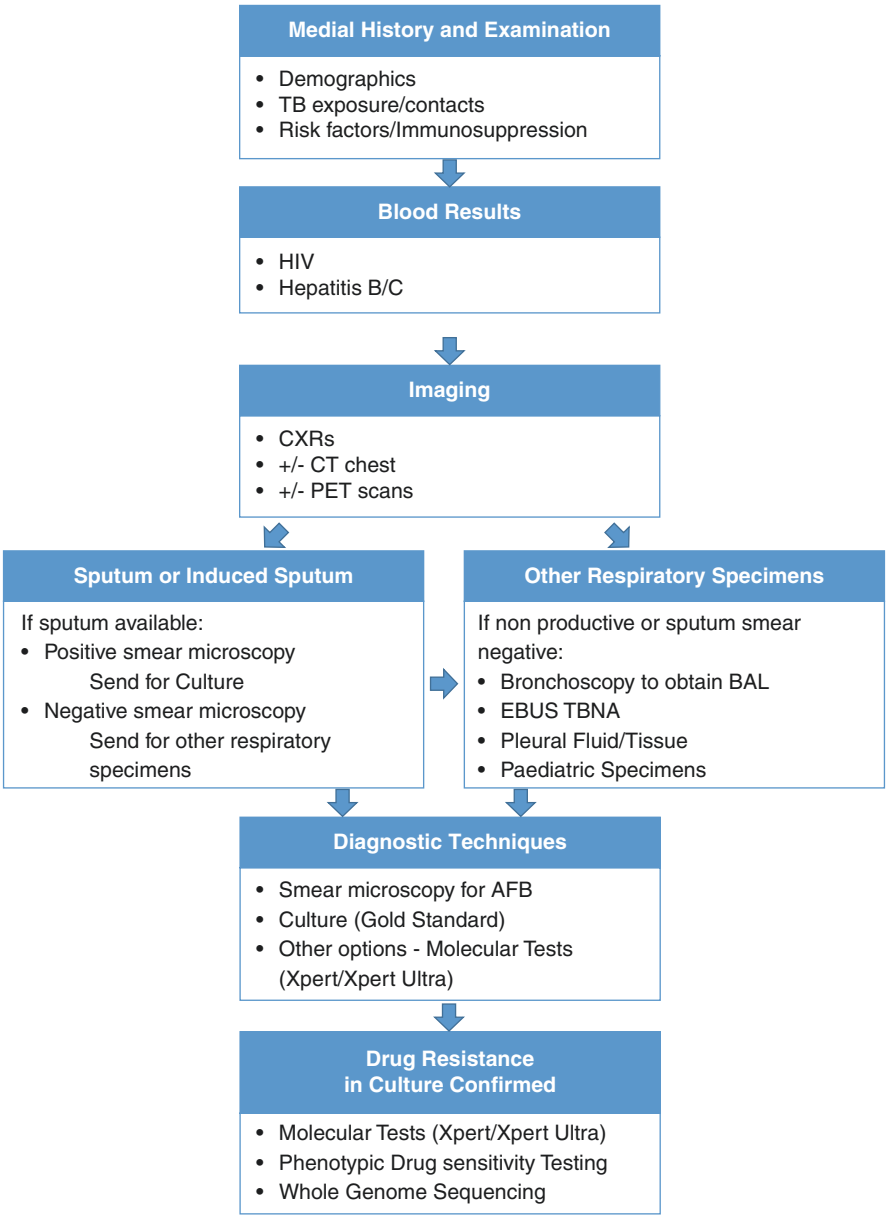

Fig. 2 Summary to show the diagnostic pathway

Imaging: Chest Radiographs and CT Scans

Chest radiographs (CXRs) are an established rapid imaging tool for TB detection and has been part of the World Health Organisation (WHO) recommendations for many years [4]. Initial investigations for symptoms suggestive of TB such as a cough lasting more than 2 weeks include a sputum sample and a CXR. Several abnormalities on CXRs which are specific for pulmonary TB such as cavities, making CXRs a useful cheap modality to support the clinical diagnosis of TB. However radiological changes are not pathognomonic and the sensitivity for conventional screening for a cough lasting for 2–3 weeks is less than 50% for active TB [5], hence microbiological tests irrespective of symptoms are required if there is a clinical suspicion.

Radiological tools have been made more accessible with the increasing availability of radiographers, low running cost and digital portable technology. New developments in digital CXRs with computer assisted diagnosis are increasingly available and used in triage and screening settings [6].

Chest radiograph appearances can vary from normal x-rays to discrete infiltrates to extensive bilateral changes with cavities depending on a host of factors including immune status, the stage of infection and the age of the patient.

Primary TB is usually self-limiting and the only radiological evidence of this is often the Ranke Complex. This consists of a calcified parenchymal scar (Ghon lesion) and a calcified hilar and/or parenchymal lymph node. In primary parenchymal TB, there is a tendency for homogenous parenchymal consolidation in the middle and lower lobes [7]. Obstructive atelectasis secondary to compression from enlarged lymph nodes can also occur most commonly causing collapse of the anterior right upper and medial right middle lobes. This is likely due to the branching angle of these lobes being surrounded by a larger plexus of lymph nodes.

About 2–6% of primary infection cases can present with miliary TB, where the host immune defence is overwhelmed and haematogenous spread of bacilli leads to the classical appearance of bilateral 2–3 mm pulmonary nodules that resemble millet seeds (Fig. 3). This occurs typically 6 weeks or more after the infection [8].

Post primary TB (reactivation TB) from a dormant residual foci spread during the primary infection mainly affects adults. This has different radiological

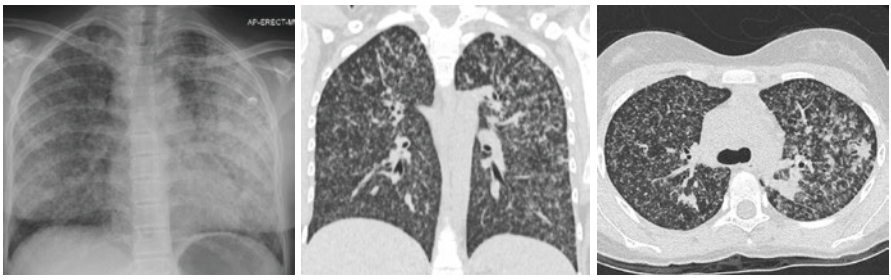

Fig. 3 CXR and CT appearance of miliary TB

characteristics compared to primary TB and generally lack abnormal lymph nodes. Tuberculomas are also seen in 3–6% of post primary TB as the main or only abnormality on a CXR. They appear as round granulomas with caseating necrotic centres caused by acid fast bacilli (AFB) surrounded by inflammatory granulomatous tissue which are 0.4–5 cm lesions and can be solitary or multiple [9].

The typical lesions for post primary TB are cavitation (Fig. 4) and 'tree in bud' appearances (Fig. 5) which can be present in 40% of cases. They tend to occur in the apicoposterior upper lobe segments and the apical segment of the lower lobes [9]. 'Tree and bud' on CT images are ill-defined micronodules and multiple centrilobular nodules with sharply linear branching opacities represents bronchogenic spread.

Endobronchial/tracheobronchial TB can also occur but have become rarer since the introduction of effective anti-TB treatment. It usually originates from a perforation of adenopathy into the bronchus and can be seen as a fistula or ulcerating granulomatous lesion bronchoscopically [9]. On CT imaging it appears as a circumferential bronchial narrowing [9].

With insidious symptoms and delayed diagnosis, radiological evidence of advance disease can be seen. Bronchiectasis as a result of pulmonary destruction and fibrosis is common. Airway stenosis can also occur. Persistent communication of the bronchial tree and the pleural space can lead to a bronchopleural fistula. Other complications of pulmonary TB include aspergillomas visible on both CXR and CT scans as a spherical nodule separated by a crescent shaped area of decreased opacity

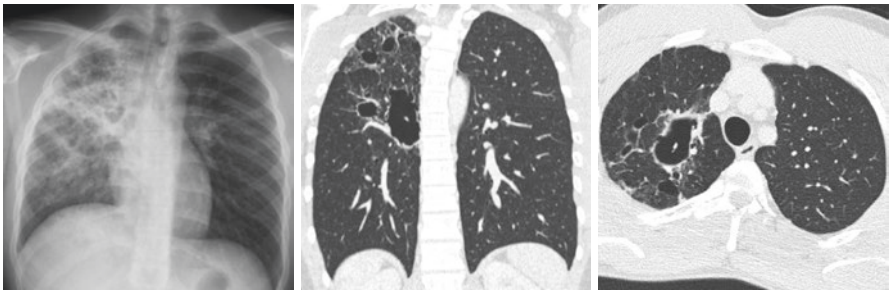

Fig. 4 CXR and CT showing cavities in the right upper lobe

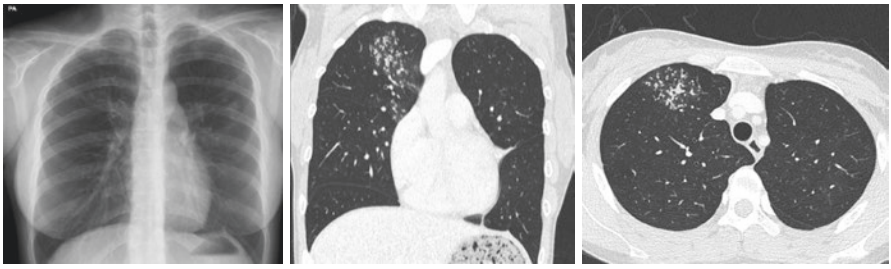

Fig. 5 CXR and CT showing tree in bud in the right upper lobe

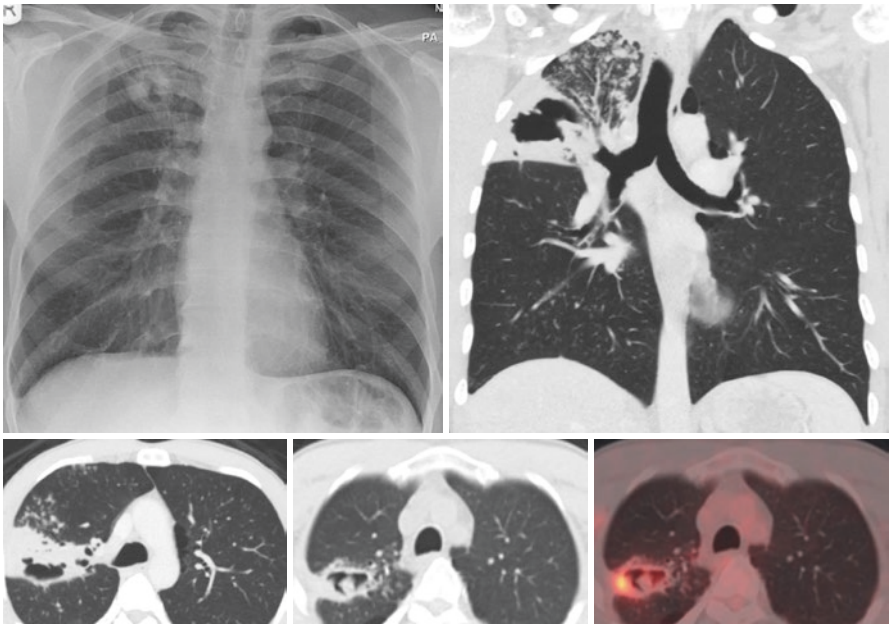

Fig. 6 CXR and CT showing right upper lobe cavity and evolution of aspergilloma over 18 month. FDT-PET showing avidity in cavity

or air from the cavity wall representing colonisation of aspergillus species in a previous TB cavity (Fig. 6). This occurs in about 11% of patients [9]. Other rarer complications of TB on imaging include fibrosing mediastinitis caused by inflammatory and reactive fibrosis of the mediastinum appearing on CT as a mediastinal mass with tracheobronchial narrowing and pulmonary vessel encasement.

In patients with HIV disease, the radiological appearances are atypical and resemble primary TB as described in more detail in the HIV chapter. Cavitation is uncommon and lower lobes are more likely to be affected. Diffuse infiltrates and intrathoracic lymphadenopathy are more frequent [1] particularly the case if the patient's CD4 T lymphocyte count is <200 cells/μL [10]. Extra-pulmonary manifestations are commoner in patients with HIV [11].

Although the typical radiological changes are described above and a summary can be seen in Fig. 7, often in a real-life clinical setting these patterns do not always apply. More details are described in the radiology chapter.

If the initial CXR and/or sputum smear is inconclusive or not available then further imaging with a CT scan can increase clinical suspicion and have a higher sensitivity for identifying cavities, nodules, lymphadenopathy and complications of pulmonary TB such as airway stenosis, tracheobronchial fistulas and bronchiectasis. A CT scan also guide potential sampling options.

Summary of Radiological Findings in Pulmonary TB	
Primary TB (often in children)	Post Primary TB (secondary of adulthood)
• Ranke Complex (Ghon lesion with calcified node) • Parenchymal consolidation • Obstructive atelectasis • Middle lower lobes • Lymph node enlargement (right intrathoracic)	• Cavity • Tree in bud • Cicatrisation atelectasis • Upper lobes, apical segment lower lobes • Bronchiectasis • Bronchopleural fistula • Aspergillomas • Fibrosing mediastinum
Characteristics persent in both • Tuberculomas • Miliary TB • TB pleuritis • Endobronchial/Tracheobronchial	

Fig. 7 Summary of radiological findings in pulmonary TB

Other imaging modalities such as positive emission tomography (PET) CT scans using fluorine-18-fluoro-2-dexoy-D-glucose, a glucose substrate which is utilised by metabolically active cells can be helpful in establishing the extent of the disease but are non-specific for malignancy as well as infection or inflammation. There have been several studies evaluating the use of PET CT in TB but the role in TB diagnostic is still yet to be fully clarified.

Sputum

The commonest and simplest method of obtaining respiratory samples for suspected TB is with spontaneous sputum. International guidelines states that at least two, ideally three deep cough sputum samples should be sent for microscopy and culture [12]. A systematic review has shown that TB diagnosis increased with pooled sputum collection and clear instructions on sample collection (before sputum collection, observed collection or together with a physiotherapy assistance). In this review early morning sputum did not seem to significantly increase the diagnostic performance [13] but in the past it has been associated with the highest AFB yield [12]. A recent study has also shown that good quality microscopy of two consecutive sputum samples is able to identify 95–98% of smear positive patients [14]. The WHO recommends that only two sputum samples are required and they may be performed on the same day [15].

If a sputum sample is not available or is smear negative, alternative methods to obtain respiratory samples such as with sputum induction or by invasive methods such as a bronchoscopy (discussed below) should be considered.

Fig. 8 Xpert MTB/RIF platform (Cepheid) and Xpert Ultra cartridge

Induced Sputum

Induced sputum is an important non-invasive way of airway sampling. It was first described in 1958 by Bickerman et al. for lung cancer [16]. Sputum induction is performed by inhaling 3–4.5% hypertonic saline through a nebuliser and coughing or expectorating any airway secretions. Precautions should be taken as the hypertonic saline can cause bronchospasm hence pre-test spirometry should be performed, as well as giving inhaled salbutamol beforehand [16]. This should all be performed in a negative pressure room to minimise infection risks. Numerous studies have shown the usefulness of sputum induction [17–19].

Sputum should be tested with smear microscopy, culture and molecular methods if available. In high burden bacillary disease such as cavitatory TB, the sensitivity of sputum smear microscopy is around 50% but drops to 10–20% for paucibacillary disease [20].

Microbiological culture remains the gold standard, but remains an imperfect test in paucibacillary disease.

Rapid molecular tests such as Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), an automated real-time polymerase chain reaction (PCR) kit has significantly improved TB diagnostics with results being available in 2 hours (Fig. 8). In addition to being more sensitive than smear microscopy [21], Xpert MTB/RIF has the added benefit of rapidly identifying rifampicin resistance. A Cochrane review has shown Xpert MTB/RIF to have a pooled sensitivity of 85% and a specificity of 98%, and 67% and 98% respectively in smear negative culture positive patients [22]. Xpert MTB/RIF Ultra (Xpert Ultra) has recently been developed with an improved sensitivity particularly when used in paucibacillary disease groups.

Bronchoscopy and Bronchoalveolar Lavage (BAL)

If sputum samples are not available, unsuccessful or in smear negative cases then the diagnostic challenge lies in acquiring adequate samples. Bronchoscopy, a semi-invasive procedure using a flexible camera with an operating channel to obtain respiratory samples can be performed. CT images can direct the bronchoscope to the area of lung most affected hence optimising the yield from the samples.

Bronchoscopy is usually performed under conscious sedation using intravenous benzodiazepines and/or opiates. Local anaesthetic spray is applied to the oropharynx and the airways. A targeted bronchial wash or a BAL is performed using 0.9% saline in 30–60 mL aliquots down the operating channel, which is then aspirated back. Numerous studies have shown the diagnostic value of bronchoscopy especially in sputum smear negative culture negative TB [23, 24].

The sensitivity for smear microscopy in BAL samples is highly variable ranging from 4.7 to 58% depending on the incidence of TB [25]. In BAL samples of sputum smear negative cases, the sensitivity of smear was 58%, Xpert MTB/RIF was 93% in culture positive cases with a culture rate of 18% [26]. Xpert Ultra is yet to be systematically reviewed for BAL samples.

Paediatric Specimens

In the paediatric population, obtaining adequate samples are difficult due to the lack of sputum and paucibacillary nature of the organism. Even in optimal conditions MTB is only isolated in fewer than 50% of suspected TB cases in children [27, 28]. A variety of samples can be taken including nasopharyngeal aspirates, gastric aspirates, stool and urine.

A small study has shown BAL samples to have a higher sensitivity than gastric aspirates for smear microscopy, 31% and 21% respectively [29]. Culture confirmation is renowned to be difficult in children with only 31% being confirmed in England in 2018 [30]. Gastric aspirates have been shown to be superior to nasopharyngeal aspirates which were superior to stool samples. An additional gastric sample increased the detection of culture positivity by 37% [31]. Xpert MTB/RIF has been shown to have a sensitivity of 62% in sputum and 66% in gastric aspirates. Xpert MTB/RIF has a higher sensitivity compared to smear but it remains significantly lower compared to the adult population. Xpert Ultra has also been evaluated in the paediatric population showing improved sensitivity [32].

Other samples such as stool and urine have been analysed in the diagnosis of pulmonary TB in children but have a lower diagnostic yield compared to other respiratory samples and are not recommended by the WHO.

Other Diagnostic Techniques and Biomarkers for Pulmonary TB

Other molecular diagnostics available include line probe assays (LPAs) such as GenoType MTBDRplus, MTBDRsl (Hain Lifescience GmbH, Nehren, Germany) and NIPRO (NIPRO Corporation, Osaka, Japan) for the detection of MTB and drug resistance (including second line treatment) but requires additional laboratory capacity. The WHO has also endorsed the use of a commercial loop-mediated isothermal amplification made by Eiken Chemical, Tokyo, Japan as a new molecular test (TB-LAMP) [33].

Lipoarabinomannan (LAM) is a promising antigen detection marker for TB diagnostics. It is a 17.5 kDa glycolipid component of MTB cell wall. It is filtered by the kidneys and hence detectable in the urine. There have been several studies looking at urinary LAM and its diagnostic performance as a TB antigen [34]. It currently offers little diagnostic utility for TB in the unselected population but may be a helpful tool in HIV infected patients with CD4 cell count of less than 200 cells/μL [35, 36]. It is currently recommended for all patients who have HIV and a CD4 count less than 100 cells/μL, seriously ill and are hospitalised. The use of LAM has also been reviewed in children with HIV [37].

Pleural TB

Pleural TB accounts for 9% of all TB cases with 418 cases in the England in 2018 [30]. In TB endemic areas, the rate of pleural involvement can be as high as 30% [38]. It is the second most common site of EPTB after lymph node TB in England [30].

Pleural TB can be the primary site accounting for around 30% of cases [38] or the reactivation site for TB. It is commoner in younger people but if it is secondary to reactivation, the age of presentation tends to be older. Pleural effusions are commoner in males representing up to 70% of cases [39].

The pathogenesis of pleural disease is thought to be related to the rupture of a subpleural caeseous foci, causing a T-helper type 1 cell mediated delayed hypersensitivity reaction [40, 41]. This hypersensitivity reaction increases the permeability of the pleural capillaries to protein and increases the protein level in the pleural fluid. The lymphocytic pleuritis obstructs the lymphatics leading to decreased pleural fluid clearance [40].

More recently, it is thought that there may be direct spread from the parenchymal lesion causing a paucibacillary infection [41]. Direct pleural infection as the mechanism for pleural effusion is supported by microbiological evidence of pulmonary disease in many cases, positive fluid culture results, TB pleural effusions being neutrophilic in early stages, as well as higher mycobacterial burden in loculated effusions [42, 43].

Clinical Presentation of Pleural TB

Patients can present with the typical symptoms of TB or be completely asymptomatic and are incidentally detected on imaging. TB pleural effusions are more common in patients with HIV who tend to have a higher incidence of disseminated disease at presentation. The illness presents over a longer duration [40].

Pleural TB usually presents as a unilateral effusion, often associated with an acute illness with commonest symptoms being fevers, pleuritic chest pain and cough. It can also present as a subacute illness with symptoms of night sweats, chills, weakness and weight loss [42]. If the effusion is sufficiently large, the predominant symptom is breathlessness [2]. Symptoms are usually present for less than 1 month.

TB empyema is a chronic infection in the pleural space which evolves from an exudative pleural collection. This becomes fibrinopurulent and then infected, leading to a consolidative phase with granulation tissue causing a calcified thickened pleura [42] visible on chest imaging.

Complications of pleural empyema involving the surrounding parenchyma can lead to alveolar-pleural or bronchopleural fistulas. These present as a secondary hydro-pneumothorax with dyspnoea and chronic chest pain. Persistent air leaks can develop as a result. Other complications such as empyema necessitans, pleural fibrosis and calcified fibrothorax may have long-term clinical implications. Residual pleural thickening of >10 mm is associated with significant morbidity: chest pain, dyspnoea and reduced lung function [44] and in some cases decortication may be indicated.

It is important to note that TB pleural effusions may slowly resolve spontaneously with time without treatment but up to 65% will progress to active TB within 5 years [45], highlighting the importance of a high index of suspicion at first presentation.

The size of the effusion can vary but 50% occupy half or more of the hemithorax [39]. The size of the effusion has no bearing on prognosis.

Diagnostic Approach

The gold standard for diagnosing pleural TB is microbiological confirmation from sputum, pleural fluid or pleural biopsy. However pleural TB is paucibacillary in nature with only less than 10% being smear positive on microscopy and only about 30% culture proven [2]. This tends to be higher in the HIV co-infected patients with a CD4 T lymphocyte count of <100 cells/μL [46]. The diagnosis is reliant on clinical suspicion, radiological appearance and evidence of a lymphocytic effusion or histological evidence of caseating granuloma [40]. The available specimens should be tested for smear and culture as a minimum alongside any other additional diagnostic techniques available to optimise the yield of MTB confirmation.

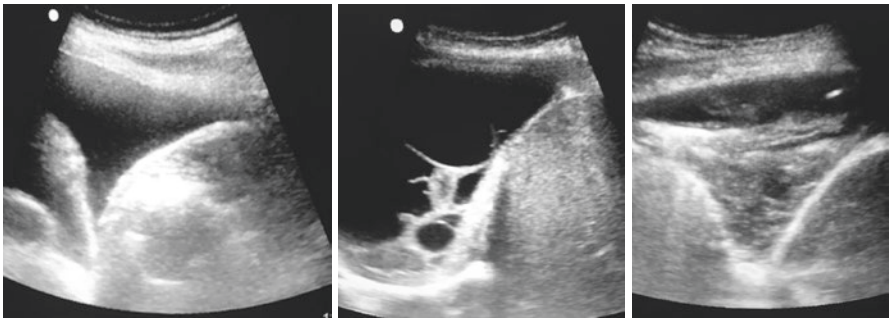

Fig. 9 US images of pleural effusions. Left: anechoic simple pleural effusion with underlying atelectasis; Middle: anechoic effusion with septations; Right: echoic complex effusion

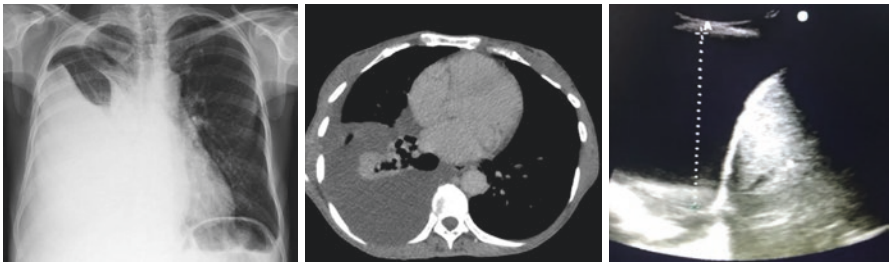

Fig. 10 CXR and cross sectional CT showing large right pleural effusion; US image showing large right anechoic effusion

Imaging

CXRs are the most accessible imaging modality to diagnose pleural effusions. Co-existence of parenchymal disease can be seen in up to 50% of cases on CXRs and up to 85% on CT scans and occur on the same side as the effusion in the majority of cases [44]. The most common finding on CT are micronodules in the subpleural and peribronchovascular area with interlobular thickening suggesting lymphatic spread [47]. CT and ultrasound (US) scans are also useful in assessing TB empyema and differentiating the different stages: (1) exudative phase with an uncomplicated effusion, (2) fibrinopurulent phase with thickened visceral and parietal pleura and (3) the organising phase with loculated pleural fluid collections and a thickened pleural peel with calcification.

Real-time US guided thoracentesis and pleural biopsy facilitates assessment and safe intervention. The appearance of pleural effusions can vary from an anechoic non-septated image in a simple effusion to an echogenic septated complex effusion (Figs. 9, 10, and 11).

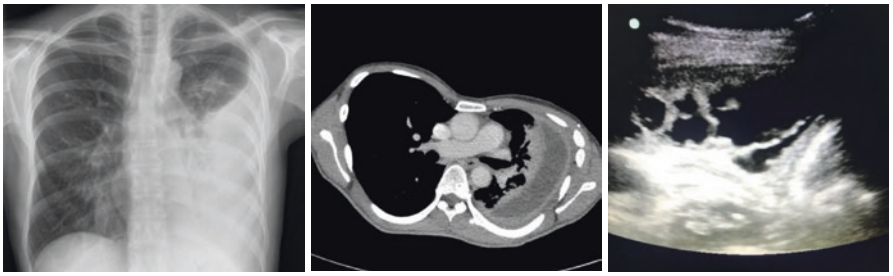

Fig. 11 CXR showing large left pleural effusion, cross sectional CT showing left pleural effusion with pleural thickening, US showing complex effusion and thickened parietal pleura

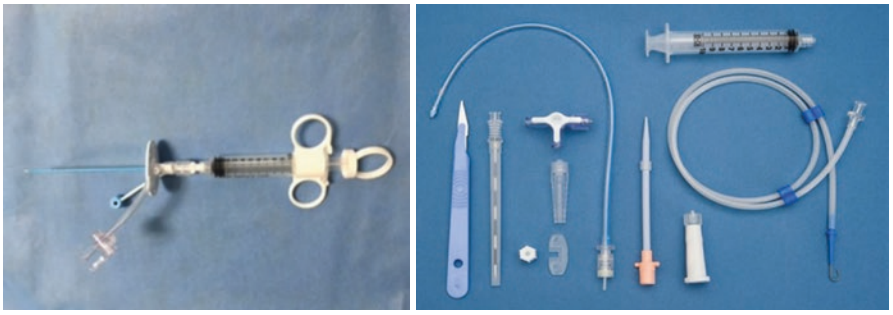

Fig. 12 Left: Aspiration kit, Right: Seldinger chest drain kit

Sputum in Pleural TB

In pleural TB, sputum samples have a modest yield. This is increased with sputum induction up to a yield of 55% even in patients without evidence of parenchymal involvement on a chest radiograph [48]. Patients with suspected TB pleural effusions should have sputum samples sent off for culture even in the absence of CXR changes.

Pleural Fluid

Pleural fluid is obtained by diagnostic or therapeutic thoracentesis or by the insertion of an intercostal chest drain (Fig. 12). This is performed with real-time US guidance to identify the optimal drain or aspiration site, and reduce the risk of organ puncture and intercostal artery puncture [49, 50].

In comparison to the diagnostic benefits of drainage, the longer-term symptomatic benefits of drainage are yet to be determined in cases of pleural TB. In comparison, TB empyemas should be managed as per bacterial empyemas.

All pleural fluid should be sent for routine chemistry to test for Light's Criteria, and is usually exudative with a protein concentration >30 g/L. Pleural fluid tends to be straw-coloured, unless an empyema is present. The fluid in pleural TB usually has a high LDH level with total nucleated white cells of around 1000–6000 cells per mm^3 [40, 41]. Most TB effusions are lymphocytic usually with a lymphocyte to neutrophil ratio of greater than 0.75. Pleural fluid collected in the first few days may be neutrophilic in nature but then becomes lymphocytic. Pleural fluid can also demonstrate a neutrophilic predominance when associated with loculations or TB empyema. Routine cytological analysis of TB pleural effusion is therefore essential, although malignant pleural effusions can give a similar picture with high lymphocytic counts.

TB effusions tend to have low glucose levels compared to serum; usually between 3.3 and 5.6 mmol/L [44]. Pleural pH is usually between 7.30 and 7.40 [40]. A very low pH <7.20 and glucose level may indicate TB empyema.

In addition to protein, LDH and cytology, pleural fluid should be sent for smear microscopy, and culture (in TB culture bottles) and molecular or additional biomarkers if available. As mentioned above, pleural fluid microscopy for MTB has a low yield of <10%, but increases to 20% in HIV co-infected patients [51], likely due to ineffective bacterial clearance. The yield of pleural fluid culture is variable around 10–37% [52, 53]. The combination of pleural fluid and sputum culture has a diagnostic yield of almost 80% [41]. Nucleic acid amplification tests (NAATs) in pleural TB have a sensitivity of 62–76.5%, with a specificity of 91–98% in previous meta-analyses [54, 55]. In the Cochrane review of Xpert MTB/RIF, pleural fluid had a pooled sensitivity against culture of 50.9% and specificity of 99.2% from 27 studies with 4006 specimens [56]. Studies using a concentrations step had a higher sensitivity of 49.1% compared to 41.6% without concentration step. Fresh pleural samples performed better compared to frozen samples [57]. A recent study evaluating the diagnostic accuracy of the new Xpert Ultra in pleural fluid showed the sensitivity in Ultra to be 44.2% compared to culture at 26.4%, Xpert MTB/RIF at 19.23% and smear microscopy at 1.4% [58].

ADA is a purine degrading enzyme found predominantly in T-lymphocytes. It is useful for its high positive predictive value in high TB burden countries. Using a value greater than 40 IU/L it carries a positive predictive value of 98% [40]. In low TB incidence countries, the negative prediction value of less than 30 IU/L has a negative predictor value of 98.9% and can be used to rule out TB [59]. It is most often useful when the pleural fluid or biopsy cultures are non-diagnostic.

IFN-ɣ is a cytokine released by activated CD4+ T lymphocyte in the normal immune response to TB. In a meta-analysis of 22 studies, IFN-ɣ had a sensitivity of 89% and specificity of 97% [60]. There is evidence that IFN-ɣ assays may be more superior to ADA for diagnostics in pleural TB but it has a slightly more complex ELISA testing and a higher cost [40]. It has been suggested that IFN-ɣ is a useful tool for pleural TB diagnostics alongside clinical and conventional tests [60].

A summary of the common characteristics of pleural effusions can be found in Fig. 13.

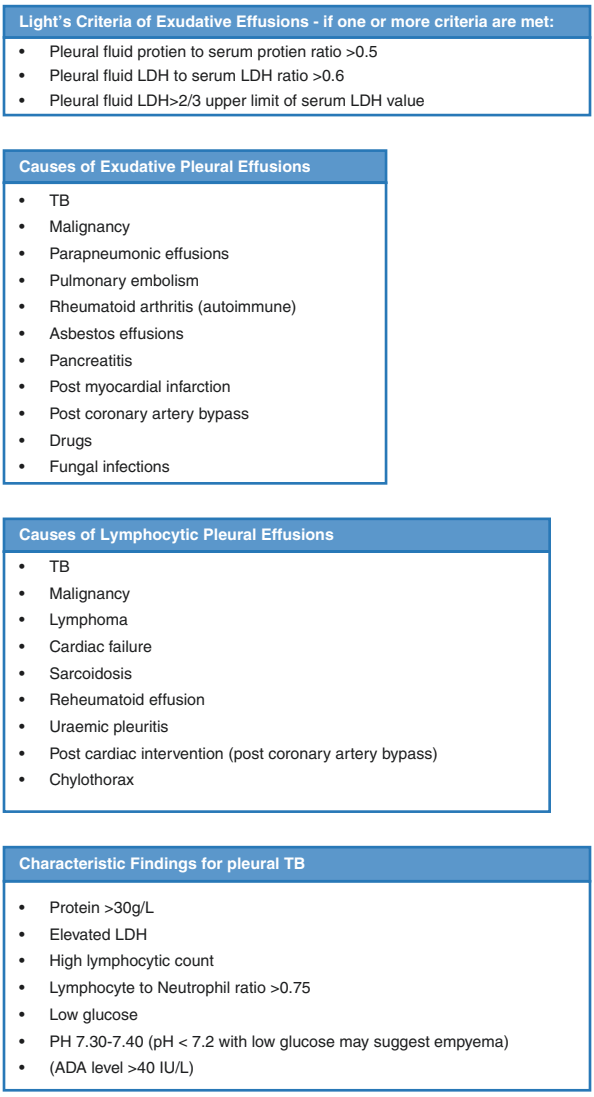

Fig. 13 Summary of the common characteristics of pleural effusions

Pleural Tissue

Pleural tissue can be obtained by either closed needle biopsies or thoracoscopic biopsies to identify AFB, cultures and granulomas on histological evaluation.

Closed Pleural Biopsies

Closed pleural biopsies were first described by Abrams and Cope in the mid-twentieth century as a less invasive technique to surgical biopsies. The initial technique was performed blindly with an Abrams needle using a reverse bevel.

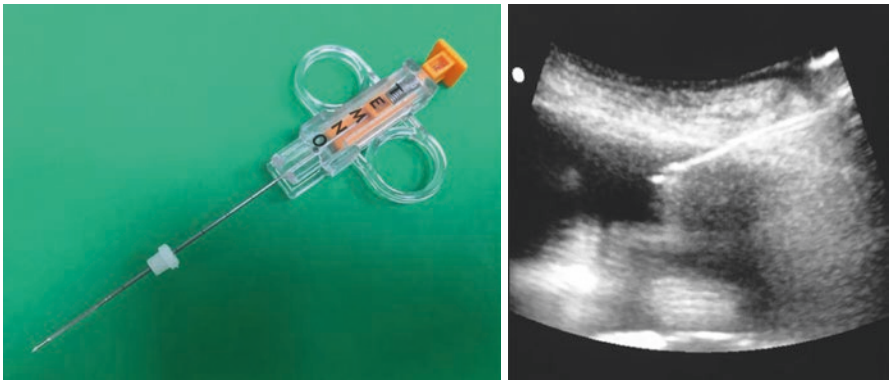

Fig. 14 Left: Core-cutting needle, Right: US image of a pleural biopsy with a true cut needle

In a prospective study comparing local anaesthetic thoracoscopy with Abrams biopsies in an area with high incidence of TB, thoracoscopy had a sensitivity of 100% when using culture and histology together compared to a sensitivity of 79% when using Abrams pleural biopsies [38]. However, given the reasonably high diagnostic rate of closed needle biopsies, they are often the initial diagnostic procedure in low resource countries with a high incidence of TB given their cost effectiveness compared to local anaesthetic thoracoscopy.

In current practice image-guided biopsies (often using core-cutting needles) (Fig. 14) are preferred over Abrams biopsies performed blindly for improved safety and yield [61, 62].

US guided biopsies have the benefit of being able to target areas of pleural abnormality whilst compensating for respiratory movements in real time and in comparison to CT guided closed biopsies, avoid ionising radiation. No formal guidelines exist but 8–10 cores pleural biopsies have been suggested and sensitivity generally increases with the number of biopsies taken [62]. Closed biopsies also have the benefit of being minimally invasive, are well tolerated by patients, and are less resource dependent compared to thoracoscopic biopsies.

Thoracoscopy

Thoracoscopic interventions have been well described for the treatment of TB by artificial induction of a pneumothorax and division of pleural adhesions. This procedure has the benefit of offering both diagnostic and therapeutic interventions.

Medical thoracoscopy is usually performed under local anaesthetic by physicians (although some larger specialist units offer general anaesthetic lists) and video assisted thoracoscopic surgery (VATS) is performed by the cardiothoracic surgeons under general anaesthesia.

Medical thoracoscopy is well tolerated and has a major complication rate of 2.3% (including empyema, haemorrhage and pneumonia). This diagnostic yield is higher than blind pleural biopsies for TB pleuritis [63]. VATS is not suitable for frail

patients with multiple co-morbidities as it requires a general anaesthetic but is has a similar high diagnostic yield and still a low complication rate with the most common side effect of subcutaneous emphysema [63].

For pleural tissue, the culture positivity rate has been reported to be 76% with the yield increasing to 90% using US guided closed pleural biopsy as the technique [64]. Pleural biopsies taken under direct visualisation via thoracoscopy has a sensitivity of up to 100% [38].

The use of Xpert MTB/RIF in using thoracoscopic pleural biopsy has been evaluated by Christopher et al. Histopathology was diagnostic in 100% of the patients with TB. The sensitivity of pleural tissue using Xpert MTB/RIF was 45%, which was higher than tissue culture at 39%. The sensitivity of pleural fluid using Xpert MTB/RIF was 14% and fluid culture was 17% demonstrating that the pleural tissue provided higher yields than pleural fluid in both Xpert MTB/RIF and culture [65].

A recent Cochrane review which included the above study demonstrated the low sensitivity for pleural tissue using Xpert MTB/RIF with a sensitivity of 30.5% with a specificity of 97.4% against culture [56].

From the evidence above, sputum samples should be sent regardless of the chest imaging. Thoracoscopic pleural biopsies are the most likely to yield a microbiological culture diagnosis of TB hence results of drug sensitivities, and when pleural biopsies are taken, they should be sent for both histological examination and culture to maximise the diagnostic rate. In resource limited areas with high incidence of TB, percutaneous needle biopsy may be more cost effective as an initial diagnostic test. Molecular tests have a variable sensitivity and specificity, and their use in clinical practice remains unclear.

Intrathoracic Mediastinal TB

TB lymphadenopathy is the commonest cause of EPTB. In England in 2018 there were 958 cases of extrathoracic and 575 cases of intrathoracic lymph node TB making up over 30% of the TB cases [30]. In countries with low TB prevalence, most TB lymphadenopathy tends to be in non-native residents or in immunosuppressed patients [66].

The pathophysiology of TB lymphadenitis is through haematogenous spread following primary TB, local extension from tuberculous infection or spread through the lymphatic system. From the regional nodes, this can continue to spread via the lymphatic system to the other and more peripheral nodes [67].

Clinical Presentation of Mediastinal TB

The clinical presentation of TB lymphadenitis depends on the area of lymph node involved. Lymph nodes are usually chronic and seldom acutely inflamed differentiating them from acute viral or bacterial infections. Cervical nodes are the

commonest and present in two thirds of TB adenitis [66] but other sites include submandibular, supraclavicular, intra-abdominal and intrathoracic nodes. Intrathoracic nodes are usually asymptomatic and are found incidentally on imaging. If the nodes are significantly enlarged, they can affect adjacent organs for example collapsing a lobe of the lung from obstruction or compressing the oesophagus causing dysphagia. If the nodes erode into adjacent organs, then more severe symptoms may be present such as aspiration pneumonia in the case of oesophageal fistulation. Other symptoms are those of general TB with systemic symptoms.

Diagnostic Approach

Imaging

Intrathoracic lymphadenopathy in TB usually presents as unilateral right sided paratracheal and hilar nodes but bilateral hilar enlargement can also be seen with the differential diagnoses including sarcoidosis, lymphoma and silicosis. Enlarged intrathoracic lymph nodes can be visualised on simple CXRs but CT is the preferred imaging modality allowing for characterisation of the nodes and a more accurate mapping of abnormal lymph nodes providing information for potential diagnostic access.

Intrathoracic lymph nodes with a diameter greater than 2 cm with an area of central low attenuation on contrast CT scans is suggestive of caseating TB necrosis [68]. The prevalence of adenopathy decreases with age hence the pattern of radiological findings alters with age. Intrathoracic lymphadenopathy is one of the most common manifestations of primary disease in children, and present in 44% of all paediatric presentations in a low incidence country [69].

Fujiwara et al. proposed a classification system to define lymph node characteristics using EBUS looking at size in both the long axis and short axis, shape (oval or round), margins (distinct with >50% of the margin visible or indistinct with <50% of margin visible), echogenicity (homogenous or heterogeneous), central hilar structures and presence or absence of central necrosis [70]. In TB lymphadenitis heterogeneous echotexture and central necrosis are characteristic features.

Endobronchial Ultrasound Guided Transbronchial Needle Aspiration (EBUS-TBNA)

Unlike peripheral lymphadenopathy where a simple needle aspiration is possible, diagnosing intrathoracic lymphadenitis is more challenging. Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) has become the standard of care for diagnosing intrathoracic TB. Compared to a mediastinoscopy, a surgical approach to obtaining biopsies through a 2–3 cm incision above the suprasternal notch under general anaesthesia, EBUS-TBNA is less invasive and can sample nodes which are commonly affected by TB lymphadenitis [71] (Fig. 15).

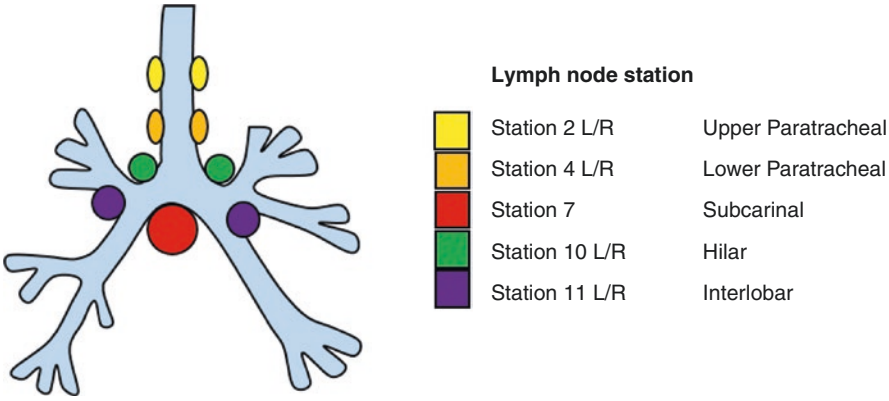

Fig. 15 Map of lymph node stations accessible by EBUS

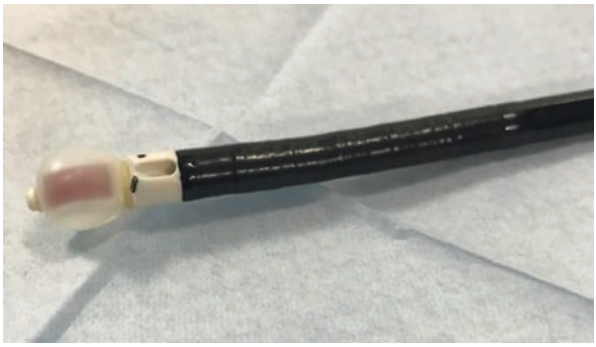

Fig. 16 EBUS scope tip with a water filled balloon, needle port and US probe

EBUS-TBNA uses a curved array US transducer to visualise mediastinal and hilar lymph nodes endobronchially and perform real time lymph node biopsies (Fig. 16). It has been used safely in adults for diagnosing a range of pathologies including lung cancer, sarcoid and TB and forms part of many adult diagnostic algorithms. It is a similar procedure to bronchoscopy and is performed under conscious sedation. An endo-bronchoscope with 19–22 gauge transbronchial aspiration needle is used to obtain TBNA samples. Nodal sampling is from areas of enlarged mediastinal nodes measuring >5 mm. The number of passes at each station often depends on the rapid on-site evaluation (ROSE) when available. If the rapid on-site evaluation is consistent with TB, further samples are taken and sent for TB PCR, smear and culture. Figure 17 shows a CT of a patient with enlarged station 4R and 7 nodes and the endobronchial US view of the enlarged node at station 7.

AFB smear microscopy has a variable sensitivity from 5 to 35% [66, 72]. Histology showing granulomas with or without caseation may be helpful in the diagnosis of TB lymphadenitis.

Dhasmana et al. looked into Xpert MTB/RIF in 116 patients in the diagnosis of mediastinal lymphadenopathy by EBUS-TNBA. A single Xpert MTB/RIF assay showed an overall sensitivity of 72.6%. Xpert MTB/RIF was consistent with all

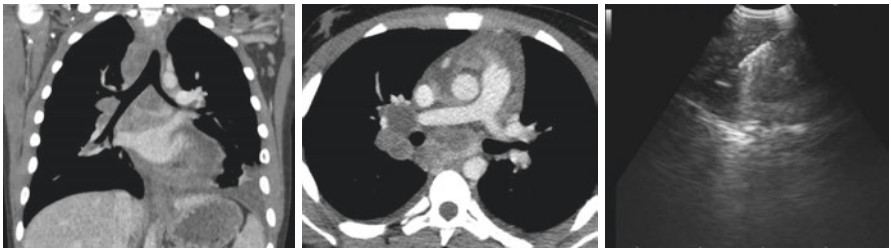

Fig. 17 Right and Middle: CT Image showing enlarged 4R and 7 necrotic nodes, Right; endobronchial US view—needling of station 7 node

	Imaging	Specimen	Routine Test	Additional Test
Adults Suspected Pulmonary TB	CXR CT chest	3 respiratory samples: • Spontaneously • Deep cough • Induced sputum • BAL	Microscopy Culture Histology	Molecular (Xpert/Xpert Ultra) Urinary LAM in HIV infected patients with CD4<100cells/µl
Children (<15 age) Suspected Pulmonary TB	CXR CT chest	3 respiratory samples: • Spontaneously • Deep cough • Induced sputum • BAL • Gastric washing • Nasopharyngeal aspirate	Microscopy Culture Histology	Interferon-gamma release assay and/or Tuberculin Skin Test
Suspected Pleural TB	CXR CT chest	3 respiratory samples: • Spontaneously • Deep cough • Induced sputum • BAL Pleural Biopsy Pleural Fluid	Microscopy Culture Histology/Cytology	ADA on pleural fluid
Suspected Mediastinal TB	CXR MRI	Mediastinal Biopsy EBUS-TBNA	Microscopy Culture Histology/Cytology	Molecular (Xpert/Xpert Ultra)

Fig. 18 Summary of investigations for suspected pulmonary, pleural and mediastinal TB (based on NICE/BTS guidelines)

positive microscopy cases and 67.6% of the microscopy negative cases. The use of Xpert MTB/RIF with cytology increased the sensitivity to 96.6% [73].

With patient selection, experienced bronchoscopists and ROSE to confirm adequate sampling, a high diagnostic rate can be achieved in diagnosing mediastinal TB.

In this chapter, the clinical presentation and the diagnostic approach for pulmonary, pleural and mediastinal TB have been discussed. A diagnostic summary, which are based on current guidelines, are shown below in Fig. 18.

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Extra Pulmonary Lymph Node, Abdominal and Pericardial Tuberculosis

Martin Dedicoat

Extra Pulmonary Lymph Node Tuberculosis

Extra pulmonary lymph node tuberculosis (TB) has been described for many centuries. The most visible form of the disease cervical lymphadenitis, previously known as scrofula, can have a chronic relapsing and remitting cause where enlarged lymph nodes develop and resolve spontaneously. In some cases, the nodes discharge and form chronic sinuses. The fact that some cases of cervical lymph node TB spontaneously heal lead to the widespread belief of the royal touch or the 'Kings Evil', where monarchs from the middle ages would touch patients with scrofula with cure observed in some cases [1].

Epidemiology

After pulmonary TB, extra thoracic lymph node TB is the most common manifestation of the disease. In England extra thoracic lymph node TB makes up 20% of all TB cases [2]. This proportion varies between populations and settings. TB lymphadenitis is a common presentation in patients born overseas who immigrate to low TB incidence settings. These patients typically present with disease several years after immigration and after a longer interval than those who present with pulmonary disease [3]. HIV infected patients frequently have lymph node involvement when they present with TB infection, often concomitantly with pulmonary disease.

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Clinical Features

Clinical features depend on the stage of disease and the patient's immune status. In immunocompetent individuals the most common site of TB lymphadenopathy is cervical, with most cases being in the anterior triangle (Fig. 1). Around 75% of cases are cervical, but TB can involve any lymph node site in the body. Often patients present with a single enlarged node that is non tender. These nodes may progress from solid in nature to fluctuant. Late presentation may include nodes that have indurated skin over them or have developed a sinus with discharge. In immunocompromised individuals especially those with advanced HIV infection there maybe multiple nodes and multiple areas involved, also the mycobacterial burden in the nodes tends to be higher with aspirated pus samples being smear positive. Also HIV infected patients are more likely to have concomitant pulmonary TB and disseminated TB.

Constitutional symptoms such as fever, night sweats and weight loss are not common in lymph node TB. HIV infected patients are more likely to have constitutional symptoms and are also more likely to have disseminated disease. In patients found to have cervical TB lymphadenitis it is always worth searching for disease at other sites. As many as 25% of TB lymphadenitis patients have been found to have an abnormal x-ray and may have pulmonary disease. This is of particular importance with regard to contact tracing [4].

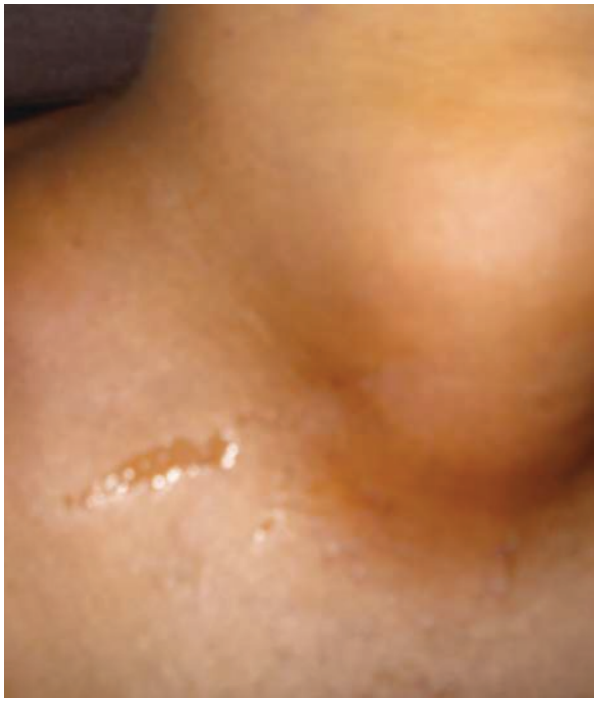

Fig. 1 A 28-year-old lady with bilateral lymph node enlargement. Biopsy showed caseating granulomas. Culture grew fully sensitive *Mycobacterium tuberculosis*

Diagnosis

Enlarged lymph nodes have a wide differential and hence both cytological/histological and microbiological assessment are essential for diagnosis. Imaging can be useful, TB infected lymph nodes go through several appearances from being simply enlarged, to a loss of normal architecture to appearing necrotic. These changes can be detected on ultrasound and computer tomography but none are specific for TB [5, 6]. Although these findings can suggest tuberculosis, especially when lymph nodes with necrotic centres are seen, none are specific for TB and microbiological confirmation of diagnosis is required. Empirical treatment without biopsy is not recommended in view of the wide range of possible diagnoses. Fine needle aspiration (FNA) may be useful although diagnostic yield can be low. Fluctuant or necrotic nodes can be aspirated for microscopy and culture. A polymerase chain reaction (PCR) test on the FNA or aspirate sample should be requested as well as smear and culture. This can give a rapid result as to the presence of *Mycobacterium tuberculosis* DNA and can give an indication if rifampicin resistance is present or not. TB PCR on lymph node samples utilising Xpert MTB/RIF has been shown to have a specificity of 74% (95% CI 69–79%) and sensitivity of 78% (95% CI 74–82%) for diagnosing TB from lymph node FNA compared to culture [7]. Excision biopsy provides the optimal amount of material for definitive histopathology examination and mycobacterial culture but is not always available and can introduce delays in diagnosis. A core biopsy is a good option having a higher diagnostic yield than FNA but being less invasive and often easier to access than a formal excision biopsy [5, 8].

Treatment

Treatment of fully sensitive lymph node TB is with standard quadruple therapy for 6 months and has been shown to be effective in several clinical trials [9] (see treatment chapter "TB Treatment and Complications"). There is little indication for extending therapy beyond 6 months but this commonly happens as clinicians continue therapy when residual lymph nodes are still palpable after 6 months therapy [10]. Paradoxical upgrading reactions where lymph nodes become bigger and new nodes appear whilst the patient is taking TB treatment or sometimes afterwards are not uncommon. This phenomenon was described before the advent of the HIV epidemic and may be due to the patients clinical condition improving as ATT commences leading to an increased immunological response. In HIV infected patients starting antiretroviral therapy with ATT especially if their baseline CD4 count is low frequently experience enlargement of their lymph nodes, known as immune reconstitution inflammatory syndrome, which can frequently be prolonged and over a year in some cases [11]. In HIV uninfected patients risk factors for upgrading reactions include younger age, acid fast bacilli seen in the sample, low lymphocyte count and the use of vitamin D supplements [12]. It may be prudent in some cases

to delay the use of vitamin D supplements at the start of ATT to prevent paradoxical enlargement of nodes. In HIV uninfected patients a large case series found 23% of patients developed paradoxical enlargement of lymph nodes a median of 46 days (interquartile range 21–139 days) after starting ATT. The nodes persisted for a median of 67.5 days (interquartile range 34–111 days) [13]. Although frequently used, steroids have not been shown definitively to be useful in managing these reactions but aspiration of fluctuant nodes maybe beneficial. If nodes appear or enlarge towards the end of a of a non-HIV patient's course of ATT, this is not an indication in itself to extend therapy. Compliance with therapy should be checked as well as the original sensitivity pattern. If there are concerns about treatment failure a repeat biopsy or aspiration sample should be obtained for mycobacterial culture before extension of treatment or retreatment is considered.

Abdominal Tuberculosis

Introduction

Abdominal tuberculosis or TB of the gastrointestinal tract can involve any part of the digestive system from mouth to anus and any intrabdominal organ. Abdominal TB makes up around 10% of all cases of TB [14]. It is commonly part of disseminated TB and more common amongst HIV infected patients. Concomitant pulmonary tuberculosis is common and occurs in around 25% of cases of abdominal TB and should always be looked for to establish if the patient is infectious and may also identify more accessible sites for taking diagnostic samples.

Clinical Features

Clinical features will be dependent on the site of disease in abdominal TB. The main sites of disease are peritoneal, intestinal and visceral organs, which are described separately below. Systemic features of fever (90%), weight loss (82%) and abdominal pain (88%) are frequently present and can help differentiate abdominal TB from other causes of abdominal disease [15].

Peritoneal Tuberculosis

Peritoneal TB is the most frequent manifestation of abdominal TB. MTB infects the peritoneal space and peritoneum from the reactivation of infection in a granuloma, direct spread from the bowel or as part of disseminated disease. Patients will usually

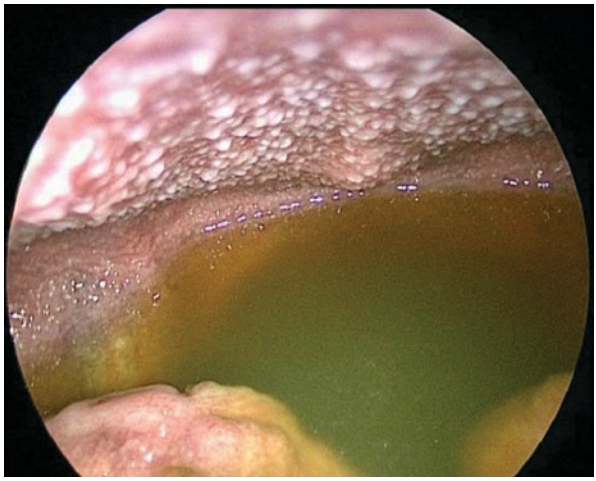

Fig. 2 Laparoscopic appearance of a patient with peritoneal tuberculosis and ascites. Ascitic culture grew *Mycobacterium tuberculosis*

have fever, weight loss, and abdominal discomfort. Peritoneal infection usually leads to the development of ascites which may cause abdominal distension and pain. Presentation initially may be as a fever of unknown origin. Imaging may reveal ascites, thickened peritoneum, thickened omentum and intrabdominal lymphadenopathy. Diagnosis is made by aspiration and culture of ascitic fluid. This can be performed by needle aspiration or laparoscopy with peritoneal biopsy. Histology showing granulomas with caseation is very suggestive of peritoneal TB and Fig. 2 shows a laparoscopic view of a patient with peritoneal TB. Aspirated ascites will have a raised lymphocyte count and the serum:ascites albumen ratio will be <1.1 g/dL. A definitive diagnosis is made by TB culture but direct nucleic acid detection has been used but lacks high sensitivity [16]. Raised adenosine deaminase (ADA) can be useful in differentiating TB peritonitis from other causes of ascites, a recent meta analysis found ADA had a sensitivity of 93% and a specificity of 94%, for ascites being due to TB [17].

In more advanced cases of peritoneal TB ascites may disappear leaving a fibrosed omentum and mesentery which clinically manifests as a 'doughy' abdomen, this is very uncommon. Risk factors associated with peritoneal TB from a series of patients in China include cirrhosis, continuous ambulatory peritoneal dialysis, diabetes, malignancy, steroids and HIV infection [18].

Intestinal Tuberculosis

Intestinal TB may present with non-specific generalised signs and symptoms of fever, night sweats, weight loss and anorexia. However it can present with abdominal pain, diarrhoea (which may be bloody), constipation and signs of obstruction.

These signs and symptoms are difficult to differentiate from other abdominal pathology such as malignancy and inflammatory bowel disease.

Around three quarters of cases of intestinal TB affect the jejunum, ileum or caecum. The most frequent site of intestinal TB is the ileocecal junction and a mass may be felt in this area [19]. TB causes ulceration of the bowel mucosa followed by healing with stricture formation and this pathology is responsible for the symptoms experienced. The parts of the bowel more preferentially affected are those rich in lymphoid tissue such as the Peyers patches in the small intestine, this may also be the reason that the ileocecal junction is commonly affected.

Any part of the gastrointestinal tract can be affected by TB. Uncommon sites are the oesophagus where patients may present with dysphagia and haematemesis. Imaging may reveal a mediastinal mass, endoscopy may show bleeding ulcerated lesions as are seen with malignancy. Diagnosis is made by biopsy. Complications include catastrophic bleeding and post treatment stricture [20]. Gastric TB is also very unusual and may present as a bleeding ulcerated lesion, pyloric obstruction or as a more widespread infiltrate mimicking linitus plastica [21–23]. Duodenal TB usually affects the third part of the duodenum and usually presents with signs of obstruction which maybe intrinsic or due to external pressure from enlarged lymph nodes, it may present as bleeding which may be catastrophic and involve fistulation into major vessels including the aorta, or rarely perforation [24, 25]. Rectal TB may present with blood in the stools, mucosal ulcers may be present which extend to the anal region. Perianal disease is not common with tuberculosis and is more common in Crohns disease.

Diagnosis

Diagnosis of intestinal TB may be suspected from the clinical presentation if constitutional symptoms are present. Computer tomographic imaging may reveal thickening of affected areas of bowel, most commonly in the ileocecal region. Several regions of thickening may be seen with evidence of partial of complete obstruction. Associated findings include local lymphadenopathy often with the nodes showing necrotic centres, para aortic adenopathy, peritoneal and omental thickening, ascites and splenic lesions. Colonoscopy is useful to establish a histological diagnosis if the lesions of interest are accessible. Findings include a patulous ileocecal value, transverse ulcers, skip lesions, nodules and strictures. These findings support the diagnosis of TB but do not definitively differentiate it from other diseases such as inflammatory bowel disease or cancer [26]. Peritoneal biopsy can be done via laparoscopy (see Fig. 3). Biopsy of lesions should be deep as changes due to TB occur into the submucosa. Granulomas with caseation are characteristic. Culture of biopsy specimens for mycobacteria should be undertaken. PCR analysis of biopsy specimens for mycobacterial DNA can be useful but has low sensitivity [27].

Differentiating Intestinal Tuberculosis from Crohn's Disease

Even in settings with access to all diagnostic modalities differentiating intestinal TB from Crohn's disease can be a challenge. There are a number of features that differ between the conditions namely clinically namely diarrhoea, blood in the stool and perianal disease are more common in Crohn's disease whereas fever and night sweats are more common in TB. Also concomitant pulmonary TB may support the diagnosis of intestinal TB, but all the features mentioned above can occur in both diseases. Imaging can help differentiate the two conditions. An Indian study found that computerised tomographic features show the involvement of the ileocecal area (70% for TB vs. 43% for Crohn's Disease), a shorter length of involvement, and presence of lymph nodes larger than 1 cm (20% for TB vs. 2% for Crohn's Disease) were more common in TB [28]. Skip lesions and left sided colonic involvement are more common in Crohn's disease. Endoscopic features mirror radiological findings to some extent but also include transverse ulcers and patulous ileocecal valve with disease crossing the ileocecal value being more common in intestinal TB. In Crohn's disease longitudinal ulcers, aphthous ulcers and cobble stoning are more frequently seen. Histology of intestinal biopsies show chronic granulomatous inflammation in both diseases. Granulomas tend to be smaller in Crohn's disease with caseation and larger granulomas being exclusive to TB. Also the finding of granulomas in surrounding lymph nodes indicates TB.

Intestinal TB is a paucibacillary disease but the demonstration of acid fast bacilli on staining or culture of *Mycobacterium tuberculosis* from biopsy samples prove the diagnosis. Because of this uncertainty models using a variety of features have been developed a recent Bayesian model found that using a variety of features including the presence of fever, night sweats, lung involvement, and ascites; transverse ulcers, patulous ileocecal valve, caecal involvement; and a positive interferon-γ release assay and pathological findings then intestinal TB could be predicted with a sensitivity 91% of and specificity of 93% [29].

Often despite the above features it is not possible to differentiate the two conditions in which case a trial of ATT may be indicated with follow up imaging and endoscopy after several months to see if the previously seen lesions have resolved.

Hepatobiliary Tuberculosis

Involvement of the hepatobiliary system is not a common manifestation of extrapulmonary TB. The liver may be involved as part of miliary or disseminated infection, hepatic hilar lymph nodes may develop focal infection along with the surrounding liver tissue that may develop into an abscess. Granulomas in the liver can develop into tuberculomas. Also isolated infection of the gallbladder can occur. In HIV infected patients hepatic TB can develop as part of disseminated infection. A case series from South Africa of HIV infected patients with histologically proven hepatic

TB found 75% of the patients had concomitant pulmonary TB, this finding had previously been reported in HIV negative patients [30, 31].

The presentation of hepatic TB includes hepatomegaly (70–96%), systematic symptoms (fever, anorexia, weight loss) (55–90%), right upper quadrant pain (65–87%), splenomegaly (25–55%) and jaundice (20–35%) [32]. Jaundice is usually the result of portahepatis node involvement or rarely cholangitis. Biochemical results reflect biliary obstruction with raised alkaline phosphatase.

Diagnosis may be suggested by the presence of TB elsewhere. Imaging findings are not usually specific for TB, ultrasound may show hypoechoic lesions and CT scan may reveal non enhancing low density lesions. Liver biopsies demonstrating caseating granulomas with acid fast bacilli support the diagnosis of TB and differentiates TB from the granulomas seen in sarcoidosis and Hodgkins lymphoma. Liver biopsies should be submitted for TB culture if this is in the differential diagnosis. Demonstration of *Mycobacterium tuberculosis* DNA by PCR or culture of MTB confirm the diagnosis.

Pancreatic Tuberculosis

Tuberculosis of the pancreas is not common but is an important and curable differential diagnosis of a pancreatic mass that can be mistaken for pancreatic cancer. Clinical symptoms can be non-specific but include abdominal pain, fever, weight loss, night sweats, backache and jaundice. Examination may reveal a palpable abdominal mass and jaundice if the mass causes biliary obstruction [33, 34]. Pancreatic TB is often associated with TB at other sites. Imaging will reveal a pancreatic mass which is hypodense often with associated enlarged lymph nodes [33]. Diagnosis requires histologic and microbiologic confirmation, this can often be achieved using endoscopic ultrasound guided biopsy [35] but ultrasound and computer tomographic guided biopsy can also be used.

Treatment

Treatment of all sites of gastrointestinal TB is with standard quadruple ATT for 6 months. Some have advocated that abdominal TB should be treated for 9 months to reduce relapse but a recent Cochrane review found that although the evidence available for analysis was relatively poor that there was no evidence that 6 months of anti TB treatment was associated with a greater proportion of relapses compared to 9 months treatment. This review did have some limitations and it is worth noting that the trials assessed did not include HIV infected patients [36]. Treatment of abdominal tuberculosis also includes management of any underlying conditions such as concomitant liver disease, and attention to good nutrition. Surgical management may be required for obstruction, strictures, fistula, perforation or bleeding.

Fibrosis, scaring and distortion of the biliary tree can occur with hepatic tuberculosis which may require surgical correction.

Pericardial Tuberculosis

Introduction

Pericardial tuberculosis is an uncommon manifestation of tuberculous disease, but can frequently lead to the development of life limiting and fatal sequelae. In the UK around 1% of reported TB cases affect the pericardium. The proportion of pericardial effusions worldwide due to TB depends on the incidence of TB in the country in question. In high TB incidence areas such as sub-Saharan Africa TB pericarditis is the commonest cause of pericardial effusions [37]. Pericardial TB is more common in HIV infected patients and this has led to a rise in presentations in all settings.

The pericardium becomes infected by TB in three ways, via a haematogenous route, via lymphatic spread or rarely by direct spread from a lung lesion.

Clinical Manifestations and Presentation

The clinical presentation of pericardial TB depends on the stage of disease. The disease progresses through four phases and may present at any stage. Initially there is an exudative effusion with is rich in polymorphonuclear cells, there are abundant mycobacteria present and the effusion has fibrinous strands, these effusive phases may lead to cardiac tamponade. Subsequently the effusion becomes lymphocytic and paucibacillary, the effusion may then be absorbed and the pericardium develops fibrosis. Finally, the thickened fibrosed pericardial layers contract and calcify, the

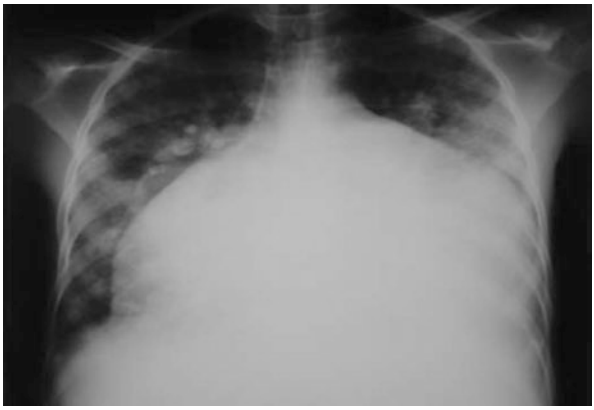

Fig. 3 Pericardial Effusion in 25 year old female patient. 900 mL of fluid was aspirated from this lady who presented with signs of cardiac tamponade. Her haemodynamic status rapidly improved after pericardiocentesis

non-compliant pericardium can impair the diastolic phase of the cardiac cycle. Patients with the earlier stages of TB pericarditis are likely to present with constitutional symptoms, possibly cardiac symptoms and signs whereas those in the later stages of disease are likely to have cardiac symptoms and signs only. Presentation can be divided in to three types, those of pericardial effusion, pericardial constriction or a mixture of both.

Symptoms can be non-specific with fever, weight loss, night sweats, anorexia and fatigue. More specific symptoms such as chest pain, cough, breathlessness and right upper quadrant pain due to liver congestion may be present. Signs depend on the stage of disease and can range from minimal signs to those of marked congestive heart failure. For patients with pericardial effusion the most common signs are, hepatomegaly (94%) increased cardiac dullness (94%), raised jugular venous pressure (JVP) (84%), soft heart sounds (78%) sinus tachycardia (77%), ascites (73%) and pulsus paradoxus (36%). When pericardial constriction has developed the most common signs are raised JVP (100%), hepatomegaly (100%), peripheral oedema (94%), ascites (89%), soft heart sounds (76%) and sinus tachycardia (70%) [38]. The risk of constrictive pericarditis following TB pericarditis varies and may be modified by ATT but has been estimated to be around 32 cases per 1000-person years [39].

Diagnosis

Diagnosis may be suspected clinically but can be overlooked especially in the early stages of disease. Clinical findings of a pericardial effusion in the presence of systemic symptoms or concomitant pulmonary or disseminated TB should raise suspicion of pericardial TB. A chest x-ray may show an enlarged cardiac silhouette in the case of a pericardial effusion or calcified pericardium in more advanced or previous disease. The electrocardiogram will be abnormal in most cases with reduced voltage complexes and non-specific ST changes. Classic ST elevation indicating pericarditis occurs in only around 10% of cases [40].

Echocardiography will confirm the presence of pericardial fluid and is an essential part of diagnosis. Findings include pericardial effusion, thickened pericardium and strands in the pericardial fluid. If there is pericardial constriction there will be specific findings related to the haemodynamic changes caused by the non-compliant pericardium. There may be distended hepatic veins and dilated inferior vena cava that do not collapse with during inspiration. These findings may also be present with cardiomyopathy. Echocardiographic signs specific for pericardial constriction are a septal ‘bounce’ with initial movement of the intraventricular septum towards the left ventricle during ventricular filing on inspiration, interventricular dependence and marked respiratory variation during ventricular filling [41, 42].

If possible an attempt at sampling pericardial fluid should be made to enable a microbiological diagnosis. In pericardial TB the fluid will be a lymphocytic exudate, but can contain polymorphonuclear leucocytes in early disease. Pericardial

fluid should be sent for Ziehl-Neelsen (ZN) staining for mycobacteria and culture. If available direct nucleic acid detection for mycobacterial DNA should be performed. The commercially available GeneXpert system has been shown to be more specific and sensitive for the diagnosis than ZN staining, and similar to culture of pericardial fluid but far quicker giving a result after several hours. A study in Saudi Arabia found GeneXpert to have a sensitivity on pericardial fluid of 84.3% and a specificity of 99.1% [43]. Pericardial biopsy for microscopy and culture can be useful and has a higher yield for TB culture but this is not widely available and is not without risk.

Indirect methods of diagnosis such as tuberculin skin testing and interferon gamma release assays when used in isolation are not routinely useful. Adenosine deaminase (ADA) levels may be helpful if available. Sensitivity and specificity depend on the cut off levels chosen. A systematic review and meta-analysis found ADA levels about 40 U/L to have a sensitivity of 88% and a specificity of 83% for pericardial TB [44]. A search for TB in other sites especially in the lung should be made as around a third of patients may also have pulmonary TB and two thirds a pleural effusion.

The diagnosis of pericardial TB may be definitive where MTB is demonstrated on culture. However a probable diagnosis can be made when there is suggestive pericardial histology, a lymphocytic effusion with a raised ADA level or where there is a pericardial effusion demonstrated on imaging with concomitant TB elsewhere or in patients with a pericardial effusion that responds to ATT.

Treatment

Treatment of fully sensitive pericardial TB is with standard quadruple therapy rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months followed by rifampicin and isoniazid for 4 months.

The use of adjunctive corticosteroids which has been standard for many years is now controversial. A trial in South Africa in the 1980's showed reduced mortality and reduced pericardial constriction in patients given steroids with ATT for the first 11 weeks of treatment [45, 46]. Subsequent to this steroids have been given routinely as part of treatment for pericardial TB. These studies also emphasised the importance of drainage of pericardial fluid. However in 2014 a large well-designed trial which randomised 1400 adults, two thirds of whom had HIV infection to receive 6 weeks of a tapering dose of prednisolone starting at 120 mg daily for the first week compared to placebo found that a composite end point of death, cardiac tamponade requiring pericardiocentesis or pericardial constriction was not different between the intervention and control arms. Also, there was an excess of HIV related cancer in the intervention group [47]. Since this trial, American Thoracic Society Guidelines for the treatment of drug sensitive TB recommend the use of adjunctive steroids only in selected cases of pericardial TB (Table 1) [48].

Table 1 Possible indications for adjunctive corticosteroids in the treatment of pericardial tuberculosis

Large pericardial effusion
Raised inflammatory cells or markers in pericardial fluid
Signs of early pericardial constriction

If a decision to use steroids is made, adults should be given 60 mg of prednisolone daily reducing the dose depending on response after 2 weeks and completing weaning over the following 4 weeks.

Aspiration of pericardial fluid is necessary to confirm the diagnosis, but is also therapeutic. Aspiration is indicated urgently if there are signs of cardiac tamponade, such as hypotension, marked pulsus paradoxus or tachycardia. An echocardiogram showing right ventricular collapse, atrial collapse and inferior vena cava plethora are signs of pericardial tamponade.

Surgical pericardiectomy may be required if pericardial constriction develops. This is less common with the advent of effective ATT but does still occur sometimes as a first presentation. Pericardiectomy is a fairly risky procedure. Optimal timing is controversial. It is indicated for patients with haemodynamic compromise despite ATT. It is appropriate if possible to see if a patient improves initially on ATT but if they still have haemodynamic compromise after 2 months, surgical intervention should be offered [49].

Patients should be carefully followed up during treatment and for several months afterwards. At follow up a focused clinical examination checking for signs of cardiac tamponade and constriction should be performed. Repeated echocardiograms should be performed if indicated to check for signs of fluid reaccumulating and the development of constriction. If constriction is demonstrated close liaison with cardiac surgeons is important to help determine if pericardiectomy is indicated and if so to determine the optimal timing.

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Spinal and Bone Tuberculosis

Jonathan Bull and Veronica White

Introduction

Tuberculosis of the skeleton, TB osteomyelitis, makes up a small but significant proportion of TB cases. Evidence of TB affecting the bone has been found in skeletons at many archaeological sites including in Egyptian mummies [1–4].

Diagnosis can be difficult and often occurs late in the patient's presentation, but the disease can cause significant morbidity due to these delays and the location of the pathology. Patients with spinal disease may be left with significant post treatment pain or neurology, paraplegic or even tetraplegic, depending on the site of the infection. Those with TB of the joints or long bones can be left with deformity, chronic pain or loss of range of movements.

Incidence

In 2018 it was estimated that there were ten million cases of TB worldwide, of which seven million were notified to national TB programmes; only 15% of these cases were reported as extra pulmonary, ranging from 8 to 24% depending on the region; it is well recognised that this is due to under reporting as well as under diagnosis [4, 5]. The true incidence of TB osteomyelitis in developing countries is therefore likely to be similar if not more than European cases, particularly with HIV co-infection [3, 4]. Active infection occurs in patients of all ages.

In England in 2018, 5–6% of TB cases were in the skeleton of which 3–4% were in the spine giving a total of 147 cases of spinal TB and 90 non-spinal bony cases [5].

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The majority of patients were born in high risk countries and are likely to have acquired their primary TB infection in earlier life [2, 4, 6–8]. Whilst the number of cases was not enormous, morbidity from TB osteomyelitis can be considerable as outlined above.

Aetiology

The TB bacillus is thought to reach the bones via the blood stream with haematological seeding, via rich vascular plexuses, including Batson's paravertebral venous plexus, that supply the spinal vertebrae [2]. Non-tuberculous mycobacterial infection is much less common, and is associated with previous injury or surgery, such as joint arthroplasty [3]. There has recently been a series of cases of Mycobacterium Chimera reported post cardiac surgery which has been found to be due to contamination of cardiopulmonary bypass heater-cooler units [9]. Mycobacterium bovis infection has been reported after intravesical Bacilli Calmette Guérin (BCG) therapy and is also thought to be spread via the venous network that links the spine and the pelvis [3, 10–12]. Multi-drug resistant tuberculosis (MDR TB) can also affect any skeletal site and requires treatment with the same complex medication as pulmonary MDR TB disease.

Spinal Tuberculosis

In the UK, Percival Pott first described spinal TB in 1779 and his name, Pott's disease, is still used to describe the infection) [1, 2, 13]. This is not to be confused with either Pott's fracture or Pott's puffy tumour which are a complex fracture of the ankle and osteomyelitis of the frontal bone of the skull respectively [14, 15].

Presentation of spinal TB can be insidious, and is often, at least initially, misdiagnosed with outcomes being variable, and despite good antibiotic and sometimes surgical treatment, can lead to long term disability.

Spinal TB tends to affect the vertebral bodies which have a rich vascular supply, skipping the intervertebral discs and radiology showing disc sparing. Frequently it affects more than one vertebra and if it is in adjacent vertebrae it may then involve the intervertebral disc. It occurs at any level and can be multi-level but most commonly affects the thoracic and lumbar spine. It is therefore important to image the whole of the spine at the time of diagnosis as lesions may be non-contiguous. Vertebral involvement and infection can lead to bony destruction and vertebral collapse which causes the typical anterior wedge fracture and wedging synonymous with Pott's disease (Fig. 1) [2, 4, 13]. Gibbus formation and kyphosis may also

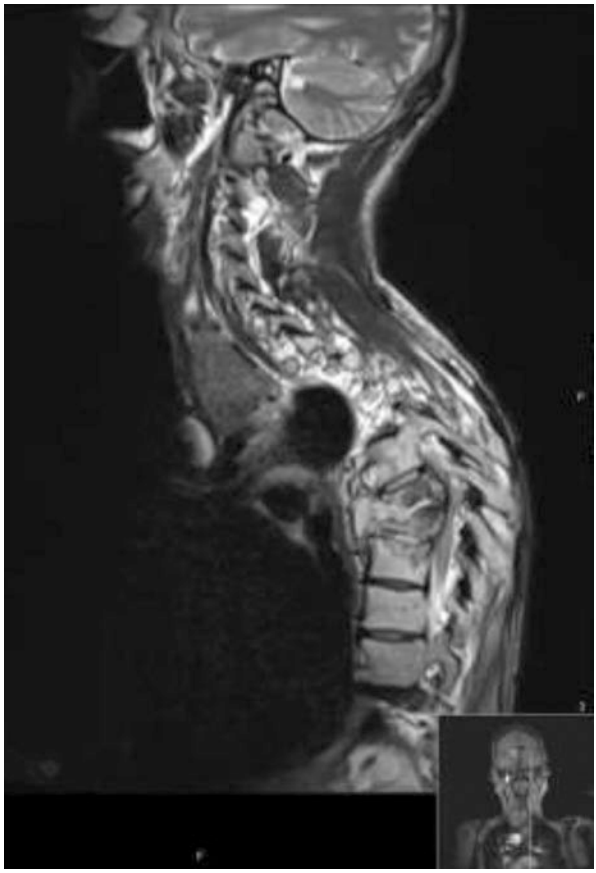

Fig. 1 MRI scan of thoracic spine showing gross destruction of thoracic spine with wedge fractures, a paraspinal abscess causing marked impingement on the spinal canal and cord compression

occur and can cause spinal cord compression and paraplegia. TB also affects the sacroiliac joints where it can present as a unilateral osteomyelitis [3].

Skeletal TB does not occur in isolation; in a third cases of active TB can be found elsewhere in the body. TB infection in the spine tends to travel along the subcostal neurovascular bundle or in the venous drainage from the vertebrae, hence further foci of infection are often found in the ribs, or the psoas or iliacus muscles, with a third of cases also have associated unilateral or bilateral psoas abscess(es). A chest x-ray is mandatory, but is often normal despite the lungs being the primary focus of infection [2, 7, 16].

Occasionally patients present in outpatients with, for example, pulmonary or lymph node TB and a gibbus will be found on examination; these patients need to be investigated urgently for spinal TB [1].

Presentation of Spinal TB

Most but not all patients with spinal TB present with back pain. About 50% of patients will present with neurology such as lower limb weakness, paraesthesia, and rarely bowel or bladder symptoms; 50% will also have at least one systemic symptoms of fever, night sweats and/or weight loss [2, 4, 8].

The difficultly in making the diagnosis arises due to back pain being a very common presentation in primary care. However, both patient and doctor often forget to acknowledge the presence of systemic symptoms, which can help in making a diagnosis.

Patient characteristics can be helpful, for example, born or lived in a high incidence area of TB, but this is not always the case and often TB exposure will have been many years if not decades before presentation.

Incidental diagnosis on a CT or MRI scan organised for other symptoms such as abdominal pain is a common presentation. Occasionally patients with, for example, pulmonary TB will be diagnosed and started on treatment, only to develop either back pain or a superficial paraspinal abscess on TB treatment. It is only at this stage that both patient and clinician are concerned about the spine and urgent investigations should be organised.

Disease in the cervical spine can present with neck and shoulder pain, brachial plexus or radiculopathic symptoms. Patients can present via the Ear, Nose and Throat specialists with dysphasia, hoarseness and dysphagia due to formation of a retropharyngeal abscess (Fig. 2). If there is spinal cord compression at the cervical spine level patients may complain of weakness and numbness of the upper and lower limbs, progressing to tetraplegia. If there is any concern about the stability of the cervical spine then the patient should be placed in a hard cervical orthosis (Fig. 3).

Thoracic spine disease commonly presents with back pain, but also radicular pain radiating anteriorly in a band like distribution to the chest wall; some patients

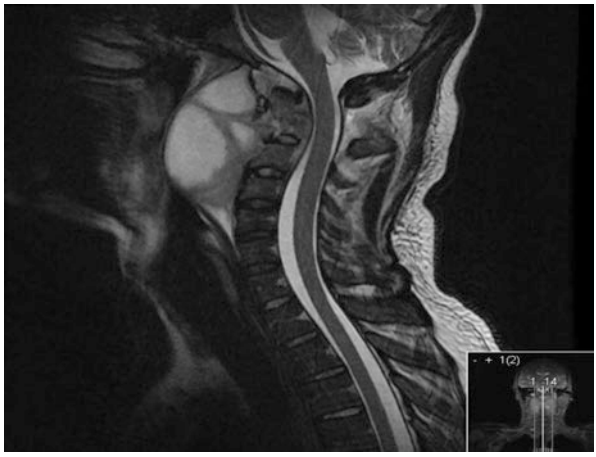

Fig. 2 MRI scan of cervical spine with evidence of a large retropharyngeal abscess, prevertebral collection and destruction of the odontoid peg; the patient presented with neck pain and nasal speech. The abscess was drained surgically, the patient placed in a halo brace and treated for TB. He made a full neurological recovery

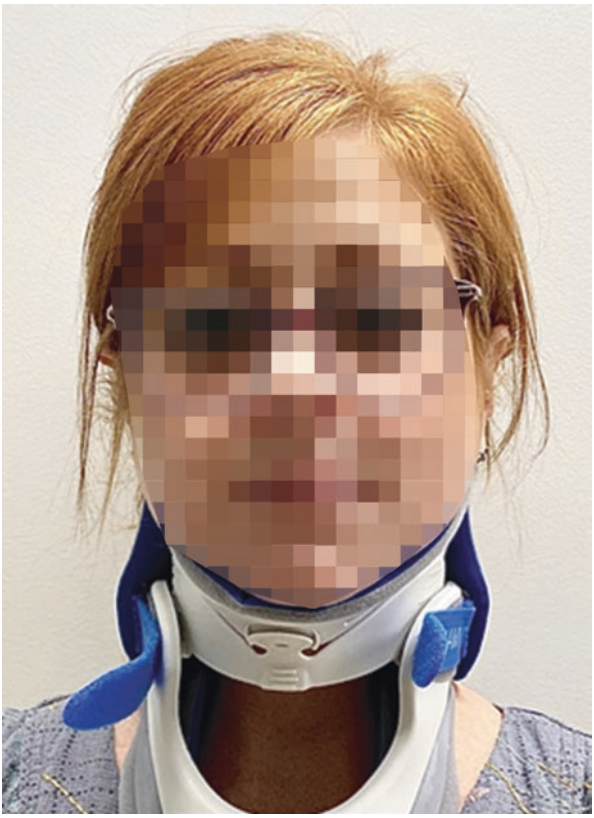

Fig. 3 Cervical orthosis or hard collar

will complain of epigastric pain which on investigation is due to referred pain. Cord compression can lead to lower limb symptoms and can lead to paraplegia (Figs. 4 and 5).

Patients with lumbo-sacral disease complain of lower back pain and difficult sitting and rising from a chair. Sacroiliac joint infection can limit walking and present with hip or buttock pain potentially leading to superficial skin abscesses. Occasionally cauda equina syndrome can be as a consequence of TB and documentation of bowel or bladder symptoms is essential.

Both thoracic and lumbar disease can be associated with a tracking of infection through the subcutaneous tissues and abscess formation on the skin, which can sometimes be the first sign of the disease. This can track to the skin surface can lead to discharging sinuses (Fig. 6).

Infection at any of these sites can initially be asymptomatic, particularly when limited to the vertebrae themselves; however, there is often formation paraspinal abscesses, or cold abscess, which if they are adjacent to the spinal cord, can cause signs and symptoms of upper or lower limb neurology and paraplegia, or if invading the nerve root, radicular pain [1–3, 8].

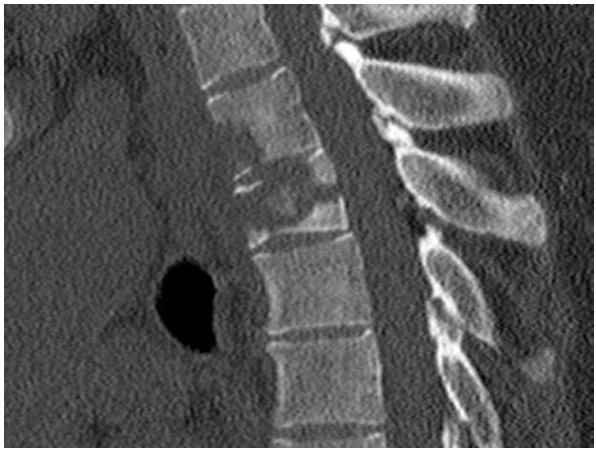

Fig. 4 31 year-old man who presented with intrascapular pain; CT scan shows anterior lesions at T3 and T4 (T4 is starting to develop a classical anterior wedge fracture)

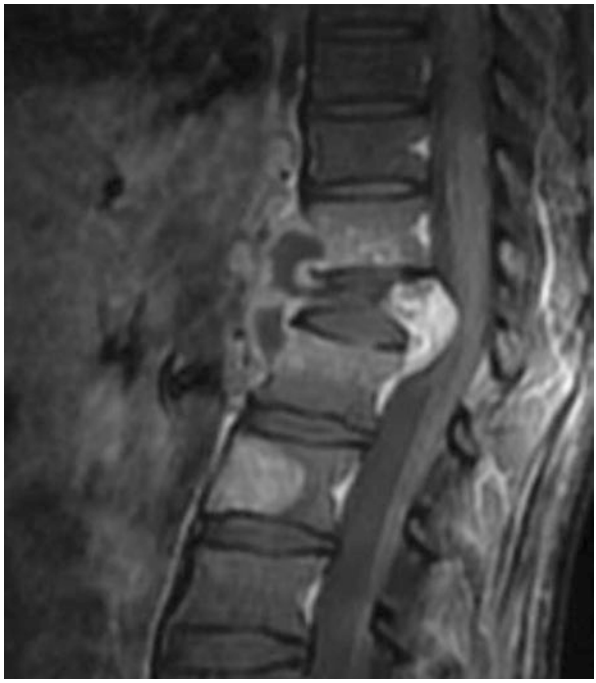

Fig. 5 23 year-old woman presented acutely with weakness, numbness, pain and needles in lower limbs; MRI scan shows complete destruction of T12 associated with an epidural and prevertebral collection

Investigation of Spinal TB

MRI scans are now the imaging modality of choice and show areas of infection and bone destruction in affected areas. T1-weighted images show a low signal and T2 weighted images a bright one. CT scans are useful when looking at the structure of the bone and bony stability. Bone scans or skeletal scintigraphy assess bone

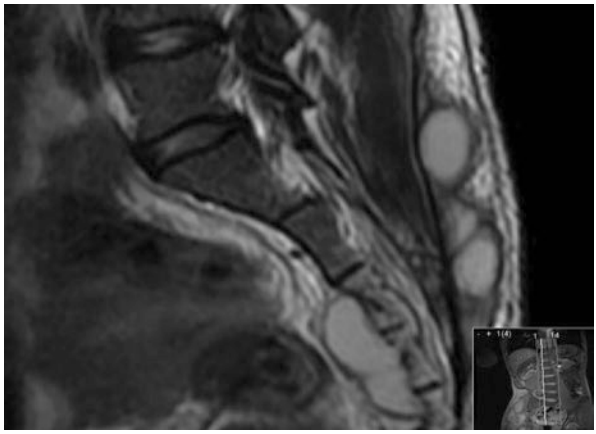

Fig. 6 40 year-old man presenting with lower back pain and a fluctuant abscess over his left gluteal region. MRI shows a presacral collection and multi loculated abscess in subcutaneous tissues

metabolism so can be used to assess whether there is an area of high bone turnover that can occur with bacterial infection, TB or metastases; PET-CT scans can similarly be used to look for evidence of multifocal infection [1, 3, 13].

Depending on the site of disease, radiological biopsy should be carried out to send samples for histopathology, standard microbiology (MC&S), and acid-fast bacilli (AFB). This can be done by CT guided biopsy or US scan guided biopsy, depending on the site of disease. Occasionally open surgical biopsy is necessary, either due to the difficult site of pathology or as part of surgical intervention to stabilise the spine. Microbiology samples can include solid tissue and/or pus and should be sent in a pathology pot dry or in saline solution; the microbiology teams are unable to process samples sent in formalin as this kills any bacteria.

Histology samples may show classic caseating granuloma, although bone biopsies are often difficult to process in the laboratory as they need to be decalcified first. Standard microbiology may reveal bacterial infection such as staphylococcus, particularly in patients who are immunocompromised. Occasionally spinal lesions diagnosed as metastatic cancer on imaging only, are then found on biopsy to be due to TB.

A chest x-ray should always be undertaken on presentation to rule out active infectious pulmonary TB and if there are any concerns about lung infection the patient should be appropriately isolated whilst in hospital and sputum samples sent (see below).

Standard blood tests should be undertaken but are generally unhelpful at confirming a diagnosis: patients who have been unwell for some time may have a normochromic, normocytic anaemia due to underlying infection or other pathology. The ESR is often raised in bony disease, but a normal result does not rule out infection. Similarly, a negative tuberculin skin test or IGRA (interferon gamma release assay—T-spot or Quantiferon) should not steer the physician or surgeon away from the diagnosis when there is a high clinical and radiological suspicion given the insufficiently high sensitivity of these tests. If patients present with multifocal lesions an immunological profile is useful to rule out a primary or acquired immunological defect.

Differential Diagnosis

Alternative diagnoses include secondary metastatic cancers, primary malignancy being much less common, and staphylococcus osteomyelitis, as outlined above; non-tuberculous mycobacterium infection does occur, particularly in patients who are immunosuppressed, for example post chemotherapy or HIV co-infection.

Presentation of Bone and Joint TB

Bone TB tends to occur in the larger joints such as the hip or knee and presents as a monoarthritis (Fig. 7). Rarely it presents as a trochanteric bursitis. Symptoms include joint pain swelling and loss of function, and is often misdiagnosed as being caused by another cause of monoarthritis. It is most commonly caused by haematogenous spread, but sometimes as the results of previous penetrating or non-penetrating trauma, instrumentation or joint replacement. Systemic symptoms are less common in bony TB which makes it more difficult to diagnose [3, 4, 17–19].

If the long bones are affected, the bone medulla tends to be infected first, unless the infection is the results of trauma or previous instrumentation. As the infection spreads, it can breach the bony cortex and spread along the subcutaneous fissure,

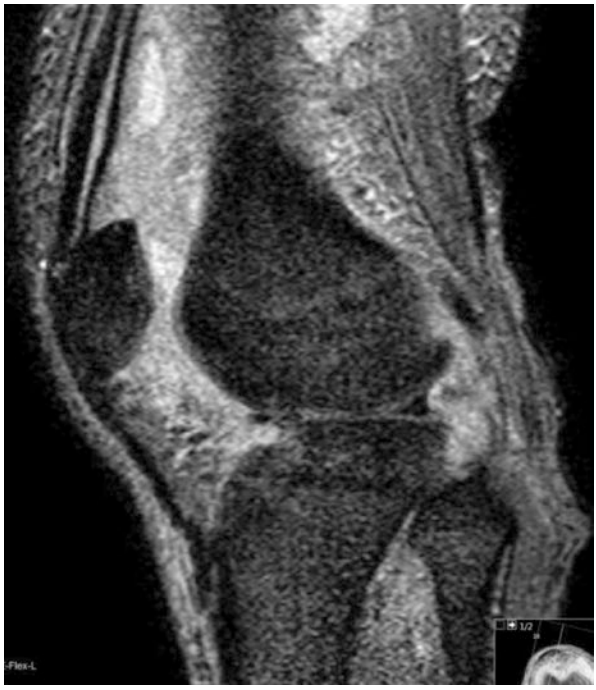

Fig. 7 MRI scan of knee joint. Whilst there is no obvious underlying osteomyelitis of the bone, there is an inflammatory arthropathy associated with a complex massive synovial thickening with joint fluid. Biopsy of the synovium showed granulomas and synovial fluid grew MTB (courtesy of Dr. Susan Cross)

and lead to subcutaneous collections. Therefore, bony TB can be associated with a chronic overlying a discharging sinus and when cutaneous TB is diagnosed in this way, care should be taken to assess the underlying skeleton, preferably with MRI imaging, to ensure that this is not an underlying associated osteomyelitis (Fig. 8).

Tuberculous dactylitis tends to occur in children and effects the tubular bones of the hands or feet [19].

TB rarely occurs in prosthetic joints sometimes many years after the original replacement. These patients may require surgical debridement and resection arthroplasty as well as standard TB therapy [3].

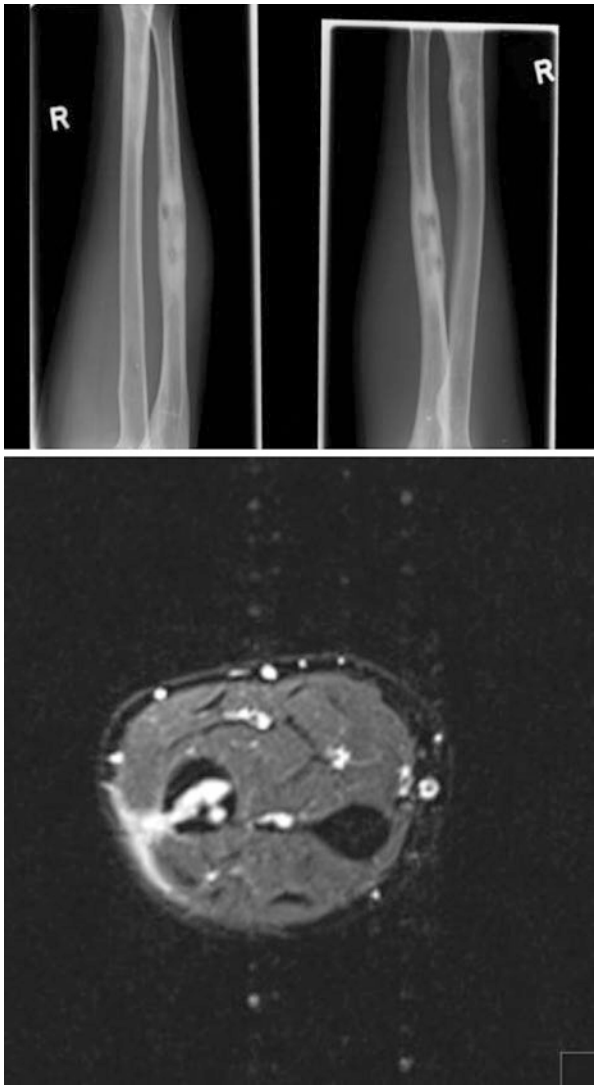

Fig. 8 Plain x-ray and MRI of right ulnar: x-ray shows mid shaft osteomyelitis with bony sclerosis and expansion. The MRI shows cross sectional imaging with breaching of the cortex and infection tracking through the subcutaneous tissues (courtesy of Dr. Susan Cross)

TB is occasional found in the sternum, often incidentally after a CT scan of the chest to investigate the underlying parenchymal disease and can occur after sternotomy following cardiac surgery [4, 20]. Active infection is also seen in the cranium and mastoids; when patients present with subcutaneous lesions the skull vault or face, underlying TB osteomyelitis should be ruled out with appropriate imaging.

Investigation of Bone and Joint TB

Plain x-ray can initially be helpful, but only if they are abnormal, and tends to show soft tissue swelling, followed by osteopenia, periosteal bone thickening and periarticular bone destruction. TB can also affect the tendon sheaths. However, it is not unusual for plain films to look completely normal, only to find multiple abnormalities on MRI (Fig. 9). Biopsies can be of the bone or synovium, which can be done under radiological guidance and synovial fluid can also be sent for MC&S and AFB, as well as cytology [4, 13]. Blood tests are as outlined above.

Differential Diagnosis

Rheumatoid arthritis, pyogenic infection, often cause by *Staphylococcus aureus*, brucellosis, actinomycosis, candidiasis, histoplasmosis and fungal infection can all mimic TB infection in the bone. Benign and malignant tumours such as enchondromas, giant cell tumours and malignant metastases [4, 19] can also imitate TB.

Isolation Precautions

Most cases of spine and bone TB are not infectious. However, when patients present, whether it be to an outpatient clinic or for admission to hospital, a chest x-ray should be one of the first investigations to be undertaken once any concern about neurological compromise is stabilised. The majority of patients will have a normal chest x-ray, but where there is doubt or obvious signs of pulmonary TB, patients should be isolated in a side room with appropriate infection control precautions. Sputum should be sent urgently for AFB and the patient kept in isolation until three negative sputa are processed. If there is concern about drug resistant TB, the patient should be isolated in a negative pressure facility.

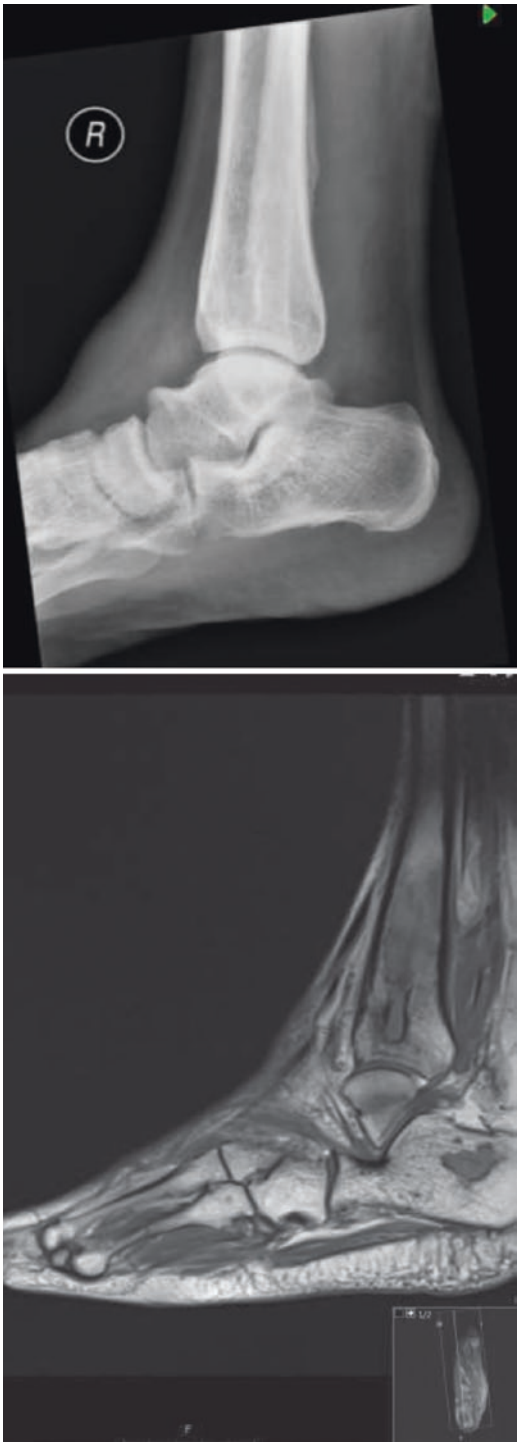

Fig. 9 Plain x-ray and MRI of the same patient's foot: the plain x-ray appears normal but the MRI shows florid changes in distal tibia and calcaneum—the sensitivity is much better on MRI for osteomyelitis and plain x-rays should not be trusted when the index of clinical suspicion is high (courtesy of Dr. Susan Cross)

Non-tuberculous Mycobacterium (NTM) and Multi Drug Resistant TB (MDR TB)

Osteomyelitis due to other members of the mycobacterium family is rare. NTM is more common in patients who are immunocompromised, after trauma or instrumentation. Depending on the organism, drug treatment can be more complex and prolonged and should be undertaken by expert in looking after non-tuberculous mycobacterium. MDR TB occurs in the bone at the same rate is pulmonary disease i.e. about 1–2% of patients and should be managed in a designated MDR TB centre [3, 10].

NTM can be found in replacement joints following surgery. Treatment may also require debridement of the affect area and removal of the prosthesis. Mycobacterium chimera has recent been found to cause infection in some patients post cardiac bypass surgery and can also affect the sternum [9].

Poncet's Disease

This refers to a painful polyarthropathy which can predate the diagnosis of active tuberculosis by many months. Also described as 'tuberculous rheumatism' it is thought to be caused by extra articular tuberculosis, most commonly active pulmonary TB, and is a reactive arthritis rather than being due to direct infection of the joints. It differs from active joint TB, which tends to be a monoarthritis, in that it affects many joints, x-rays tend to be normal and aspiration of the joints shows a sterile arthritis. It is thought to be caused by an immunological reaction. The symptoms settle once the underlying TB infection is treated [4, 19, 21, 22].

Treatment of TB Osteomyelitis

Both the British, American and WHO guidelines on management of TB recommend 6 months treatment for spinal and bone TB [23–25]. However, many specialists treat spinal TB for 9–12 months, sometimes times longer, partly due to concerns about multi-level spinal involvement and also involvement of the central nervous system, particularly when there is evidence of infection that is directly involving the spinal cord [1]. Length of treatment can also be influenced by the greater availability of MRI scans: clinicians use them to monitor progress, and when the site of infection still appears to be active, there is a tendency to continue TB treatment. What is unclear is at which point the infection resolves and the imaging is simply showing residual inflammation that will settle over time. Treatment should be guided by symptoms rather than imaging appearances.

Particularly with spinal TB, patients should be warned that once they start treatment, they should urgently report any changes in neurological symptoms. Similar to lymph node TB, encapsulated TB infection in the spine tends to enlarge at the start of TB treatment. Particularly if the infection is close to a nerve root or is part of a para spinal abscess adjacent to the spinal cord, a very small increase in size of a TB abscess can lead to progressive neurology and even lead to paraplegia which, if not addressed urgently, can lead to permanent disability. If patients are in hospital at the beginning of treatment, they should be told to report any new symptoms and examined neurologically on a daily basis; outpatients should be instructed to present to the nearest Emergency department if concerned about new neurology.

There are no clear guidelines on the use of steroids in spinal or bony disease and they should not be used routinely [13]. Steroids are rarely used in the treatment of bone TB. However, in spinal disease where there are neurological symptoms on presentation with spinal disease or when there is concern that an enclosed lesion close to important neurological structures such as the spinal cord with impending spinal cord compression, steroids may be started concomitantly with TB treatment using either iv or oral dexamethasone or oral prednisolone. Again, there is no specific guidance on the length of course, and the dose of steroids generally has to be doubled when rifampicin is used in the treatment regime. The authors would recommend a decreasing dose over an 8–12 week period. Treatment with steroids is more complex in patients with HIV who develop immune reconstitution syndrome (IRIS).

The side effects of steroids must be considered. Common effects include increased appetite and weight gain, acne and skin striae, osteopenia and osteoporosis. Patients should always be considered for bisphosphonates. Some patients develop psychological side effects including depression and/or hypomania. Clinicians should also consider a 9 am cortisol 2 weeks after finishing a prolonged course of steroids to ensure that there is not prolonged adrenal suppression. Very occasional patients can develop avascular necrosis of the hip as a result of high dose steroid use.

A well recognised side effects of treatment with isoniazid is a peripheral neuropathy, often presenting in a glove or stocking distribution. In patients with spinal disease it can be difficult to conclude whether new neurological is due to drug side effects or worsening burden of infection.

Non-pharmacological Treatment

Typically, it is possible to manage patients with spinal TB in a spinal brace, in part to manage their pain and to prevent or diminish the chance of progressive deformity. The risk of the deformity not only being cosmetic but also with a risk of long-term pain. Braces can be used for lesions in all locations in the spine and images of cervical and thoraco-lumbar orthoses are illustrated (Figs. 3 and 10).

Occasionally large joints may require temporary support with a brace; in generally however, the patients should be encouraged to exercise and mobilise both to use

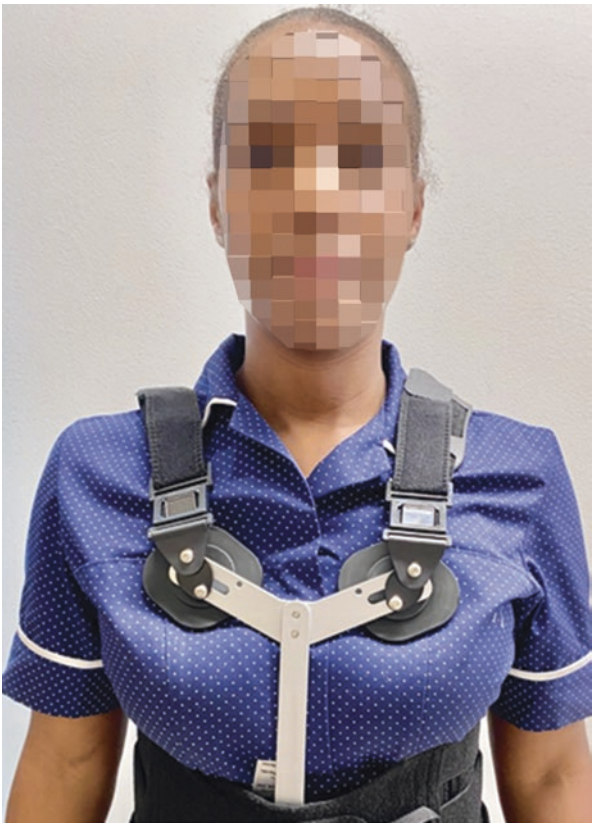

Fig. 10 Thoraco-lumbar orthosis or TLSO brace

the joint and encourage muscle strength in the surrounding structures. Physiotherapy and hydrotherapy can be helpful in some patients and patients with healing spinal infection should be encourage to attend Pilates classes and swim at least twice a week.

Diet and weight can also be important: any patient who has become immobile for whatever reason, and particularly if they have been given a course of steroids, tend to gain weight which puts further stress on the affected spine or joint. We also recommend the measurement of Vitamin D levels and appropriate replacement when needed.

Surgical Intervention

Different approaches to the surgical management of spinal TB are, to some extent, based on geography. This is particularly pertinent in developing countries with access to health resources can be limited and is coincident with patients travelling longer distances for their care. In such situations, the luxury of regular reviews of

patients is not practical and a single definitive single treatment such as surgery is undertaken [26, 27]. Surgical intervention with debridement and instrumentation will reduce the burden on the patient and facilitates with an early return to their home where TB chemotherapy can be continued without recourse to prolonged surgical follow up.

In developed countries it is possible to regularly review patients and potentially run a more conservative approach with TB chemotherapy using spinal orthosis and regular imaging to assess for the development of deformity. If the patient is not managing in terms of pain or signs and symptoms progress then timely surgical intervention can be undertaken.

Indications for surgery are progressive deformity and pain that cannot be managed with a brace and analgesia alone [28]. In patients that have neurological deficit that is progressing then surgery is indicated although it can be possible to manage a stable deficit with conservative treatment and this may improve as the patient responds to TB chemotherapy.

Deformity (gibbus) may well need correction as it can lead to long term pain in spite of TB typically resulting in fusion across the affected segments [28, 29]. Timing of surgery can be complex; experience in resource limited environments suggests that even early surgery with instrumentation when the patient has had only a very short course of treatment does not typically result in persistent infection. This is in the context of extensive surgical debridement.

In general TB of the spine without neurological deficit can be managed conservatively. Where surgery is considered a multidisciplinary approach can be helpful to ensure all options are explored (Fig. 11).

The majority of long bone or joint TB is treated conservatively with antituberculous therapy. However, infection may lead to bony destruction and deformity which may require debridement, joint replacement or reconstruction, the latter being generally recommended once TB treatment has been completed. However, surgery can take place if necessary whilst the patient is on treatment. Mycobacterial infection in prosthetic joints may require early debridement and removal of the prostheses which is replaced whilst on treatment or once the infection is completely cleared.

Outcomes and Long-Term Morbidity

The outcome of spinal TB is partially dependent on the original site of the disease, the degree of neurological involvement on presentation, any delay in diagnosis, as well as success of treatment and motivation of the patient to engage in exercise programmes. Aiding long term recovery can at least in the first instance be about managing expectations. All patients should be warned at the beginning of treatment that they may experience long term mild to moderate back pain, similar to many patients with mechanic back pain who have not had the burden of an infective episode. As outlined above, physiotherapy and an incremental increase exercise can

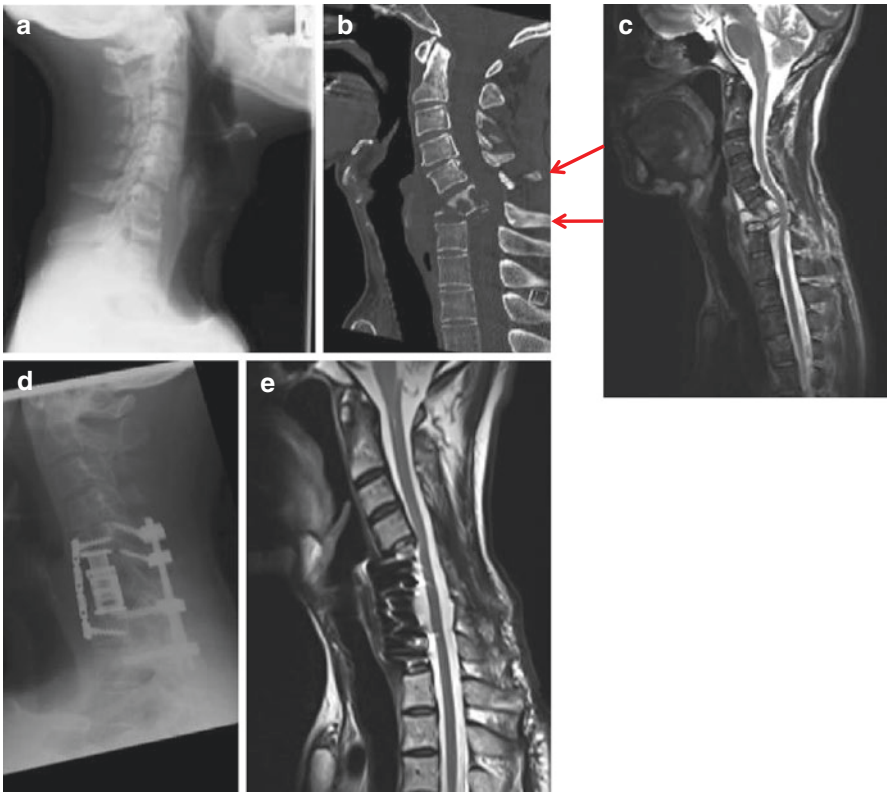

Fig. 11 48 year-old man with 9 months of neck pain who had initially presented to his emergency department 4 months previously with the same neck pain (**a**) he was discharged with a diagnosis of degenerate spondylosis. Represented with worsened neck pain CT (**b**) and MRI (**c**) show complete destruction of C7 vertebral body and partial destruction of C6 (note the two red arrows pointing to the spinous processes of C6 and C7) with retrolisthesis and canal compromise without neurological deficit. He was initially fitted with a HALO brace and started on TB Chemotherapy. After 2 weeks of treatment when it was felt that the disease burden had been reduced he underwent an anterior and posterior fixation where the deformity was corrected. [Post OP x ray (**d**) and MRI (**e**)]

often be the key to a successful pain-free recovery and should be discussed from the initiation of treatment.

At least half of patients with spinal disease can be expected to make a complete recovery, with or without intermittent back pain. Others may be left with long term neurological sequelae such as foot drop, bladder instability, radicular pain or paraesthesia. At worse a very small percentage of patients may be left with either paraplegia or tetraplegia as a result of TB infection. Patients with long bone and joint TB can be left with bony deformities, limitation of movements and chronic pain.

Patients with long bone and joint TB can be left with bony deformities and limitation of movements; joint infection may lead to bony destruction and deformity

and which may require debridement, joint replacement or reconstruction in the future, which are general recommended once TB treatment has been completed. However, surgery can take place if necessary whilst the patient is on treatment.

Some patients continue to require multidisciplinary care with neurorehabilitation, pain specialists, physiotherapy, occupational therapy and spinal or orthopaedic specialists.

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Tuberculosis of the Central Nervous System

Hanif Esmail and Graham S. Cooke

Epidemiology

Tuberculosis (TB) disease of the central nervous system (CNS) is estimated to affect approximately 100,000 people each year, representing only 1% of the total number of TB cases worldwide [1]. However, CNS disease has the most unfavourable outcome resulting in death or severe disability in 50%. Even in high resource settings, such as the United Kingdom, mortality is approximately 10% [2]. The two main manifestations of CNS TB are TB meningitis and tuberculomas, space occupying lesions within the brain parenchyma or spinal cord. CNS disease can occur as an isolated manifestation of extra-pulmonary disease or associated with disseminated or miliary disease. As the latter is more common in children under 5 years and immunocompromised adults, particularly with advanced HIV infection, so too is TB meningitis.

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Pathogenesis

The pathogenesis of TB meningitis is well understood, largely from the detailed histopathological studies of Arnold Rich and Howard McCordock in the 1930s [3]. During the initial dissemination of bacilli (prior to the development of an effective acquired immune response) or as a part of disseminated miliary disease, small tuberculous granuloma termed Rich foci may emerge within the brain parenchyma, spinal cord or meninges following a vascular distribution. Rich foci that are superficially located within subpial or subependymal regions and subsequently progress, may extend into the subarachnoid space or ventricles resulting in meningitis. Foci located deeper within the brain parenchyma that progress, may develop into space occupying tuberculoma or abscesses [3, 4].

The inflammatory response accompanying meningeal involvement, results in the development of a dense, proteinatious, cellular exudate typically accumulating over the basal surface of the brain and the basal interpeduncular and supraseller cisterns, due to cerebro-spinal fluid (CSF) flow patterns. This thick exudate may obstruct the CSF flow resulting in hydrocephalus and raised intercranial pressure. In addition, it can coat blood vessels of the vertebrobasilar system and circle of Willis at the base of the brain with the inflammation resulting in vasculitis which may lead to ischaemia, infarction and stroke like syndromes [5].

Clinical Features

TB meningitis (TBM) in adults usually present sub-acutely, with symptoms usually developing over greater than 5 days. Typical symptoms include, low-grade fever (60–95%), headache (50–80%) and neck stiffness (40–80%) which may be accompanied by vomiting (30–60%). Anorexia or weight loss is present in 60–80%. Confusion or a reduced Glasgow come score is present in 30–60%. Cranial nerve palsies, as a result of direct involvement as cranial nerves as they exit the brainstem within the inflammatory exudate or intercranial pressure, occur in 30–50% with VI, VII and III nerves being most commonly involved. Other focal neurology such as hemiparesis occurs either as a results if stroke-like symptoms resulting from vasculitis or mass effect from tuberculoma and are present in 10–20%. Seizures occur uncommonly in adults and as part of presentation in 5% [5, 6]. Patient co-infected with HIV presenting with TBM frequently have disseminated disease, however their neurological presentation is not significantly different [7]. CD4 count at presentation is typically <150/mm^3. In children the pace of disease is frequently more accelerated, seizures are more common occurring in up to 50% and headache may be less prominent.

Metabolic complications of TBM are also common in adults and children with hyponatraemia occurring in 50% of cases. Hyponatraemia is usually accompanied

by hypovolaemia and is attributed to cerebral salt wasting or a hyponatraemic natriuretic syndrome, the mechanism for which is incompletely understood. A syndrome of inappropriate ADH secretion (SIADH) however may also be present in some individuals [8].

Patients with CNS TB presenting with meningitis, frequently also have tuberculoma identified by subsequent imaging. However, in patients with isolated CNS tuberculoma, clinical presentation will depend on their anatomical location, size and number. Symptoms are similar to other causes of space occupying lesion with headache, focal neurology and seizures being common. Constitutional symptoms such as fever and weight loss may also be present but are often minimal.

Prognosis

Overall prognosis and risk of death relates to conscious level which largely reflects the presence of hydrocephalus or cerebral vasculitis. The modified British Medical Research Council (MRC) criteria, initially developed for use in trials, remain a simple and useful clinical score classifying patients into three grades. Grade I patients are alert with a Glasgow Coma Score (GCS) of 15 and no focal neurology. They have a mortality of 15–20% (though this will be less in high resource settings). Those in Grade II have focal neurology or a GCS of 10–14, with a mortality of 30–40%. Those in Grade III have GCS < 10 and a mortality of 50–75% (Table 1). Patients co-infected with HIV typically have a worse outcome [5, 9].

Diagnosis

The key challenge with diagnosis of TBM relates to the paucibacillary nature of disease. As a result, microbiological approaches to detect organisms are less sensitive than, for example, in adult pulmonary disease. Given the high mortality of the condition, empiric treatment is often initiated without or before microbiological conformation, hence, a thorough clinical assessment remains important. In particular, factors that might affect the pre-test probability of TBM should be carefully considered for example, recent exposure, travel to or migration from areas of high TB incidence, evidence of TB disease at other sites and HIV co-infection.

Table 1 Prognosis of TB meningitis by modified British MRC grade

Modified British MRC grade	Criteria	Mortality (%)
Grade I	GCS 15; no focal neurological signs	15–20
Grade II	GCS 11–14, or 15 with focal neurological signs	30–40
Grade III	GCS ≤10	50–75

CSF Examination

CSF examination remains the most important diagnostic intervention and should be undertaken promptly if TBM is suspected. Given the paucibacillary nature of disease it is crucial that a large volume (ideally 8–10 mL) is taken for microbiological evaluation as bacillary load in the CSF rarely exceeds 100–1000 colony forming units (CFU)/mL [1, 10]. The opening pressure is typically raised and will be over 25 cm H_2O in 50% of cases [6]. The CSF is usually clear. Older literature suggests a spiders web coagulum, due to fibrin fibres, may be visible within the CSF but this is rarely seen and not specific to TBM. The CSF white cell count is usually elevated with a lymphocyte predominance. CSF protein and lactate concentration can be markedly raised and the CSF:serum glucose usually <50% (Table 2). However, no specific cut-off can be used to rule-in or rule-out the disease. A number of clinical scoring systems have been developed using features of patient demographics, clinical presentation, initial blood tests and CSF cell count [6]. However, these clinical scores perform poorly outside the settings in which they were derived and shouldn't be used in isolation to initiate or withhold treatment.

A number of microbiological investigation can be undertaken to help confirm the diagnosis. Microscopy for acid fast bacilli by Ziehl Neelsen (ZN) staining generally has a poor sensitivity, 10–20%, as direct visualisation is unlikely if the bacillary concentration if less than 10,000 CFU/mL. As sensitivity is dependent on concentration, when large volumes of CSF (>10 mL) are concentrated by centrifugation prior to microscopy, sensitivity can be increased to 50%. The experience of the microscopist and duration of time spent reviewing the slide have also be shown to improve sensitivity [1].

Culturing the CSF in liquid media remains the gold standard investigation, however it is rarely positive prior to 10 days incubation and may take as long as 6 weeks. The limit of detection is approximately 10 bacterial colonies/mL but sensitivity remains around 80% against a clinical diagnosis of TBM, hence a negative culture does not completely rule out the diagnosis [1].

Table 2 Comparison of CSF findings in TB, bacterial, viral and cryptococcal meningitis

CSF feature	Normal	TB meningitis	Bacterial meningitis	Viral meningitis	Cryptococcal meningitis
Opening pressure	<20 cmH_2O	⇑	⇑	Normal	⇑⇑
Appearance	Clear	Clear/cloudy	Turbid	Clear	Clear/cloudy
CSF WCC	<5 cells/mm^3	⇑ (lymph predom)	⇑⇑ (neut predom)	⇑ (lymph predom)	⇑ (lymph predom)
CSF protein	0.15–0.45 g/L	⇑⇑	⇑⇑	⇑	⇑
CSF lactate	1–2.4 mmol/L	⇑	⇑⇑	Normal	⇑
CSF glucose CSF:serum	>0.6	⇓⇓	⇓⇓	Normal	⇓

The Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) is a rapid, automated, nucleic acid amplification test (NAAT) principally developed for the initial diagnosis of pulmonary TB from sputum and evaluation of rifampicin resistance. Sample processing is minimal with results available within 2–3 h, a similar timeframe as smear microscopy. It has subsequently be validated and approved for use in other sample types such as CSF [11]. The limit of detection of the standard Xpert assay is approximately 114 CFU/mL and in comparison to CSF culture as gold standard sensitivity and specificity are 80% and 99% respectively [11]. Recently, the Xpert MTB RIF Ultra assay has been developed incorporating two different multi-copy amplification targets (IS6110 and IS1081) and a larger DNA reaction chamber which has further reduced limit of detection to 16 CFU/mL and further increased the sensitivity to 95% [12]. CSF interferon gamma release assay and adenosine deaminase do not play a useful role clinically in the diagnosis of TBM owing to poor specificity [1].

Diagnostic Imaging

Imaging of brain, spine and lung play an important role in the assessment of patients with TBM. Gadolinium enhanced MRI brain has greater sensitivity for abnormalities over contrast CT, however 15% of those in early stages of TBM (MRC grade 1) will still have a normal MRI [1]. Common findings on brain imaging are basal meningeal enhancement, hydrocephalus, infarction (with diffusion weighted MRI increasing sensitivity to detect early areas of ischaemia) and tuberculoma. Patients with TBM frequently have spinal cord lesions which are easy missed unless an MRI whole spine is undertaken. A chest radiograph of all patients with suspected TBM should be undertaken to assess for evidence of pulmonary or miliary disease, which may be helpful both diagnostically and have implication for infection control and patient isolation. All those with abnormal chest imaging should have sputum investigation attempted though the CXR is normal in 50% [1]. Further cross sectional imaging of the chest abdomen and pelvis may also be useful to identify sites of extra CNS disease and enable sampling elsewhere to confirm or increase the yield of microbiological testing.

Differential Diagnosis

Other infectious causes of a subacute lymphocytic meningitis include cryptococcus (the most important differential in HIV infected individuals), viral infection, Lyme disease, syphillis, partially treated bacterial meningitis, other fungal infection and brucella (Table 3). Investigation should be guided by exposure history and risk factors, though all patients should ideally have CSF cryptococcal antigen (CRAG) testing, viral PCR and routine microscopy, culture and sensitivity (MC&S) as a minimum.

Table 3 Differential diagnosis for subacute lymphocytic meningitis with supportive features highlighted

Condition	Supportive features
TB	History of TB contact, history of living in a high TB burden country, HIV co-infection
Cryptococcal	Very high opening pressure, HIV co-infection (low CD4 count), positive cryptococcal antigen tests (CRAG)
Syphilis	Risk factors of acquisition, HIV co-infection, positive syphilis serology
Lyme	History of tick bite or erythema chronicum migrans, 7th nerve palsy, positive Lyme serology
Partially treated bacterial	Acute presentation with recent antibiotic use
Brucella	Ingestion of unpasteurised milk/cheese or uncooked animal product from a Brucella endemic country

Drugs for Treatment of CNS Tuberculosis

The drugs recommended for treatment of CNS TB are often the same as for non-CNS TB (see Chap. 14 'TB Treatment and Complications'), although there are few high quality studies exploring alternative treatments and dosing. Many clinicians use higher doses than those recommended in guidelines, informed by an understanding of drug levels in the CSF. There is limited data that this benefits clinical outcomes but this is an area of active research.

First Line TB Drugs in the Treatment of TB Meningitis

Isoniazid is a key drug for treatment of CNS disease with good penetration of the blood brain barrier and bacteriocidal activity. It is arguably the most important of the first-line TB therapies in treating TB meningitis. Rifampicin, a key drug for treatment of non-CNS disease does not penetrate the CSF as well. There is some evidence that higher doses of intravenous therapy (and higher CSF levels) are associated with improvement mortality [13] but in a much larger study comparing 15/mg/kg orally (with levofloxacin) to 10 mg/kg, no benefit on mortality was seen [14].

Ethambutol does not cross the blood brain barrier well, even when it is inflamed. It is likely to have minimal activity in the setting of sensitive disease but is still recommended in some guidelines while the question of the best alternative "4th drug" to ethambutol remains debated. The respiratory fluoroquinolones (moxifloxacin or levofloxacin) are commonly used alternatives.

When second line TB treatment is used, either because of first line treatment toxicity and/or presence of drug resistance, it is important that the regimen chosen is considered with regard to CNS penetration. The principles of MDR treatment are discussed chapter "Therapeutic Drug Monitoring in Tuberculosis" but second line drugs that penetrate the CNS well include protionamide, amikacin and cycloserine (see Chap. 16 "Therapeutic Drug Monitoring in Tuberculosis"). Bedaquiline is thought

to have poor CNS penetration and there is little data for delamanid. Newer methods of measuring drug penetration may help to define dosing more accurately in future.

Duration of Treatment for TB Meningitis

Although some guidelines suggest 9 months of therapy may be sufficient for TB meningitis [15], 12 months is usually recommended; 2 months induction with at least four drugs (RHZE/RHZM) and 10 months of maintenance with RH. As with many recommendations on duration of therapy, these need to be interpreted in the context of an individual patient, their response to treatment, toxicity and adherence. There is rarely any role for imaging in decision on duration of treatment for TBM, but repeated imaging may be helpful in patients whose symptoms persist or worsen.

Adjunctive Therapy for CNS Tuberculosis

There is a strong evidence base to support the use of adjunctive steroids in patients with TB meningitis, regardless of Grade of disease (see above). Randomized controlled trials [9, 16–19] found improvement in end-points including mortality, death or severe disability, and disease relapse when patients were treated with steroids in addition to anti-TB treatment.

Recommended adjunctive therapy is dexamethasone at an initial dose of 0.3–0.4 mg/kg/day, in divided doses and tapered over 6–8 weeks and adjusted according to interactions with rifampicin. The addition of steroids can reduce the incidence of significant hepatotoxicity resulting from TB treatment and this may be important in avoiding interruptions to therapy and sequential reintroduction of drugs. Sub-group analysis of patients with HIV/TBM suggests a possible benefit from steroids in this group and this is being evaluated in trials.

It should be remembered when treating patients that there may be long-term consequences of steroids use (particularly on increased risk of infection, diabetes and bone density). Alternative immunomodulators used in practice have included thalidomide and anti-TNF antibodies, though the evidence to support their use is limited. Given that ischaemic stroke appears to be an important cause of long term disability in some patients with TBM, there is emerging interest in the potential role of high dose aspirin [20], but it is not yet a recommended therapy.

Additional Supportive Measures

Severe sequelae of TBM in any patient are likely to be multifactorial, and good supportive management is essential. Raised intracranial pressure is commonly recognized and may be due to mass effect, obstruction to CSF flow and/or oedema. Poor

oxygenation of the brain is increasingly thought to be important and hyponatraemia is common (see above) [21].

Hydrocephalus, usually communicating, is common in patients with severe TBM as a consequence of decreased CSF reabsorption in the setting of inflammation. There is a little high quality evidence to inform management but medical management with acetazolamide and sequential lumbar puncture is often recommended. Drain insertion (or shunt) is generally reserved for those with obstructive hydrocephalus or those who are deteriorating clinically.

Management of Cerebral Tuberculomas

In general, the choice and duration of therapy for cerebral tuberculomas is the same as for meningitis, with similar considerations of local concentration and toxicity. Cerebral tuberculoma may be isolated or multiple and may co-exist with TB meningitis. Tuberculoma can become more prominent as part of "paradoxical" reactions in approximately a third of patients. Despite adequate TB therapy, inflammation causes enlargement and/or oedema around existing lesions that may not have been clinically detectable [22]. In such cases prolonged courses of immunomodulation may be required, but the evidence base is limited by comparison to TB meningitis. Prednisolone is the most commonly used treatment, but there are reports of thalidomide and infliximab being effective if alternative agents are required.

HIV Treatment in the Setting of TBM and Tuberculomas

In patients with advanced HIV and proven (or presumptive) tuberculous meningitis, other pathogens should be actively sought as more than one may be present (particularly cryptococcal meningitis).

Early initiation of HIV treatment in the setting of TB is recognized as important factor for preventing morbidity and mortality from tuberculosis. However, recommendations for the timing of HIV treatment in patients with CNS tuberculosis are more cautious compared to non-CNS tuberculosis. The main concern with initiating HIV treatment is the development of IRIS (see chapter "TB/HIV"). In general, IRIS is often mild and self-limiting. However, when IRIS occurs in the brain, small areas of oedema and/or inflammation that result can have profound clinical consequences, depending on anatomical location of disease.

In a placebo controlled trial comparing early (immediate on trial entry) versus late (2 months after randomization) HIV treatment initiation in 253 patients with TBM, immediate HIV treatment did not improve 9 month mortality or new AIDS events with more severe adverse events in the immediate initiation arm [23].

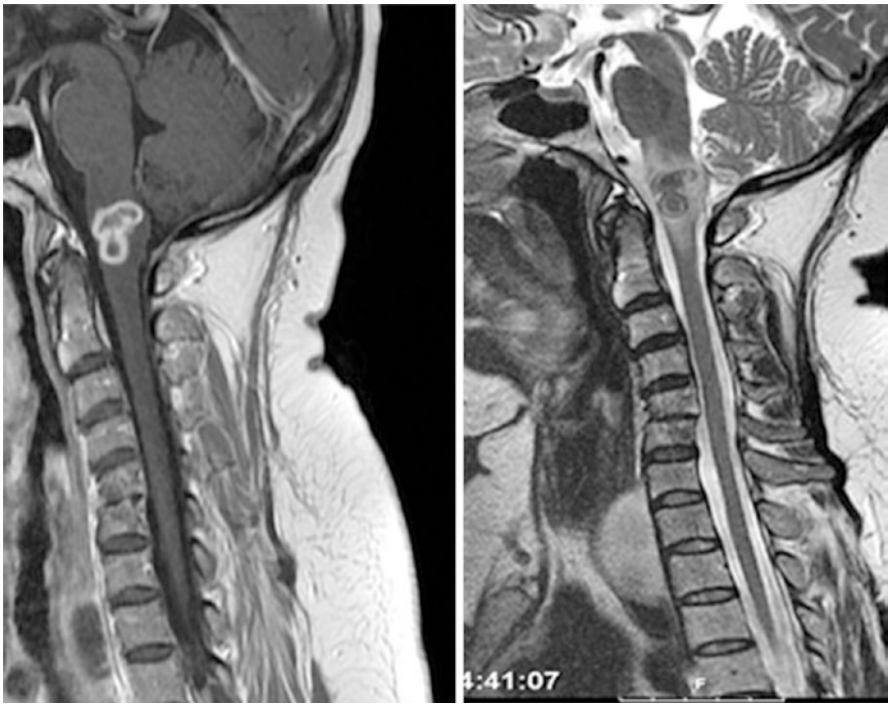
HIV treatment should usually be started within 2 months of TB therapy in those with CNS tuberculosis. The choice of treatment for HIV does not differ from treatment that would be given for non-CNS TB, other than consideration needs to be given to likely drug-drug interactions.

Case Vignette

A 35 year old male, originally from Uganda, presented with tuberculous meningitis and was newly diagnosed with HIV (CD4 count 46 cells/mm^3, HIV plasma viral load 110,000 copies/mL). Treatment was initiated with standard doses of RHZE but transaminitis led to isoniazid being replaced with moxifloxacin. HIV treatment was initiated after 6 weeks of TB therapy and he was transferred to out-patient services in a district hospital. For the continuation phase he remained on rifampicin and ethambutol for tuberculosis. Despite good adherence he represented 2 months later with smear (and culture) positive CSF and obstructive hydrocephalus requiring shunting. He had significant nursing needs and was transferred to nursing facility for long-term care. The case highlights the importance of achieving good CSF levels of therapy throughout treatment.

Images

Cerebral tuberculoma with significant oedema in the midbrain seen with MRI T1 (left) and T2 (right) imaging. The patient had significant limitation in movement from increased tone in the legs and required prolonged TB therapy (18 months) with further adjuvant steroid therapy for over 2 years until symptoms eventually resolved.



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Tuberculosis in Renal Disease

Heather Milburn

Introduction

Tuberculosis presents a number of specific challenges in patients with chronic kidney disease (CKD), both in the diagnosis of latent infection (LTBI) and active disease and also in their management. Patients are often complex and a standard approach may need some adjustment. Patients with CKD are at increased risk of active tuberculosis (TB) compared with those with normal renal function, due to immunodeficiency associated with uraemia, co-existing conditions and the drugs used to prevent graft rejection following transplantation [1]. Furthermore, ethnic minorities from countries with a high incidence of TB are at increased risk of not only TB but also CKD [2].

What Do We Mean by CKD?

CKD is the term now used by most renal physicians to describe all levels of renal disease and is categorised into five stages according to underlying creatinine clearance, renal replacement therapy (RRT) and transplantation (Table 1).

Stages 1 and 2 would not be considered on their own to increase the risk of infection; figures are not yet available for Stage 3. Stages 4 and 5, RRT and transplant are, however, considered important for an increased risk of TB.

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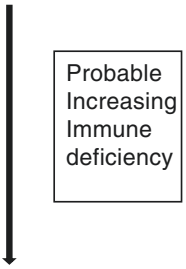
Table 1 Stages of renal disease (Chronic Kidney Disease)

CKD:	
Stage 1 normal function but structural abnormality	
Stage 2 Creatinine Clearance 60-90mls/min;	
Stage 3 Creatinine Clearance 30-60mls/min;	
Stage 4 Creatinine Clearance 15-30mls/min;	
Stage 5 Creatinine Clearance <15mls/min.	
Renal Replacement Therapy:	
Continuous Peritoneal Dialysis	
Haemodialysis	
Transplant	



Incidence & Prevalence of LTBI & active TB in CKD

Figures for the incidence and prevalence of LTBI and active TB disease in CKD patients vary depending on the populations being considered and degree of CKD. There is very little work on evidence of LTBI in varying stages of CKD and renal replacement therapy (RRT). One study from a tertiary referral centre in Taiwan used the *QuantiFERON-TB Gold In-tube* (QFT) interferon-γ release assay (IGRA) to determine LTBI [3], and found that 11% of patients with CKD stages 4 and 5 and not receiving RRT had a positive IGRA compared with 25% of patients receiving haemodialysis (HD) ($p = 0.015$). Not surprisingly, they also found that independent predictors of a positive IGRA included evidence of previous TB on chest radiograph (OR 2.90[CI 1.45–5.83]). Further predictors of LTBI as measured by a positive QFT were older age (OR 1.03[1.01–1.04] per year increment); increased serum albumin (OR 2.59[1.63–4.11] per 1 g/dl increment), and the need for dialysis (OR 2.47[1.02–5.95]). Indeterminate results were associated with malignancy (OR 4.91[1.84–13.10] and low serum albumin (OR 0.22[0.10–0.51] per 1 g/dl decrease). Fonseca and colleagues [2013] [4] in Brazil used up to three tuberculin skin tests in dialysis patients to demonstrate a mean annual risk of infection of 1.19%, which was similar to that reported for the general population.

Many studies looking at rates of active disease have been from countries with high background rates of infection and disease [5–9]. The cumulative incidence of TB disease over a 16 year period in recipients of a renal transplant in Brazil was 1.32%; TB occurred at any time following transplantation (median time 18.8[IQR 7.2–60] months) and was influenced by the immunosuppressive regimen used [10]. A recent study from the UK showed that patients receiving haemodialysis (HD) had a cumulative incidence of TB 85 times that of the background rate; this was 37 times the background rate following successful transplantation [11]. Although the relative risk of

active disease in patients receiving peritoneal dialysis (CAPD) tends to be less than that in HD patients, CAPD patients appear to be at increased risk of peritoneal TB in particular [5, 11, 12, 13]. A meta-analysis of published studies showed a median incidence of active TB of 26.6 (range 1.3–52.0) per 1000 population in patients undergoing HD and 5.1 (no range given) in those following organ transplantation [14]. It can be seen that there is plenty of evidence from around the world that these patients are at increased risk of TB, and diagnosis of both active TB and LTBI is crucial in patients with CKD, and particularly those receiving RRT or renal transplant.

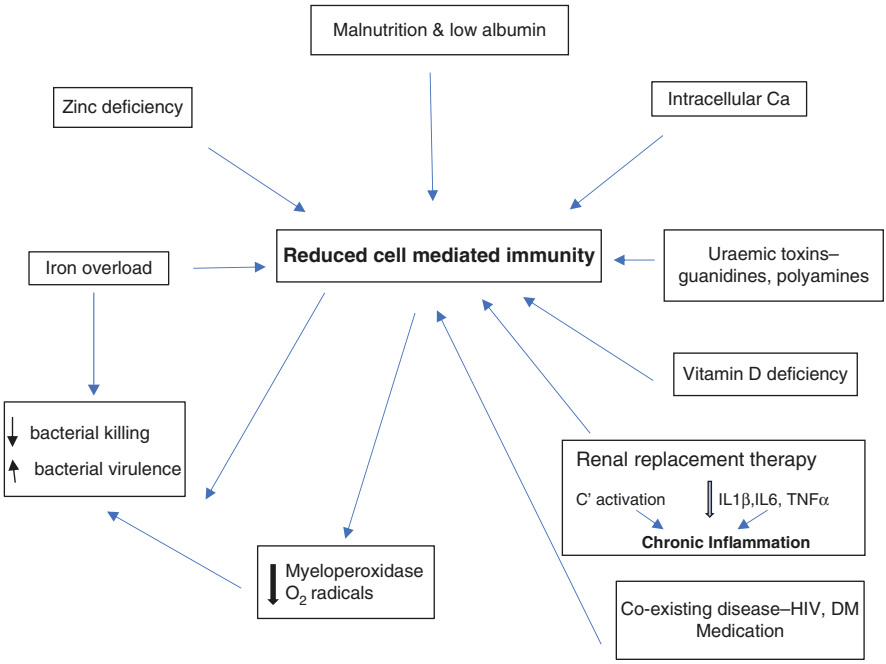
Reasons for Susceptibility to Infection and Disease

Many of these patients have co-existing conditions which contribute to impaired immunity to infections, and these are themselves important for the development of renal disease, such as HIV and diabetes mellitus. Immunosuppressive therapy is used to control underlying disease and also to suppress graft rejection following transplantation. In addition, uraemia is itself an acquired immunodeficiency state, with functional abnormalities found in neutrophils, lymphocytes, monocytes and natural killer cells, as well as defective chemotaxis, cell adherence and phagocytosis. These changes will all contribute to impaired cell mediated immunity [15–17]. Haemodialysis can also exacerbate these abnormalities and result in chronic inflammation by complement activation and upsetting the balance between regulatory and inflammatory cytokine production. Some older studies have shown specific effects depending on the type of HD membrane used [18]. Most of these patients also suffer from deficiency of vitamin D, which has been found to be important for immune function [19, 20]. Furthermore, iron overload is common in renal patients and this is associated with increased susceptibility to TB, as well as contributing to successful mycobacterial growth and virulence [21, 22]. Figure 1 is a schematic summary of these complex contributions to increased susceptibility to TB infection and disease in these patients.

Patients undergoing transplantation who already have LTBI are likely to reactivate the disease when starting additional immunosuppressive therapy to prevent graft rejection, and disease can also be transferred with the allograft itself, albeit rarely [23].

Screening

Where possible we should aim to reduce the risk of active disease by effective screening and management of latent infection. There is, however, no perfect screening tool available for use in these patients. Both the 2010 British Thoracic Society (BTS) Guidelines for the diagnosis and management of TB and LTBI in CKD [24] and the 2016 UK NICE guidelines [25] for the diagnosis and management of TB, suggest that all patients with renal disease need a risk assessment based on risk



Abbreviations: Ca calcium; O_2 oxygen; DM diabetes mellitus; HIV human immunodeficiency virus; C' complement; IL1β Interleukin-1β; IL6 interleukin-6; TNFα tumour necrosis factor-α

Fig. 1 Factors contributing to reduced cell mediated immunity and resulting increased susceptibility to infection in uraemia

factors for TB infection, including time spent in a country with medium-high background rates of TB and contact with an infected person, as well as the presence and severity of immunocompromise. An assessment for active disease should also be made, and these patients should have a baseline chest radiograph at presentation. This will demonstrate any evidence of previous disease and will also be a useful reference in times of future respiratory infections. Specific screening should be with an IGRA test with or without the tuberculin skin test (TST).

Tuberculin Skin Test (TST)

The immunodeficiency associated with uraemia results in skin anergy in up to 50% of these patients, making the TST have low sensitivity in this group [24]. Therefore, a negative test cannot be assumed to be a true negative, while a positive test should prompt further investigation. It is therefore usually more useful to use the TST with an IGRA. In the meta-analysis by Getahun et al. (2015) [14], the median percentage

prevalence of LTBI as determined by a positive TST was 21.9% (range 2.6–42.1) in HD patients compared with figures for QFT and the *TSpot-TB* (33.4% [17.4–44.2] and 43.6% [23.3–58.2]) respectively.

Interferon Gamma Release Assays (IGRA)

Although the IGRA response is also reduced in immunocompromised patients when compared with immunocompetent controls, it remains higher than the TST in CKD patients [26]. Both the commercially available IGRAs (*TSpot-TB,* Oxford Diagnostic Laboratories, UK; QFT, Qiagen, Netherlands) have increased specificity than the TST with no cross reactivity with the BCG and the majority of non-tuberculous mycobacteria. In a recent study of 95 patients receiving HD, the QFT was reported as having 100% sensitivity and 62% specificity for active TB [27]. The IGRAs are not, however, usually used for diagnosis of active disease but as evidence of LTBI, and a positive result is presumed to identify those with evidence of likely progression to active TB. Most studies, however, have been in immunocompetent patients as part of contact tracing.

In an earlier meta-analysis of studies investigating the positive (PPV) and negative (NPV) predictive values of the IGRAs and TST in various at risk groups, the pooled PPV for progression was 6.8% (CI 5,6–8.3%) and 2.4% (CI 1.9–2.9%) for the IGRAs and TST respectively [28]. The NPVs for both IGRAs and the TST were > 99% with narrow CIs. One study in renal transplant patients reported that 5.6% of these patients with a positive IGRA result developed active disease if left untreated [29].

A large European study compared both commercially available IGRA tests together with the TST in five separate groups of immunocompromised patients and a group of immunocompetent controls [30]. These groups included 270 patients with various stages of CKD and 197 patients with mixed organ transplants. The frequency of a positive test result in CKD patients was 25.3–30.6%, but only 9–20.0% among transplant patients. These results probably reflect the multifactorial nature of immunodeficiency which is not purely T-cell mediated in CKD, whereas drug-induced suppression of T-cell function occurs following transplantation [23, 31]. There is also the very small possibility that some patients had converted their response following chemoprophylaxis for LTBI at the time of transplant (a frequent practice in renal units), although once a patient has had active TB or LTBI with a positive IGRA/TST, these tests frequently do not return to normal with treatment, and we have no evidence when, if ever, they do [32]. High levels of indeterminate IGRA results were found in this collection of immunocompromised patients (up to 20%), with the highest rates found in those considered to be most immunodeficient (including transplant recipients) and lowest rates found in CKD patients. These results together suggest that immunodiagnostic assays are more adversely affected the greater the underlying immunodeficiency.

It is currently unclear which test is preferable for immunodiagnostic testing. There is higher between-test agreement between IGRAs than between either IGRA and the TST, and IGRAs also had a higher rate of positivity and were more strongly associated with *M. tuberculosis* exposure [30]. The evidence suggests that in immunocompromised patients, results from two or three positive assays are generally better associated with a greater likelihood of exposure to TB, whereas only one positive test was less likely to be linked to exposure variables [30]. This study also demonstrated that neither of the IGRAs nor the TST could adequately predict those at risk of later developing TB. Positive results should, however, prompt further investigation, while negative results cannot be assumed to be a true negative. The advice following indeterminate results is generally to repeat the test and/or add another.

When and How to Screen?

Which CKD patients should we be screening for LTBI and active disease? It is likely that not all patients with CKD have the same level of immunodeficiency, but that those with stages 4/5 or on RRT are at greater risk of infection than those with Stages 1–3 (Table 1). There do not appear to be any studies examining the performance of the different screening tests in different stages of CKD. There is, however, evidence of a significantly increased risk of active disease in patients on HD [11]. Consideration should be given to screening HD patients originating from countries with a high background risk of active disease as well as those with a clear history of contact.

Following transplantation, it is accepted that patients are at increased risk of activating previous infection [23, 25], and pre-transplant screening is recommended by both the European TB Research Network (TBNET) [23] and NICE [25]. Unfortunately, there does not appear to be any desire in renal units to screen all those on the transplant list, for example, as not all of these patients will necessarily proceed to transplant (M. Ostermann, personal communication). This has led to many renal units giving isoniazid chemoprophylaxis to all patients following transplant, whatever their likely risk of LTBI. It is our own experience that this is not always effective, however, as any suggestion of side effects (eg a marginal rise in liver enzymes) often results in discontinuation of isoniazid with no later introduction or use of an alternative, resulting in cases of significant active disease [33]. Furthermore, a study from London showed the highest rates of active TB were found in HD patients, suggesting this group could benefit from screening, whether or not they then proceed to transplant [11]. Also, it is usually clinically easier to treat patients for LTBI prior to transplant as there is less likelihood of interaction with immunosuppressive medication. Despite published guidelines from the UK and Europe [23, 25] a recent survey of UK renal units showed that only one third are acting in accordance with the latest guidance, screening with IGRAs is rarely used,

Table 2 Screening for LTBI Summary

Screening in CKD:
Check history of contact, previous TB, LTBI and treatment received.
Check chest radiograph with earlier X-rays.
Use IGRA with or without TST, particularly in at risk patients without prior disease.
A negative test cannot be assumed to be a true negative; do further investigations including ruling out active disease.
A positive test should result in further investigation in patients without a prior history of active or latent disease; rule out active disease.
Indeterminate results may be frequent especially in more severely immunocompromised patients; repeat test and/or add another.
Consider screening patients on RRT.
Consider screening pre-transplant.
There is no perfect screening test; the greater the immunosuppression, the less likely any test can currently give a wholly reliable result.
A positive IGRA with or without a TST is usually sufficient to commence chemoprophylaxis.

and dosing and length of treatment for LTBI was incorrect in nearly 50% of cases [34].

As detailed above, there are limitations to all the screening tests currently available, particularly in immunocompromised patients, and difficulties in the clinical interpretation of IGRAs have been highlighted by numerous studies. A more detailed review of IGRAs and further developments are found in Chap. 13 'The Tuberculin Skin Test and the IFN-γ Release Assays'. At the time of writing there is, however, no data on their performance in CKD or transplant patients.

A summary of screening is shown in Table 2.

Presentation of Active TB

Presentation of disease is often atypical and this can contribute to delay in diagnosis. There is a greater proportion of both extrapulmonary and disseminated disease, with miliary TB a well recognised complication [11, 35–38] (Fig. 2). Most patients present with fever but weight loss can be difficult to interpret in a patient with fluid imbalance. Cavities are rarely seen on chest radiograph, but lower lobe shadowing or multiple lobar involvement can often be found. Pleural effusions are fairly common in dialysis patients due to heart failure, uraemic pleuritis and hypoproteinaemia, so pleural TB can easily be missed. Levels of adenosine deaminase (ADA) in pleural fluid tend to be elevated in tuberculous effusions [39, 40], but unfortunately the activity and hence diagnostic usefulness of ADA, is reduced in uraemia and HD [41, 42]. Nucleic acid amplification tests for *M. tuberculosis* in pleural fluid have good specificity for the diagnosis of tuberculous pleuritis (96–98%) but poor and variable sensitivity (43–77%) [43]. Similarly, pericarditis, pericardial effusion and ascites are often dialysis related but abdominal TB is a frequent complication of

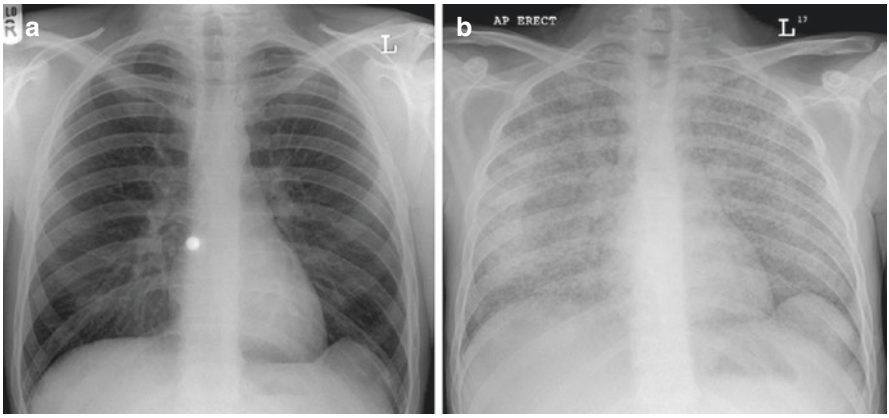


Fig. 2 Chest radiograph showing miliary TB presenting in a renal patient with a PUO not immediately obvious on original radiograph (**a**), apparent on chest radiograph after two weeks (**b**)

continuous ambulatory peritoneal dialysis (CAPD). While these patients are also subject to peritoneal infections with organisms other than *M. tuberculosis* leading to a cloudy dialysate, TB should always be considered when presented with a cloudy dialysate and appropriate samples sent.

Diagnosis of Active TB

All patients should be assessed for active disease by taking a detailed clinical history, including contact with TB and previous history of active TB or LTBI and whether these were treated, with what and for how long. Symptoms of cough, fever, weight loss, night sweats and lymphadenopathy should be investigated as with any patient. It must, however be remembered that 30–50% of CKD patients present with extra-pulmonary TB and symptoms may not always be classic. TB should always be considered in any patient presenting with a pyrexia of unknown origin (Fig. 2), and TB must always be in the differential of any CAPD patient presenting with abdominal infection [11, 12].

All CKD patients should have a chest radiograph as part of their original workup (whether or not they have chest related symptoms) as this will be helpful in showing evidence of previous disease, as well as being useful for comparison at a later date should the patient develop symptoms. Any new infiltrates should then prompt further investigation, which may include a CT scan, induced or spontaneous sputum specimens or fibreoptic bronchoscopy, as outlined in previous chapters. Further site-specific investigations should be considered based on symptoms. These might include abdominal ultrasound, CT or spinal MRI scans.

As in all patients with possible TB, every effort should be made to obtain samples for microscopy and culture, such as three early morning sputum specimens, induced sputum, bronchial lavage and biopsies. Intrathoracic lymphadenopathy can

be investigated using endobronchial ultrasound (EBUS) and biopsy. Involvement of extra-thoracic sites should be investigated by aspirated pus, fine needle aspiration biopsy (FNA) or tissue biopsy. These should be examined histologically for the presence of granulomata, which are suggestive of TB disease, stained for acid fast bacilli (AFBs), and sent for cultures. It is imperative that specimens are sent either in a plain pot or in normal saline and not in formalin as this will prevent culture of the organism [24, 25].

Management of LTBI

Unlike patients with normal renal function, there is an increased risk of side effects from chemoprophylaxis in patients with CKD, making any treatment challenging [11, 24]. This is not, however, a reason for reducing the dosage of drugs as this just reduces the efficacy of treatment as these drugs demonstrate concentration-dependent activity, and a reduced dosage could result in development of drug resistance [24]. With chemoprophylaxis, however, this should not be a problem and drug regimens are discussed in more detail in the following section.

One approach has been to treat all transplant patients with chemoprophylaxis, both to mitigate the high incidence of active TB found in HD and transplant recipients and the mixed evidence around IGRA testing in immunocompromised groups. This, however, presents two problems:

1. it fails to identify patients with active disease, and
2. chemoprophylaxis itself is not without risk.

Both isoniazid and rifampicin can cause drug induced hepatitis, and this may outweigh the risk of developing active disease in those at low risk and with no evidence of exposure or LTBI. Some centres do limit chemoprophylaxis to those at higher risk, but without a screening programme, some of those with no perceived risk may have LTBI which reactivates post-transplant. Unfortunately, in the UK there is still a marked variation in chemoprophylaxis policy between renal units, with no clear association with local TB incidence and a broad discrepancy in length of chemoprophylaxis, ranging from none to lifelong. Guidelines do not appear to have been followed and clinical practice in some units has failed to follow the evidence for appropriate chemoprophylaxis [34, 44].

Chemoprophylaxis

Both isoniazid and rifampicin are metabolised by the liver and poor renal function should not present a problem in the appropriate use of these drugs. Hepatic toxicity with both drugs can of course occur but should not present a greater problem in CKD [24]. Isoniazid can be associated with peripheral neuropathy and central neurological disturbance, and these effects seem to be increased in CKD patients,

although this is not common [45–49]. Ototoxicity has also been reported in patients receiving isoniazid plus other drugs, but excluding the aminoglycosides [50]. Patients with underlying diseases such as Alport's Syndrome and Wegener's granulomatosis may also rarely develop hearing loss due to axonal uraemic neuropathy [51] and increased susceptibility to ototoxins [52, 53]. It is therefore important that pyridoxine is added to any isoniazid containing regimen [24].

The three commonly used regimens are:

- 6 (or 9) months of isoniazid 300 mg daily plus pyridoxine [24, 45, 54];
- 3 months of isoniazid plus rifampicin based on weight plus pyridoxine [24, 54];
- 4 months of rifampicin alone [24, 54–56].

A review of the evidence for the relative efficacy of the shorter and longer isoniazid regimens is discussed in Myall and Milburn 2016 [57].

The regimen of four months of rifampicin alone appears to be better tolerated than isoniazid-containing regimens [54, 56]. There should be no problem with the use of rifampicin in CKD patients, including those on RRT, but post-transplant, most centres prefer to use isoniazid alone because of the interactions between the rifamycins and the immunosuppressive drugs necessary to prevent graft rejection. A recent review and meta-analysis, however, showed that rifampicin containing regimens for three months or more, even though shorter, were potentially more effective than isoniazid monotherapy [56, 58]. Twelve weeks of isoniazid plus rifapentine also had similar efficacy to 9H [59].

These large studies would support future screening of dialysis patients at risk and appropriate chemoprophylactic treatment, whether or not they then proceed to transplantation. It is generally clinically easier to use rifampicin containing regimens in patients not yet on immunosuppression to support a graft. Those who have completed chemoprophylaxis should have a reduced risk of active TB unless they are later re-infected. The reduced incidence of active disease found in recent studies in transplant patients compared with HD patients may well be the result of the sometimes indiscriminate use of chemoprophylaxis in all transplant recipients, although this is not without problems as outlined above [11, 25].

While it is not necessary to complete chemoprophylaxis prior to transplantation, all patients will require careful monitoring for both drug-drug interactions and drug toxicity.

Management of Active TB

Treating TB in renal patients should involve input from a TB specialist as these patients will need careful monitoring, and guidelines should be followed [24, 25]. Four drugs should be used in the first instance: rifampicin (R), isoniazid (H), pyrazinamide (Z), and either ethambutol (E) or moxifloxacin (M), with pyridoxine (p). This is assuming there is no suspicion of drug resistance. Generally CKD patients should be treated for six months, with two months of four drugs (RHZE/M + p) followed by four months of RH + p [24, 25]. One year of treatment is needed for

central nervous system TB as per guidelines (2RHZE/Mp, then 10RHp) [24, 25]. Drug resistance is covered in the BTS Guidelines Appendix 1, with emphasis on specialist management [24]. Further information on specialist drugs for resistant disease can be found in Chap. 15 'Multi-drug Resistant Tuberculosis Management'.

As with rifampicin and isoniazid, pyrazinamide is metabolised by the liver, although excretion of its metabolites may be impaired in CKD stages 4 and 5 and on HD. This will result in uric acid retention and gout. Pyrazinamide and its metabolites are significantly eliminated from the body by HD, with 45% appearing in the dialysate [60]. No data are available for CAPD. Ethambutol, however, is 80% renally excreted and accumulates in renal failure, as do the aminoglycosides. Moxifloxacin is often substituted for ethambutol in patients with CKD, on RRT or following transplantation, but can only be given as a daily dose and is not suitable for three times weekly regimens. Moxifloxacin is usually well tolerated but there is evidence for connective tissue disorders with the quinolones in general. Dysglycaemia may occur with gatifloxacin, and liver dysfunction and a long QT interval with moxifloxacin (reviewed by Mehlhorn and Brown) [61]. If ethambutol or the aminoglycosides are used, then monitoring of drug levels is essential [24, 25, 62] (Table 3).

Table 3 Recommended doses of first line drugs in chronic kidney disease for standard sensitive disease (adapted from British Thoracic Society Guidelines 2010) [24]

	CKD Stages 1–3	CKD Stages 4–5	Haemodialysis[a]	Post Renal Transplant[b]
Isoniazid[c] 6 months	300 mg daily	300 mg daily or 15 mg/kg max 900 mg 3x/week	300 mg daily or 15 mg/kg 3x/week max 900 mg 3x/week	300 mg daily
Rifampicin 6 months	<50 kg 450 mg daily ≥50 kg 600 mg daily	<50 kg 450 mg daily ≥50 kg 600 mg daily or < 50 kg 600 mg 3x/week ≥50 kg 900 mg 3x/week	<50 kg 450 mg daily ≥50 kg 600 mg daily or < 50 kg 600 mg 3x/week ≥50 kg 900 mg 3x/week	<50 kg 450 mg daily ≥50 kg 600 mg daily
Pyrazinamide[d] 2 months	<50 kg 1.5 g daily ≥50 kg 2.0 g daily	<50 kg 2 g 3x/week ≥50 kg 2.5 g 3x/week	<50 kg 2 g 3x/week ≥50 kg 2.5 g 3x/week	<50 kg 1.5 g daily ≥50 kg 2.0 g daily
Ethambutol[e,f] 2 months	15 mg/kg daily	15–25 mg/kg 3x/week plus TDM	15–25 mg/kg 3x/week plus TDM	15 mg/kg daily
Moxifloxacin[f] 2 months	400 mg daily	Not suitable for 3x/week	Not suitable for 3x/week	400 mg daily

[a]Haemodialysis – give medication immediately after dialysis
[b]Can give 3x/week regimen post transplant
[c]Always give with pyridoxine in renal disease
[d]Check uric acid levels and monitor for gout
[e]Check baseline colour vision and visual acuity and warn patients to report any changes in red/green discrimination or visual acuity. Check peak and trough drug levels (TDM)
[f]Can be discontinued if organism is found to be fully sensitive before two months

Special Considerations when Treating TB in CKD Patients

Patients with CKD should be managed by physicians experienced in the management of TB, because of the increased risk of side effects, possible drug accumulation, and risk of drug-drug interactions. The assistance of a renal pharmacist can also be helpful.

Physicians are always rightly concerned about toxicity of the TB drugs in renal patients because of accumulation. Lowering the dosages, however, is not the answer as these drugs exhibit concentration-dependent activity and dose reduction can lead to decreased efficacy and also the development of resistant disease. Rifampicin and isoniazid should be given at normal doses together with pyridoxine, but for patients with CKD stages 4 and 5 and those on RRT, *increasing the dose interval* of pyrazinamide and ethambutol to 3x weekly is recommended. Moxifloxacin can be substituted for ethambutol but is only suitable for daily dosing. If ethambutol is used, therapeutic drug monitoring (TDM) is needed [24, 25, 62].

Haemodialysis

There are two possibilities for dosing in patients on HD, both with positive and negative considerations:

1. TB medication given 4–6 hours before dialysis: advantage of reduced toxicity of pyrazinamide and ethambutol, but risk of premature drug removal. Also, this is unacceptably difficult in terms of timing for patients receiving morning dialysis.
2. TB medication given immediately after dialysis: avoids above disadvantages and potentially facilitates directly observed therapy (DOT) and therefore compliance. This is balanced against the risk of increased drug levels between dialysis sessions. Monitoring of peak (one hour post-dose) and trough (pre-dose) levels of ethambutol (and the aminoglycosides if used) is therefore mandatory.

Peritoneal Dialysis

Our current knowledge of the pharmacokinetics of TB drugs in CAPD is not comprehensive. One study showed that CAPD patients did not require adjustment of these drugs [63]. Our own experience is that only small amounts of rifampicin, however, are found in the dialysate due to its high molecular weight, lipid solubility and protein binding capacity, and levels of the other drugs also appear to be variable. Therefore, the dose of rifampicin may need to be increased in peritoneal TB, while levels of pyrazinamide, isoniazid and ethambutol need to be carefully monitored in these patients and doses adjusted accordingly [33]. Enlisting pharmaceutical expertise can be very helpful when managing these patients.

Post-Transplant

The rifamycins upregulate cytochrome P450, resulting in increased metabolism of many of the immunosuppressive drugs and possible loss of the graft [64]. This affects the efficacy of steroids and drugs such as mycophenylate mofetil, tacrolimus and ciclosporin used to suppress the rejection response and protect the graft. This problem can be reduced, however, by the use of TDM followed by appropriate adjustments in doses of immunosuppressants [24]. The dose of steroids should generally be doubled but the other drugs require careful TDM and adjustment until a therapeutic level is reached. Rifabutin can be used instead of rifampicin as it is a weaker inducer of cP450 so the interaction with the immunosuppressant drugs is much less, leading to its increasing use post-transplant [65] Using rifabutin in combination with the macrolides, however, increases the risk of uveitis [66]. Rifabutin may also induce neutropoenia [66–68]. A significant decrease in neutrophil count has been found after fourteen days of rifabutin monotherapy, and the incidence of neutropoenia ranged from 10–26% in a multicentre study looking at the interaction between rifabutin and azithromycin [65]. It is therefore recommended that the white cell count is monitored for one week after initiation of rifabutin therapy and thereafter at two to four weekly intervals [67].

Summary

Until all the problems with screening can be overcome, it is likely that CKD patients on RRT and those receiving transplants will continue to face an increased risk of both latent infection and active disease. There is no agreed protocol for when and how to screen for LTBI but evidence certainly presents a case for screening those CKD patients on RRT, whether or not they then proceed to transplant. Currently, however, screening is rarely undertaken, practice is variable and often does not follow published guidelines. At the very least, all patients should undergo a risk assessment for both levels of immunosuppression and risk of TB exposure together with a routine chest radiograph. Although there is still no perfect test for LTBI, there is, however, sufficient evidence that a positive test from either of the two commercially available IGRAs with or without the TST, is usually sufficient to commence chemoprophylaxis in this significantly immunocompromised group. It is crucial to exclude active disease in any patient with CKD and to treat it appropriately. Recognition of TB can be difficult in these patients, but TB should always be in the differential of any presenting infection and the correct specimens sent. Treatment of TB presents some unique difficulties in CKD patients, but with care and the sensible use of TDM, these can be overcome. Moxifloxacin can be used instead of ethambutol and rifabutin is a useful alternative to rifampicin post-transplant. Finally, doses of TB drugs must not be reduced, but the *dosing interval increased* in order to prevent drug accumulation.

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Tuberculosis in Children and Adolescents

Elizabeth Whittaker, Steven B. Welch, Jonathan Cohen, and James A. Seddon

Introduction

Children and adolescents have historically been ignored in the battle against the tuberculosis (TB) epidemic. Considered non-infectious and therefore not contributing to disease propagation, they were felt not to be a public health threat, rather an unfortunate consequence. However, attitudes have changed dramatically over the last decade with the recognition that children frequently do transmit *M. tuberculosis,* that they present a reservoir from which future cases will emerge and that paediatric TB contributes significantly to overall child mortality and morbidity [1].

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When exposed to an infectious case of tuberculosis (TB), contacts may breathe in droplet nuclei of *M. tuberculosis*. If the organisms overcome the physical barriers of the lung and the innate components of the immune system, they are likely to encounter macrophages in the terminal alveoli. If the adaptive elements of the immune system are found to be sensitized, as evidenced by a positive tuberculin skin test (TST) or interferon gamma release assay (IGRA), the contact is said to have TB infection. If immunological constraints are overcome and the mycobacteria proliferate, the contact will develop signs and symptoms of TB disease [2, 3].

Although, arbitrary in nature, for reporting and recording purposes, children are defined as those <15 years with adolescents those 10 to <20 years. Modelling studies suggest that currently 67 million children have TB infection [4] and the World Health Organization (WHO) estimates that one million of these children develop TB disease each year [5], of which 30,000 have multidrug-resistant (MDR)-TB (disease caused by organisms resistant to isoniazid and rifampicin) [4, 6]. It is estimated that an additional half a million adolescents aged 15 to <20 years develop TB annually [7].

The risk of progression from TB infection to TB disease, as well as the pattern of disease, is influenced by age at initial infection, as well as sex, nutrition and immunological status [8]. Young children are at high risk of disease progression, as well as rapid disease progression following infection. They tend to develop either more limited intra-thoracic lymph node disease or severe forms of disseminated disease, such as TB meningitis or miliary TB. Generally, they are not infectious. Risk falls to a nadir in the primary school age before rising again as children enter puberty, with the rise in girls starting earlier than boys. Adolescents typically have pleural effusions, parenchymal breakdown and cavities, often in the apical regions [9]. They are frequently infectious. Children with malnutrition are at increased risk of disease progression following infection [10], as are children living with any form of immunodeficiency, particularly human immunodeficiency virus (HIV) [11].

The aim of this chapter is to provide an oversight of TB in children and adolescents and to give practical advice on the approach to investigating and managing children and adolescents with TB infection and TB disease. It builds on the WHO childhood TB guidelines [12], the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) guidance [13] and the best available evidence.

Diagnosis

Children may be identified as contacts of a known case of TB, or they may present with symptoms, signs or investigation findings suggestive of TB disease. The diagnosis of TB in children requires the clinician to piece together different types of evidence. Diagnosis is straightforward in children with positive microbiology and

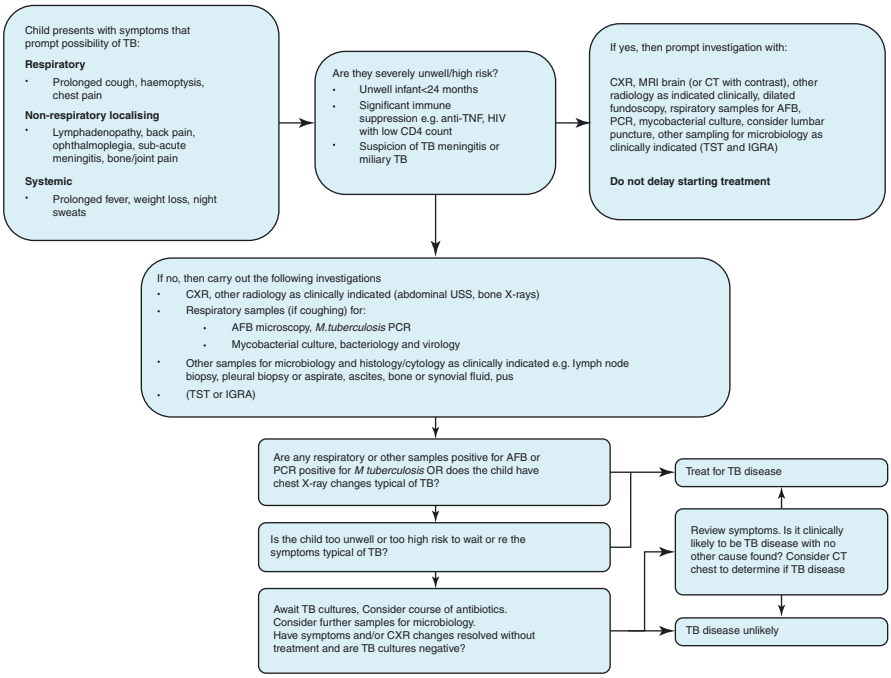

Fig. 1 A suggested algorithm for the investigation of children and adolescents with possible tuberculosis. *TB* tuberculosis; *TNF* tumour necrosis factor; *HIV* human immunodeficiency virus; *CD* cluster differential; *CXR* chest x-ray; *MRI* magnetic resonance imaging; *CT* computed tomography; *AFB* acid-fast bacilli; *TST* tuberculin skin test; *IGRA* interferon-gamma release assay; *USS* ultrasound scan; *PCR* polymerase chain reaction

typical clinical and radiological features, but for most children with TB this will not be the case. The history, examination, radiology, immune-based tests and microbiology (when positive) need to be combined to arrive at a diagnosis, like assembling pieces of a jigsaw. This is outlined in Fig. 1 with the strengths and weaknesses of different tests shown in Table 1.

Household Contacts

Children exposed in their household to infectious cases of TB are at high risk of TB disease; systematic reviews showing that 5–10% of TB-exposed children <15 years in high-prevalence countries have TB disease at the initial time of screening [14, 15]. A study from the UK showed that 12% of household contacts had prevalent disease [16]. Other non-household forms of exposure can also be high risk if the

child has had high intensity exposure, or exposure of long duration with an infectious TB case. In addition, about half of children exposed in their household have evidence of TB infection [14, 15], and without TB infection treatment they remain at high risk of progression to TB disease. The first step when screening a child contact is to evaluate them for evidence of TB disease based on history, examination and chest x-ray. Those children with TB disease often have early pathology and the diagnosis is easily missed, as symptoms and radiology may be subtle or non-specific, and microbiology confirmation rates are low. If TB disease is ruled out, an evaluation for TB infection then needs to be performed.

Table 1 Diagnostic options in children suspected of tuberculosis, with summary of advantages and disadvantages

Diagnostic Approach		Advantages	Disadvantages
Clinical	History	Easy to undertake and only cost associated is time of clinical staff	Requires training. Poor sensitivity and specificity
	Examination	Easy to undertake and only cost associated is time of clinical staff	Requires training and appropriate environment. Poor sensitivity and specificity
	Scoring systems	Allows risk assessment without requiring clinical expertise	Not validated and poor sensitivity and specificity
Radiology	CXRs	Relatively inexpensive and available, low radiation	Often of poor quality and few features pathognomonic for TB. Interpretation highly variable
	Computed Tomography	Demonstrates intrathoracic lymph nodes with greater clarity than CXR	Expensive, not widely available, large radiation dose
	Magnetic Resonance Imaging	No radiation, excellent definition for soft tissues	Very expensive, very uncommonly available, often requires general anaesthetics in young children
	18F-FDG positron emission tomography/ computed tomography	Provides insight into location and metabolic activity of lesions	Very high radiation dose, rarely available
	Ultrasound scan	No radiation, portable, good for visualisation of fluid and consolidation	Poor visualisation through air-filled structures, requires training, subjective

Table 1 (continued)

Diagnostic Approach		Advantages	Disadvantages
Microbiology—Sampling	Expectorated Sputum	Easy and cheap, acceptable	Not possible in children under about 6 years, infection control risk needs to be considered
	Gastric Aspirate	Easy and cheap to perform	Requires equipment, needs to be performed early in the morning after an overnight fast, invasive. Not accepted in some communities. May be unpleasant for child.
	Induced Sputum	Can be performed as outpatient and at any time of day on any age of child	Requires equipment and monitoring, invasive, some infection control concerns
	Nasopharyngeal Aspirate	Can be performed as outpatient and at any time of day on any age of child	Requires equipment, invasive, not well tolerated in older children
	Stool	Easy and cheap to perform	Sensitivity and specificity less good than for respiratory samples
	Fine-needle aspiration biopsy	Easy to perform and can be done as an outpatient under local anaesthetic, good yield	Can be distressing
	Tissue Biopsy	Often gives definitive diagnosis	Usually requires general anaesthetic, invasive
	Endobronchial ultrasound	Allows sampling at site of disease in lungs, high yield	Requires expensive equipment and training, usually requires a general anaesthetic
	Bronchoscopy	Permits visualisation of airways and allows sample collection at the site of disease	Requires expensive equipment and training, usually requires a general anaesthetic
	Body fluids, e.g. CSF, pleural fluid, pericardial fluid or ascites	Allows evaluation of microbiology as well as other tests—biochemistry etc.	Low yield, invasive

(continued)

Table 1 (continued)

Diagnostic Approach		Advantages	Disadvantages
Microbiology—Laboratory	Smear	Easy and quick to perform, cheap	Low sensitivity
	Xpert MTB/RIF (Ultra)	Better sensitivity than smear, results within 2 hours and provides information on drug resistance	Expensive, needs servicing, requires power supply and IT capability
	Microscopic Observation Drug Susceptibility Assay	Cheap and robust, provides information on drug resistance	Takes days for results, kits not widely available
	Line-probe assay	Provides information on DST to multiple drugs and for multiple mutations	Requires laboratory infrastructure and training, for children rarely possible to perform directly on clinical specimens Although can be performed directly on clinical specimens, results are often negative and usually requires a cultured isolate leading to time delay
	Solid Culture	Relatively cheap, easy to use	Takes weeks for results, requires laboratory infrastructure and training
	Liquid Culture	More sensitive than all other investigations to detect *M tuberculosis* and drug resistance	Takes weeks for results, requires laboratory infrastructure, expensive
	Whole Genome Sequencing	Provides information on multiple genes associated with resistance, permits evaluation of relatedness of strains for epidemiological surveillance	Still unclear correlation between genotype and phenotypic resistance, for children rarely possible to perform directly on clinical specimens. Expensive
Immunological tests	Tuberculin skin test	Cheap and relatively easy to use	Requires two visits, imperfect sensitivity especially in young children and children living with HIV, specificity impaired by BCG and NTM
	Interferon-gamma release assay	Improved specificity; only requires one visit	Expensive and requires laboratory infrastructure, imperfect sensitivity, especially in young children and children living with HIV

Table 1 (continued)

Diagnostic Approach		Advantages	Disadvantages
Histology	Histological examination	May give supportive information to aid diagnosis. Inexpensive	Requires biopsy, and trained laboratory staff. May not give definitive diagnosis
Host RNA biomarkers		Could assist in the diagnosis of TB disease in children who are microbiologically unconfirmed	Still at experimental stage. Likely to be highly expensive for several years.

Adapted from Schaaf HS, Marais BJ, Carvalho I, Seddon JA. Challenges in childhood tuberculosis. *In*. Migliori GB, Bothamley G, Duarte R, Rendon A. eds. Tuberculosis (ERS Monograph). Sheffield, European Respiratory Society. 2018; pp. 234–262 [84]. *CXR* chest x-ray; *TB* tuberculosis; *CSF* cerebrospinal fluid; *DST* drug susceptibility test; *HIV* human immunodeficiency virus; *BCG* Bacillus Calmette–Guérin; *NTM* non-tuberculous mycobacteria; *RNA* ribonucleic acid; *IT* information technology

Table 2 Differential diagnoses for children with symptoms of tuberculosis or with granuloma identified

Common differential diagnoses of tuberculosis	Differential diagnoses of granuloma
Bacteria: Bartonella, Lyme, Brucella, Non-Tuberculous Mycobacteria	Bacterial: Bartonella, Leprosy, Non-Tuberculous Mycobacteria
Viral: HIV, EBV, CMV, Adenovirus	Fungal: Histoplasma, Coccidiomycosis
Fungal: Aspergillus, Candidiasis, Histoplasma, Coccidiomycosis	Parasitic: Schistosomiasis, Cryptococcus
Sarcoid	Inflammatory: Crohns, Rheumatoid, Wegeners, Sarcoid
Malignancy (in particular lymphoma)	Immune: Chronic granulomatous disease
Immunodeficiency with an opportunistic infection	Other: Foreign Body, Berylliosis

HIV human immunodeficiency virus; *EBV* Epstein Barr Virus; *CMV* cytomegalovirus

Children Presenting with Symptoms or Abnormal Investigations

TB disease should be considered as part of the differential diagnosis in any child with suggestive symptoms or investigation results. A list of differentials for TB are shown in Table 2. Children in this category are either inpatients, seen in the Emergency Department or are referred from primary care or radiology. Children can present with a variety of non-specific symptoms which can prompt TB being considered. Presenting symptoms are varied and include persistent lymphadenopathy (including hilar adenopathy on chest x-ray), chronic cough, prolonged fevers, failure to thrive, lethargy, weight loss or, less commonly, symptoms of disseminated TB or TB meningitis. They can sometimes present acutely, with the child

very unwell. TB disease should be suspected in children with any of these presentations. The best predictive symptom for a clinical diagnosis of TB disease in young children is persistent cough, especially if also combined with systemic symptoms such as weight loss [17, 18]. It is common for parents of infants and young children to give a history of chronic cough and poor feeding which often reflect recurrent viral infections and parental anxiety about diet. A detailed history is needed to distinguish a truly persistent or worsening cough from recurrent episodes of cough with well periods in between. The risk of disease progression is highest in young infants, in whom clinical symptoms and radiology are least specific. Infants are also most likely to have paucibacillary disease and to present the greatest difficulty in obtaining samples, both of which reduce rates of microbiological confirmation.

Remembering to consider TB as a possible diagnosis is the most important step; this is more often considered when there is a history of risk factors such as known TB exposure, previous TB infection or disease, travel to a high-incidence area, or personal or family origin from a high incidence area. TB endemic areas include much of Eastern Europe, Russia, Central and Southern Asia, South America and Africa [5]. The possibility of TB is often overlooked if there is no obvious risk factor, especially if the onset of symptoms is insidious.

When children present symptomatically, and TB is considered in the differential diagnosis, assessment should include a history of TB exposure, any TB symptoms, or any risk factors for TB. It also should include a full clinical examination and chest x-ray. If symptoms suggest pulmonary TB, appropriate microbiological sample collection (induced sputum/gastric aspirate) is required, whereas if symptoms or examination findings suggest any extrapulmonary disease, then other radiology, and additional samples for microbiology, may be required. Immune testing (TST and/or IGRA) is not essential for the diagnosis of TB disease but may well add a valuable piece to the jigsaw; a negative test does not rule out TB disease. Equally, in somebody who has a high background probability of TB infection, a positive immune test for TB itself may not necessarily increase the likelihood that the current symptoms are due to TB disease. Investigation should be done promptly and should not delay treatment in children with symptoms suggestive of TB who are unwell or at high risk of disease severity progression. This includes infants, children of any age with significant immune suppression (including HIV/primary immunodeficiency or on immunosuppressive therapy), children suspected of having miliary TB or TB meningitis, or those who are severely unwell requiring intensive care. (Fig. 1).

It is always important when children present with symptoms of possible TB to ask about TB symptoms in household members and other contacts, as the child may be the first to present but have an undiagnosed source case in the household [19]. Consideration should be given to arranging chest x-rays and, if coughing, sputum samples for other household members as part of the diagnostic workup of the presenting child.

Radiology

Chest Radiology

A chest x-ray is used routinely to assess for pulmonary TB in children, although it lacks both specificity and sensitivity. The most common pattern of abnormal radiology in children with TB disease is primary disease with hilar lymphadenopathy and adjacent consolidation. There is a high degree of inter- and intra-observer variability in the diagnosis of hilar lymphadenopathy in paediatric chest x-rays, even with experienced radiologists [20, 21]. Other patterns of abnormality on chest x-ray in paediatric TB include other intrathoracic lymphadenopathy, lobar or multi-lobar collapse or consolidation, cavities, miliary disease and pleural effusions. Characteristic chest x-ray images are shown in Fig. 2. Extrapulmonary disease may be incidentally seen on chest x-ray as pericardial effusions, soft tissue or bony infection or extrapulmonary lymphadenopathy. Pulmonary TB is unlikely in the absence

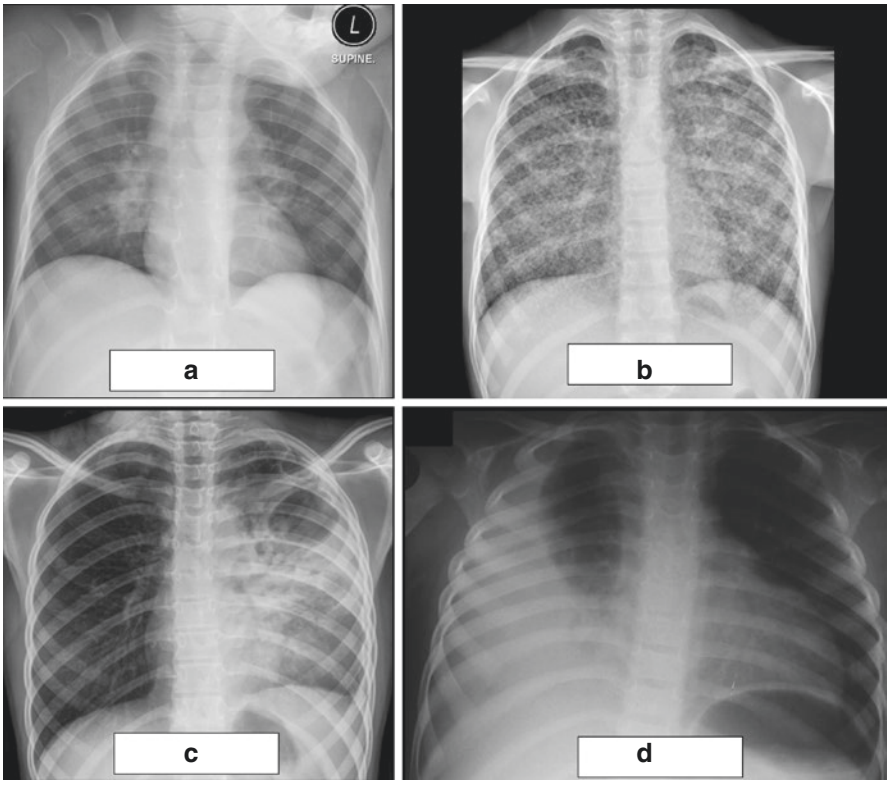

Fig. 2 Chest radiograph images of children with features suggestive of tuberculosis. (**a**) Hilar lymphadenopathy (**b**) Miliary pattern (**c**) Cavities (**d**) Pleural effusion

of any lymphadenopathy at all, but lymphadenopathy cannot be excluded by plain radiography.

Plain chest x-rays are helpful when clearly normal, or characteristic of TB disease, but may often be abnormal but not clearly suggestive of TB. Changes that are characteristic of TB are also likely to be more common in children for whom it is usually possible to diagnose TB by other means—children with a cavity are likely to have characteristic symptoms and positive microbiology from sputum, and children with pleural effusions are likely to have positive immunological tests. There is also always a differential diagnosis, even of characteristic findings,—a cavity may be caused by staphylococcal pneumonia, or by fungal infection; there are various other causes of pleural effusions; and lymphoid interstitial pneumonitis can be mistaken for miliary TB in children with HIV infection.

Computed Tomography (CT)

Chest CT is more sensitive and specific than plain radiography at picking up changes of TB, especially in detecting minor degrees of lymphadenopathy. However, it involves higher exposure to radiation, and should be used selectively. If a child is being investigated as a TB contact and has immunological evidence of TB infection and a normal or equivocal chest x-ray, a decision whether to treat as TB infection or TB disease can be based on symptoms without using a CT to look for minor degrees of lymphadenopathy. CT may be particularly useful if there is uncertainty as to the TB diagnosis, no microbiological confirmation and a particular need for making the correct diagnosis (e.g. after contact with drug-resistant TB, child has symptoms and normal chest x-rays, or no symptoms and equivocal chest x-ray). CT may also be useful to assess complications of TB disease such as collapse secondary to airway obstruction, or to guide a diagnostic bronchoscopy/endobronchial ultrasound [22].

Other Radiology

18F-FDG-PET (Positron Emission Tomography)/CT scanning may be particularly useful in distinguishing TB disease from other causes of anatomically visible lesions but is not widely used in children because of the high radiation dose involved. Radiological imaging of non-pulmonary sites is guided by clinical signs and symptoms. CT and MRI scans should be contrast enhanced. Ultrasound (US) is increasingly being used in children suspected of TB. For children suspected of having pulmonary TB, US can be a useful investigation, particularly in young children. Findings of pleural effusion, abdominal lymphadenopathy and splenic microabscesses indicate TB [23, 24]. For children suspect of having extra-pulmonary TB, US should be a first-line investigation.

Microbiology

Microbiological confirmation is the gold standard for the diagnosis of TB disease in adults, but positive rates of microscopy of acid-fast bacilli (AFB), PCR for *M tuberculosis* and mycobacterial culture are lower in children than in adults [25–27]. Nevertheless, every effort should be made to obtain samples for microbiology. This allows a definitive diagnosis to be confirmed and offers the possibility of follow-up testing to confirm cure. It is also the only way to establish whether there is antibiotic resistance, even if this may be inferred from the resistance patterns of any source case within the household. The additional information that may be gained when whole genome sequencing is available is a further reason to encourage sampling.

There is a possibility of *M tuberculosis* being isolated from respiratory samples of children undergoing primary infection which they will subsequently contain, but it is reasonable to interpret all positive microbiological samples as indicating TB disease.

Specimen Collection

Respiratory samples from children may be collected by a variety of means. Spontaneous sputum production is the method of choice in children aged above 10 years and should be tried in children from age 5 years (and sometime younger). In younger children induction of sputum with nebulised hypertonic saline [28, 29], aspiration from a nasogastric tube [30, 31] and nasopharyngeal aspiration have all been used [32–34]. Gastric aspiration is relatively invasive, and unpleasant for some children; sputum induction carries an infection control risk. Children should not be put through these procedures simply to go through the motions and produce a poor-quality sample which has little chance of yielding positive microbiology results. It is important that whoever is collecting the sample is familiar with the procedure, and units collecting samples infrequently should liaise with their microbiology laboratories to discuss sample collection and handling. Being familiar with a particular technique to collect adequate volumes of high-quality samples is probably more important than which technique is selected. Collecting several good-volume samples by different techniques at the same time may be more useful than sending serial samples [29, 32, 33].

Bronchoalveolar lavage (BAL) and endobronchial ultrasound (EBUS) to sample intrathoracic lymph nodes are more invasive alternatives and are not always readily available. BAL has not been shown to be superior to gastric aspiration in increasing microbiological yield and should be reserved for specific cases [35]. EBUS may be useful when there is intrathoracic lymph node disease only [36]. In addition, there is increasing interest in using stool samples as an alternative to gastric aspirates as a source of identifying bacteria from swallowed sputum [37, 38].

Obtaining samples other than sputum should be guided by symptoms and imaging for extrapulmonary sites. The most common other sample would be lymph nodes [39], but other samples include pus, cerebrospinal fluid (CSF), pleural fluid, pericardial fluid, ascites, urine, tissue biopsies, synovial fluid or bone. How and whether to obtain samples should be guided by the degree of uncertainty of diagnosis and the relative ease of obtaining the sample. Pleural biopsies give higher microbiological yields than pleural fluid alone, and allow histological examination, but require a more invasive intervention [40, 41].

Laboratory Tests

Sputum, induced sputum, BAL and EBUS samples should be examined by microscopy for AFB; gastric aspirate and stool samples have a high rate of false positives for microscopy for AFB. The current standard remains for three specimens to be sent, and one of each type of specimen should be tested by PCR, and all also by culture. Other samples from sterile sites should also be tested by PCR and culture, although PCR is often not validated for this.

Sputum smear positivity rates in children, other than adolescents with cavitating disease, remain very low [25]; culture confirmation rates vary between <10 to >50% [29, 42, 43]. PCR confirmation rates may be up to 45–70% of culture-confirmed cases in children; the turnaround time for a positive PCR result is much more rapid than culture [26, 27]. PCR therefore essentially takes the role of smear microscopy for rapid confirmation of TB disease in children, although a negative PCR does not rule out the diagnosis of TB. Given that it is associated with the greatest sensitivity in children, all samples should be sent for culture.

Histology

When samples are taken that include tissue (such as lymph nodes, pleural biopsies or biopsies from other sites) they should be examined by histology as well as microbiology in order to look for typical histological changes such as caseating granulomas, as well as AFB.

Immunological Tests

In a child with symptoms consistent with TB (but also consistent with other aetiologies), a positive TST or IGRA can lend weight to the diagnosis of TB. Of the two, TSTs are less specific due to cross-reactivity with BCG and non-tuberculous mycobacteria. Previous TB disease or infection is a contraindication to doing a TST but not to doing an IGRA.

Clinical Diagnosis

Despite best efforts, there will remain many cases where microbiology is negative, there is no supportive histology, and radiology is non-diagnostic. Exposure history and immune testing are strongly supportive of TB, but do not diagnose TB disease alone. Clinical symptoms then remain the cornerstone of diagnosis. There is no substitute for a longitudinal weight chart, but this is often missing; a detailed symptom history, supplemented by clinical examination, remains paramount. Repeated studies have shown that prolonged unremitting cough together with constellations of multiple systemic symptoms (especially fever, anorexia and weight loss) are the best predictors of TB disease [17, 18]. Time is also an important component of a clinical diagnosis. For most children with pulmonary TB who are not acutely unwell, there is no urgency to initiate treatment. A review in 10–14 days without TB treatment (with or without empiric broad-spectrum antibiotics such as amoxicillin) will provide a useful triage, as many infections that can cause similar symptoms will resolve in that time. A child with symptoms persisting beyond this period is more likely to have TB disease.

Novel Tests

Several non-sputum tests are in development [44]. An RNA gene expression study has demonstrated that a 51-transcript signature is able to differentiate TB disease from TB infection and other diseases in children [45]. A T-cell activation marker assay (TAM-TB) has also demonstrated promise [46]. If it is possible to translate these research tests into truly point-of-care tests, and retain good sensitivity and specificity, while keeping costs low, the landscape for childhood TB diagnostics may change considerably.

Treatment

Treatment Regimens

The principles underlying the design of treatment regimens for children are similar to those of adults. For drug-susceptible disease, three or four drugs are used during an intensive phase (usually two months) followed by two drugs during a continuation phase (usually for a further four months). Currently isoniazid, rifampicin and pyrazinamide (with or without ethambutol) for two months followed by four months of isoniazid and rifampicin is the most commonly used regimen [12, 13, 47]. This regimen is associated with good outcomes in children. With a fully susceptible organism, in an immunocompetent child with good adherence, the addition of

Table 3 First-line anti-tuberculosis drugs, dosages and associated adverse events

Drug	Abbreviation	Dose (range) (mg/kg/day)	Max daily dose (mg)	Preparations	Most common adverse events associated with medication
Isoniazid	H or INH	10 mg/kg (7-15 mg/kg)	300	50 mg & 100 mg tablets Rifinah 300/150 Rifinah 150/100 Rifater 120/50/300 Voractiv 150/75/400/275 Macleods FDC (RHZ 75/50/150 or RH 75/50)	Peripheral Neuropathy Hepatitis
Rifampicin	R or RIF or RMP	15 mg/kg (10-20 mg/kg)	600	150 & 300 mg capsules Rifinah 300/150 Rifinah 150/100 Rifater 120/50/300 Voractiv 150/75/400/275 Macleods FDC (RHZ 75/50/150 or RH 75/50)	Hepatitis Discoloration of secretions Drug interactions with multiple other medications
Pyrazinamide	Z	35 mg/kg (30-40 mg/kg)	2000	500 mg tablets Voractiv (RHZE) 150/75/400/275 Macleods FDC (RHZ 75/50/150)	Hepatotoxicity Arthralgia/arthritis
Ethambutol	E	20 mg/kg (15-25 mg/kg)	1600	100 mg &400 mg tablets Voractiv (RHZE) 150/75/400/275	Red/green colour blindness Optic Neuritis

ethambutol is not essential. Shorter regimes may be effective and safe in children, especially those with paucibacillary disease. This is currently under investigation in the SHINE trial comparing outcomes with four- and six-month regimens [48].

The dosages recommended by WHO were increased in 2011 following a review of pharmacokinetic data [47]. Studies are underway to evaluate much higher dosages of rifampicin in children [49]; if this is found to be safe, it may also help in reducing treatment duration. Current recommendations are shown in Table 3 and include rifampicin 15 mg/kg (range 10-20 mg/kg), isoniazid at 10 mg/kg (range 7-15 mg/kg), pyrazinamide at 35 mg/kg (range 30-40 mg/kg) and ethambutol 20 mg/kg (range 15-25 mg/kg [12]. Doses are now recommended in weight-bands, enabling treatment using both single drug tablet formulations and fixed drug combination (FDC) tablets (Table 4). Such FDCs are advantageous in avoiding the need for liquid formulations, especially if they are dispersible and can therefore be used in younger children unable to swallow whole tablets. They are more palatable than

Table 4 Dosing of first-line anti-tuberculosis medication by weight band and available preparations

Weight band	Rifampicin 15 mg/kg	Isoniazid 10 mg/kg	Pyrazinamide 35 mg/kg	Ethambutol 20 mg/kg	Available preparations
4-7 kg	75	50	150	100	• Macleods FDC (RHZ 75/50/150 or RH 75/50) 1 tablet
8-11 kg	150	100	300	200	• Rifinah 150/100 1 tablet *[Pyrazinamide 500 mg ½ tab plus syrup 50 mg]* • Macleods FDC (RHZ 75/50/150 or RH 75/50) 2 tablets
12-15 kg	225	150	450	250	• Rifinah 150/100 1 tab plus ½ 100 mg tab Isoniazid & 75 mg Rifampicin syrup • Macleods FDC (RHZ 75/50/150 or RH 75/50) 3 tablets
16-24 kg	300	200	600	400	• Rifinah 150/100 two tabs • Macleods FDC (RHZ 75/50/150 or RH 75/50) 4 tablet
25-40 kg	450	300	1.5 g	500	• Rifinah 150/100 one tab and rifinah 300/150 one tab
>40 kg	600	300	2 g	15 m/kg	• Rifinah 300/150 two tabs, • Rifater 5 tabs

liquids and avoid the excessively large volumes that otherwise need to be stored, carried by families and carers and swallowed by children. Availability of FDCs suitable from newborns upwards has been supported by the WHO, UNICEF and TB Alliance [50, 51].

The design of treatment regimens for drug-resistant TB in children again follows similar principles to adults. Second-line agents have greater adverse effects and lack of availability of appropriate formulations to use in children add to the challenge of treatment, especially for MDR-TB. This is particularly true for the desire to avoid injectable agents with very high risks of sensorineural hearing loss [52], devastating at an early stage of development. For less extensive disease, there is increasing data suggesting acceptable outcomes with shorter and less intense regimes than the traditional 18–24 month regimens recommended for adults with MDR-TB [53].

Adverse Effects and Monitoring

Otherwise healthy children usually tolerate TB medications well without adverse effects requiring interruption of treatment [54]. It is important to assess the likelihood of adverse events and monitor accordingly. Concurrent liver disease or

potentially hepatotoxic medications should lead to proactive monitoring of liver function whilst on therapy. It should be noted that mild-moderate rises in liver transaminases are expected on therapy and are not of themselves an indication to interrupt treatment. Monitoring liver function on treatment is not necessary in all children especially if baseline liver function tests are normal. In this regard it is important to test for co-infection with hepatitis B and hepatitis C, as well as HIV. Patients and families/carers need to be counselled about expected side effects such as discolouration of urine and secretions. Written information leaflets and support from TB specialist nurses can be very beneficial in providing the reassurance that is required. This is important in maintaining good adherence to therapy. Two months therapy with the currently recommended dose of ethambutol appears to have a low risk of optic neuritis [55]. However, where children are old enough to report visual symptoms, this should be proactively asked about.

Drug Interactions

As well as closer monitoring for adverse effects, certain concurrent medications may necessitate alteration of TB drug doses and use of therapeutic drug monitoring. A paediatric pharmacist should be involved in decisions on drug monitoring and dose manipulation. Anti-TB medication may also affect levels of other medication. Rifampicin is a potent inducer of the cytochrome P450 enzyme system in the liver and can cause problems with dosing for multiple other drugs [56]. One of these is the oral contraceptive pill which may be used in adolescent girls for contraception or menorrhagia. Patients should be counselled to use other means of contraception. Another important interaction is with antiretroviral medications, and potentially with anticonvulsants and with steroids.

Follow up

It is important to regularly follow up children on treatment for TB disease. This is to ensure they are responding well to treatment, do not have any adverse effects of therapy and to help maintain adherence through to completion. Many children will not need follow up in clinic beyond treatment completion, such as for cervical lymphadenitis, or for small volume pulmonary disease with complete symptom resolution and without reported impairment of exercise tolerance. The need for follow up beyond successful treatment completion depends on the site and extent of disease, and the impact it has had on organ function because of disease. Children may require more specialist ongoing input, for example from neurodevelopmental services for CNS disease or for respiratory services for post-TB pulmonary impairment.

Adherence

Maintaining adherence to therapy for the duration of the treatment course is key to ensuring cure. Poor adherence not only increases the likelihood of treatment failure but risks leading to the evolution of resistance to the agents that have been used. This is particularly the case when some but not all drugs are taken, or the drugs are taken intermittently. Adherence can be challenging in children who quickly become asymptomatic. Support for the child and the family/carers from healthcare professionals is key to this success. Compared to self-caring adults, all children require an extra degree of enhancement to case management. For many there will be confidence that parents/carers can provide assurance that medication is being taken. Where there are challenges with swallowing or accepting medication, it is important to engage healthcare professionals with experience in supporting medication adherence, such as play specialists, paediatric pharmacists and TB nurses. In certain cases, it may be preferable to undertake training use dummy pills or small sweets to achieve success. Where there is lack of assurance about adherence and for cases of MDR-TB and TB meningitis, direct observation of swallowing of medication by healthcare professionals may be necessary. This may be done remotely observing time-stamped video recordings of medication being swallowed [57].

Adolescents require support around adherence as this is a period of life during which adherence to medications is frequently poor [58]. Adherence support needs to be delivered in an adolescent-appropriate environment and using appropriate language. Websites, leaflets, or even peer support groups can help, as can text messaging. Educational and behavioural interventions may be of use and specialist nurses or psychologists can perform a vital role.

Future of Treatment

The aim of treatment is to use as few drugs for as short a time as is required for cure and prevention of relapse without the risk of resistance development. Ideally the regimen would be tailored to the individual based on host and pathogen factors. This is not currently possible, hence the duration of regimens in published guidance often reflects a compromise that is expected to cure the majority without undue toxicity. In time, it is likely to become more feasible to stratify patients in routine practice in terms of extent of disease and pharmacokinetic profile. Combined with whole genome sequencing of isolated organisms, the future may be much more personalised with regimens tailored to the combination of host and pathogen. It is hoped this would lead to maximal cure, minimal duration and few adverse effects.

Central Nervous System Disease

TB can cause a spectrum of disease in the central nervous system (CNS), including most commonly, tuberculomas, TB meningitis and spinal TB. In children with focal neurology or altered consciousness, a CT brain should be performed urgently and discussed with neurosurgeons, with subsequent MRI of brain and spine. MRI may show characteristic cerebral tuberculomas (discrete ring-enhancing lesions) or basal enhancement in the case of meningitis. Dilated fundoscopy should always be performed in suspected TB meningitis to look for retinal tuberculomas. In the absence of contra-indications such as raised intracranial pressure, a lumbar puncture should be performed (ideally with opening pressure) and samples sent for MC + S, glucose, protein, AFB, PCR and TB culture, alongside the other differential diagnostic tests. Note that the diagnostic yield of PCR from CSF increases with increased volume of CSF. It is safe to take 2-4 ml of CSF from a term neonate, 6-9 ml from an infant and 10-15 ml from an adolescent [59]. Current recommendations are to treat CNS TB for 12 months (the standard 2 months of intensive phase and 10 months continuation phase). This remains the current WHO guidance [12], yet is based on limited evidence [60]. Replacing ethambutol with agents with better CNS penetration (such as ethionamide/prothionamide, moxifloxacin or levofloxacin), and increasing the dosage of the drugs, may permit shorter duration of treatment in TB meningitis, as has been reported in cohorts in South Africa [61]. This is being investigated currently in the TBM-KIDS [62] and the SURE trials [63].

In addition to anti-microbiological therapy, it is increasingly recognised that it is also important to modify the damaging host-mediated responses that lead to excessive inflammation and tissue damage. Corticosteroids are advised for CNS TB as well as for other indications, such as TB pericarditis and for intrathoracic disease that compresses the airways [12]. Other host-directed therapies are under evaluation.

HIV Co-infection

Globally, HIV infection is an important risk factor for TB in children, with HIV increasing the likelihood of developing TB almost eight-fold in children [11]. Conversely, children with known HIV infection in low-prevalence settings have rates of TB disease substantially higher than the general population, and at least three times higher than children with similar risks of exposure to TB [64]. All children diagnosed with TB disease should have an HIV test, and some guidelines recommend testing for HIV in all children screened for TB infection (as well as considering screening for hepatitis B and C) [13].

All children living with HIV should be screened for TB infection and disease at diagnosis and regularly on review. TB disease can hasten progression of HIV

infection, and the reduced immunity of HIV increases disease progression risk for TB. Treatment with antiretrovirals mitigates but does not remove the additional risks. There are also multiple potential drug interactions (especially rifampicin-induced metabolism of antiretrovirals) and increased risks of side effects from combining anti-TB and antiretroviral medication. There is also a risk of paradoxical worsening of TB symptoms during immune reconstitution after starting antiretroviral medication (Immune Reconstitution Inflammatory Syndrome) [65]. Nevertheless, data show that initiation of antiretroviral treatment as soon as possible after starting TB treatment improves prognosis (with the possible exception of TB meningitis) [66, 67]. It is essential that children with TB/HIV coinfection are managed according to national guidelines, and by clinicians experienced in managing both conditions [68, 69].

Decision-Making around Tuberculosis Infection Treatment

Immune-Based Tests

Both the TST and IGRA measure host immune response to mycobacterial antigens and demonstrate evidence of prior exposure to TB. They cannot distinguish between infection and disease, nor between past resolved and ongoing infection. These tests should be regarded as a "rule in" test for TB infection. They are less reliable in the diagnosis of TB disease. The tests must be used and interpreted with caution as false negative rates of up to 20% are seen due to malnutrition, steroids and TB disease itself. The IGRA is more specific than the TST as it is not influenced by previous BCG vaccination or non-tuberculous environmental mycobacterial exposure [70]. There are two, main commercial IGRAs currently used, the QuantiFERON-TB (the most recent generation is the QuantiFERON-TB Gold Plus) and TB ELISpot (the T-SPOT.TB).

To perform a TST, purified peptide derivative (mycobacterial antigen) 2 IU (0.1 ml of 20 units/ml strength) is injected intradermally into the left anterior forearm. The reaction is read at 48–72 hours and any lateral induration is measured. Induration indicates possible TB infection with the greater the diameter of the induration the greater the likelihood of TB infection. There is differing guidance between countries and international guidelines regarding how to interpret the TST results. This reflects the incorporation of several different factors including differing pre-test probabilities based on TB prevalence rates, use of BCG vaccine and national cost-effectiveness assessments. The current UK cut off for TST positivity after TB exposure is now >5 mm, regardless of BCG vaccination status [13]; WHO recommends a cut-off of 10 mm [12].

Management of TB Infection

All children should be evaluated for evidence of TB disease with history, examination and chest X-ray. If the child does not have TB disease, then a decision needs to be made regarding the provision of TB infection treatment. Given the high risk of disease progression in the youngest children and the limitations of the tests of infection in this age group, we recommend all exposed children under two years of age are assessed by a paediatrician with TB expertise. Given the higher risks of both infection leading to disease and rapid disease progression, many clinicians treat all children under the age of two years who have been exposed to an infectious TB case, without testing with TST or IGRA due to concern about the ability to confidently rule out infection with immune-based tests. Neonates (babies under four weeks) can be given isoniazid (10 mg/kg daily, although 5 mg/kg should be considered in premature or low birthweight babies) [71] with pyridoxine (5 mg daily) for six months. Children between four weeks and two years of age can be treated with either three months of both daily isoniazid (10 mg/kg) and rifampicin (15 mg/kg) or 6 months of daily isoniazid alone [72]. If the child has not received the BCG vaccine, then at the end of treatment, they should have a TST or IGRA, and if negative, BCG should be given.

As the risk of disease progression is lower in older children, and as the tests of infection perform better, most clinicians use these tests from the age of about two years to inform treatment decisions. Initially, children of this age can be evaluated by the community TB team without necessarily needing referral to see a doctor. If they have any symptoms of TB disease, they should be referred for medical review. There are several approaches for the evaluation of these children, including use of TST alone, IGRA alone, IGRA then TST or TST then IGRA. If the child has been recently exposed, it may be necessary to repeat tests of infection as the child may have become infected but have not yet mounted an immune response necessary to cause a test of infection to become positive. A suggested algorithm is outlined in Fig. 3. WHO policy is to treat all child TB contacts younger than five years for TB infection, and in recognition of this, many centres have a low threshold for starting patients aged two to five years of age on a TB infection regimen, as this group is at higher risk of primary progressive disease and dissemination than older children. Generally, once all investigations and treatment are completed, and if the child has not previously had BCG, a BCG vaccine is recommended. Treatment can be with isoniazid daily alone for six months or with isoniazid and rifampicin both daily for three months [13, 73–75]. Emerging regimens include (1) weekly isoniazid and rifapentine for three months [76, 77], (2) daily isoniazid and rifapentine for one month [78], and (3) daily rifampicin for four months [79, 80].

Adherence to TB infection treatment can be poor as the child is not unwell [81]. It is important to invest the time to explain to children and parents the reason for their treatment and the severity of TB disease should it occur. Use of leaflets and websites can help. Families should be warned about the common effects of taking the medications, particularly around the discoloration to secretions that rifampicin causes. Rare side effects should also be discussed, such as hepatotoxicity (all

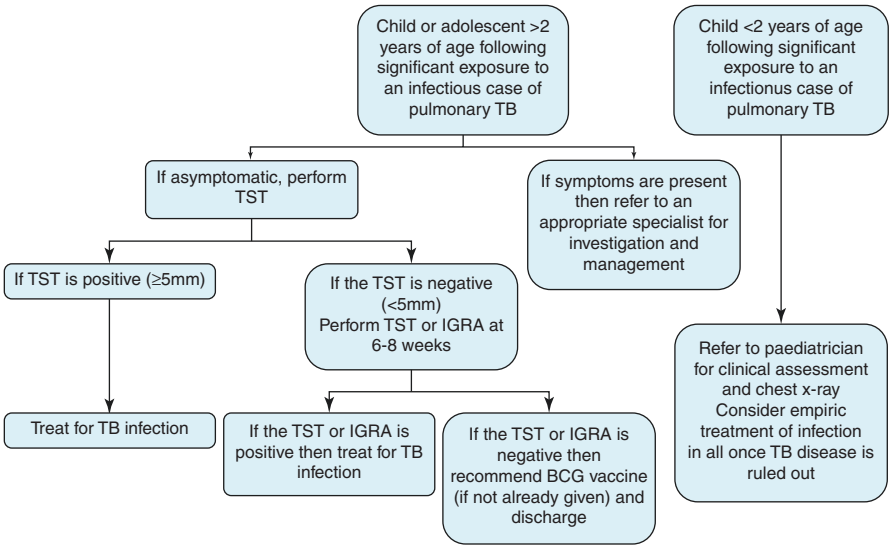

Fig. 3 A suggested algorithm for decision-making around the provision of tuberculosis infection treatment in children and adolescents. *TB* tuberculosis; *TST* tuberculin skin test; *IGRA* interferon-gamma release assay; *BCG* Bacillus Calmette–Guérin

rifamycins and isoniazid) and peripheral neuropathy (isoniazid). The family should be told what to do should they have any concerns about these adverse events and whom to contact. Risks of drug-induced hepatitis are even lower than for pyrazinamide containing treatment regimes, so it is not necessary to monitor whilst on therapy if baseline is normal. In children it is usually not necessary to test liver function prior to prescribing TB infection treatment and not necessary to do so routinely while on treatment. However, should the treating team have any concerns, either prior to, or during treatment, they should have a low threshold for evaluating function. Practice regarding follow up of children post completion of TB infection treatment is varied—many clinicians follow up the youngest children for a year. Older children who are well probably do not need to be seen after they have completed their treatment. For children treated for TB infection, follow up chest X-rays are not required in the absence of new symptoms.

Other Issues

Infection Control

Although children generally have paucibacillary disease, and are therefore less infectious, it is good practice to put all patients suspected of having pulmonary TB disease in isolation, ideally in negative pressure cubicles where available, until

infectiousness status determined [82]. Parents are often the index case and should be screened with chest x-ray, sputum examination and TB immune test (IGRA/TST) as soon as possible, and should wear surgical masks in communal hospital areas until confirmed to be non-infectious. This also serves to identify potentially infectious family members who may have been the source case for the child. If symptomatic they also require sputum testing and clinical assessment. Staff and well parents/relatives/friends should wear FFP3 masks to prevent nosocomial transmission when in the cubicle. Unwell children should wear surgical masks when leaving the cubicle until assessment of infectiousness is complete. As with adults, infectious individuals with fully susceptible *M. tuberculosis* cease to be infectious approximately two weeks after commencing effective medical treatment for drug-susceptible TB, or when previously positive sputum has become negative for AFB.

Impact on School and Education

Older children and adolescents with infectious TB disease will be required to miss two weeks of school until the risk of transmission has decreased. The national education union (NEU) in the UK has information for schools on the approach to cases of TB in schools, both in terms of TB screening within the school and supporting the individual child with TB disease [83]. Timing of treatment may impact on school, and working with families to develop a routine that can be adhered to is vital. Children with MDR-TB who require longer hospital admission and experience more adverse effects face the greatest impact on schooling and education, and a multi-disciplinary approach including the family, clinical nurse specialists and teachers may be required to limit the impact for the child.

Child Protection

Children with TB infection and disease who are not brought to medical appointments or do not adhere to treatment represent a high clinical risk and a safe-guarding assessment should be performed if this is a regular occurrence. If, following discussion and explanation with the family there are ongoing concerns, or any other safe-guarding concerns identified, a child protection referral should be made.

Conclusions

Children and adolescents represent an important component of the overall TB epidemic. Due to diagnostic and treatment challenges, they require an approach which is holistic and inclusive and meets the needs of the family as well as the child. In the

youngest children, a microbiologically confirmed diagnosis is less common, and TB disease frequently must be diagnosed clinically, on a basis of contact history, symptoms, signs and radiology. For adolescents, the diagnosis is less challenging but creating an environment that is welcoming and inclusive is crucial to supporting them through treatment for both infection and disease. New scientific developments in diagnosis and treatment of TB in children are likely to be translating from the bench to the bedside in the coming years and it is hoped that a TB-free generation will be seen soon.

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HIV and TB

Hazel Morrison, Ian Cropley, and Marc Lipman

Introduction

From the first consistent reports in 1981 of Acquired Immunodeficiency Syndrome (AIDS), it is estimated that over 35 million people worldwide have died as a result of infection with the causative organisms—Human Immunodeficiency Viruses 1 and 2 (HIV) [1, 2].

Worldwide, there are currently an estimated 37 million people living with HIV (PLWHIV) [2]. Their risk of developing TB disease is around 20 times that of an HIV negative population [3]. This is due to an increased risk of both progression to active TB disease in primary infection and reactivation of latent TB infection (LTBI) [1, 3]. TB remains the leading cause of death among PLWHIV, accounting for nearly one third of all HIV-related deaths.

HIV infects and damages cells that display CD4 antigen molecules on their surface, in particular the T-helper 1 subset of CD4+ T lymphocytes. Dysregulation of adaptive immunity by depletion of CD4 cells is a key pathway through which HIV increases the risk of TB. However, unlike the opportunistic infections (OI) typically associated with severe disease in PLWHIV, the risk of TB is increased at all stages of HIV infection compared to HIV uninfected people. This includes early in HIV

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infection when the CD4 count remains high. In TB endemic settings, an increased risk also remains in patients using HIV antiretroviral treatment with high blood CD4 counts and undetectable HIV loads. This strongly suggests that CD4 T cell depletion is not the only mechanism by which HIV impairs host defences against TB. Other aspects of the immune system, including macrophages and cytokines (such as tumour necrosis factor alpha TNFα and interferon gamma IFN-γ) play key roles in the control of *M. tuberculosis* infection and are known to be detrimentally affected by HIV [4].

HIV and TB exist in a dangerous synergy, as infection with TB can also worsen the clinical course of HIV. Proinflammatory cytokine production in response to *M. tuberculosis* may lead to increased viral transcription and therefore disease progression [5, 6]. A key clinical practice message is that all patients diagnosed with TB should be offered testing for HIV, and risk of TB should be considered in all those diagnosed with HIV. To achieve best patient outcomes in both high and low burden countries, it is essential that HIV and TB services are integrated, as successful treatment of one condition is fundamentally related to the other.

Epidemiology

TB/HIV co-infection occurs throughout the world, with the highest burden seen in southern Africa (Fig. 1). The WHO estimates that ten million people developed tuberculosis in 2017 and 920,000 (9%) were living with HIV. 72% of these co-infected cases occurred in the WHO Africa region [2, 3].

In 2017, tuberculosis caused 1.6 million deaths. 300, 000 (19%) of these were in PLWHIV. Countries where HIV, TB and drug resistance overlap face the highest burden from these pandemics (Fig. 2).

The number of deaths from tuberculosis in PLWHIV has fallen by 44% since 2000 [3]. Most of this reduction has occurred in African countries and is attributable predominantly to increased HIV testing and antiretroviral therapy (ART) coverage. However, TB remains the number one cause of death among people with HIV in Africa, and a leading cause of death in PLWHIV worldwide, accounting for 1 in 3 HIV-related deaths [2].

While overall cases of tuberculosis continue to fall in the WHO European region, HIV/TB co-infection numbers are rising. The proportion of TB in PLWHIV has increased from 3% in 2008 to 13% in 2017 [3]. In the UK, under 3% of people with TB are coinfected with HIV. The majority of these are born outside of the UK [7].

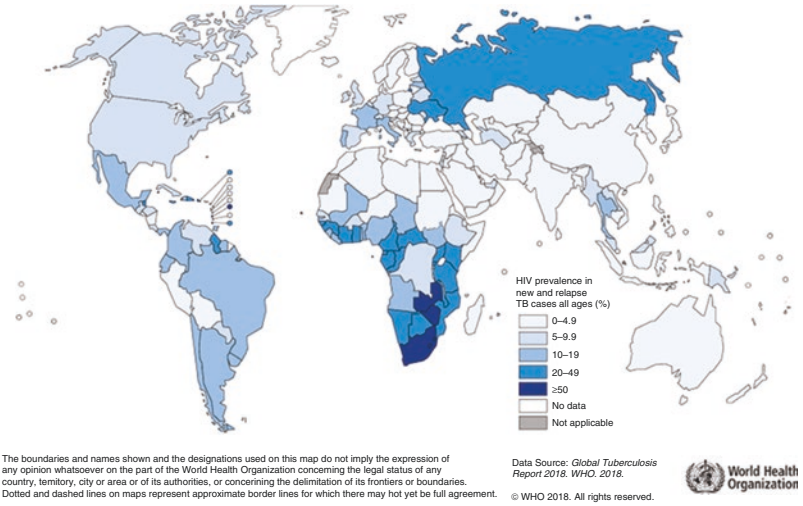
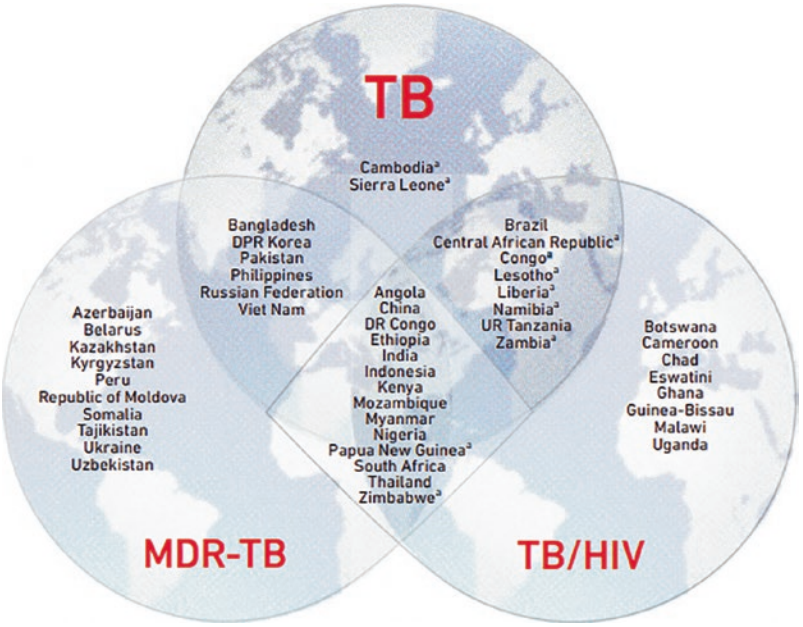


Fig. 1 Estimated HIV prevalence in new and relapse TB cases, 2017. Reprinted from Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Chapter title: Chapter 2. Global commitments to end TB and multisectoral accountability. Page 24. Copyright World Health Organisation (2018)



[a]Indicates countries that are included in the list of 30 high TB burden countries on the basis of the severity of their TB burden (i.e. TB incident cases per 100 000 population per year), as opposed to the top 20, which are included on the basis of their absolute number of incident cases per year.

Fig. 2 WHO High-burden country lists 2016–2020 for TB, TB/HIV and MDR-TB and their overlap. Reprinted from Global tuberculosis report 2018. Geneva: World Health Organization; 2018. Chapter title: Chapter 3. TB disease burden. Page 38. Copyright World Health Organisation (2018)

Table 1 Factors associated with an increased risk of active TB in people living with HIV

Patient-related factors	HIV-related factors	TB-related factors
Lower socio-economic group	Not on ART	From a TB endemic country
Low BMI (<18.5 kg/m2)	Advanced clinical stage of HIV (WHO stage 3 or 4)	Previously reported TB[a]
Haemoglobin <100 g/L	Low blood CD4 count	
	High plasma HIV load	

[a]some studies only

Risk Factors for Tuberculosis in HIV Infection

Many studies have looked at specific risk factors for the development of tuberculosis in PLWHIV, with a number of variables being potentially implicated (Table 1). The strongest and most consistent associations are with impaired host immunity (reflected in low blood CD4 count, poor adherence to ART and more advanced stage of HIV) and system factors, such as lack of access to ART (Table 1) [8, 9, 10]. This is an important message for both healthcare providers and policy makers wanting to reduce the global impact of HIV/TB co-infection.

Clinical Features and Diagnosis of TB in HIV Co-infection

Tuberculosis is infectious to everyone, irrespective of their immune status. Therefore, its management (including diagnosis and treatment) is a public health priority. Tuberculosis can occur at any stage of HIV infection and accurate diagnosis can be challenging, as HIV infection and its resulting immune dysregulation modifies the clinical presentation of TB.

Symptoms and signs are often not those characteristically associated with TB. This is particularly so in people with advanced HIV disease, reflected in a blood CD4 count of <100 cells/μL (normal >400 cells/μL). Here, the presentation may be with non-specific symptoms such as fever, weight loss and marked systemic upset. During assessment, the differential diagnosis and associated investigation needs to be broad—including for other systemic infections such as disseminated fungal disease, as well as malignancies in particular lymphoma.

Extrapulmonary and disseminated TB are more frequently seen in PLWHIV; although pulmonary TB (PTB) is still its most common manifestation. Here the presentation may be with typical features of TB (cough, sputum, haemoptysis and malaise as well as fevers and weight loss) or there can be few specific symptoms [1].

It is well recognised that some PLWHIV are asymptomatic, despite microbiological evidence of active tuberculosis, and are only detected when formally screened for TB disease. Inevitably this is particularly so in TB and HIV endemic areas, where it has been reported in up to one in four of evaluated subjects [11, 12].

Diagnosis of Pulmonary TB in HIV

In many settings smear microscopy and chest radiographs (CXR) remain the cornerstone of TB diagnosis. CXR appearances may be more difficult to interpret in HIV, depending on the stage of immunosuppression, with atypical features increasingly common in more advanced immune dysfunction (Table 2) [13, 14].

People with advanced HIV are more likely to be sputum smear-negative than those who are HIV uninfected. In patients unable to produce a good quality sputum sample spontaneously, induced sputum or bronchoalveolar lavage (BAL) should be considered. Patients should be asked to provide at least two sputum samples when being investigated for TB. Although BAL and even induced sputum sampling are unlikely to be performed more than once during diagnostic work-up, it is important to maximise sample collection when these are done. A good practice point, therefore, is to ask patients to collect any sputum they produce post-procedure as this can often add to the overall diagnostic yield.

Just as in HIV negative populations, current mycobacterial Interferon Gamma Release Assays (IGRA) used in the diagnosis of latent TB infection (LTBI) are neither sensitive nor specific for TB disease in PLWHIV and should not be regarded as a test to diagnose or exclude active TB [15].

Molecular Testing in Pulmonary TB

Molecular testing methods are increasingly part of the routine diagnostic work-up for TB. The Xpert MTB/RIF (Cepheid, Sunnyvale, USA) is a rapid, cartridge-based nucleic acid amplification test that can detect MTB complex DNA and the *rpoB* gene mutations that confer resistance to rifampicin (in itself generally a good indicator of multidrug resistant TB). It is designed to be used on primary samples, such

Table 2 Presentation of Pulmonary TB (PTB) depends on stage of HIV infection

PTB Features	HIV negative & early HIV disease	Late HIV infection (blood CD4 count < 100 cells /μL)
Overall picture	Resembles post-primary (reactivation) PTB	Resembles primary PTB
CXR	"Typical appearance" Cavitation Upper lobe involvement, often predominantly unilateral	"Atypical appearance" Cavities rare Consolidation/interstitial infiltrates, may have basal predominance Intrathoracic (hilar/mediastinal) lymphadenopathy Miliary disease Pleural effusions CXR may appear normal
Sputum smear	More likely to be smear positive	More likely to be smear negative

as sputum and some extrapulmonary fluids. Results are available within two hours, which is of particular benefit in settings where access to healthcare is difficult and people are less likely to attend for return visits and results [16].

In high prevalence TB settings Xpert MTB/RIF has a sensitivity of 88% and a specificity of 99% compared to culture in adult pulmonary TB. In contrast the sensitivity of microscopy is around 50–60%. However, the sensitivity of Xpert MTB/RIF is reduced in PLWHIV to only 79% [17].

The newer Xpert MTB/RIF Ultra (Cepheid) has improved sensitivity in patients with pauci-bacillary sputum such as PLWHIV. This increase in sensitivity does come with the cost of a decrease in specificity. The overall sensitivity for PTB in PLWHIV is 90% with specificity of 96% (compared to 98% for Xpert) [18]. Xpert Ultra was endorsed by the WHO in 2017 for sputum and selected extrapulmonary samples.

In the UK, it is recommended that molecular testing is performed on all smear positive respiratory samples. This allows early discrimination of MTB complex from non-tuberculous mycobacteria plus rapid detection of likely rifampicin resistance. It may also be considered in smear negative samples where the index of suspicion for TB is high. Molecular tests should be performed in conjunction with confirmatory culture and drug susceptibility testing [15].

Whole genome sequencing (WGS) can give detailed genotypic drug resistance information and identify patterns of MTB transmission. This may be of particular use in populations such as PLWHIV who are at increased risk of active TB. However, it requires a positive culture and cannot yet routinely be performed on primary specimens. It has been shown to be feasible for use in high resource settings with a low TB burden. It has yet to be validated in low resource settings with high rates of HIV/TB co-infection [19].

Diagnosis of Extrapulmonary TB in HIV

The risk of extrapulmonary and disseminated TB increases with more advanced HIV disease, reflecting the inability of the damaged immune system to contain the infection. Lymph node (usually cervical) and pleural disease are most common. However, any site can be involved including the central nervous system (TB meningitis, cerebral tuberculoma), soft tissues (psoas muscle), bones (particularly the thoracic spine), gastrointestinal tract (ileocaecal, peritoneal) and pericardium [1]. Some reports have found disseminated HIV-associated TB (involving multiple organ systems) in 90% of post-mortem cases [20]. Starting treatment promptly can avoid some of these deaths—with best outcomes being achieved when multiple diagnostic samples are obtained from suspected cases pre-treatment. These include mycobacterial blood cultures, early morning urine and stool samples [20, 21].

Pleural TB

In HIV endemic settings, TB is the most common cause of a lymphocyte-predominant pleural effusion. In the immunocompetent host, TB pleuritis is paucibacillary in nature and smear microscopy of pleural fluid is almost always negative. However, in PLWHIV microscopy may be positive in up to 20% of cases and this can increase further with lower blood CD4 counts [22]. Investigation is similar in HIV positive and negative individuals (Table 3). Pleural biopsy (via closed needle

Table 3 Diagnostic tests in pulmonary and selected extrapulmonary sites of TB with HIV co-infection

Disease site	Radiology	Samples	Diagnostic Tests	HIV specific features
Pulmonary	CXR CT thorax	Sputum Induced sputum BAL Endobronchial biopsy	Smear microscopy Culture Xpert MTB/RIF [Ultra]	Atypical CXR and smear negative more likely in advanced HIV
Pleural	CXR Thoracic US	Pleural fluid Pleural biopsy (+ Induced sputum/ BAL)	Pleural fluid cell count Adenosine Deaminase Microscopy Culture Xpert MTB/RIF [Ultra] on fluid and biopsy samples	Microscopy more sensitive in HIV
Lymph Node	US lymph nodes	FNA Excision biopsy	Microscopy Culture Xpert MTB/RIF [Ultra]	
Gastro-intestinal	US/CT abdomen	Biopsy Ascitic fluid Stool	Microscopy Culture Xpert MTB/RIF [Ultra] on biopsy samples	Abdominal lymphadenopathy more common and ascites less common in HIV [30]
CNS	MRI brain CT brain	CSF	CSF cell count, protein, glucose Xpert MTB/RIF [Ultra] Microscopy Culture	CSF may be acellular in advanced HIV
Disseminated	CT MRI brain	Sputum Blood CSF Urine	Mycobacterial blood cultures Urine LAM	Urine LAM if CD4 count ≤100; or if patient severely ill

ADA adenosine deaminase, *BAL* bronchoalveolar lavage, *CSF* cerebrospinal fluid, *CT* computed tomography, *CXR* chest radiograph, *FNA* fine needle aspiration, *LAM* lipoarabinomannan, *MRI* magnetic resonance imaging, *US* ultrasound

biopsy or medical thoracoscopy) increases the likelihood of positive microscopy and culture and is recommended if available [23].

Central Nervous System TB

TB meningitis (TBM) is the commonest manifestation of CNS TB and the most severe form of tuberculosis. It has a high morbidity and mortality (up to 50% in some case series), in part due to diagnostic delays from its insidious and variable presentation [24]. An altered level of consciousness may be seen more frequently in PLWHIV [25]. Cerebral infarcts are also more commonly present on cranial imaging [26]. Investigation of suspected TBM is the same as HIV uninfected individuals, although the differential diagnosis for potential CNS infection in HIV is broader—including for example fungal infections and lymphoma. It is important to note that CSF may be acellular in advanced HIV disease [24].

Disseminated TB

Disseminated TB occurs following lymphatic or haematogenous spread of TB bacilli from the lungs to multiple other body sites. It is more common in advanced HIV infection and may present with a range of non-specific symptoms, creating diagnostic difficulty. Mycobacteraemia may be detected, and blood cultures for MTB should be obtained [27]. TB blood cultures are up to 5 times more likely to be positive in HIV positive than negative individuals [28].

Detection of mycobacterial lipoarabinomannan (LAM) in the urine is an adjunctive indicator of disseminated TB. Determine TB-LAM is a commercial low cost, point of care urine dipstick test. It has poor sensitivity when used for screening in the general population and is optimal in those with low CD4 counts. It has been shown to identify patients at high risk of death and leads to reduced mortality in severely ill patients, who particularly benefit from early commencement of treatment for TB. Urine LAM testing is recommended by WHO in adults with HIV infection, signs and symptoms of TB and CD4 counts of 100 cells /μL or less [29]. New assays are being developed which have greater sensitivity, and hence may be more broadly-useful rule out tests in PLWHIV with suspected active TB.

Treatment of active TB/HIV Co-infection

Effective antiretroviral therapy became a reality in 1996. It is generally a combination of three drugs that target the HIV replication cycle, and to which the specific virus is susceptible.

Combination ART is not a cure for HIV infection but can lead to near total suppression of HIV replication and plasma viral load, with remarkable and sustained improvements in health [31].

Timing of ART Initiation

The WHO recommends ART is started in all PLWHIV, regardless of CD4 count or clinical stage. HIV and TB are often diagnosed concurrently. Treatment for TB should be initiated first, in order to reduce the risk of TB immune reconstitution inflammatory syndrome (TB-IRIS, see next section). The timing of ART initiation in HIV/TB co-infection requires careful consideration of the risks and benefits of early versus late introduction—these being defined as within two weeks and greater than 8 weeks from starting treatment for TB respectively.

Early ART initiation places a high pill burden on the patient, increases the risk of drug-drug interactions and additive side effects, and the likelihood of TB-IRIS. All of these may contribute to decreased patient adherence. However, if ART initiation is delayed, there is a risk of developing further opportunistic infections and death rates are higher (Fig. 3). This is particularly true in patients presenting with advanced HIV disease and low CD4 counts (<50 cells/μL) [32, 33].

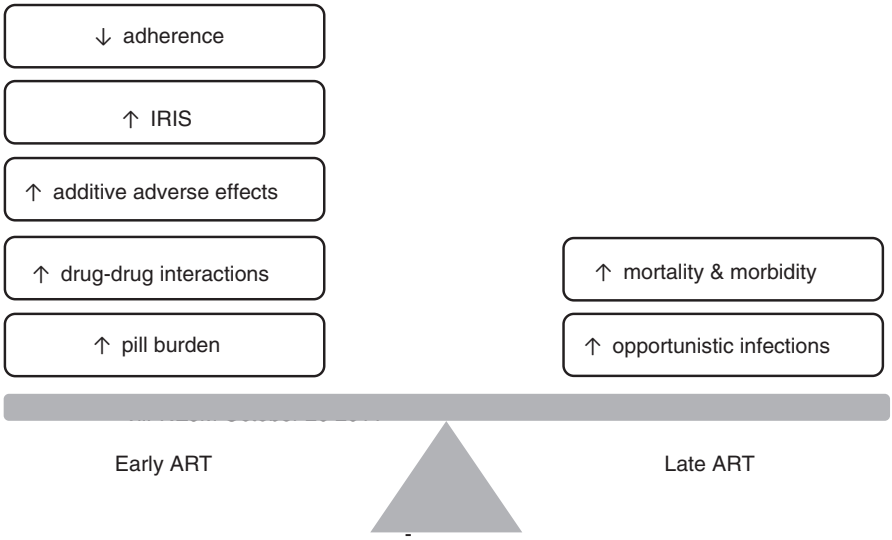


Fig. 3 A balancing act—when to start ART in TB/HIV Coinfection

It is recommended that all PLWHIV diagnosed with TB should be started on ART within 8–12 weeks of starting TB treatment. The greatest mortality benefit with early ART initiation is seen in the most immunosuppressed patients. Therefore, in patients with a blood CD4 count below 50 cells/μL, ART should be commenced as soon as treatment for TB is tolerated and certainly within 2 weeks. The only exception to this is CNS TB infection, where IRIS has a high associated mortality and therefore ART initiation should be delayed [15, 32].

Choice of ART Initiation in HIV/TB Co-infection

Types of ART

Antiretroviral medications act to disrupt various steps in the lifecycle of HIV. Nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) act on the HIV viral enzyme reverse transcriptase to prevent viral replication. Protease inhibitors (PIs) block the viral enzyme protease from cleaving long polypeptide chains into mature viral proteins. PIs are often combined with another medication (ritonavir, itself a PI, or cobicistat, a CYP3A Inhibitor) that acts as "boosters" by slowing down metabolism of the main drug. Integrase inhibitors or integrase strand transfer inhibitors (INSTIs) block the integrase enzyme, preventing the insertion of viral genomic material into the host DNA. Entry inhibitors block HIV from entering host CD4 T lymphocytes and include fusion inhibitors and chemokine receptor 5 (CCR5) antagonists (Table 4) [34, 35].

Table 4 Commonly used antiretroviral drugs

Class	Examples
Nucleoside Reverse Transcriptase (NRTI)	Abacavir (ABC), Emtricitabine (FTC), Lamivudine (3TC), Tenofovir alafenamide (TAF), Tenofovir disoproxil fumarate (TDF)
Non-Nucleoside Reverse Transcriptase (NNRTI)	Efavirenz (EFZ), Nevirapine (NVP), Rilpivirine (RVP), Doravirine (DOR)
Protease Inhibitors (PI)	Atazanavir (ATZ, ATZ/r, ATZ/c), Darunavir (DRV/r), Lopinavir (LPV/r)
Integrase Inhibitors (INSTI)	Dolutegravir (DTG), Elvitegravir (EVG/c), Raltegravir (RAL), Bictegravir (BIC)
CCR5 Inhibitors	Maraviroc (MVC)
Fusion Inhibitors	Enfuvirtide (T20)

Listed alphabetically by class with abbreviations in brackets. Where drugs are boosted r (ritonavir) or c (cobicistat) are added

Drug-Drug Interactions in HIV/TB Co-infection

Overlapping drug toxicities and interactions must be carefully considered when choosing or changing TB treatment and ART regimens. See Box 1 for useful resources to check HIV drug interactions.

Box 1: Useful Resources in HIV Drug Interactions
Liverpool University HIV drug interactions website: www.hiv-druginteractions.org
Toronto General Hospital website: https://hivclinic.ca/druginformation/drug-interaction-tables/

Antiretroviral medications can be co-administered with ethambutol, pyrazinamide and isoniazid without significant interactions or need for any planned dose adjustments. The main ART interaction is with rifamycins (rifampicin, rifabutin and rifapentine). Rifamycins, normally as rifampicin, form the backbone of drug-sensitive TB treatment. Non-rifamycin containing regimens require longer treatment durations and are less effective [36].

Rifampicin is the most potent known inducer of cytochrome P450 enzymes (CYP450) and interacts with many other drugs. Co-administration of rifampicin causes increased metabolism and therefore decreased serum concentrations of PIs, NNRTIs and INSTIs, rendering them less effective (Table 5). NNRTIs and PIs themselves also affect CYP450, resulting in bidirectional drug-drug interactions. There is no interaction between rifampicin and NRTIs, however triple NRTI ART regimens are less effective [31].

Rifabutin is a less potent enzyme inducer and can be used an alternative to rifampicin. It has been shown to be efficacious against TB but there are not sufficient studies to determine if it is as effective as rifampicin across all patient populations [37]. Rifabutin is also more expensive than rifampicin. The same applies to rifapentine, which is even less studied in the treatment of active TB. Its longer half-life may offer some advantages within certain therapeutic regimens.

Choice of ART Regimen in HIV/TB Co-infection

This section aims to give a basic overview of widely used ART. It must be remembered that new antiretroviral drugs are being regularly developed and introduced into clinical practice. National (for example British HIV Association BHIVA) [15] and international (for example WHO) [31] guidelines are frequently updated to reflect this and should be consulted for current best practice advice. The general principle is to form an NRTI "backbone" with two NRTI medications and then add an additional third medication from another class.

Table 5 Interactions between certain antiretroviral drugs and rifampicin/rifabutin [15]

ART	Rifampicin	Rifabutin	Notes
NRTIs	✓✓	✓✓	No significant interactions[a]
Efavirenz	✓	✓	Rifampicin is the rifamycin of choice with EFZ Standard EFZ dose is recommended Rifabutin dose should be increased (450 mg OD) with EFZ
Nevirapine	x	✓	Use nevirapine with caution in rifabutin, use standard doses
Rilpivirine	x	✓/ x	Rilpivirine with rifabutin not recommended in UK Increased rilpivirine dose to 50 mg OD with rifabutin in US
Protease Inhibitors	x	✓	Boosted and unboosted PIs should be avoided with rifampicin Rifabutin dose should be reduced to 150 mg OD or thrice weekly
Integrase inhibitors	✓	✓✓	Increase dolutegravir dose to 50 mg BD with rifampicin Increase raltegravir to 800 mg BD with rifampicin
CCR5 inhibitors	✓	✓✓	Maraviroc dose should be 600 mg BD with rifampicin Avoid with rifampicin if also on EFZ or NVP

BD twice daily, *CCR5* chemokine receptor 5, *EFZ* efavirenz, *NRTIs* nucleoside reverse transcriptases, *NVP* nevirapine, *OD* once daily, *PIs* protease inhibitors, *UK* United Kingdom, *US* United States of America

✓✓No interaction, can safely be used together

✓Interaction, can be used together but dose adjustments may be needed (see notes)

x Significant interaction, should not be used together

[a]Rifamycins and tenofovir alafenamide interact but the clinical significance is not yet known

Recommended first line NRTI backbones include tenofovir disoproxil fumarate, TDF (which has the added advantage of activity against hepatitis B) and emtricitabine or lamivudine. As tenofovir can cause nephrotoxicity, abacavir can be used as an alternative in patients with renal impairment and does not require dosage adjustment [1, 15]. However, this drug is associated with hypersensitivity (in around 3% of PLWHIV—and where available testing for HLA-B5701 should be performed before using it). It is also rather less effective than TDF at high starting HIV loads, and has been associated with an increased risk of significant cardiac events, so should be avoided if the patient has a strong history of cardiac disease.

Tenofovir alafenamide is a newer antiretroviral, that has greater antiviral activity that the older TDF. Pharmacokinetic studies have shown a significant reduction in plasma tenofovir levels when rifampicin and tenofovir alafenamide are co-administered but intracellular tenofovir levels remain greater than those seen with standard TDF. Currently, the clinical significance of this is unknown and UK guidelines do not presently recommend tenofovir alafenamide containing ART regimens in patients receiving rifamycin-based treatment for TB [15].

Efavirenz-based ART regimens are recommended for patients receiving rifampicin as part of treatment for TB. Rifampicin co-administration has been shown to reduce serum efavirenz concentrations and previously weight-based increased doses of efavirenz had been recommended. More recent studies have shown that rifampicin-based treatment for TB does not have a significant or sustained effect on efavirenz levels and standard dosing (EFZ 600 mg OD) can be safely used [15, 38].

Nevirapine, all protease inhibitors and drugs boosted with cobicistat should be avoided in ART naïve individuals with TB co-infection [15]. Nevirapine concentrations are significantly decreased by rifampicin, with area under the curve (AUC) decreases of 20–50%. Rifampicin causes AUC reductions of up to 75% for protease inhibitors and attempts to counteract this by increasing doses of PIs leads to unacceptable levels of gastrointestinal side effects including hepatoxicity. Integrase inhibitors such as raltegravir and dolutegravir can be used as alternatives if efavirenz is contraindicated, such as in those with a history of mental health problems. It is recommended that the doses are increased if used with rifampicin, and given twice rather than once daily [15].

Patients on Established ART

While it is common for HIV and TB to be diagnosed concurrently, active TB can also present in PLWHIV, even if they are already on ART. If a patient has an undetectable HIV load, it is recommended that they continue on their current ART regimen. If this includes a protease inhibitor, rifabutin should be substituted for rifampicin to treat rifampicin-sensitive TB. Here too interactions are a potential issue, as the plasma concentration of rifabutin is increased (and hence the prescribed dose should be reduced), when using concurrent PIs that reduce its metabolism [15].

Choice of TB Treatment in HIV/TB Co-infection

Standard daily administration of first line therapy for TB (RHZE + pyridoxine) is recommended for PLWHIV with drug sensitive TB.

Fixed dose combination tablets for both TB and HIV should be used where possible to reduce pill burden and improve adherence.

TB IRIS

The term immune reconstitution inflammatory syndrome (IRIS) refers to the paradoxical worsening of either known or sub-clinical pre-existing infectious conditions after the initiation of ART in PLWHIV. Restoration of immune function results in an exaggerated local or systemic inflammatory response. It is most commonly seen

with mycobacterial, herpes-virus and invasive fungal infections. This usually occurs in the first few months after the initiation of ART [39].

Tuberculosis-associated IRIS (TB-IRIS) presents in one of two ways. Paradoxical TB-IRIS occurs when there is a worsening or recurrence of tuberculosis disease after ART initiation, in patients already established on treatment for TB. Unmasking TB-IRIS refers to a new diagnosis of previously subclinical TB, usually with particularly acute inflammatory features, shortly after ART initiation [40].

Paradoxical TB-IRIS is common, affecting 8–43% of patients with tuberculosis starting ART. Its frequency is maximal with early initiation of ART. Patients with lower blood CD4 counts/ higher plasma HIV loads are at greatest risk [41]. Immunological studies suggest IRIS is a complex hyperinflammatory process, involving both innate and adaptive immune responses. It is most often seen where there is a high antigen burden from multi-bacillary lesions and pre-ART profound immune suppression. Potentially implicated mechanisms include an increase in activated monocytes and circulating pro-inflammatory cytokines, dysregulated matrix metalloproteases and an expansion of mycobacterial specific Th1 CD4+ T cells [42, 43].

Clinical Features and Diagnosis of TB IRIS

There is no validated diagnostic test for TB-IRIS. Diagnosis relies mainly on clinical parameters. Features include new or enlarging lymph nodes, recurrence of fever, worsening of respiratory symptoms and new CXR findings, such as pleural effusion or worsening pulmonary infiltrates (Fig. 4). In addition, there may be conversion of tuberculin skin test or IGRA from negative to positive. Many biomarkers are being evaluated in the study of IRIS, but none have yet been validated as a diagnostic tool. Of note in routine clinical practice, CRP may be significantly elevated with TB-IRIS [42, 44].

Consensus definitions of paradoxical TB-IRIS vary but include a confirmed diagnosis of TB with initial response to anti-TB treatment, diagnosis of HIV with recent ART initiation (usually within 3 months) and deterioration in clinical condition due to an inflammatory process, with exclusion of other causes. One widely used definition is the International Network for the Study of HIV associated IRIS (INSHI) case definition (Box 2), which has been validated for use in low resource settings [40, 45].

Although IRIS is confined to PLWHIV started on ART, a similar phenomenon can be observed with the introduction of effective treatment for TB by itself in PLWHIV not using ART or people known to be HIV negative—where it is termed a TB paradoxical reaction (PR). The estimated frequency of these reactions is between 2–23%. It is a phenomenon that has been observed for many years and predates the recognition of TB-IRIS. It is generally less inflammatory than IRIS [46, 47].

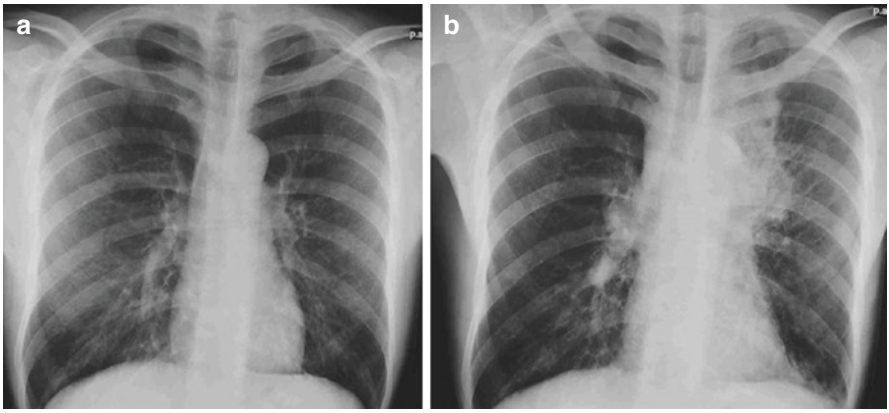


Fig. 4 Paradoxical IRIS following initiation of antiretroviral therapy**. Panel A**—Normal Baseline chest radiograph at start of treatment for cervical lymph node TB in newly diagnosed PLWHIV with blood CD4 count 230 cells/μL. Patient commences antiretroviral therapy one week later. **Panel B**—Chest radiograph (CXR) at week 3 following onset of new cough, fever and malaise for 4 days. CXR shows increased upper mediastinal widening and left upper zone consolidation consistent with lymphadenopathy and parenchymal changes. Investigation revealed no other disease process, drug sensitive lymph node TB and the symptoms and signs resolved during investigation with no need for specific further treatment

Box 2 INSHI TB-IRIS Case Definition 2008

Antecedents	
• Diagnosis of TB fulfils WHO criteria pre-ART • Initial response to TB treatment pre-ART	
Clinical Criteria (1 major or 2 minor)	
Major Criteria	Minor Criteria
• New or enlarging lymph nodes, cold abscess or other focal tissue involvement • New/worsening radiological features of TB • New/worsening CNS TB • New/ worsening serositis (pericardial or pleural effusion)	• New/worsening constitutional symptoms (weight loss, fevers, night sweats) • New/worsening respiratory symptoms (cough, dyspnoea, stridor) • New/worsening abdominal pain (peritonitis, hepatosplenomegaly, abdominal adenopathy)
Exclude alternative explanations for deterioration where possible	
Poor adherence Failure of treatment for TB due to drug resistance Another opportunistic infection or neoplasm Drug toxicity	

Outcomes and Treatment of TB IRIS

IRIS associated with tuberculous meningitis (TBM-IRIS) may complicate up to 47% of ART naïve TBM/HIV co-infected patients started on ART [48]. PLWHIV at highest risk of TBM-IRIS include those with CSF culture positivity at time of TBM diagnosis and people with higher CSF neutrophil counts [48]. Morbidity and

mortality are high in CNS TB-IRIS, with death occurring in almost 30% in some studies [49]. This forms the basis for the current recommendation that ART initiation should be delayed in PLWHIV diagnosed with CNS TB.

Excluding CNS disease, mortality in TB IRIS is low and both TB-PR and paradoxical TB-IRIS are often self-limiting [50]. Investigations must be undertaken to rule out other explanations for clinical deterioration, such as additional infection or drug resistance. Treatment is largely supportive, including analgesia, antiemetics and intravenous fluids where indicated. Abscesses may require surgical or percutaneous drainage. Treatment for TB and ART should not be interrupted if at all possible.

Dampening down the excessive immune response with corticosteroids should be undertaken in clinically significant IRIS. For example, starting with 40 mg of oral prednisolone and tapering down over 6–8 weeks. The clinical course varies and may take weeks or months resolve.

Recent randomised-controlled trial (RCT) data from the PredART trial showed a reduction in the risk of paradoxical TB-IRIS by 30% when prednisolone was started concurrently with ART initiation in patients with CD4 counts <100.There was also a reduction in the severity of IRIS, with no increase in significant adverse effects [51]. Steroids may therefore play a role in preventing as well as treating TB-IRIS in selected at-risk patients in future.

Diagnosis and Treatment of Latent TB Infection in HIV

Latent TB infection (LTBI) is defined as a state of persistent immune response to *M. tuberculosis* without clinically-manifest evidence of active TB disease. Prevention of progression from latent infection to active disease is a cornerstone of efforts to prevent new TB cases. People living with HIV are at higher risk of progression from LTBI to active disease, with the risk increasing with lower CD4 counts. ART reduces the risk of progression to active TB disease but additional treatment for LTBI may also be indicated [15].

All patients with HIV should be screened for active TB disease with a clinical assessment and consideration of a CXR as a minimum. Once active TB has been excluded, it may be appropriate to screen for LTBI. All PLWHIV who are close contacts of people with infectious TB should be offered screening for LTBI, in line with national TB standards [15].

Interferon Gamma Release Assay (IGRA) testing is recommended over tuberculin skin testing (TST) as a first line test for LTBI in PLWHIV. If a borderline test (i.e. one which falls around the positive/negative cut-off) or an indeterminate result (failure of the positive or negative controls within the test kit) is obtained, the IGRA should be repeated. If the initial and repeat IGRAs remain borderline or indeterminate, then clinical judgment on risks and benefits on an individual patient basis will be required to determine if additional treatment for LTBI should be offered [15, 52].

Specific treatment for LTBI in PLWHIV is the same as that in HIV negative individuals. Currently recommended regimens of widely available drugs include either 6 months of isoniazid (with pyridoxine); 3 months of rifampicin and isoniazid (with pyridoxine) or 4 months of rifampicin. Isoniazid-only regimens may be preferred if there is concern of rifampicin interactions with existing ART regimens [52].

In high incidence TB settings, the WHO currently recommends that PLWHIV who do not have active TB disease receive at least six months of isoniazid preventative therapy (IPT), without necessarily waiting for specific tests for LTBI. There is evidence that IPT for 36 months may be safe and beneficial in very high-risk environments such as prisons, where there is likely continuous exposure to infection. This approach is not recommended in low incidence settings. Despite WHO endorsement, uptake of IPT has been poor, with fewer than 25% of PLWHIV receiving it—with South Africa alone accounting for the majority of this figure [1, 3].

Shorter treatment regimens for LTBI in PLWHIV are currently being explored. Three months of weekly rifapentine plus isoniazid has been shown to be as effective and safe as 9 months of daily isoniazid alone [53]. More recently, a one-month course of daily rifapentine plus isoniazid has been shown to be non-inferior to 9 months of daily isoniazid [54]. In both cases, the shorter regimens had similar rates of adverse reactions and better treatment completion rates compared to the standard arms. Currently rifapentine is not easily available in many low- and middle-income countries and this, plus its relatively high cost, may prove a barrier to implementation.

Drug Resistant TB in HIV

HIV infection is a risk factor for all forms of TB, both drug-susceptible and drug-resistant. However, it is not clear whether HIV positive individuals have a specifically increased risk of multidrug resistant (MDR) or extremely drug resistant (XDR) TB [55].

In PLWHIV with isoniazid mono-resistance (the most common form of drug resistance), a 6-month regimen of rifampicin, ethambutol, levofloxacin and pyrazinamide is recommended [15].

Management of MDR/XDR TB in patients with HIV is complex and should be undertaken in conjunction with regional centres of expertise. In resource-rich settings, use of whole genome sequencing (WGS) to give faster, more comprehensive resistance profiles is leading to more individualised treatment regimens for MDR-TB. Detailed discussion of interactions between antiretrovirals and drugs used to treat MDR/XDR-TB are beyond the scope of this chapter, but further information can be found using the links in resource Box 1.

An important practice point is the recent WHO endorsement of bedaquiline as a key first line drug and hence its likely wider use. This is important to consider as PLWHIV and MDR/XDR-TB may be on therapy such as efavirenz, which can decrease bedaquiline levels or cobicistat- or ritonavir-boosted protease/integrase

inhibitors, which can significantly raise levels, by increasing or impairing drug metabolism respectively [56].

All patients with MDR-TB and HIV not already on ART should be commenced on ART as soon as they have been stabilised on treatment for TB.

Key Messages

- TB/HIV co-infection is common. All patients diagnosed with active TB should be offered an HIV test; and all patients diagnosed with HIV should be screened for active TB
- Diagnosis of TB in HIV may be difficult and a high index of suspicion should be maintained. Mycobacterial blood and urine cultures, plus urine LAM may be useful in disseminated disease.
- Start treatment for TB prior to ART. Aim to start ART within 2 weeks if CD4 count <50 and as soon as practicable in other cases (certainly by 8–12 weeks). Delay starting ART in CNS TB infection due to increased risk of IRIS-related severe disease
- TB-IRIS is common. Prednisolone should be used for treatment of clinically significant paradoxical TB-IRIS
- Testing for latent TB in PLWHIV should be considered in all patients. ART significantly reduces the risk of active TB. Specific treatment for latent TB is also of additional value in selected populations

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Radiology of Tuberculosis

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Introduction

Despite the availability of long-established anti-microbial chemotherapy, tuberculosis (TB) remains a leading cause of death as a result of infection and a major public health concern worldwide [1]. Early diagnosis is critical to initiating prompt effective management and limiting further transmission of the disease.

Often considered the great mimic and the benign imposter, TB can manifest with a myriad of non-specific imaging appearances leading to confusion with other granulomatous diseases like sarcoidosis and fungal infections, but also with neoplastic processes [2]. Familiarity with the classical appearances of TB and also the wider more non-specific imaging spectrum of tuberculosis is desirable for a more nuanced and contextual approach to imaging findings.

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Imaging Tuberculosis: The Modalities

The modern radiology armamentarium offers a number of different imaging modalities to diagnose, characterise and follow-up the manifestations of TB in various organ systems. This ranges from Chest Radiography (CXR), Computed Tomography (CT) and Ultrasound (US) for thoracic and body imaging, Magnetic Resonance Imaging (MRI) for musculoskeletal and neurological manifestations of TB and Positron Emission Tomography (PET)-CT for troubleshooting diagnostic and treatment related dilemmas. In addition, CT and US guided directed biopsies complement other sampling strategies, whilst interventional techniques of vascular catheterisation are used in the emergency management of complications such as haemoptysis related to TB.

Imaging Considerations in Pulmonary and Abdominal Tuberculosis

Conventional chest radiography (CXR) is central to first-line imaging in suspected pulmonary TB [3]. It is readily available and affords a reasonable overview of parenchymal, pleural and lymph nodal manifestations of pulmonary tuberculosis. Being two-dimensional however, subtle findings such as micro-nodular patterns can be elusive on CXR. Nonetheless, CXRs remain a vital tool at the start of and over many time points in the TB journey of the patient. It is also important to note that negative chest radiographs should not be taken as the last word in the immunocompromised patient, as they can sometimes look normal despite disease.

Computed Tomography (CT) is the workhorse in thoracic, abdominal and pelvic imaging. It has the major advantages of being rapidly performed, relatively inexpensive and readily available with in-depth anatomical information in three-dimensions, enabling detection of radiographically occult abnormalities. Attendant with CT is a higher radiation dose; use must be judicious, especially in younger patients. Recent improvements in dose optimisation methods in modern CT scanners allows a thoracic CT to be achievable with effective doses as low as 2.0–2.5 milli-Sieverts (mSv) [4]. To put that into perspective, this is roughly equivalent to the average natural environmental radiation accrued in 1 year [5]. The use of iodinated contrast enhancement improves diagnostic potential but comes with a theoretical risk of contrast induced nephropathy. Towards this, generic guidelines are in place and the radiologist should be consulted, especially when scanning patients with known renal impairment [6]. Ultrasound (US) is useful in the assessment of complex pleural effusions, elucidating features such as debris and loculation and facilitating safe targeting of diagnostic and therapeutic drainage procedures [7]. US is useful in the assessment of solid abdominal viscera, notably the liver, pancreas, spleen and the genito-urinary system. It is sensitive in assessing for small traces of

free intraperitoneal fluid. Given that it is a radiation-free modality, it is a particularly valuable tool in imaging children [8]. MRI has a complementary role in abdominal TB imaging. It is a radiation free modality.

Radiology of Pulmonary Parenchymal, Pleural and Nodal Tuberculosis (See Tables 1, 2, and 3)

Pulmonary disease is the most common manifestation of tuberculosis. However, it is important to note that the vast majority of immunocompetent individuals exposed to *M. tuberculosis* do not develop clinical disease. It is estimated that between 5–15% of individuals infected progress over months to years to clinically active TB disease [9]. Traditional radiological classifications dichotomise pulmonary TB into *primary* and *post-primary* forms, based on time from first exposure. After the first or index exposure, the fate of an inhaled bacillus is either elimination by an effective innate immune response, or containment. Containment may result in the bacillus lying dormant or *latent* until it reactivates, potentially progressing to active *primary TB* (see Chap. 2).

Primary TB manifestations range from the relatively self-limiting focal lung granuloma, the well-described *Ghon focu*s, that forms after first exposure, to a more clinically apparent triad of enlarged regional lymph nodes, pneumonic air-space consolidation and pleural effusion, referred to as *progressive primary TB.* (Table 1). *Post-primary TB* on the other hand, is related to reactivation or reinfection in a previously exposed host. A key feature of post-primary TB is a cavitary response within air space consolidation or nodules and characteristic distal small airway involvement with endo-bronchial exudative plugging. This classification of TB offers key pathophysiological insights into the modes of disease spread; the key radiological features in these two sub-groups are summarised in Table 1. It is noteworthy that *primary TB* typically affects patients of a young/paediatric age group in endemic regions. In

Table 1 Radiology of primary and post-primary pulmonary tuberculosis

Primary/Progressive TB	Post-primary TB
– Intra-thoracic lymph nodal disease (ITLND)(children 80–90% > > adults)	– Nodal disease (ITLND) increasingly demonstrated on CT series, but less common compared to primary disease
– Often asymmetric ipsilateral	– Air-space consolidation—upper lobe predominance
– Air space consolidation—any lobe	– Bronchogenic (tree-in-bud) cavitary nodular disease
– Adults 80–90% > children	– Pleural fluid 10–30% (unilateral > bilateral)
– Pleural effusion (unilateral > bilateral)	– Miliary TB
– Adult 30–40% > children	
– Miliary TB 2–4% (children > adults)	

Table 2 Features of Disease activity on Imaging (Pulmonary TB)

Disease Activity	Inactive Disease
– Thick walled or new cavitation – New consolidation – New nodules centrilobular / tree-in-bud – ITLND—necrotic nodes / new nodes – Pleural effusion – FDG PET positive nodes, parenchymal scarring / nodules	– Architectural distortion / volume loss – Nodal calcium – Bronchiectasis – Stable (> 6 months) fibro-nodular scarring

Table 3 Complications & Sequalae of Intra-thoracic Tuberculosis

Complications & Sequalae of Intra-thoracic Tuberculosis	
Pleuro-pericardial – Fibrothorax (restrictive) – Constrictive pericarditis – Bronchopleural fistula – Pneumothorax – Chronic empyema – Empyema necessitans – Chest wall TB	**Parenchymal** – Distortion, volume loss – Fibrosis – Cavity aspergilloma colonisation – Vascular inflammation and invasion – Long term risk of scar carcinoma
Airway complications: – Traction broncheactasis, – Tracheo-bronchial stenosis – Broncholith **Mediastinal complications:** – Mediastinal fibrosis, – Oesophageal strictures, traction diverticulae or fistulae	**Haemoptysis** What to look for? – Active cavitary disease – Bronchiectasis – Cavitary aspergilloma colonisation – Hypertrophied bronchial artery or pulmonary artery branch pseudo-aneurysm

parts of the world where effective public health measures have reduced overall disease prevalence, the demographic is shifting with more patients exposed for the first time as adults.

Whilst such considerations of natural history have a bearing on the spectrum of radiological features, it is now increasingly appreciated, through research into finger printing of mycobacterial strains and a better understanding of host susceptibility, that the clinico-radiological patterns are predicated more on immune competence of the host, rather than time from exposure. This is best exemplified in HIV wherein the immune status, reflected by CD4 counts, is a predictor of the radiological spectrum of disease. Therefore, the imaging findings in TB are more pragmatically viewed as having features of active TB infection, (transmissible in the context of active pulmonary TB) or latent TB infection (LTBI) (an asymptomatic and non-transmissible state) [10]. It is also clinically more relevant to separate the active from the inactive disease, rather than distinguish between primary and post-primary tuberculosis, which is academic in relation to patient management) [10, 11]. Indeed, with increased use of CT imaging, it is becoming more apparent that radiological manifestations in *primary* and *post-primary* TB categories show considerable overlap and the distinctions may be more blurred than otherwise

thought. Elucidated below are the key features of active pulmonary TB in the categories of parenchymal, pleural and nodal pulmonary tuberculosis, that we expect to encounter in routine clinical practice. Whilst not specific or pathognomonic, these manifestations should, in the correct context, trigger more investigations to rule out TB.

Intra-thoracic Lymph Nodal Tuberculosis (ITLNTB)

Nodal involvement is the hallmark of childhood TB (*primary TB*) [7]. It tends more often to be asymmetric and ipsilateral to pneumonic insult (often right-sided), a helpful feature to distinguish it from the more bilateral symmetric patterns common in sarcoidosis [7]. (Figs. 1 and 2) illustrate how nodal enlargement can be assessed on chest radiographs with due attention to anatomical landmarks. Lymph nodes are better visualised on CT; a classical feature of TB lymph nodes is central hypoattenuation and peripheral enhancement (Fig. 3). This pattern corresponds to the pathological findings of central caseous necrosis with surrounding granulation tissue [7]. Nodal enlargement can potentially, albeit infrequently, lead to extrinsic bronchial compression or direct invasion of the bronchus with subsequent lobar collapse with potential for bronchial strictures or stenosis as a late complication [11]. ITLNTB is increasingly recognised on CT series in patients with the constellation of post-primary reactivation features, with a frequency between 15% and 43% in immunocompetent patients [12].

Parenchymal TB

Lung parenchymal findings after an index exposure are usually self-limiting, manifesting as a focal pneumonitis/consolidation resulting in an organised granulomatous nodule, known as a *Ghon focus*. The combination of a lung granuloma and lymphadenopathy along its drainage pathway is known as a *Ghon complex*. Calcification in such burnt out nodal and parenchymal scarring marking the site of original infection, forms the *Ranke complex* [13]. Patients with previous infection with TB often have evidence of these tell-tale features on imaging. If however, the disease is not self-limiting, more extensive consolidation can occur almost anywhere in the lung. In adults with such progressive primary disease, air-space consolidation (Fig. 4) is a significant feature and findings may be indistinguishable from a community acquired pneumonia.

Parenchymal disease in the immunocompetent host in the context of reactivation or reinfection usually manifests as ill-defined patchy consolidation with or without nodular foci that predominate in the apico-posterior segments of upper lobes and superior segments of the lower lobes [3] (Fig. 5). This is postulated to relate to

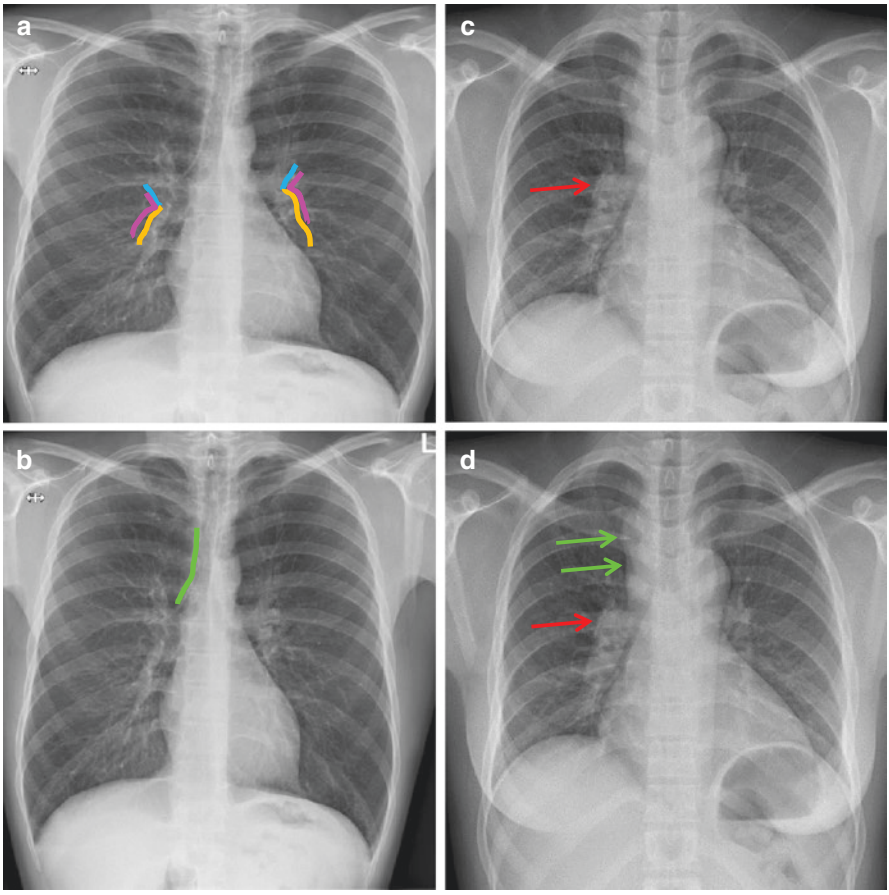

Fig. 1 (**a**) A normal frontal chest radiograph. The pink lines delineate normal hilar points, made up of the intersection between the upper lobe pulmonary veins (lateral borders delineated by the blue lines) and the lower lobe pulmonary veins (denoted by the orange lines). The left hilar point should always be above the right hilar point on a normal chest radiograph. (**b**) Normal right paratracheal stripe constituted by the soft tissue density tracheal wall against a lung air interface. (**c** and **d**) Thickened right paratracheal stripe with a lobulated lateral contour (green arrows) with obscuration of right hilar point by enlargement of the right hilum (red arrows). CT subsequently confirmed typical caseous nodal disease in both locations

relatively reduced lymphatic drainage and increased oxygen tension in these regions, facilitating bacillary replication [11]. In a minority of cases, a non-calcified nodule known as a tuberculoma (5–40 mm) may be the predominant manifestation with or without small satellite nodules [11]. Overall, cavitation is a prominent feature of post-primary TB; whilst discernible radiographically (Fig. 5a), cavities are better appreciated on CT (Fig. 5b). Endobronchial small airways involvement with

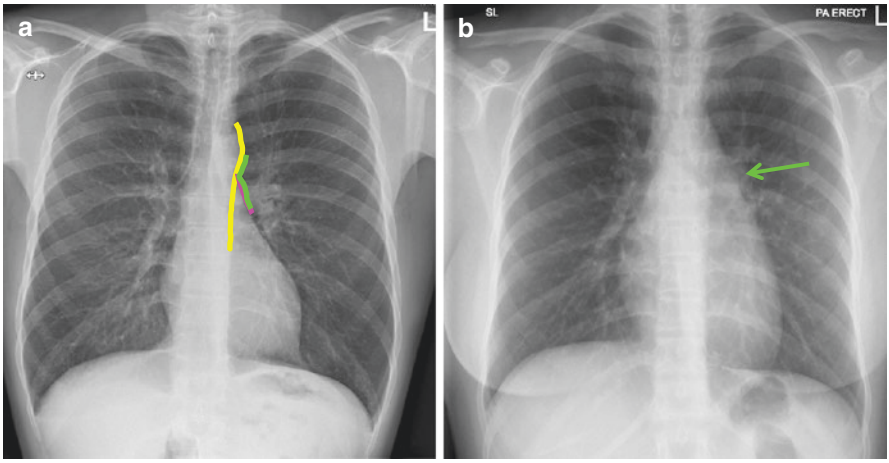

Fig. 2 (**a**) The aortopulmonary window (AP window) should have a concave lateral contour (green line). It is formed as the aortic arch (yellow line) intersecting the main pulmonary trunk (pink line). (**b**) Convex bulging of the AP window(green arrow) should raise suspicion of lymphadenopathy

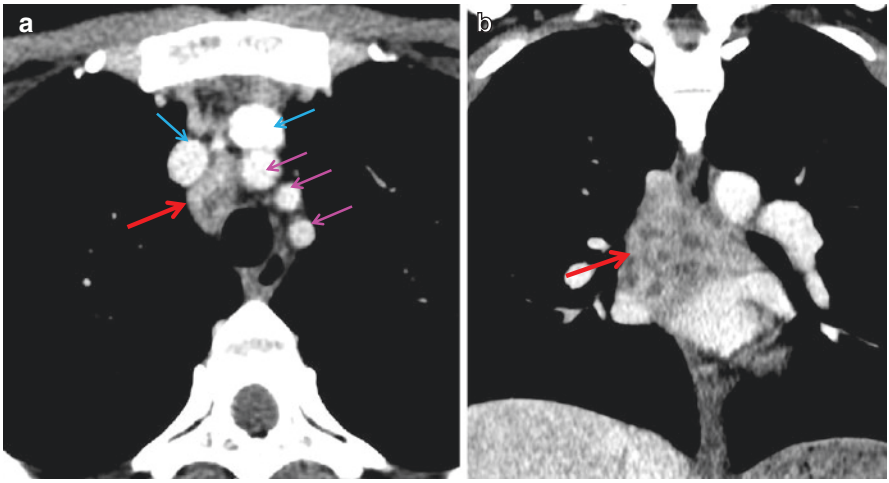

Fig. 3 (**a**) Axial slice of a contrast enhanced CT thorax at the level of the superior mediastinum There is an enlarged right para-tracheal lymph node (red arrow) with peripheral enhancement and low attenuation centre. These appearances are typical of caseous necrosis seen in TB. Note vascular structures, 3 aortic arch branches (pink arrows) and 2 brachiocephalic veins (blue arrows). (**b**) Coronal slice of the same patient at the level of the left atrium. A cluster of abnormal enlarged subcarinal nodes (red arrow) with typical necrotic appearances of caseous nodes

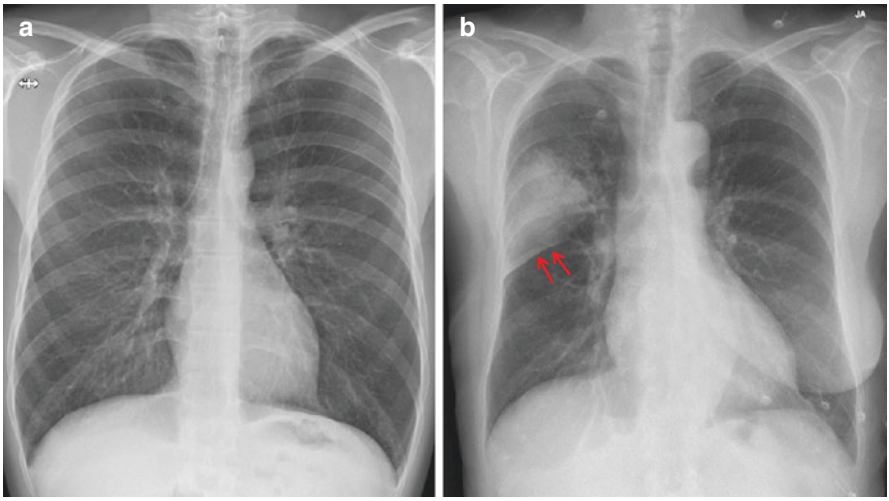

Fig. 4 (**a**) Normal Chest Radiograph (**b**) Right upper lobe consolidation abutting the superior aspect of the horizontal fissure (red arrows)

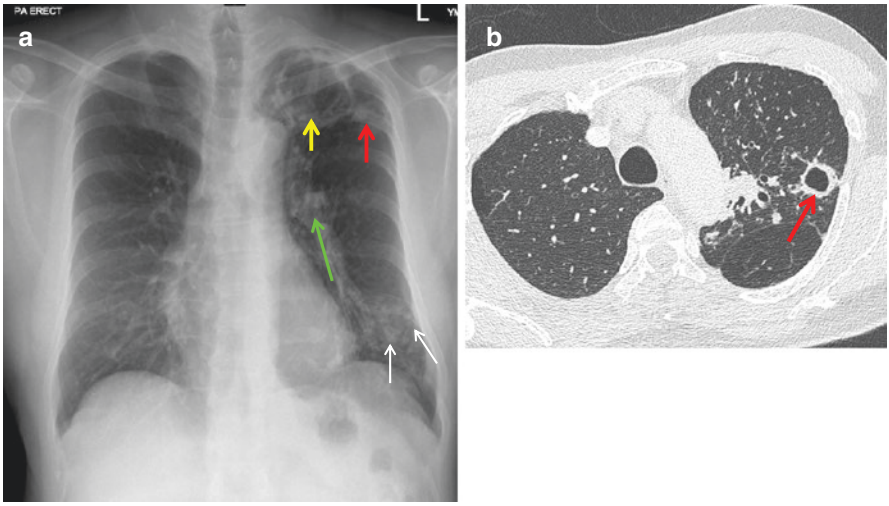

Fig. 5 (**a**) Chest radiograph with a left apical thin-walled cavity (yellow arrow) with an adjacent small opacity (red arrow). Further nodular shadows in the left lower zone (white arrows). Left hilar elevation (green arrow) in keeping with left upper lobe volume loss. (**b**) Axial CT slice of a follow-up CT thorax inferior to the level of the large radiographically visible apical cavity. This shows the subjacent nodule is also cavitary in nature. Surrounding centrilobular nodularity is also noted

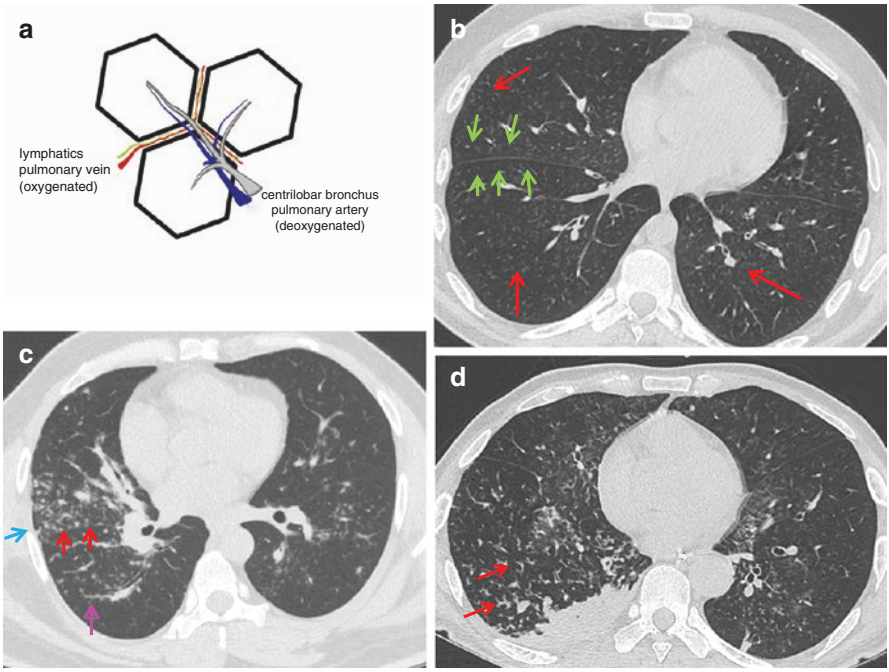

Fig. 6 (**a**) A schematic sketch of secondary pulmonary lobule architecture. The terminal bronchiole and pulmonary artery give off branches that extend to the centre of the hexagonal pulmonary lobule. Pulmonary vein and lymphatics run along the interstitium, depicted in black. *Illustration—Dr Aisling Fagan, Radiology Registrar, Imperial College Healthcare NHS Trust.* (**b**) Axial CT lung image. *Centrilobular nodules distribution*: multiple tiny nodules throughout (red arrows). Sparing of lung immediately adjacent to major fissures (green arrows) and pleural surfaces, also a feature of centrilobular nodules. (**c**) Axial CT lung image *peri-bronchovascular / peri-lymphatic nodular distribution* (in a patient with sarcoidosis): characteristic distribution along fissures (red arrows), sub-pleural interstitium (blue arrow) and interstitial compartment within bronchovascular sheaths (pink arrow). (**d**) Axial CT lung image *with tree-in bud nodular morphology*: In addition to right basal consolidation, there is extensive nodularity that has a branching morphology of interconnected lines and dots that resemble tiny 'V' and 'Y' shapes (red arrows). This pattern is a key feature of TB, but the morphology simply signifies involvement of small airways and is not pathognomonic to any one disease

plugging is another hallmark in reactivation TB disease in immunocompetent subjects. This filling of small airways and terminal alveolar spaces with granulomatous inflammatory exudate, manifests as centrilobular nodules and the typical tree-in-bud nodularity [7] on CT (Figs. 6d and 7). A basic structural and pathological basis of these nodular patterns is illustrated in (Fig. 6) These patterns are not exclusive or specific to TB, but in the right context, they are highly supportive. TB cavities, whilst a key feature of active disease, may persist after treatment and become a nidus for and predispose to bacterial superinfection and fungal ball/mycetoma colonization as well as other secondary sequelae.

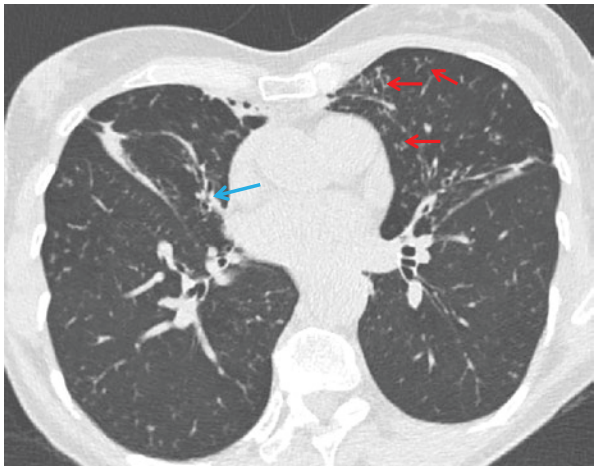

Fig. 7 Axial CT lung slice demonstrates tree-in—bud nodularity most noticeable in the lingula (red arrows). Associated cylindrical bronchiectasis, for instance in the right middle lobe (blue arrow). This relatively anterior distribution of changes is quite typical of non-tuberculous mycobacterial (NTM) infection

Pleural TB

Whilst more typically described in primary TB, especially in adults, pleural effusions can occur in both primary and reactivation tuberculosis [14–18]. The incidence of pleural involvement may be as high as 30% in adult cohorts, in high-burden TB settings, especially where HIV is also endemic [19].

Pleural effusions secondary to TB are largely unilateral with a slight right-sided predominance [14]. The long-held belief that TB pleuritis is purely a delayed hypersensitivity reaction has recently been challenged with the advent of improved culture media. TB pleural effusions are thought to be a manifestation of low level, paucibacillary pleural mycobacterial infection associated with a protracted lymphocyte driven immune reaction [14, 15, 20]. Most are lymphocyte-rich effusions that are free-flowing, debris free and appear clear of any echogenic complexities i.e. anechoic on ultrasound and like any other effusion on plain radiographs and CT. Pleural fibrosis or fibrothorax is a well-described complication of such pleuritis; residual pleural thickening on radiographs and CT (≥10 mm). This may be associated with chronic chest pain and impairment in lung function [21] (Table 2).

Chronic TB empyema is less common and represents a distinct entity of chronic active infection within the pleural space. It is characterised by purulent fluid with neutrophilic response; may occur due to progression of a TB pleuritis or direct extension of infection from nodes and cavities or haematogenous spread [15, 20, 21]. CT is very useful in imaging both pleura and lung to visualise disease extent and assess the empyema in more detail. The radiology of the empyema mirrors the pathological stage of evolution from the viscous effusion to the fibrino-purulent and then to an organizing phase. In the fibrino-purulent phase, CT typically shows thickened visceral and parietal pleura separated by fluid, known as the "split pleura" sign [13, 14] (Fig. 8a). In the later organizing phase, CT may reveal a loculated pleural

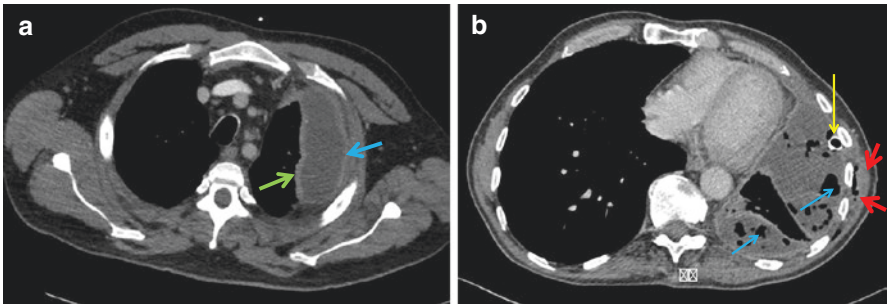

Fig. 8 (**a**) Axial contrast enhanced CT slice demonstrating a left sided pleural collection / TB empyema, with an apparent split pleura sign demonstrating smooth enhancement of the visceral pleura (green arrow) abutting the lung and the parietal pleura (blue arrow) abutting the chest wall. (**b**) Axial contrast enhanced CT slice with a complex loculated left sided pleural collection with smooth pleural enhancement and multiple gas locules (blue arrows). The pleural collection communicates with fluid and gas pockets in a chest wall collection superficial to the ribcage. This constitutes an empyema necessitans. There is a large bore left sided chest drain in situ (yellow arrow)

fluid collection, thickened pleura and variable calcification. Based on stage, the US appearances can range from simple anechoic to complex with visible septations, with or without internal echogenic foci [22]. On CT, gas can ordinarily be seen within an empyema. In some cases, a larger amount of gas can be an indicator of an abnormal communication between lung airspaces/airways and pleural space, a so-called bronchopleural fistula. The majority of empyemas resolve leaving a thickened, scarred, and possibly calcified pleura, however this process may be complicated by the extension and decompression through the chest wall. This is known as empyema necessitans [23, 24] (Fig. 8b).

Miliary TB

Miliary disease occurs when haematogenous seeding of the bacteria results in widespread disease. It can manifest as an isolated pulmonary infection or as a multisystem process usually with profound illness. It may be seen in both primary and post-primary contexts, simply signalling a point at which host's defences are overwhelmed. Patients with impaired immunity, such as those with HIV, are at increased risk [25]. In the lungs, innumerable tiny pulmonary nodules (resembling millet-seeds) are typical. These usually measure 1-3 mm, and can become larger and confluent if left untreated [25]. Miliary disease has a classical chest radiographic appearance, but findings can sometimes be more subtle, [25] manifesting as changes in overall texture (Fig. 9a). Again, CT is more useful. The hallmark of miliary nodules is their random distribution, in that they can occur anywhere within the secondary pulmonary lobule [26] (Fig. 9b).

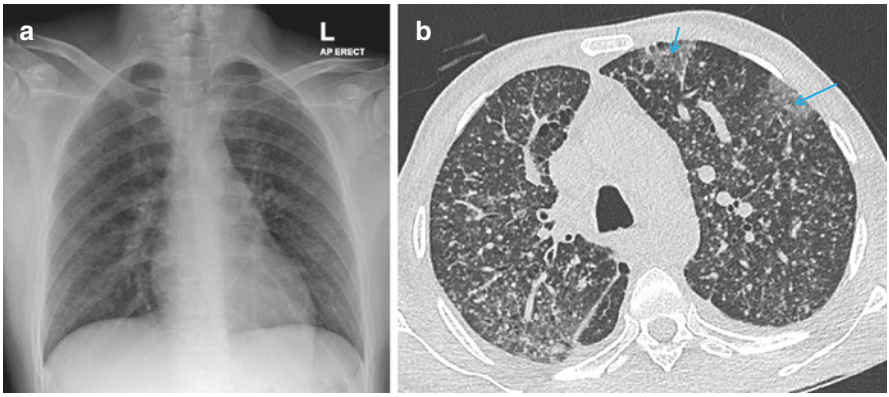

Fig. 9 (**a**) AP chest radiograph demonstrates subtle diffuse nodularity throughout both lungs, giving the lungs an overall abnormal texture in miliary TB. (**b**) Axial CT Lung slice confirms a miliary pattern of nodularity. Miliary nodules do not conform to the typical distribution of peri-lymphatic, tree-in-bud or centrilobular nodules. Interestingly, this patient with confirmed TB also tested positive for COVID-19. Note the well defined peripheral ground glass opacities in the anterior aspect of the left upper lobe (blue arrows)

Non-tuberculous Mycobacteria

Non-tuberculous mycobacteria (NTM) are ubiquitous organisms that can colonise the respiratory tracts of individuals leading to more chronic, drawn out non-specific symptoms [27]. Often the diagnosis is initially suggested based on its characteristic imaging appearances. These typically feature bronchiectasis and bronchiolitis, with associated centrilobular nodules and or tree in bud opacification. In NTM infection, changes typically favour the anterior regions of the lungs. Disease confined to or predominating in the middle lobe and lingula should always raise suspicion of NTM [28] (Figs. 7 and 10). Non-specific patterns similar to those seen in TB can occur.

TB in the Immunocompromised Host & TB-IRIS

Immunocompromised patients in general are at a higher risk of developing tuberculosis. This includes patients on cancer chemotherapy or immunosuppressants, patients with malnutrition, and diabetes mellitus to name a few. Among such risk factors for TB, HIV infection is the strongest; 12% of all new active TB disease cases occur in HIV-positive individuals [29].

Various series quote between 5–21% normal chest X-Ray rates in HIV patients with active TB, more frequently with CD4 counts of <200 per mm3 [7, 30, 31]. In addition, in immunocompromised states, imaging findings of miliary and extrapulmonary disease (EPTB) are more commonly encountered [32].

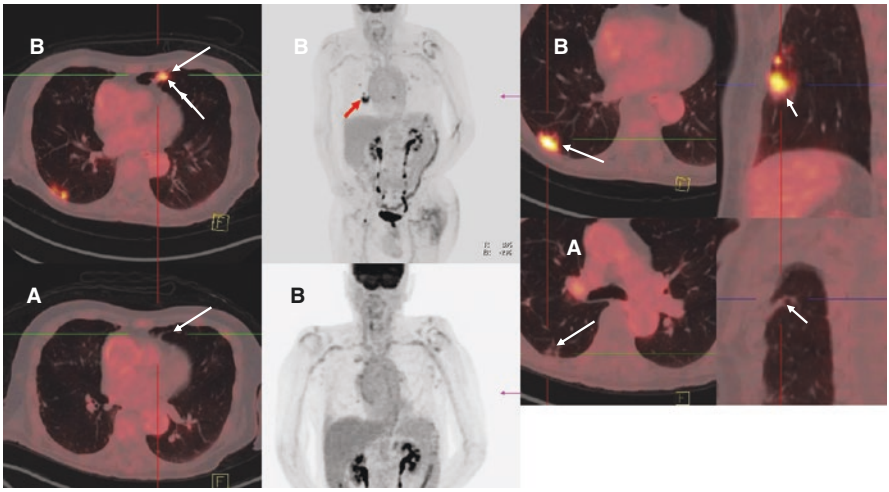

Fig. 10 FDG PET Scans A (2018) and B (2019) in a patient with known culture positive non-tubercular mycobacterial (NTM) multi-drug resistant (MDR) infection. Scans (**A**) axial and coronal and FDG MIP's after treatment in 2018, demonstrate relative tracer quiescence i.e. lack of FDG activity within the peripheral parenchymal changes. Scans (**B**) in 2019 performed when symptoms recurred, show FDG positive focal nodular consolidation (white arrows) in keeping with recurrence of an active infection

Many cases of active TB in adult HIV patients are probably related to reactivation, however, the observed radiological pattern is dependent on the level of immunosuppression [30]. If the cellular immune function is relatively intact, findings tend to be similar to non-HIV immune-competent individuals. Therefore, with preserved CD4 counts (>200/mm3), a reactivation *post-primary* tuberculosis pattern occurs more often, with infiltrates in upper zones possibly with associated cavity formation [30]. However, when CD4 counts are reduced (<200/mm3), a primary TB pattern is more frequently seen, in which nodal disease (ITLND) predominates [32].

It is also worth keeping in mind, that in HIV positive patients who are on treatment, a classic post-primary TB radiology pattern can emerge as restoration in cell mediated immunity occurs. In this context, it is important to be aware of the immune reconstitution inflammatory syndrome (TB-IRIS) that may occur as impaired immunity is allowed to rebuild during TB treatment [33]. Whilst this IRIS response can also occur in non-HIV patients, it is commoner in HIV positive individuals on highly active antiretroviral therapy (HAART) [34–36]. In response to HAART, an improving CD4 T lymphocyte count may unmask previously undiagnosed latent tuberculosis infection [21] or cause deterioration of known TB i.e. provoke a *paradoxical reaction* [37, 38]. Diverse radiological manifestations are reported. Of these, the commonest is enlargement of lymph nodes throughout the

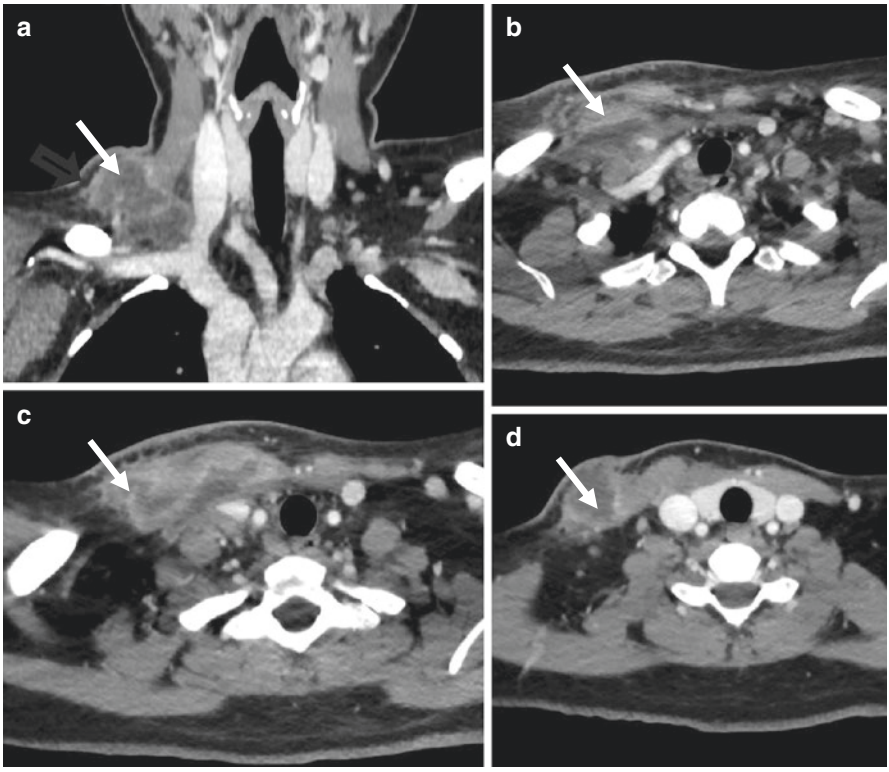

Fig. 11 Necrotic cervical lymphadenopathy in a case of TB paradox: Post-contrast CT in the coronal (**a**) and axial (**b-d**) plane demonstrate a large, peripherally enhancing collection in the right supraclavicular fossa

body (Fig. 11). Pulmonary infiltrates, nodules, miliary disease and pulmonary abscesses are also reported [33, 36, 39]. Differentiating TB-IRIS from failure of treatment can be challenging. It is a diagnosis of exclusion and radiological appearances have to be put into context of the clinical and pathological findings with a multidisciplinary approach. Such reactions may occur within a few days or many months after the commencement of anti-tuberculosis treatment; when the disease process takes a very exaggerated course, it can be responsive to corticosteroid therapy [35, 38, 40].

Latent TB and Radiological Markers of Disease Activity (Table 2)

Strictly speaking, latent TB infection (LTBI) refers to positive findings on laboratory screening tests (Tuberculin skin test or an interferon-γ release assay) in clinically silent individuals with no radiological evidence of active disease [11]. Whether latent TB progresses to active TB is largely a function of host immune status. Amongst the spectrum of risk factors (diabetes, chemotherapy, immune-modulating drugs, renal failure, malnutrition, steroid use etc.), HIV infection is the strongest known risk factor. One of the strategies for successful containment of TB is to diagnose and treat latent TB in at-risk patients, or contacts of smear positive TB patients and prevent future progression to *active* disease.

Broadly, it is practical to consider latent TB and all inactive TB (previously treated) together [11], to understand the role of radiological stratification in these patients. Given the treatment regimen of LTBI differs from that of *active* TB, it is vital to recognise and pin-point any signs of disease activity. Chest radiographs or CT in patients suspected of LTBI show no active disease but may demonstrate residual tell-tale features of past exposure by way of focal calcific lung granulomas, stable fibro-nodular parenchymal scarring or nodal calcification [7]. In previously treated patients, the distinction between active and inactive disease can be challenging especially on radiographs, due to architectural distortion and scarring. In this context, CT is useful. Stability and lack of temporal evolution is helpful in gauging lack of disease activity [7]. Conversely, new nodules, consolidation, cavitation, tree-in-bud nodularity or pleural effusions should trigger a work up for active tuberculosis. In this respect, PET-CT (discussed in a forthcoming section) has shown itself to be of use in predicting disease activity on a metabolic basis [41–44] (Fig. 10).

Cardiac TB

The commonest manifestation of cardiac TB is pericarditis, which can arise through lymphatic, haematogenous or direct contiguous spread from an adjacent structure (for example, a ruptured necrotic mediastinal node) [45]. On both echocardiography and CT, this can be demonstrated as a simple pericardial effusion or can be associated with nodular pericardial thickening (Figs. 12 and 13). An added benefit of CT imaging (versus echocardiography) in this context, is that ancillary supportive features of TB, such as lymphadenopathy and pleuro-parenchymal disease can be demonstrated. These features can help narrow the differential diagnosis for an otherwise non-specific finding of a pericardial effusion.

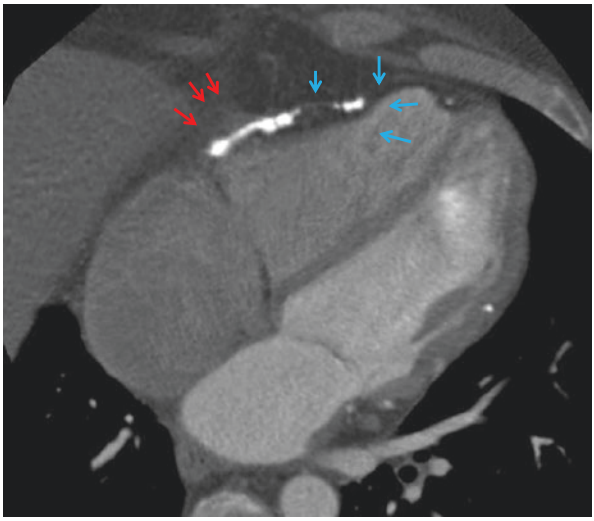

Fig. 12 Contrast enhancement gated cardiac CT reconstructed in a 4 chamber view. There is pericardial calcification (red arrows), ventricular distortion (blue arrows) and bi-atrial enlargement all in keeping with constrictive pericarditis (*image courtesy of Dr Tarun Mittal, Consultant Radiologist, Harefield Hospital, UK)*

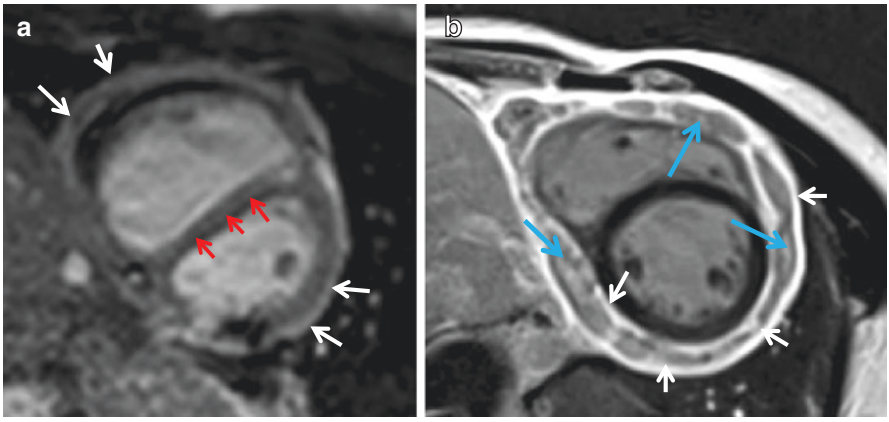

Fig. 13 (**a**) Cardiac MRI-left ventricle short axis (LVSA) images demonstrating septal flattening (red arrows) and a D-shaped ventricle on inspiration in keeping with constrictive physiology. There is pericardial thickening (white arrow heads) (**b**) Cardiac MRI Post contrast, phase sensitive delayed myocardial enhancement image demonstrating extensive pericardial enhancement of the thickened, two layers of pericardium (white arrows) associated with a complex, intermediate signal pericardial effusion (blue arrows). (*Image courtesy Dr Ben Ariff, Consultant Radiologist, Imperial College NHS Healthcare Trust UK)*

Constrictive pericarditis is a common sequela of pericardial TB. Distortion of the shape of the cardiac chambers underlying a pericardial abnormality is suggestive of constriction, particularly with the correct correlating clinical picture [46] (Figs. 12 and 13). Pericardial calcification is an occasionally encountered incidental finding whilst reading CT scans for unrelated problems. This can indicate old TB

pericarditis [46]. Myocardial spread of TB occurs by the same routes, but does so less commonly. It is a difficult diagnosis to make and may only be detected post mortem. However, modern cardiac MRI tools in expert hands, can be useful when applied in a focussed manner with a high degree of suspicion. Like other cardiomyopathies, TB myocarditis usually manifests with an abnormal pattern of enhancement of the late myocardial gadolinium enhancement imaging [47].

Role of Interventional Radiology in Management of TB

Chronic inflammatory changes in TB fibro-cavitary disease can recruit blood vessels from systemic bronchial arterial supply arising from the aorta [48]. In difficult to manage cases of haemoptysis refractory to conservative management, the treatment of choice is prompt radiological intervention and embolization of these feeding vessels supplying the abnormal lung (Fig. 14). In such circumstances, it is important that the clinician discusses the nature of the clinical problem with the radiologist, rather than proceed straight to CT. The protocol and timing of contrast phases on CT is critical to ensuring both systemic and pulmonary arterial systems

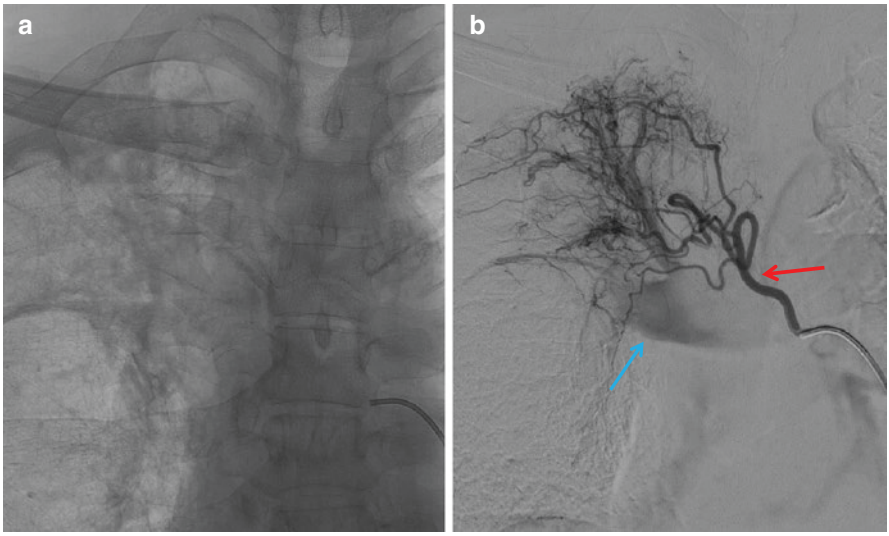

Fig. 14 (**a**) Control film from intercosto-bronchial arteriograms showing right apical scarring and ill-defined increased opacification in the right upper zone. (**b**) Right intercosto-bronchial arteriogram (red arrow) showing hypertrophy of the bronchial and intercostal arteries with bronchial and non-bronchial systemic to pulmonary artery shunting. Note the marked retrograde opacification of the right main pulmonary artery (blue arrow). *(Image courtesy Dr Ali Alsafi, Consultant interventional Radiologist, Imperial College Healthcare NHS Trust UK)*

are identified, to identify sites for embolization. Other than bronchial arteries, other systemic arterial branches from intercostal arteries, the thyrocervical trunk [48] and the inferior phrenic arteries can be potential feeder vessels. Importantly, another potential source of bleeding, the *Rasmussen's pseudoaneurysm* arises from the pulmonary arterial tree [49]. This is an important entity, as it represents a potential cause for re-bleeding in a patient who has had a successful embolization of the aforementioned systemic arteries. When identified in advance of invasive angiography, this can prompt, the interventional radiologist to perform more focused evaluation of the pulmonary arterial tree.

Abdominal and Pelvic TB

Although pulmonary TB is the most common presentation, the disease can spread to virtually any tissue or organ by haematogenous or lymphatic dissemination or direct spread.

In the abdomen/pelvis, the commonest manifestations are of peritoneal disease and lymphadenopathy, although gastrointestinal tract and solid abdominopelvic viscera can also be involved [50]. TB associated nodal disease usually has a characteristic appearance of caseous necrotic nodes with peripheral enhancement and central low attenuation, as previously alluded to in the ITLNTB section [50]. This is not pathognomonic or specific to TB, but should raise suspicion.

Peritoneal TB

A common manifestation of intra-abdominal tuberculosis is peritonitis. It is thought that this arises through haematogenous dissemination and/or lymphatic spread from rupture of a tuberculous lymph node. Another recognised route is of peritoneal spill from an involved fallopian tube [51]. There are three broad types of pathological peritoneal TB entities crucial to the appearances on radiology (Fig. 15). *Wet-type* peritoneal involvement is predominantly characterised by generalised ascites or organised into loculated pockets of fluid. The fluid in peritoneal TB is often higher density (20–40 Hounsfield units HU) than water (0 HU) due to its proteinaceous content [51]. Ascites may be associated with generalised smooth peritoneal thickening (Fig. 15) compared to normal peritoneum which is barely perceptible. *Dry-type* peritoneal disease tends to feature nodular deposits along the mesenteries, omentum and peritoneal reflections and vague fat stranding or 'misting' of the mesentery. There may also be mixed ascites and mesenteric adhesions associated with dilated obstructed bowel loops. Again, typical necrotic caseous mesenteric lymph nodes can be seen [50]. *Fibrotic-type* peritoneal disease features larger cake-like deposits in the mesentery and omentum with thick fibrotic adhesions that can result in matting together of bowel loops

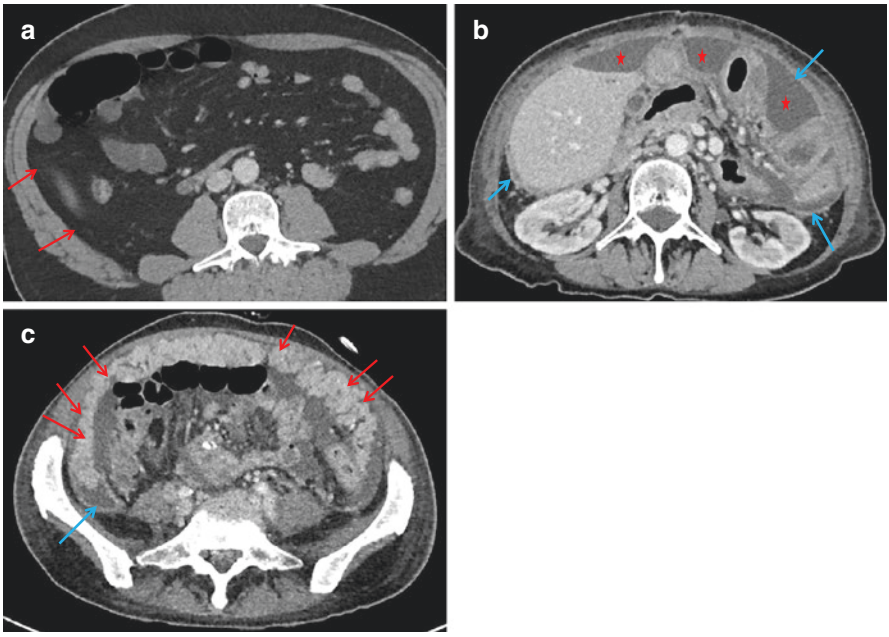

Fig. 15 (**a, b & c**) Axial enhanced normal and abnormal CT abdomen of peritoneal TB (**a**) Normal scan with normal pencil thin / barely perceptible peritoneum (red arrows). (**b**) Abnormal scan demonstrating TB ascites / loculated pockets of fluid ascites (red stars). Peritoneal lining is smoothly thickened and enhances diffusely (blue arrows). (**c**) Abnormal scan demonstrating TB omental cake: Extensive nodular soft tissue peritoneal conglomerate masses in omentum (red arrows). This omental *caking* seen in fibrotic type TB peritoneal disease. Ascites with smooth thickening of overlying peritoneum also seen (blue arrow), notably at the right iliac fossa reflection

[50] (Fig. 16). Importantly TB peritoneal features, are not specific for TB and it is important to exclude other differential diagnoses notably neoplastic disease [51].

Gastrointestinal Tract TB

The most commonly affected part of the gastrointestinal tract (~90%) is the ileo-caecal region [50]. This usually results in concentric bowel wall thickening with inflammatory change within the mesentery and localised necrotic lymphadenopathy. This can be demonstrated on CT or MRI. With time, this can lead to architectural distortion in the right iliac fossa leading to a shrunken retracted appearance of the caecum and tethering of adjacent loops (Fig. 16). Complications of disease includes bowel wall perforation and abscess formation as well as interloop fistulation [50]. Whilst ileo-caecal disease is most common, any part of the gastrointestinal tract can be involved. Again, when other areas are involved, findings tend to be non-specific. For example, with gastro-oesophageal TB, disease manifests with

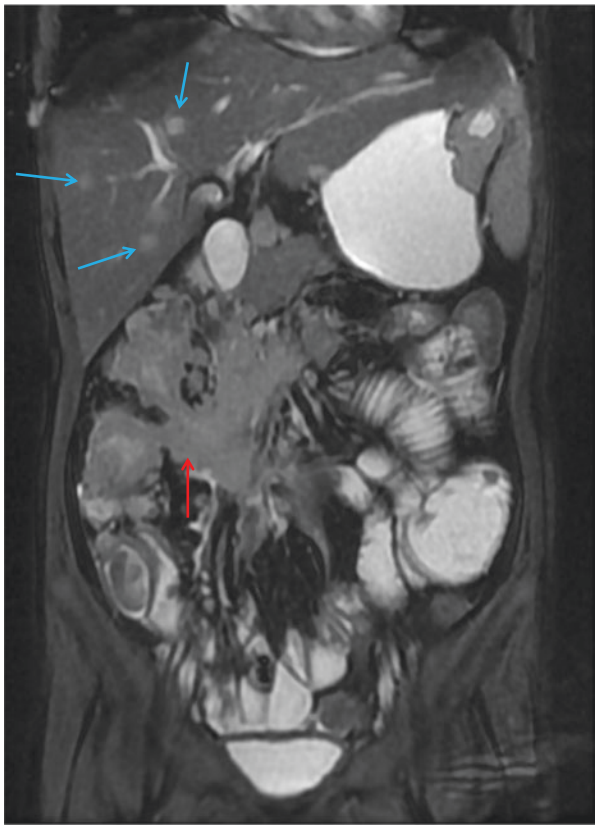

Fig. 16 Coronal MRI slice (T2 weighted sequence). Fluid is bright on this sequence. The study demonstrates an enterocolitis in a patient with known miliary pulmonary TB. Abnormal thick-walled bowel loops are noted in the right side of the abdomen. The thickened caecum and distal ascending colon are distorted and drawn medially, into an area of matted inflamed distal ileal loops. There is apparent tethering and ileo-colic fistula formation at this site (red arrow). Associated multiple T2 hyperintense liver lesions in keeping with systemic dissemination of miliary TB (blue arrows)

ulceration, stricturing and stenosis [52]. Hence, fluoroscopy still offers a role in assessing this. This involves administering an oral contrast agent that is ingested and then dynamically imaged using X-rays. This allows for assessment of peristalsis and demonstration of strictures and stenoses. Double contrast studies using effervescent agents are less often performed to assess for ulceration and mucosal irregularity in favour of endoscopy [52]. Other than imaging the oesophagus, investigation has moved away from conventional barium studies in favour of cross-sectional studies [53]. MRI is preferred owing to its lack of exposure to ionizing radiation and for its ability to dynamically image bowel peristalsis. The findings in GI TB are not specific and have a differential diagnosis which includes other infectious and inflammatory aetiologies, such as Crohn's disease. Equally, malignancy should be considered and excluded. Clinical context is especially important and concurrent chest findings are helpful in making the distinction [50].

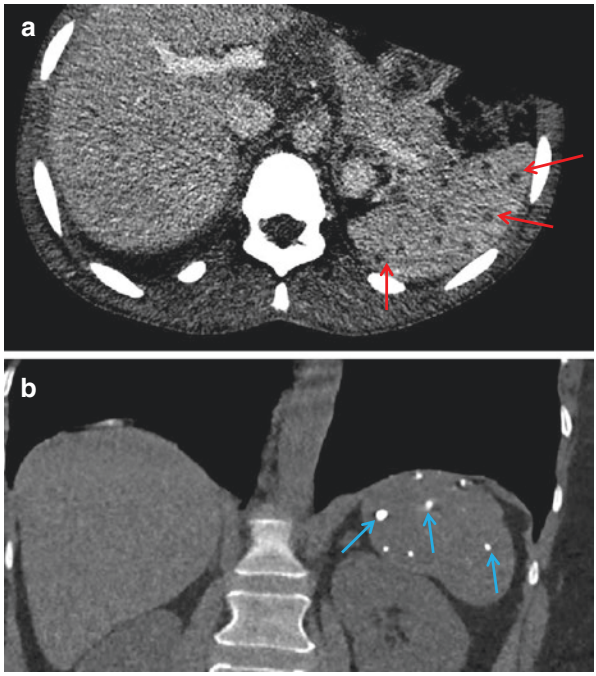

Fig. 17 (**a**) Axial contrast enhanced CT slice of the liver and with small low attenuation nodules in the spleen. The pattern of nodules demonstrated is typical of active granulomatous splenic infiltration. (**b**) Coronal slice of an unenhanced CT shows multiple tiny calcified foci in the spleen in keeping with evidence for old healed splenic granulomas /TB

Hepatic and Splenic TB

Granulomatous infiltration of the liver and spleen can occur in haematogenously disseminated TB with a miliary pattern of diffusely distributed hepato-splenic 2-4 mm low-attenuation lesions on CT. (Fig. 17a). On MRI, these lesions tend to be low signal on T1 weighted imaging and higher signal than background liver parenchyma on T2 weighted imaging (Fig. 16). Some of these larger nodules may be associated with peripheral enhancement. Diffuse infiltration of the liver and spleen can lead to enlargement [50, 51], and such a pattern is usually seen in conjunction with pulmonary TB. In the liver, a macronodular pattern can also be seen with nodules that measure up to 30 mm, [51] but this is less common. Similar to disease in the lungs, once hepatic and splenic granulomas resolve, they can leave small residual parenchymal calcifications (Fig. 17b) [50].

Adrenal TB

Adrenals are a relatively common abdominal site; interestingly, the leading cause of Addison's disease worldwide is tuberculous infiltration. The imaging manifestations include bilateral expansion of the glands with nodular contours and internal

low attenuation [50], whilst shrunken distorted glands with dense focal calcification are features of old TB.

Genitourinary TB

Urinary tract TB: Contrast enhanced CT Urography has by and large replaced two-dimensional Intravenous Urography (IVU) and involves multi-phasic contrast enhanced assessment of the renal parenchyma, collecting system and urinary bladder. Knowledge of the normal anatomy of the renal medulla, minor and major renal calyces (which have sharply outlined edges), is key to appreciating pathology (Fig. 18). Granulomatous inflammation and microvascular damage leads to renal papillary necrosis which manifests on imaging with blunting of the sharp edges of

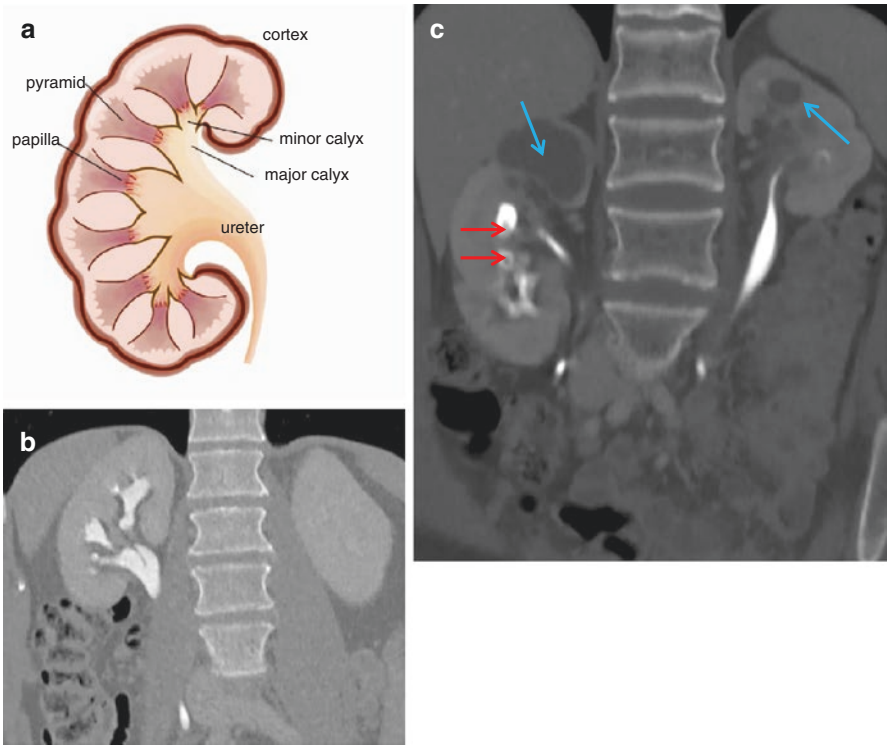

Fig. 18 (**a**) schematic drawing of the macroscopic architecture of the kidney in longitudinal cross section. *Illustration-Dr Aisling Fagan, Radiology Registrar, Imperial College Healthcare NHS Trust.* (**b & c**) Coronal oblique slice right kidney excretory phase CT-IVU. (**b**)**:** Normally opacified calyceal system. Note, calyces have sharp funnel shaped edges (**c**) CT-IVU demonstrates filling defects and underfilling of mid-pole renal calyces (red arrows) due to urothelial thickening and distortion, with balloon dilatation of un-opacified upper pole calyces (blue arrows) due to calyceal infundibular strictures

the renal calyces which become irregular and club shaped [54]. The contrast filled calyces can develop an irregular moth-eaten appearance with sloughed debris resulting in filling defects [51] (Figs. 18 and 19). Disease can extend to the renal parenchyma resulting in a TB pyelonephritis with generalised heterogenous enhancement on CT [55]. This correlates with focal areas of reduced echogenicity on ultrasound [56] and patchy attenuation on contrast enhanced CT (Figs. 19 and 20). In addition to generalised pyelonephritis, focal parenchymal granulomatous nodules can form and can potentially result in Intra-renal or perinephric abscesses. These typically appear hypodense on CT with peripheral enhancement [55] (Figs. 19 and 20). On

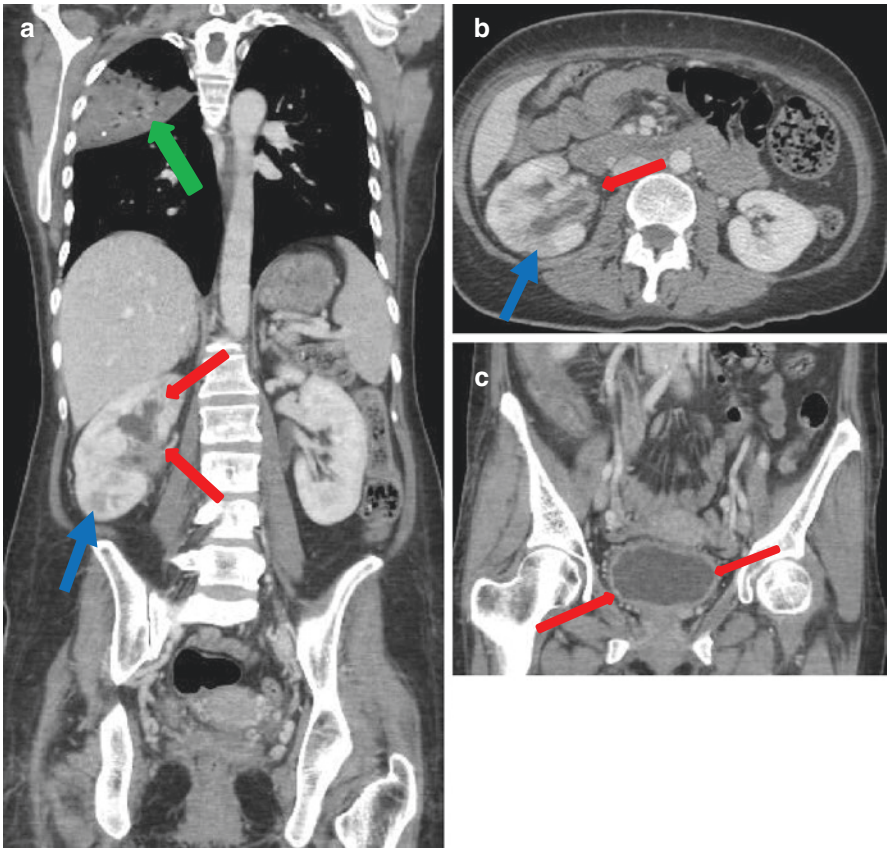

Fig. 19 (**a, b, c**) Lung, renal and urothelial TB. Contrast enhanced Coronal Body CT (**Image a**) with axial CT (**Image b**) show urothelial thickening with associated upper pole calyceal dilatation (red arrows image **a** & **b**) due to structuring of upper pole infundibulum. Associated renal right lower pole patchy cortical enhancement (blue arrows **a** & **b**). Associated bladder wall thickening and inflammation (**Image c** coronal pelvic CT, red arrows). Constellation of features in keeping with urothelial and renal cortical TB. Associated lung consolidation right upper lobe (green arrow image **a**) *Image courtesy Dr Uday Patel, Consultant Radiologist, St George's Hospital NHS Trust, London, UK*

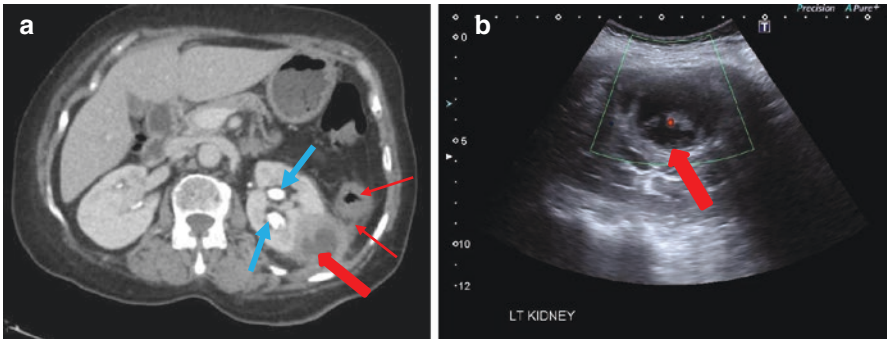

Fig. 20 (**a**) Contrast enhanced axial CT scan slice. (**b**) Ultrasound left kidney. Findings: left kidney, on contrast CT (Image **a**) shows low attenuation necrotic focus with enhancing rim in keeping with a cortical renal abscess (thick red arrow). Note the peri-nephric stranding and reactive thickening of adjacent bowel loop (fine red arrows). Contrast is also noted within the left renal collecting system (blue arrows). Ultrasound (Image **b**) demonstrates a complex partly echogenic septated abscess (thick red arrow). Diagnostic aspirate performed under ultrasound (US), revealed culture positive mycobacterium tuberculosis. *Image courtesy Dr Uday Patel, Consultant Radiologist, St George's Hospital NHS Trust, London, UK*

ultrasound these appear as hypoechoic rounded foci which have internal avascularity on Doppler, compared with the rest of the hyper-vascular inflamed kidney [56] (Fig. 20). In untreated cases, parenchymal granulomas can lead to a spectrum of findings with necrosis, parenchymal distortion, and eventually destruction with extensive calcific debris conforming to the shape of the shrunken renal parenchyma. This auto-nephrectomy appearance or 'putty kidney' [57], is rarely seen nowadays. However, this can still be encountered as an incidental finding on unrelated radiological investigations. Descending infection into the ureters and bladder is more rare than renal involvement. On CT Urography, ureteric involvement is typically demonstrated with thickening of the walls of the contrast opacified ureters. This inflammation can lead to stricturing and associated focal ureteric dilatation [55]. Tuberculous bladder involvement and can manifest as focal or diffuse bladder wall thickening with or without calcification (Fig. 19). However, bladder calcification is more often related to other causes, such as Schistosomiasis [51].

Genital tract TB: In men, this most commonly involves the prostate, albeit with non-specific imaging features. Typically, on CT, hypoattenuating lesions with peripherally enhancing rims are seen, but MRI is a more sensitive modality and more subtle changes can be detected (Figs. 21 and 22). Appearances are often indistinguishable from prostatic inflammation and abscesses from other causes [50]. Calcific foci can persist in patients with previous tuberculous prostatitis [55]. Prostatic disease can spread to involve the rest of the male genital tract. Potential sites of involvement can include the seminal vesicles and vas deferens, which can lead to infertility as a complication. Scrotal involvement is also encountered. This manifests as epididymitis that can progress to involve the testes [58]. Ultrasound is the best modality to assess for this and typically demonstrates a thickened hypoechoic

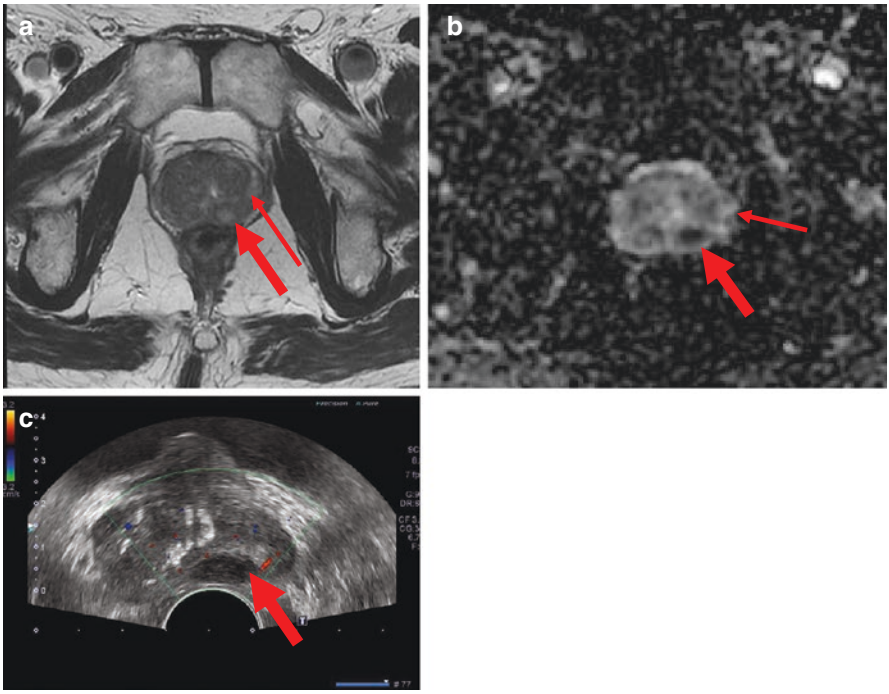

Fig. 21 Prostate TB after intra-vesical BCG treatment for early bladder cancer. (**a**) Axial T2 weighted image demonstrates focal areas of increased signal (bright foci) in the left peripheral zone (red arrows), (**b**) Axial diffusion weighted sequence (ADC) demonstrates associated diffusion restriction (dark spots) (more notably labelled with the thick red arrow), (**c**) Trans-rectal US shows that the larger peripheral zone abnormality corresponds with a hypoechoic lesion (dark focus) (thick red arrow). US guided biopsy showed granulomas and culture positive mycobacterium tuberculosis. *Image courtesy Dr Uday Patel, Consultant Radiologist, St George's Hospital NHS Trust, London, UK*

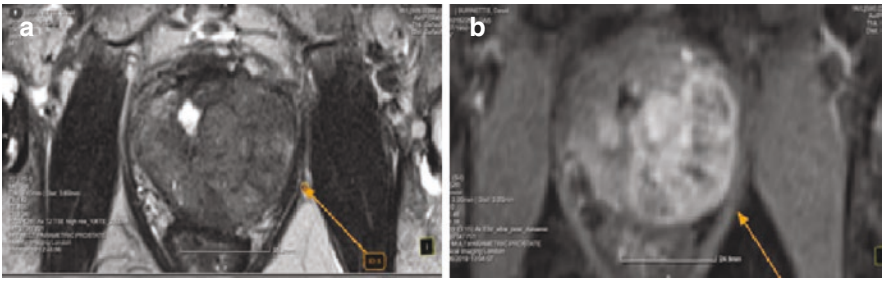

Fig. 22 Prostatic TB: MRI prostate Coronal T2 (*Image **a***) and contrast enhanced coronal images (*Image **b***) showing intense contrast enhancement bilaterally but predominantly in the left half of the gland (*yellow arrows). Image courtesy Dr Uday Patel, Consultant Radiologist, St George's Hospital NHS Trust, London, UK*

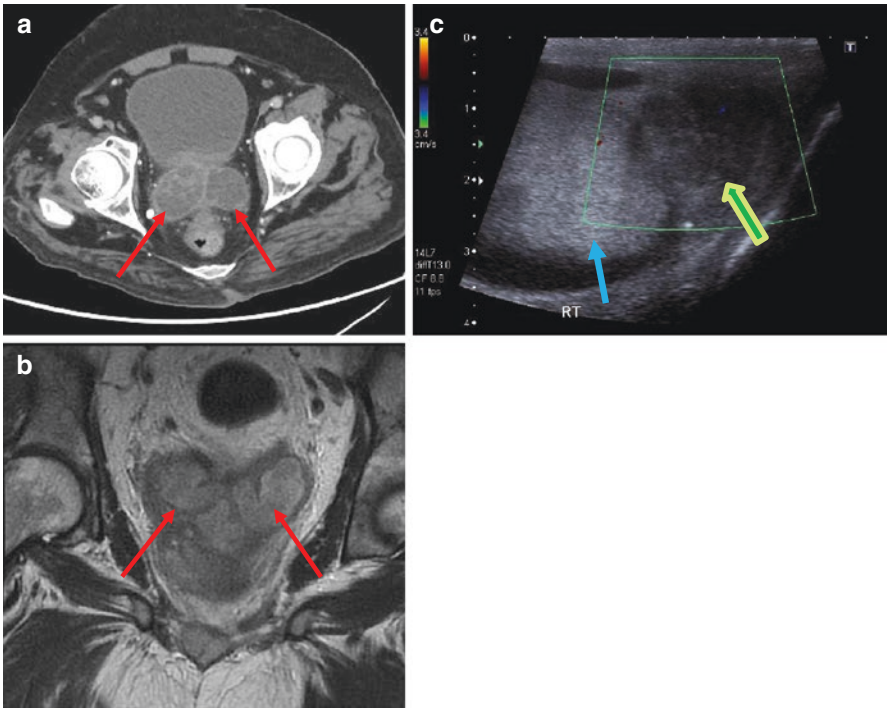

Fig. 23 Epididymal and seminal vesicle tuberculosis: (**a**) Axial contrast enhanced CT through base of bladder shows grossly distended seminal vesicles (red arrows). (**b**) Coronal T2 weighted MRI sequence also demonstrates gross dilatation of the seminal vesicles. (**c**) Ultrasound testis (blue arrow) with a swollen inflamed epididymis at the lower pole of the testis (green arrow) on **Image c.** *Image courtesy Dr Uday Patel, Consultant Radiologist, St George's Hospital NHS Trust, London, UK*

epididymis and/or heterogeneous areas of reduced echogenicity within the testes [59] (Fig. 23).

In women TB can result in salpingitis, the scarring sequelae is best demonstrated on fluoroscopic hysterosalpingography (HSG) [51]. The HSG involves instillation of uterine cavity and fallopian tubes with contrast via cannulation of the cervix [60]. In TB salpingitis, multi-focal strictures of the fallopian tubes can be observed [51]. The more active disease manifestations of tubo-ovarian abscesses, are amenable to ultrasound detection, and an inflammatory phlegmon can potentially spill into the peritoneal cavity resulting in a peritonitis [50].

Bone and Joint TB

Skeletal TB is the third most common form of extra-pulmonary TB. Estimates range from 5%–20% in endemic and non-endemic regions and across all age groups [61–64]. In adults, 50% of all skeletal TB is spinal, whilst in children one third of bone related TB is spinal [61, 62]. This propensity for the spine, is thought to be related to the rich vertebral blood supply, given that spread is predominantly hematogenous. The consequences of untreated spinal TB can be devastating with potential for compression of the spinal cord. *The subject of spinal TB imaging is discussed in detail in section-2 of this chapter.*

Extra-spinal Bone and Joint TB

Extra-spinal skeletal TB manifests predominantly as TB arthritis (60–70%) or TB osteomyelitis (30–40%). A small incidence of isolated soft tissue findings such as tenosynovitis and bursitis is also recognised [61, 62, 65]. Extra-spinal skeletal TB is important, not because it is common, but because the diagnosis is often delayed [66, 67]. Given that appendicular skeletal TB is less frequent and because symptoms are often non-specific, doctors may overlook the diagnosis. Imaging is helpful in the diagnosis of spinal and extra-spinal bone TB, but an index of suspicion on behalf of the clinicians is critical to initiating timely imaging. Early diagnosis is key to preventing permanent sequelae, notably serious debilitating neurological consequences (related to spinal TB), deformity and disability. The mainstay of bone and joint imaging in TB is MRI.

Extra-spinal skeletal TB, commonly affects weight bearing bones and joints. Imaging often starts with plain radiographs. These may be very useful when disease has been present for some time allowing bone or joint changes to become more obvious. Abnormalities on plain radiographs and indeed CT depend on a degree of bone loss (such as osteolysis, peri-articular osteopenia, erosions around articular surfaces) and sufficient attrition and damage to cartilage (with reduced joint space and sub-articular/sub-chondral cysts) (Fig. 24). Once such signs are present, it is reasonable to assume the pathology has been present for some time. A normal plain radiograph does not exclude pathology. Therefore, normal plain films should not preclude further imaging if clinical suspicion is high. MRI is more sensitive to early and subtle signs of inflammation in the synovium, cartilage and sub-chondral bone and importantly the adjacent soft tissues. MRI has a higher negative predictive value.

TB infection can seed (most commonly from a hematogenous source) to the bony metaphysis or directly to the synovium of affected joints. When the process starts in the metaphyseal bone, granulation tissue and caseation can lead to bone

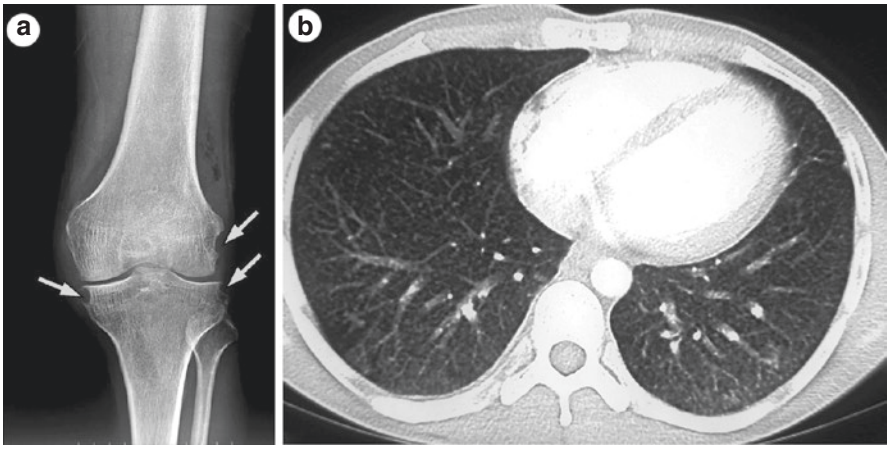

Fig. 24 *The Phemister triad: Reproduced with permissions from The Lancet Volume 391 Issue 10,135 (May 2018) Arghya Chattopadhyay, MD, Prof Aman Sharma, MD, Prof Kirti Gupta, MD, Prof Sanjay Jain.* Anteroposterior x-ray left of knee (standing) showing multiple marginal erosions (arrows), periarticular osteopenia, and reduced joint space (**a**) and high-resolution chest CT showing subtle miliary mottling (**b**)

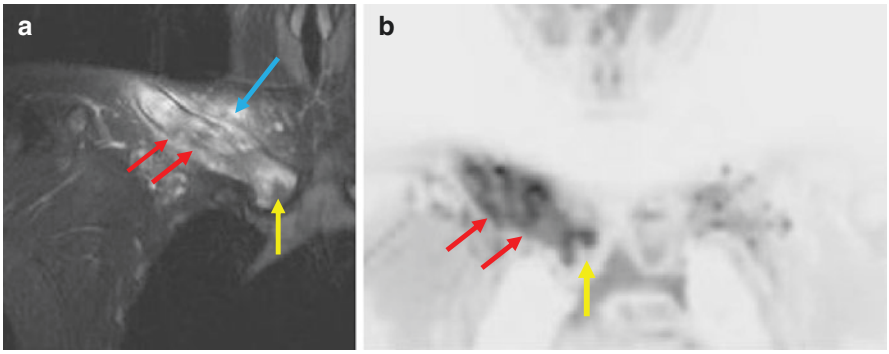

Fig. 25 Chronic Clavicular TB Right clavicle: MRI T2 fluid sensitive (**Image a**) and Diffusion weighted Imaging (DWI) (**Image b**) Findings are of diffuse bone based abnormal signal on MRI with oedema and remodeling deformity, the latter reflecting chronicity. Associated sub-articular erosions at sternoclavicular articular surface and surrounding oedema. (*Image courtesy Dr Afshin Alavi, Consultant Radiologist, Imperial College Healthcare NHS Trust UK)*

necrosis. This reflects on imaging as an eccentric osteolytic lesion of TB osteomyelitis. Infection may extend into adjacent soft tissue, forming a soft tissue 'cold' abscess, or result in contiguous joint involvement. In children, this trans-epiphyseal spread of infection, has the potential to disrupt epiphyseal growth. The combination of bone-based and joint-based infection present together raises TB as a key differential as such trans-epiphyseal spread of osteomyelitis is traditionally thought to be typical of TB [51, 65, 68] (Fig. 25). It is now more widely recognised that such

spread is though not exclusive to TB and also possible in pyogenic osteomyelitis [69]. Given the granulomatous process is relatively slow and insidious, compared to pyogenic infections, it is more likely that in TB, the problem only becomes clinically apparent in a delayed fashion, when the joint also becomes involved and pain begins to limit joint mobility.

MRI is very sensitive in detecting early bone inflammation as abnormalities in marrow signal. Unlike other causes of marrow oedema, the granulomatous response in TB can manifest as intermediate to low signal intensity on the key MRI T1 and T2-weighted MRI sequences [65, 70, 71]. Caseous necrosis can have high or intermediate signal components on fluid sensitive sequences. Soft tissue abscesses are also well delineated on MRI. TB abscess tend to have thin and smooth walls relative to the irregular ill-defined thick margins, seen in pyogenic abscesses. This is due to the comparatively lesser degree of inflammation in TB together with a more chronic insidious course of the disease [71].

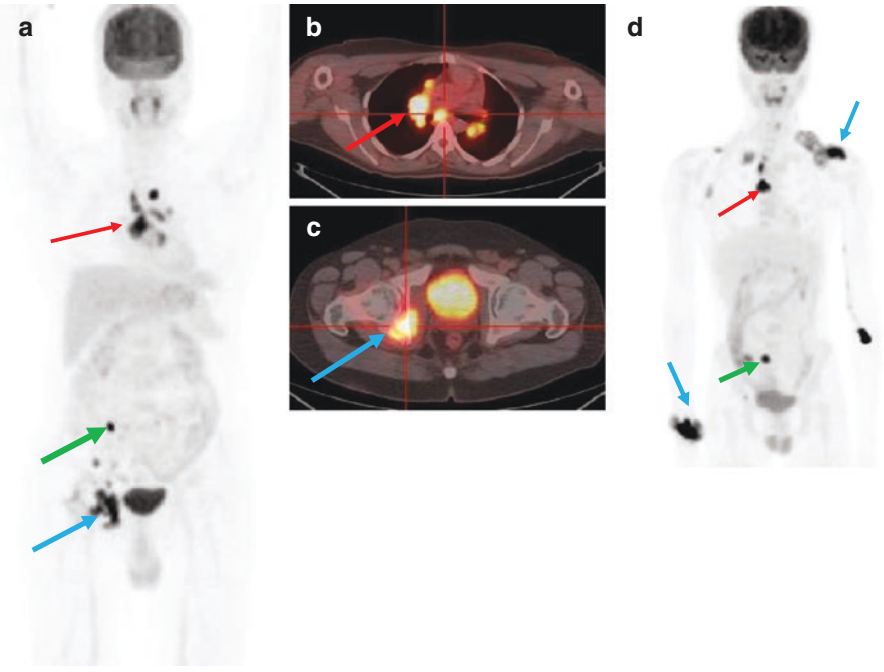

Fig. 26 Multi-focal TB on FDG PET CT. **Image a, b, c:** FDG PET MIP and fused PET-CT axial slices through the thorax and hips with FDG tracer activity at the right hip (blue arrows), within intra-thoracic lymph nodes (red arrows) and intra-abdominal right iliac fossa lymph nodes (green arrow) **Image d:** FDG PET MIP image in another case with multi-focal TB with tracer active foci of nodal disease (red arrow intra-thoracic nodes and green arrow intra-abdominal node) and osteoarticular TB (blue arrows—right wrist and left shoulder). In both cases FDG PET CT helped to identify accessible target tissue for sampling, leading to a confirmed diagnosis of TB. *Images Courtsey: Dr Rajnish Sharma, Director, Molecular Imaging & Research Centre (MIRC), INMAS, Delhi*

A single site of TB osteomyelitis is more common, but multiple sites of involvement may be seen, (Fig. 26) especially in children or immunocompromised hosts [65, 71]. In children, the metaphysis of the long bones tend to be affected, whereas in adults, the axial skeleton (skull, shoulder girdle, pelvis) is involved [65, 71]. The

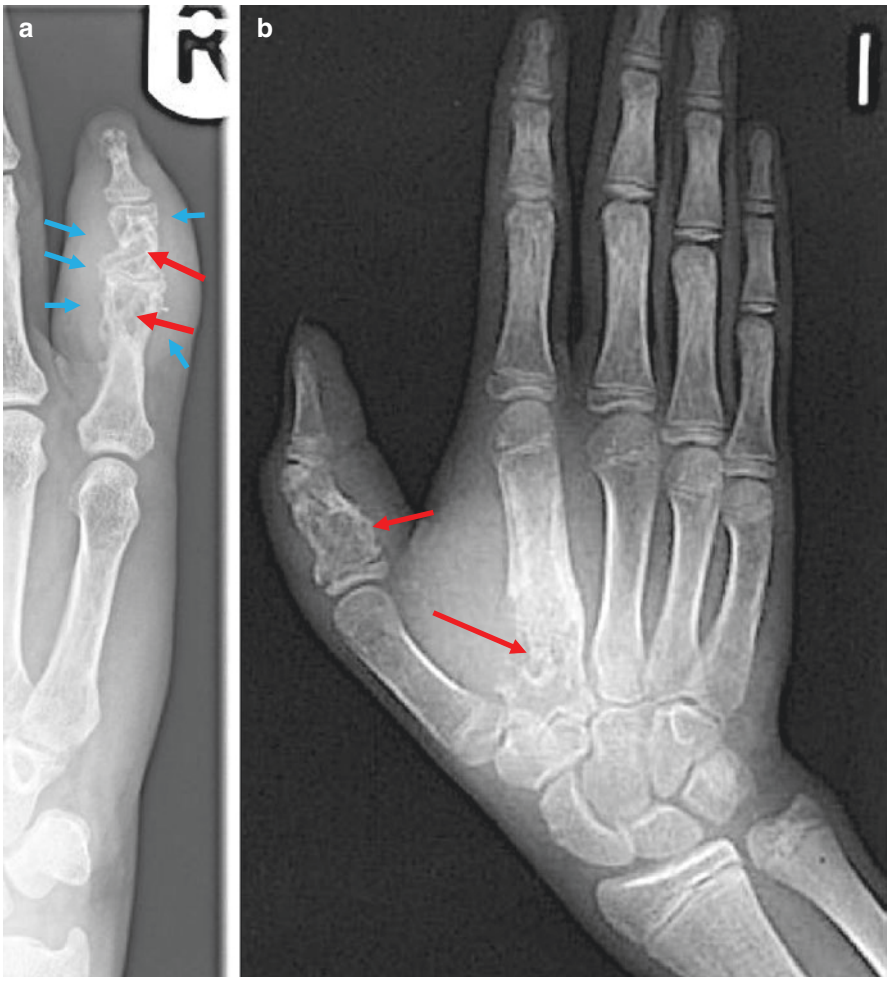

Fig. 27 TB Dactylitis: (**a**) Extensive soft tissue swelling (blue arrows) little finger with a lytic process and remodelling involving the proximal and middle phalanx (red arrows) with sparing of inter-phalangeal joints. Sarcoid or a tuberculous dactylitis are key differentials. *Reproduced with permissions from* https://radiopaedia.org/cases/spina-ventosa-2 *Case courtesy of Melbourne Uni Radiology Masters, Radiopaedia.org, rID: 42142* (**b**) Expansile and lytic process involving involving the thumb (proximal phalanx) & base of the index finger metacarpal, the latter with more overt cortical destructive changes. *Reproduced with permissions from* https://radiopaedia.org/cases/tuberculous-dactylitis *Case courtesy of Radswiki, Radiopaedia.org, rID: 12043*

ribs are another site of chronic TB osteomyelitis and should be kept in the differential for pathology at these sites. Another peculiar pattern of bony involvement is TB dactylitis with characteristic fusiform swelling of the small tubular bones in the hands and feet. This also occurs more frequently in children [71] (Fig. 27). Tuberculous dactylitis, may be painless and present on plain radiographs. It can feature periostitis, a coarsened trabecular pattern and acro-osteolysis, sometimes, with adjacent joint involvement. In some cases, this can involve the adjacent small joints of the hand. This presentation is not exclusive to TB and differentials includes pyogenic or fungal infections, sarcoidosis and hyperparathyroidism [71].

TB arthritis can occur as a primary process when mycobacterial seeding is synovial or as a secondary process, when infection spreads from an adjacent bone-based TB osteomyelitis. TB arthritis is often mono-articular. The hip and knee are commonly affected in most reported series [61, 62, 65, 71]. The typical plain radiographic findings of TB arthritis that make up the eponymous Phemister Triad (Fig. 24) are juxta-articular osteopenia/osteoporosis (loss of bone density around the joint as a consequence of inflammation), peripheral osseous erosions (small areas of bone/peri-articular lysis around the joint), and narrowing of joint space (from loss of articular cartilage) [72]. These features are not specific for TB, but should raise suspicion for an inflammatory or a septic arthritic process. On MRI, findings can be detected at an earlier stage with joint effusion and thickening and enhancement of synovium. Tubercular arthritis is characterised by synovial proliferation which is typically hypointense or intermediate signal on T2-weighted images, unlike other inflammatory arthropathies [65, 70, 71] (Fig. 28). This characteristic signal is thought to be related to haemorrhage, fibrosis and inflammatory debris [70]. Articular cartilage damage, subchondral bone erosions and oedema are also depicted in the earlier stages on MRI before joint space loss occurs. Surrounding soft tissue extension and sinus tract formation is also best demonstrated on MRI. When the process is advanced, CT gives a better picture of extent of bone destruction. Should the infection remain untreated, severe joint destruction is the end result and ankylosis of the joint can occur. In contrast to pyogenic arthritis, the development of bone ankylosis is uncommon and the ankylosis in TB is more commonly fibrous in nature [71].

Whilst lower limb, notably hip and knee joints, are key sites of TB arthritis, no joint is exempt. Amongst others, sterno-clavicular and sacro-iliac joints are notable sites [73]. An asymmetrical or unilateral sacroiliitis should prompt an index of suspicion for infective etiologies, TB included, such that diagnosis is not delayed and intra-articular steroid injections are not used for pain management. It is also important to keep in mind the eponymous entity of Poncet arthritis; a non-infectious form of reactive polyarthritis that can occurs during an episode of acute TB infection [74]. Whilst it is very rare, mycobacterium bovis related bone and joint infection can occur after intravesical bacillus Calmette-Guérin (BCG) therapy for non-invasive bladder cancer [61]. In addition, observed cases of skeletal NTM, whilst rare, increased following the AIDS epidemic in 1980s [61].

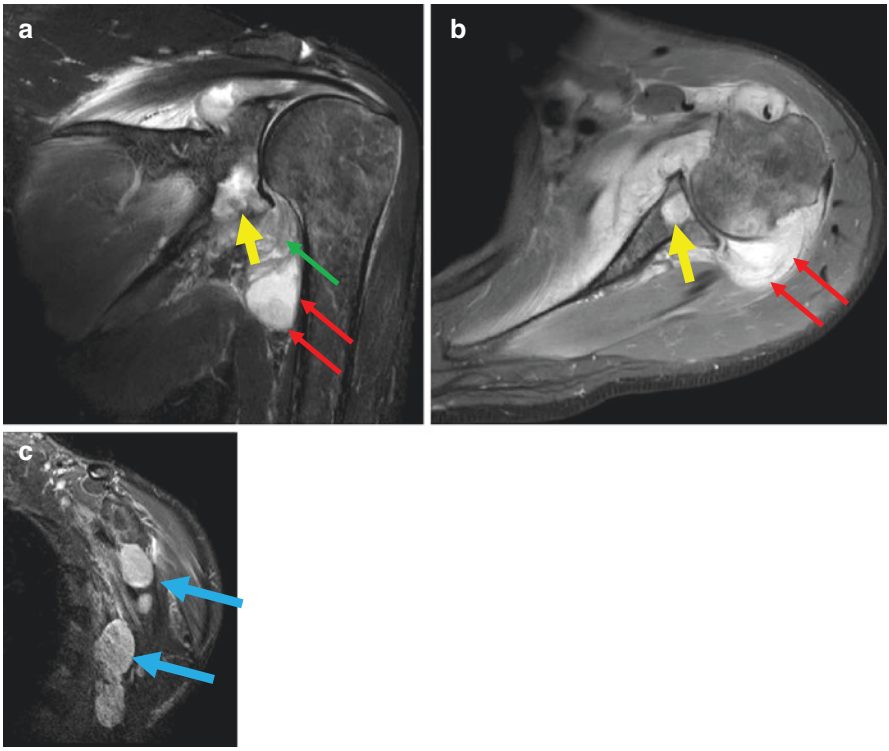

Fig. 28 Left Shoulder Tubercular arthritis MRI: Image a & c—Coronal STIR, Image b Axial SPAIR (All fluid sensitive sequences). Large complex mixed signal left shoulder effusion distending the capsule (red arrows) with marked synovial thickening (green arrow) and surrounding soft tissue oedema. Associated glenoid high signal reflects bone lysis (yellow arrows). Associated bulky axillary lymph nodes (blue arrows, Image c). *Image courtesy Dr Michael Khoo, Consultant Radiologist, Royal National Orthopaedic Hospital, Stanmore, UK*

A key question from a clinical perspective is—can radiology/MRI differentiate between pyogenic and tubercular osteomyelitis and arthritis. Indeed, whilst there are features that may favour tuberculosis (insidious onset, minimal sclerosis, paucity of periosteal reaction, relative preservation of joint space in early stages, low to intermediate, as opposed to high T2-weighted MRI signal related to synovial granulomatous infiltration), these are not pathognomonic for TB and there is overlap with other aetiologies (eg. brucellosis, non-infective inflammatory arthropathy). Confirmation of aetiology is based on tissue sampling with aspiration or biopsy. In this context, ultrasound is very useful if the collection is soft-tissue based, whilst CT guided percutaneous bone biopsy can help avoid an open surgical procedure.

Imaging of Intracranial Tuberculosis Infection
(See Tables 4 and 5)

General Imaging Considerations

The key imaging modalities used in imaging the brain are computed tomography (CT) and magnetic resonance imaging (MRI). CT is used in acute settings and as a screening tool; it is particularly good for rapidly answering emergency management questions, for example whether there is a large haemorrhage or acute hydrocephalus, and also for evaluation of bone. However, it is less useful in determining the presence and nature of intracranial infection. MRI is much more sensitive to signs of intracranial infection and is generally used to detect and determine the extent of disease.

In neuroimaging, a number of MRI sequences are key for diagnosis and tend to be performed as standard. The box in Fig. 29, identifies the key features to help identify each sequence. As a general rule, T2-weighted imaging (which includes fluid-attenuated inversion recovery (FLAIR) images) is the most useful for highlighting pathology, as oedema is hyperintense. The T2 characteristics of focal brain lesions are particularly helpful in tuberculosis infection.

T1-weighted imaging is most helpful for delineating anatomy and assessing for haemorrhage, and also is used for post-contrast imaging with gadolinium-based contrast agents; GBCAs do not cross the blood-brain barrier in normal circumstances, so enhancement again usually indicates pathology.

Diffusion-weighted imaging (DWI) can highlight very cellular material that can be useful for identifying tuberculosis mimics, for example pus in a pyogenic abscess or cellular tumour in intracranial lymphoma. When interpreting diffusion weighted imaging both the high-b value diffusion weighted images and the constructed apparent diffusion coefficient (ADC) map must be evaluated together, with true restricted diffusion defined as increased DWI signal and decreased signal on the ADC map. Finally, susceptibility-weighted imaging identifies substances with paramagnetic properties; practically speaking this includes blood, blood degradation products and calcification, all of which are again particularly relevant when imaging tuberculosis.

Table 4 Key points—Neuroimaging in TB

Neuro-imaging of Tuberculosis
– MRI with contrast is the modality of choice for assessment and follow up of intracranial and spinal TB
– Rupture of intracranial Rich focus leads to leptomeningeal spread & a basal meningitis
– Significant associated morbidity and mortality
– Complications of TB meningitis include hydrocephalus, vasculitis, and cerebral infarcts
– Spondylodiscitis with paravertebral and epidural extension is most common spinal manifestation

Table 5 Key points—Imaging patterns in Spinal tubercular and pyogenic infection

Spinal Infection	Pyogenic	Tuberculous
Disc	Primarily involved	Often spared in early disease
Subligamentous spread	Absent	May be present +/− Non-contiguous multilevel involvement
Paravertebral/epidural collections	May be present Often thick-walled	Frequently present Larger and thin-walled
Bone destruction	Mild to moderate	Severe in longer term
Patient condition	Unwell	Well relative to appearance on imaging

BRAIN	Grey Matter	White Matter	CSF
T1	Darker	Brighter	Dark
T2	Brighter	Darker	Bright
FLAIR	Brighter	Darker	Dark
DWI (B1000)	Similar to FLAIR but lower resolution		
ADC	Brain dark, CSF bright, lower resolution		
SWI	Veins and calcification very dark		

SPINE	Fat (Bone Marrow)	CSF
T1	Bright	Dark
T2	Bright	Bright
STIR	Dark	Bright

Fig. 29 Quick guide to MRI sequence recognition. *FLAIR* Fluid Attenuated Inversion Recovery. *DWI* Diffusion Weighted Imaging. *ADC* Apparent Diffusion Coefficient map. *SWI* Susceptibility Weighted Imaging. *STIR* Short Tau Inversion Recovery

All sequences can be imaged in multiple planes or acquired volumetrically, so that they can be reconstructed in the plane desired; it is worth becoming familiar with local protocols in order to be comfortable interpreting pathological findings.

Intracranial Pathology

As in the lungs, there are multiple potential presentations of intracranial tuberculosis infection and the presentation will depend on the chronicity of infection and the immune status of the patient, among other considerations. Unlike pyogenic meningitis which tends to arise from haematogenous spread, tuberculous infection tends to originate from the formation of a Rich focus, a granuloma which forms in the subcortical region or in the meninges, and then ruptures, spreading infection most frequently through the leptomeninges [75]. The most common presentation of intracranial tuberculosis infection is therefore tuberculous meningitis, but there are many other potential imaging manifestations and complications which we will discuss in this section.

Meningeal Disease

Leptomeningeal disease usually occurs because of the rupture of a Rich focus; rarely there can be contiguous spread from bone but this is much less common [76]. Cell-mediated immunity gives rise to a thick gelatinous exudate which causes the characteristic imaging findings [76]. This typically affects the internal layers of the meninges, the pia and arachnoid mater (known collectively as the leptomeninges). In the setting of leptomeningeal infection, there is localised breakdown of the blood-brain barrier leading to replacement of the normal cerebrospinal fluid with gelatinous exudate and thickening and nodularity of the leptomeninges. In TB this tends to occur in the basal cisterns and in the Sylvian fissures (the so-called 'basal meningitis'), although can extend to the cerebral convexities if the infection is severe.

The consequent imaging features are thick, nodular enhancement (as compared to the smooth enhancement in bacterial and viral meningitis) in the affected regions, and there can be replacement of the normally dark cerebrospinal fluid on FLAIR with iso—or hyperintense material. The enhancement is most commonly seen only on contrast-enhanced MRI, but may also be visible on contrast-enhanced CT. It often leads to hydrocephalus, with the inflammatory exudates or focal tuberculomas blocking cerebrospinal fluid drainage (Fig. 30).

These findings are nonspecific in that other forms of meningitis may have similar appearances (other infections, particularly fungal, as well as carcinomatous meningitis and other granulomatous diseases such as sarcoidosis and IgG4 disease); however, in the correct clinical context these imaging features are fairly characteristic.

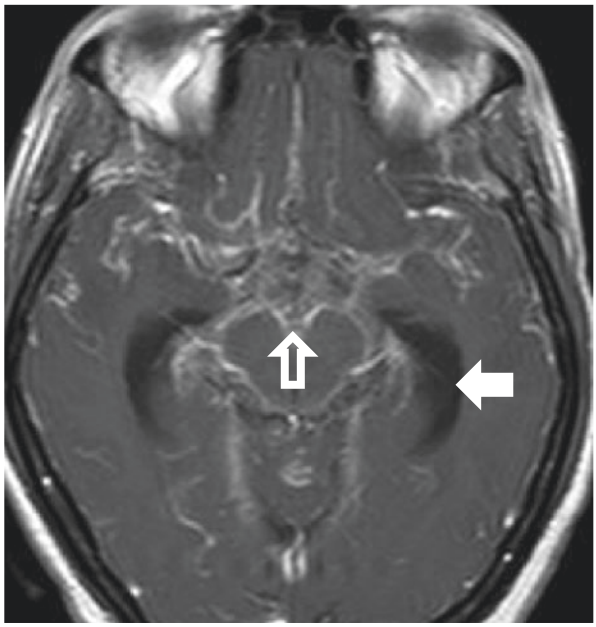

Fig. 30 Widespread leptomeningeal enhancement in a patient with tuberculous meningitis. There is particularly florid, thickened leptomeningeal enhancement in the basal cisterns (open arrow). Also note prominence of the temporal horns in keeping with secondary hydrocephalus (closed arrow)

Pachymeningeal Disease: Less commonly, the outer layers of the meninges (arachnoid and dura mater, collectively known as the pachymeninges) can be involved. This is thought to be related to more chronic infection and granulomatous disease, rather than the exudates seen in leptomeningeal disease. MRI demonstrates bulky pachymeningeal thickening and enhancement, which may be hypointense on T2-weighted images (Fig. 31), and this responds to antituberculous treatment. The differential diagnosis again includes other granulomatous diseases, particularly IgG4 and sarcoidosis, as well as malignancy, particularly lymphoma [77].

Parenchymal Disease

There are a variety of intraparenchymal manifestations of tuberculous infection, including tuberculomas, abscesses, and cerebritis.

Tuberculomas: Tuberculomas are the most common parenchymal manifestation of TB. Tuberculomas are granulomas forming in reaction to tuberculous bacilli, and their appearance can change depending on the stage they are in: they are initially solid (noncaseating) and then become centrally caseating, which can progress from solid to liquid caseation, each of which can have slightly different imaging characteristics [76]. However, the distinction between stages is sometimes a rather academic exercise and the most common imaging appearances are more helpful to bear in mind.

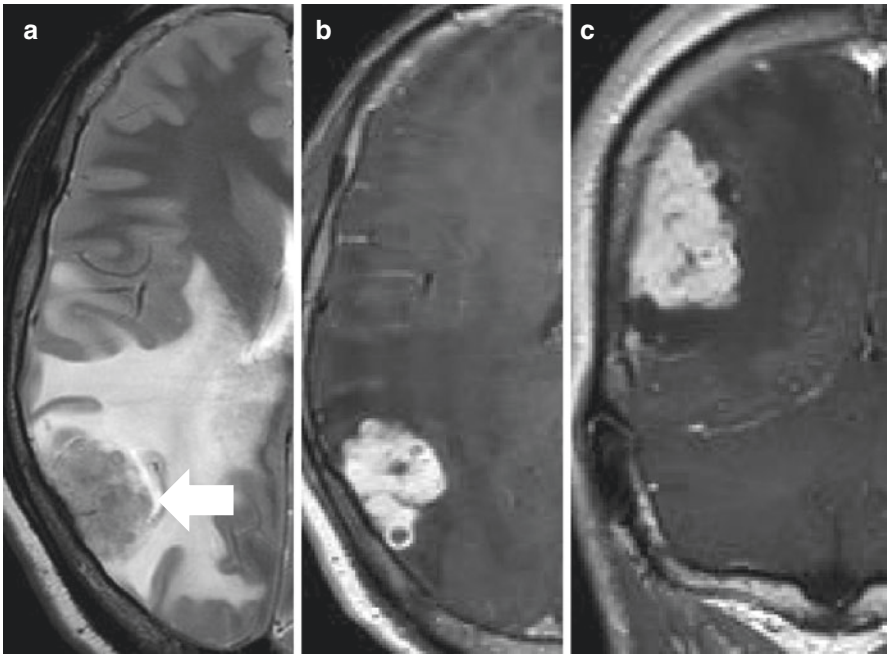

Fig. 31 Durally based tuberculosis infection. There is an extra-axial durally based lesion which is hypointense on T2-weighted images (**a**, arrow), and demonstrates avid contrast enhancement on axial (**b**) and coronal (**c**) post-contrast T1-weighted images. Also note the extensive surrounding oedema, best seen on the T2-weighted imaging (**a**)

On CT, the lesions may have central calcification and either solid or ring enhancement, and may be difficult to detect on non-contrast studies unless there is significant surrounding oedema.

The most typical appearance on MRI is of one or multiple focal intraparenchymal lesions with central T2 hypointensity and peripheral enhancement, with surrounding vasogenic oedema (Fig. 32). The central signal may increase on T2 as the lesion liquefies [76]. Miliary TB in the CNS describes the pattern of multiple small tuberculomas (2-5 mm) scattered throughout the brain parenchyma, and often occurs in immunocompromised patients via haematogenous spread [78].

The T2 hypointense rim and central calcification, if present, can be helpful imaging signs to alert the radiologist to the likelihood of TB, but in general the appearances tend to be nonspecific and the differential diagnosis includes many other forms of infection (including neurocysticercosis and toxoplasmosis) as well as metastases.

Abscess: TB abscesses are more rare, and essentially represent encapsulated pus and tuberculous bacilli without the granulomatous reaction seen in tuberculomas [76]. These are very difficult to differentiate from pyogenic abscesses, presenting similarly with a T2 hyperintense centre and enhancing rim with internal diffusion restriction. Slower progression and increased thickness and nodularity of the

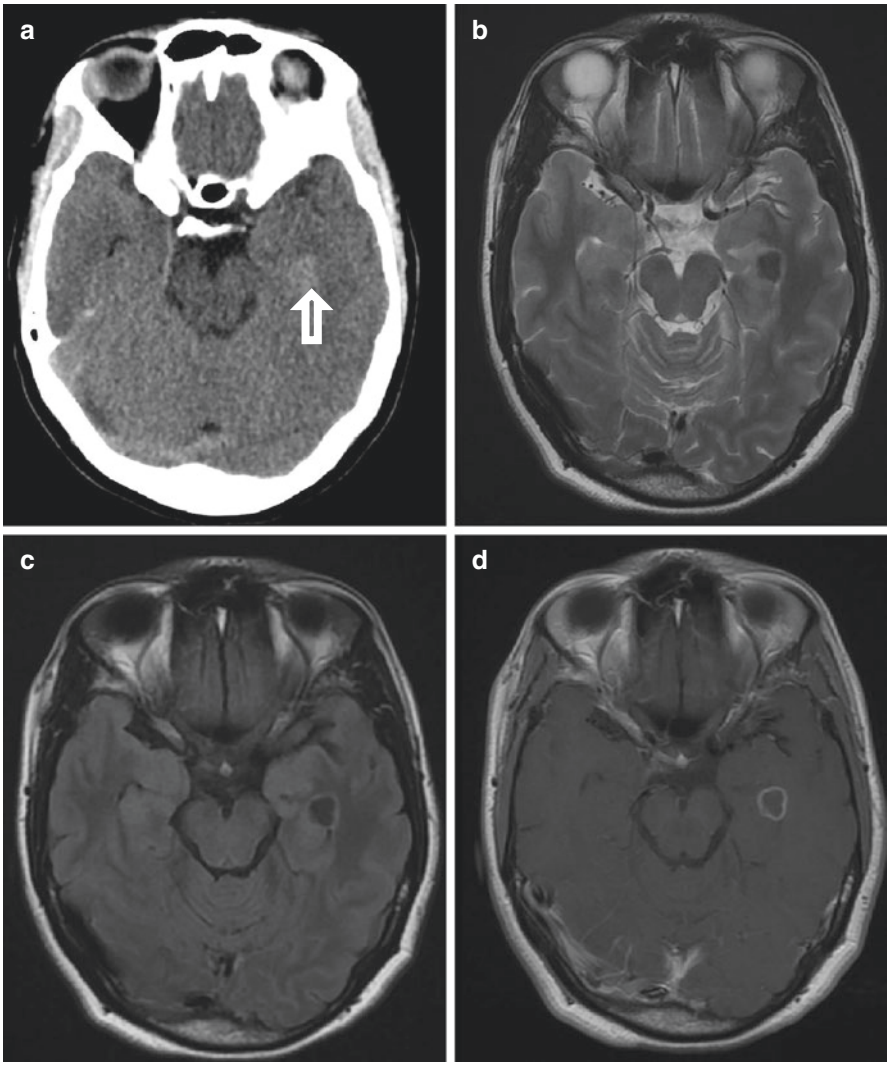

Fig. 32 Tuberculoma. There is a focal lesion in the left temporal lobe which is hyperdense on CT (**a**, arrow), hypointense on T2 (**b**) and FLAIR (**c**) weighted MR images, and demonstrates peripheral contrast enhancement on the post-contrast axial T1 weighted image (**d**). Note the surrounding oedema seen on the T2-weighted image (**b**)

enhancing rim may differentiate them from pyogenic abscesses. They tend to be larger than liquefied caseating granulomas, and internal diffusion restriction can also help to distinguish the two. There may be a role for spectroscopic and magnetization transfer imaging but this may not be practical to obtain and interpret in most centres [79].

TB Cerebritis Infection of the brain itself may occur either alone, or more frequently in conjunction with meningitis. The typical imaging characteristics are of oedema (hypodense on CT, hyperintense on T2/FLAIR and hypointense on T1) with patchy contrast enhancement.

Tuberculous Encephalopathy This is not strictly an infective manifestation, but a hypersensitivity reaction to the bacillus, which occurs mainly in children and has a high morbidity and mortality. This presents with an imaging phenotype similar to acute disseminated encephalomyelitis (ADEM), with diffuse white matter T2 hyperintensity and patchy contrast enhancement [80].

Complications

The major secondary complications of intracranial tuberculosis infection tend to arise from tuberculous meningitis, and include hydrocephalus, vascular compromise and ventriculitis.

Hydrocephalus: Hydrocephalus in the setting of TB infection is most often communicating, thought to relate in part to obstruction of the arachnoid granulations by exudate, but there may also be obstructive hydrocephalus directly secondary to a tuberculoma.

This can be easily identified on CT with enlargement of the ventricles, signs of raised intracranial pressure, and hypodensity in the periventricular white matter representing trans-ependymal fluid shift. The earliest signs are said to be a disproportionate increase in the size of the temporal horns of the lateral ventricles (Fig. 30), and then rounding of the frontal horns and downward displacement of the floor of the anterior recess of the third ventricle seen on the sagittal view [81]. This is an emergency and requires urgent neurosurgical assessment.

Vascular Complications: The basal exudate in tuberculous meningitis often surrounds the major intracranial arteries of the circle of Willis, and a secondary vasculitis in these vessels leads to focal infarcts. In one study, 50% of those with TB meningitis suffered cerebral infarcts [82].

The distribution of infarcts tends to involve the deep perforator and cortical branches rather than main trunks of cerebral arteries, and infarcts are most commonly seen in the basal ganglia as a result of lenticulostriate artery involvement [83] (Fig. 33).

On imaging, infarcts are seen as focal areas of restricted diffusion in the acute stage, with evolution of imaging characteristics depending on the age of infarct [84]. Involvement of the intracranial arteries may be demonstrable on angiographic imaging; digital subtraction angiography is the most sensitive to detect multiple focal stenoses in the intracranial arteries, but these are often visible on CT or MR angiography [82]. Vessel wall imaging, a technique which suppresses the signal from the lumen of the artery so that the enhancement pattern of the arterial wall can be evaluated, may be useful to assess the degree of arterial involvement [85].

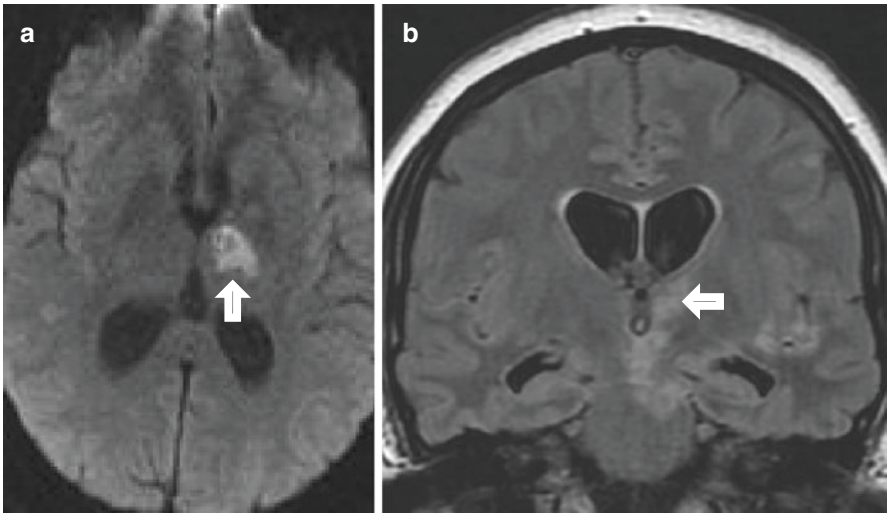

Fig. 33 Infarct. In this patient with tuberculous meningitis, there is abnormal DWI (**a**) and FLAIR (**b**) signal in the left thalamus compatible with an infarct (arrows)

Ventriculitis: Ventriculitis (infection of the ependymal lining of the ventricles) is a much less common complication of tuberculous meningitis than pyogenic meningitis, but nevertheless has been reported. Imaging will demonstrate abnormal hyperintense T2/FLAIR signal and enhancement of the ependyma, and there may be swelling and increased enhancement of the choroid plexus as well as intraventricular tuberculomas [86].

Spinal Tuberculosis

General Imaging Considerations

As in the brain, standard imaging protocols exist for imaging the spine in the setting of infection. In the emergency setting, CT is again the first line modality of choice, and is ideal for the assessment of bony involvement. This can be performed without contrast, but post-contrast imaging allows the characterisation of the paravertebral soft tissues, and post-contrast CT is often performed in the setting of chest or abdominal infection on which spinal disease may also be identified. CT is also frequently used for image guidance to sample the bone itself or the paraspinal collections in the setting of infective spondylodiscitis.

MRI of the spine is more useful for the evaluation of the spinal cord and the vertebral canal, and differentiating the compartment in which the infection resides (for example paravertebral, epidural, or intramedullary). The typical sequences performed include T1 and T2, usually performed in the sagittal planes with axial slices

acquired through areas of pathology, and short tau inversion recovery (STIR) which is a sequence that suppresses fat signal. The advantage of this is that in suppressing the fat signal in bone marrow, it can identify oedema within the bone with much greater sensitivity. This is key in the detection of osteomyelitis, among other pathologies. Post contrast imaging can also be performed with or without fat saturation. In the setting of potential TB infection, it is often important to image the whole spine rather than just the area of pain/deformity, because of the predilection for multilevel involvement which may not be contiguous [87].

Spinal Pathology

The main compartments to consider in the spine are the vertebral column, infection of which leads to spondylitis, discitis or osteomyelitis; the vertebral canal, which incorporates disease outside the dura (epidural) and within the dura (subdural/intradural); and finally, the spinal cord itself.

Vertebral Column: The three terms used above refer to slightly different entities—*spondylitis* refers to inflammation of the vertebral body, *discitis* to the inflammation of the disc, and *osteomyelitis* to inflammation of the bone more generally, and there is some overlap in how these terms are applied in practice.

Spondylodiscitis is non-specific in imaging appearance and can be due to a number of infective organisms, of which TB is one. A general imaging appearance of spondylodiscitis is of T2 hyperintense signal within the disc space, associated with adjacent oedema in the surrounding vertebral bodies and contrast enhancement around the disc and within the bone.

In comparison with pyogenic infection, TB is more often associated with the thoracolumbar junction region, large paraspinal and psoas collections (Fig. 34), and subligamentous spread to multiple vertebral levels which may not be adjacent [88, 89]. The paraspinal collections may be large at presentation, in a surprisingly well patient, and may be visible as a paravertebral mass on X-ray, a peripherally enhancing low density collection on CT (which may contain calcifications), and a loculated T2 hyperintense, T1 hypo-or hyperintense collection with thin peripheral enhancement on MRI (Fig. 35). However, the collections can also be more solid-appearing [90]. TB infection is more likely than pyogenic infection to spare the intervertebral disc until later in the disease (*as in* Fig. 35), but the appearance of the disc can be variable and is not in itself pathognomonic [90]. Over time, there tends to be anterior vertebral destruction, with relative sparing of the posterior elements, which can lead to significant deformity. The differential diagnosis includes other granulomatous infections such as fungal infection and brucellosis, and malignant causes such as lymphoma should also be borne in mind [87].

Vertebral Canal: Often when there are paraspinal collections these can be contiguous with epidural collections (*as in* Fig. 34), and the vertebral canal should be carefully scrutinised for these in the axial and sagittal planes. These have similar imaging appearances to the more common pyogenic epidural abscesses and are

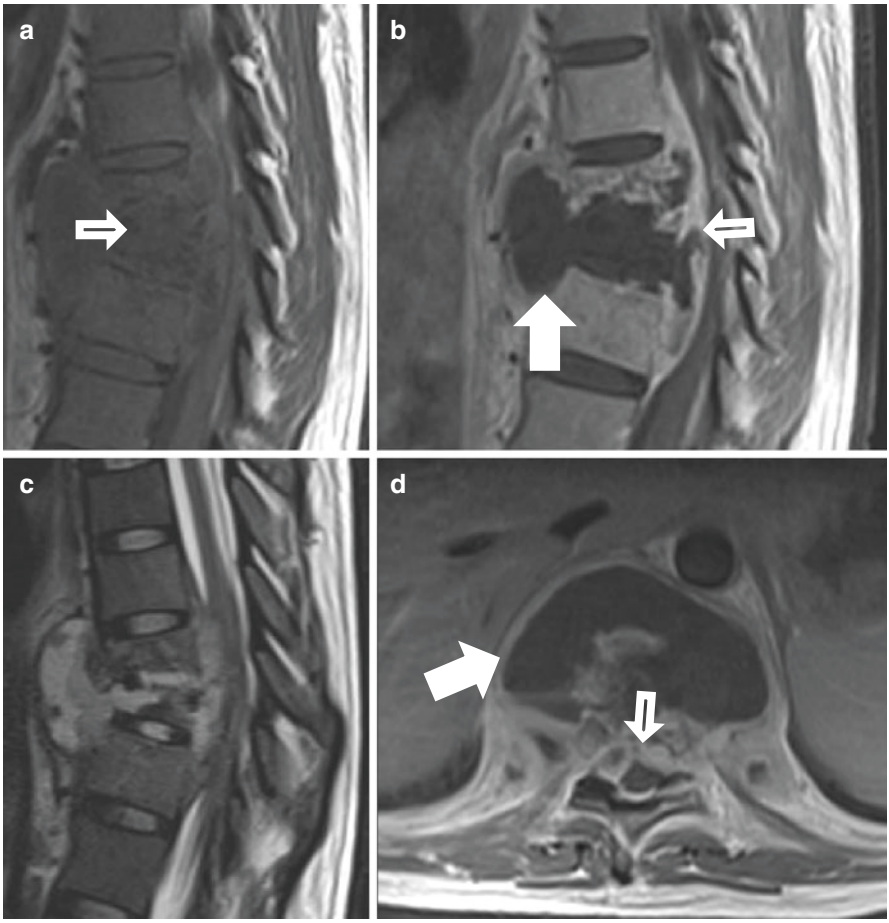

Fig. 34 Spondylodiscitis. Sagittal T1 (**a**), T1 post contrast (**b**), T2 (**c**), and axial T1 post contrast (**d**) images demonstrate destruction of a lower thoracic vertebral body (open arrow, **a**) with a large, peripherally enhancing collection extending into the anterior paravertebral soft tissues (solid arrow, **b** and **d**) and with a large epidural component (open arrow, **b** and **d**)

usually seen as a convex, T2 hyperintense, peripherally enhancing collection within the canal which displaces the thecal sac and may indent or compress the spinal cord [87]. Care must be taken as these can be non-liquefied (phlegmon) and therefore may be difficult to drain.

The spectrum of disease within the spinal canal, involving the leptomeninges and nerve roots, is known as tuberculous radiculomyelitis and is usually associated with intracranial disease. On CT this can be difficult to delineate although nonspecific intracanalicular soft tissue may be visible. On MRI, there may be loss of outline of the spinal cord with septated intradural peripherally enhancing collections, and thick, nodular enhancement along the meninges and nerve roots [91] (Fig. 36).

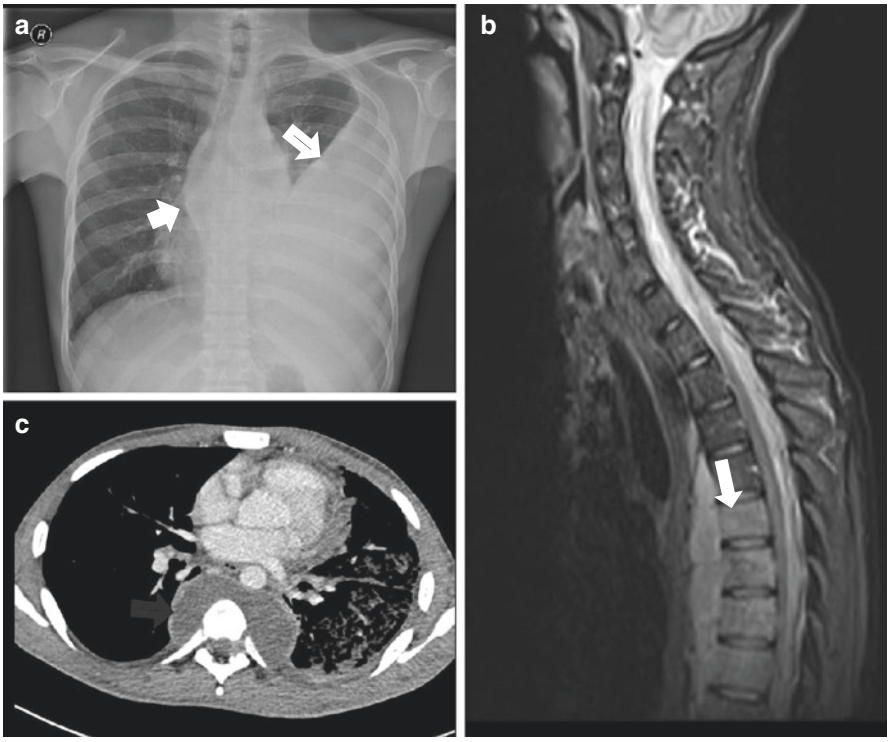

Fig. 35 Spondylitis. Chest X-ray (**a**) demonstrates a large left pleural effusion (meniscus indicated by open arrow) and a fusiform paravertebral mass (closed arrow). This is confirmed to be a large paravertebral abscess on CT (open arrow, **b**). Sagittal STIR MRI (**c**) demonstrates oedema within the lower thoracic vertebrae (open arrow) and subligamentous spread of infection with preservation of the intervertebral discs

There may also be arachnoiditis of the cauda equina, with clumping and enhancement of the cauda equina nerve roots (Fig. 37), although on its own this may be less specific and other (predominantly neoplastic) causes should be considered. Potential complications include spinal cord infarcts and development of syringomyelia.

Spinal Cord: Involvement of the cord parenchyma is similar to that seen in the intracranial compartment; there may be tuberculomas, intramedullary abscess, or myelitis. This is the rarest manifestation of spinal tuberculosis, and it is important to note that signal abnormality within the cord in the setting of spinal TB has a number of non-infective causes; it may be secondary to compression by abscess or vertebral deformity, relate to arterial or venous ischaemia and potentially para-infective/post-inflammatory demyelination in the form of transverse myelitis [90, 92].

Tuberculomas again typically demonstrate internal hypointense T2 signal and peripheral enhancement on MRI, or simply small ring-enhancing lesions [90] (Fig. 38). An abscess may demonstrate internal diffusion restriction or centrally

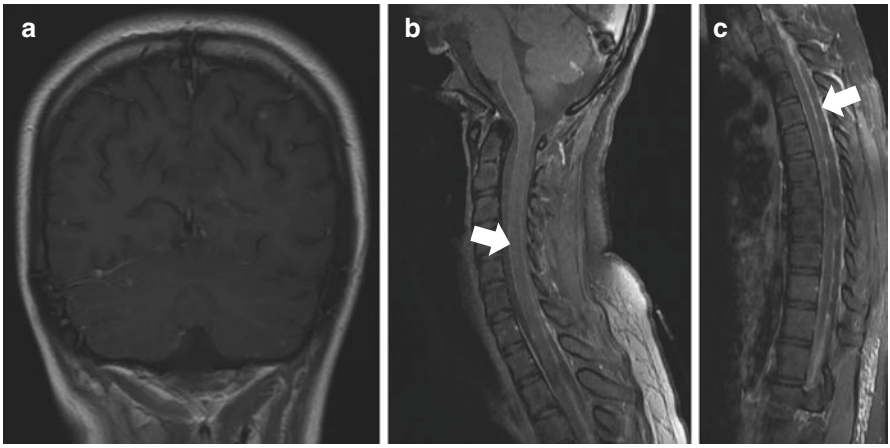

Fig. 36 Patient with military TB and intradural disease. Coronal T1 post gadolinium MRI (**a**) demonstrates multiple foci of enhancement compatible with miilary disease. Sagittal fat-saturated T1 post contrast spinal MRI demonstrates leptomeningeal enhancement (solid arrow, **b**) and a peripherally enhancing dorsal subdural collection (solid arrow, **c**)

hyperintense T2 signal and peripheral enhancement. Myelitis demonstrates nonspecific T2 signal abnormality, usually involving more than one spinal segment [92].

Head & Neck Tuberculosis Infection

10–35% of extrapulmonary TB infection involves the head and neck [93]. The vast majority of these presentations are within the cervical lymph nodes, but other sites such as the salivary glands, larynx, orbits, temporal bones and pharynx may also be involved [94]. Frequently the imaging appearances are nonspecific and similar to other granulomatous disease, but the possibility of TB should be kept in mind, particularly if there is concurrent pulmonary TB. The most common manifestation is a cervical lymphadenitis, and the presentation is often with an enlarging neck lump in an otherwise well patient. The typical progression of imaging features, seen on ultrasound, CT or MRI, is of multiple homogeneously enlarged and (on cross sectional imaging) enhancing lymph nodes, typically along the internal jugular chains and in the posterior triangle. This progresses to central nodal necrosis, with central fluid seen on all modalities. These can develop to large trans-spatial, peripherally enhancing abscesses, often at the lower level of the internal jugular chains (Fig. 11). In the longer term, the nodes become fibrotic and calcified [95]. Ultrasound is often the most useful investigation in this setting as the lesions can be sampled by fine needle aspiration or core biopsy, but cross-sectional imaging can help delineate extent of disease.

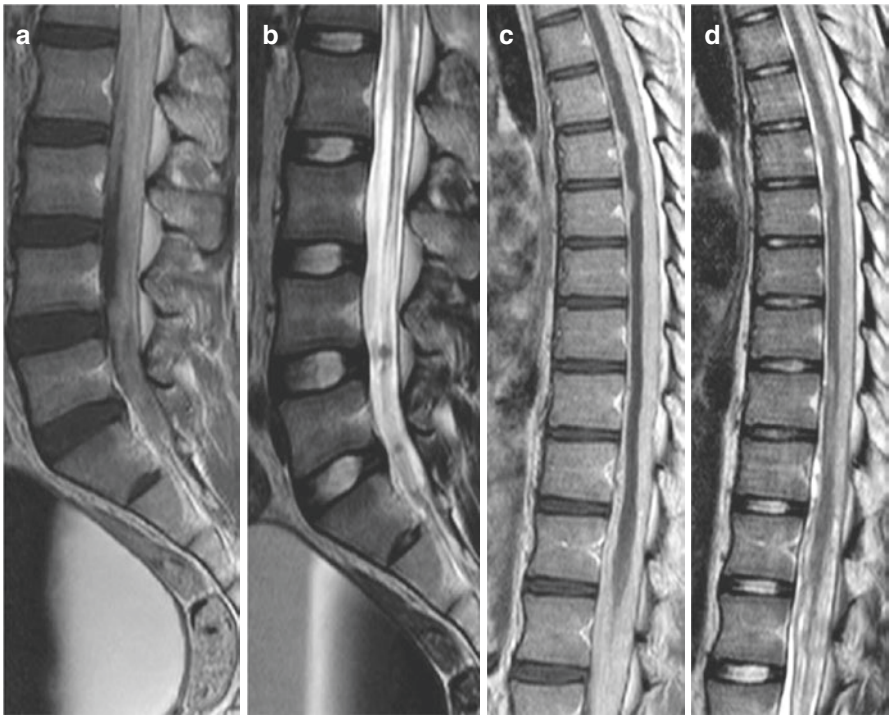

Fig. 37 Intradural disease and arachnoiditis. Sagittal T2 (**a**, **c**) and T1 post contrast (**b**, **d**) MRI demonstrate intradural enhancing material and lower down focal nodularity and clumping of the cauda equina nerve roots compatible with arachnoiditis

CNS Tuberculosis in Immunodeficiency

The immune status of patients is very important when interpreting neuroimaging, particularly when tuberculosis infection is suspected because the list of potential differential diagnoses grows significantly. However, the imaging features of CNS TB infection in immunodeficient and immunocompetent patients are generally similar—although abscesses are said to occur more frequently in immunocompromised patients—and a third category, patients with immune reconstitution, also demonstrate a similar spectrum of imaging characteristics [96].

Immune reconstitution inflammatory syndrome (IRIS) is an exaggerated immune response to a pre-existing pathogen following administration of antiretroviral therapy for HIV. This is rare in the setting of CNS TB, but can present as rapid progression of pre-existing disease, with an increase in size of lesions and increased perilesional oedema, and it is important to recognise this to allow correct treatment to be instituted [97]. There is also a risk of unmasking or reactivating latent TB when starting immunosuppressive therapies, such as monoclonal antibodies.

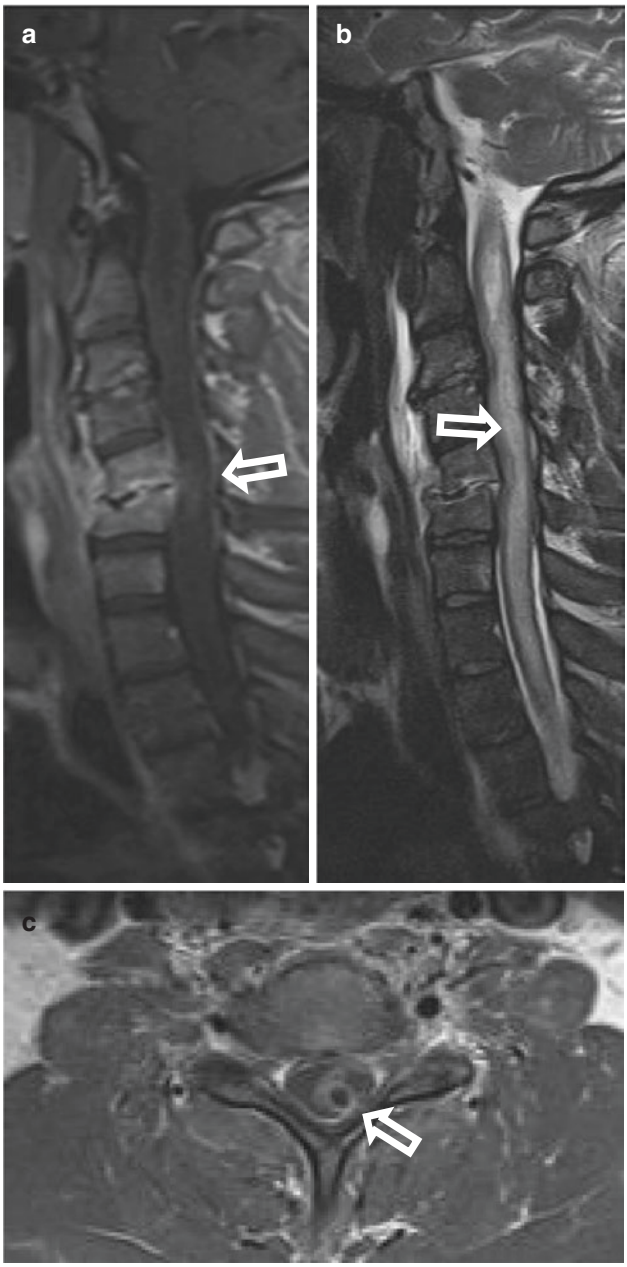

Fig. 38 Intramedullary disease. Sagittal T2 (**a**) and T1 post contrast (**b**) and axial T1 post contrast (**c**) images demonstrate in addition to spondylodiscitis with retrolisthesis and a prevertebral collection that there is extensive intramedullary cord signal change (open arrow, a) and focal enhancement within the cord (open arrow, b) which demonstrates a ring morphology on axial imaging (open arrow, **c**)

Role of F18 -fluorodeoxyglucose (F18-FDG) PET-CT in Tuberculosis (Table 6)

PET-CT is a technique that utilizes an array of radioactive positron emitting tracers, to trace and map metabolic and functional pathways in various organ systems. A three-dimensional functional map of the tracer distribution (PET) is fused with anatomical imaging derived from CT scans to give a powerful combination of metabolic and structural imaging information. The most widely used tracer, F18-fluorodeoxyglucose (F18-FDG) is a glucose analogue, that maps out glucose metabolism in tissues. Cancer cells are inherently hungry for glucose, by virtue of their rapid metabolic turnover. This makes FDG a an extremely useful cancer biomarker in staging and evaluating response to treatment.

Borrowing from this oncological paradigm and principle, the use of FDG PET CT in tuberculosis capitalizes on the glucose hunger of activated inflammatory cells notably macrophages and lymphocytes, involved in in the granulomatous process. The FDG uptake is therefore not specific for TB, and both malignant and non-tubercular inflammatory/infective pathologies can be FDG-avid, (Figs. 39, 40, 41, and 42). Used in the correct clinical context, FDG PET CT is however a sensitive and powerful biomarker.

PET-CT is not routine standard of care in tuberculosis, but it is used as a problem-solving tool on a case-by-case basis. The authors clinical experience and several observational series support the value of PET in characterising extra-pulmonary TB with greater sensitivity, as well as detecting multi-organ involvement, that may not always be otherwise apparent [98–100]. Often this may translate to selecting the most appropriate site to sample (Figs. 26, and 42). FDG PET CT is potentially useful in assessing response to therapy, especially when structural changes persist on CT and active disease cannot be discriminated from scar tissue [42, 101, 102]. A specific emerging application in this context is the use of FDG PET CT in multi-drug-resistant TB to prognosticate response at early time points and define status at end of treatment [42, 101, 102]. Demonstrable reduction in activity at early follow up and tracer quiescence at the end of treatment, is considered prognostically favourable (Figs. 10 and 43). FDG PET is also potentially useful in complementing

Table 6 Key points—FDG PET CT in TB

F18 FDG PET CT in Tuberculosis
– Not standard of care for routine evaluation. Used on a case-by-case basis for troubleshooting
– FDG activity is not specific for TB; findings interpreted in clinical context, correlating with structural CT morphology
– Known to uncover more extra-thoracic sites of infection than conventional imaging
– Helpful to select sites for tissue sampling, based on degree of metabolic activity
– Useful as a non-invasive biomarker, notably in multi-drug resistant TB. Complementary to MRI in evaluation of treatment response in bone and spinal TB

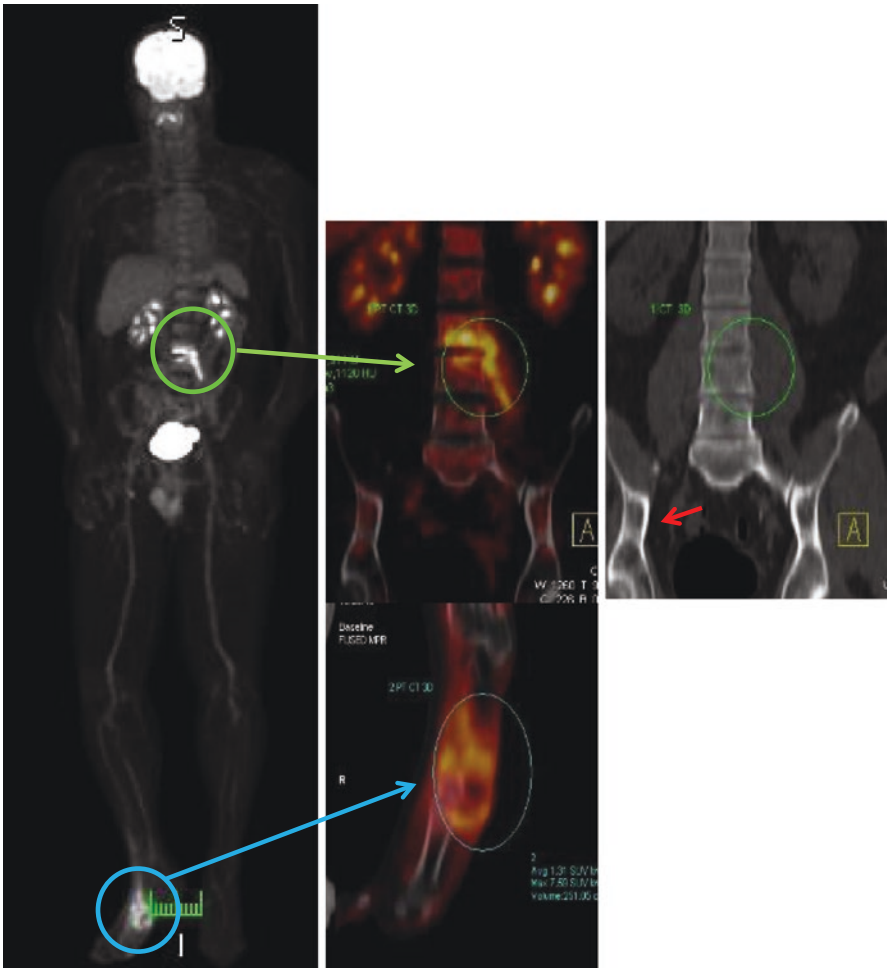

Fig. 39 All diskitis is not TB: 42y M with previous history of treated TB, with right foot cellulitis treated with antibiotics, but persistent fever, normal CT chest & abdomen. A FDG PET CT shows right mid-foot diffuse bone and soft tissue tracer uptake and L3/4 lumbar disko-vertebral activity with left sided para-vertebral activity in the left psoas muscle. CT abnormalities at L3/4 end plate are subtle. Tubercular diskitis was suspected on account of the previous history. CT guided L3/4 aspiration grew staphylococcus aureus with no mycobacterial growth and complete resolution following a prolonged course of antibiotics. TB diskitis and pyogenic diskits can have similar features, so tissue diagnosis is vital

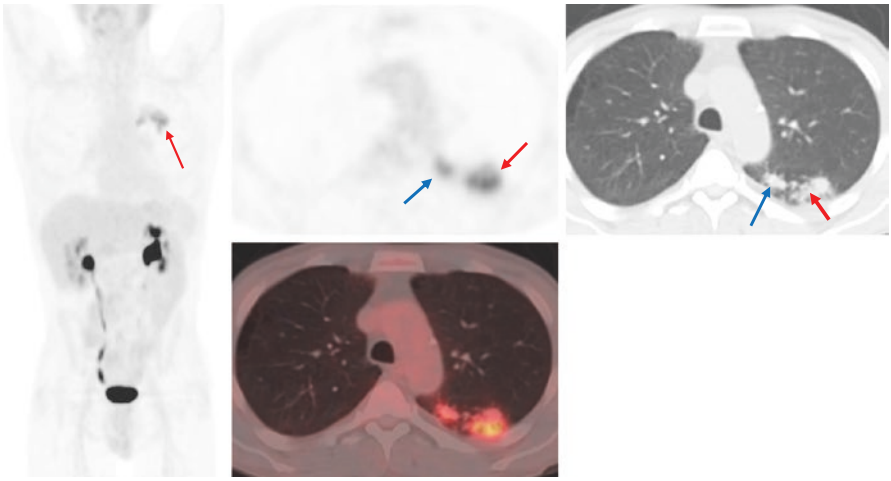

Fig. 40 TB-the great mimic. 74 year old male smoker. PET imaging demonstrates left upper lobe FDG positive mass-like consolidation (red arrow) with a satellite lesion (blue arrow), suspicious for a bronchogenic primary tumour. Biopsy confirmed caseating granulomas with culture positive TB and no evidence for malignancy. (*Image courtesy Dr Tara Barwick, Consultant Radiologist, Imperial College Healthcare NHS Trust UK)*

MRI in the follow-up of difficult cases of skeletal TB, especially at the treatment end-point [100]. The fundamental principle in these applications of FDG PET CT is to reliably differentiate active from inactive disease, a distinction not always possible on conventional imaging.

Of note, tubercular disease can also be elusive on FDG PET CT, if normal biological activity of FDG obscures pathology. This especially pertains to intracranial disease that can be potentially obscured by normal brain parenchymal FDG metabolic activity and renal and urinary bladder disease, potentially masked by physiological excretion of FDG tracer. All things considered, given that FDG PET CT is a relatively expensive test, mainly available at larger centres and also entails significant radiation exposure, it is not part of standard routine pathways. It is most useful on a case-by-case basis, applied judiciously to problem solve diagnostically ambiguous cases when conventional imaging does not provide an answer.

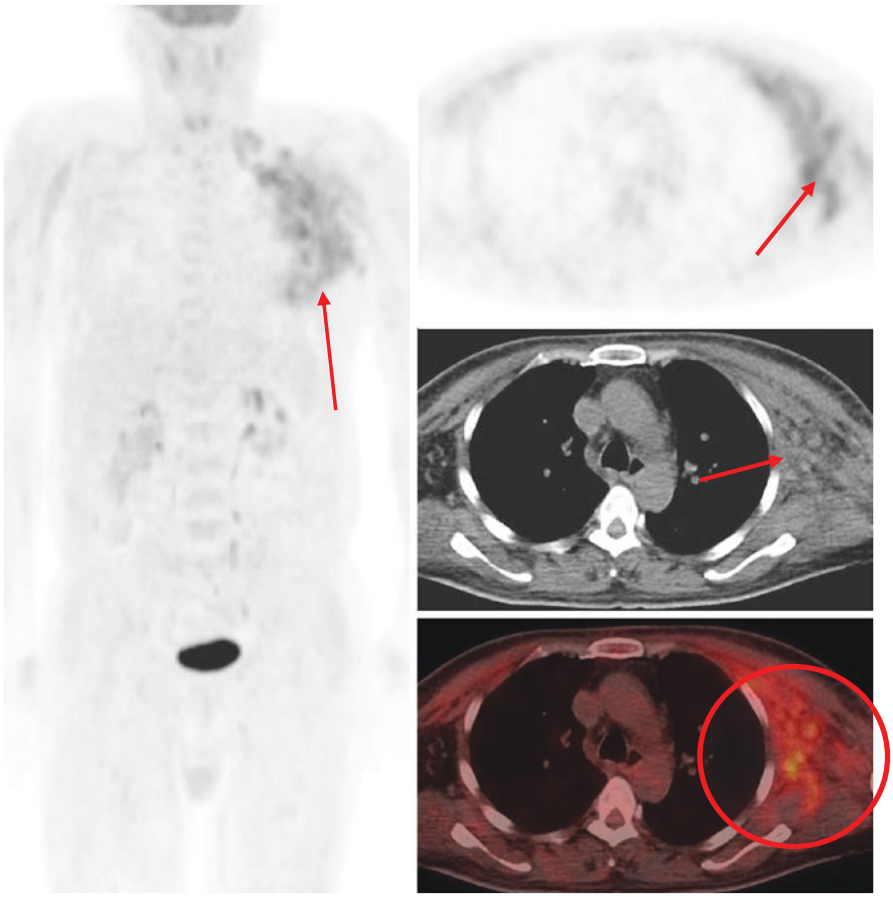

Fig. 41 Many faces of TB: 64 year old with axillary lymphadenopathy—The differential includes lymphoma and other neoplastic aetiologies. Biopsy demonstrated caseating granulomas with culture positivity confirming the diagnosis of TB lymphadenitis. (*Image courtesy Dr Tara Barwick Consultant Radiologist, Imperial College Healthcare NHS Trust UK)*

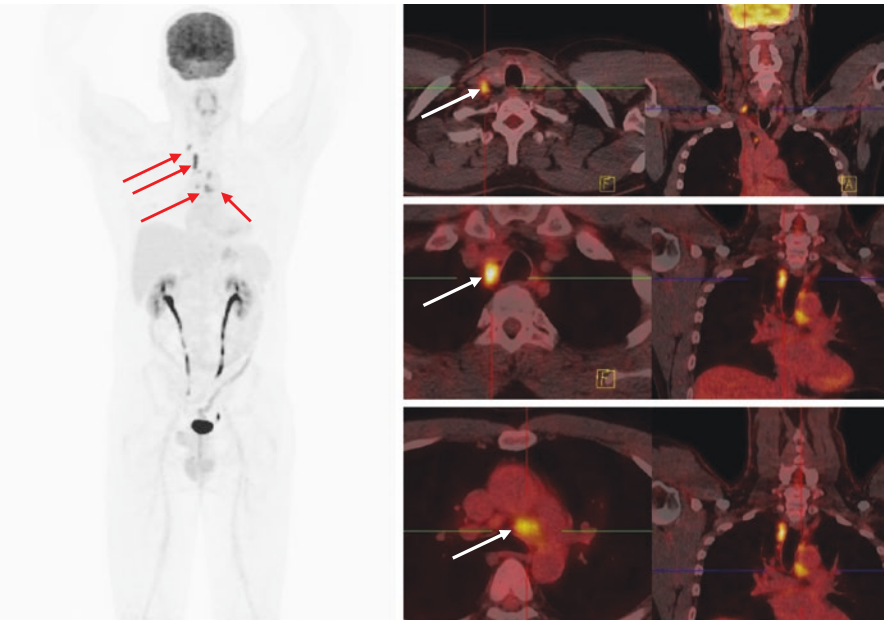

Fig. 42 FDG PET CT performed to look for potential systemic causes in a case of bilateral uveitis. This demonstrated FDG-avid intra-thoracic right paratracheal, aorto-pulmonary window and right supraclavicular lymph nodes (borderline by CT size criteria, red arrows). Endobronchial ultrasound guided fine needle aspiration of the right paratracheal nodes (white arrows) showed non-caseating granulomas. TB PCR negative, positive quantiferon test. On this basis anti-tubercular therapy was started, resulting in improvement of the eye symptoms

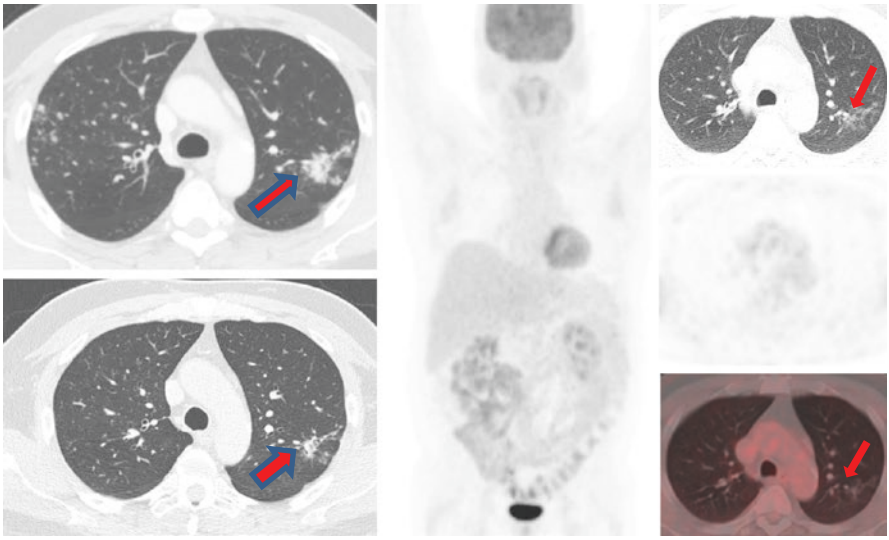

Fig. 43 FDG PET CT to assess response to treatment in a case of multi-drug resistant (MDR) TB: MDR TB on sputum culture with confluent nodularity in the left upper lobe and tree in bud nodularity in both upper lobes. CT at 4 months (upper left image) and 18 months (lower left image) post-treatment show progressive response on CT. The residual left upper lobe changes on CT are FDG negative on PET CT at 18 months, suggesting a complete metabolic response. (*Image courtesy Dr Tara Barwick, Consultant Radiologist, Imperial College NHS Healthcare Trust UK)*

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Laboratory Diagnostic Techniques

Giovanni Satta

Introduction

Tuberculosis (TB) is an infectious disease caused by bacteria of the *Mycobacterium tuberculosis* complex. *M. tuberculosis* is the most common human pathogen but other members of the complex such as *M. bovis* (including the vaccine strain *Bacillus Calmette-Guérin*), *M. africanum*, *M. canettii* and *M. caprae* are able to cause the disease in humans. The two other species currently in the complex, *M. microti* and *M. pinnipedii* are generally associated with other mammalian hosts, but some case reports have been described in immunocompromised patients [1]. Nontuberculous mycobacteria (NTM) are all other mycobacterial species other than the *M. tuberculosis* complex. With increasing numbers of immunocompromised patients (including those with HIV infection and hematological disorders), as well as patients with cystic fibrosis and chronic lung disorders, the role of NTM as a cause of human, and in particular pulmonary, disease has become apparent, with recent reports indicating a worldwide increase [2, 3]. This chapter will mostly focus on the diagnosis of TB, but the laboratory methods described will be sufficient to also identify the majority of NTMs causing human disease. International standards regarding the diagnosis of TB have been published by the World Health Organization (WHO) as well as by authoritative American and British guidance bodies [4–6].

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Specimen Collection

TB generally affects the lungs (pulmonary TB), but every organ can be infected, in particular the central nervous system, lymphatic system, gut, kidneys, spleen and bones (Fig. 1) and this will influence the type of specimen that can be processed in the laboratory. In terms of pulmonary TB, three separate sputum samples have been traditionally considered the gold standard, although the WHO has reduced its global recommendation from three to at least two serial samples [4]. This is to reduce the time to diagnosis, accelerate the initiation of treatment and to decrease the workload where laboratory resources are limited. Ideally, those samples should be taken before or within 7 days of starting treatment. Alternatively, gastric lavage, induction of sputum or bronchoscopy lavage fluid are a valid substitute where a sputum sample is not available. The diagnosis of extra pulmonary disease can be challenging. Any other sterile fluid (i.e. cerebrospinal or ascitic fluids, urine), tissue and biopsy samples (i.e. bone, lymph node) can be sent to the laboratory for processing in a sterile container. Of note, swabs are not suitable for TB microscopy or culture as well as stool samples. Biopsy tissue taken endoscopically should be sent to the laboratory for the diagnosis of gastrointestinal TB. In general, all tissue samples should normally be sent for both microbiological and histological investigations, bearing in mind that samples for culture should not be fixed. Considering the current limited sensitivity of culture in cases of paucibacillary disease, histological examination can often reveal the presence of necrotizing granulomas and help to achieve a diagnosis of tuberculosis in these challenging cases.

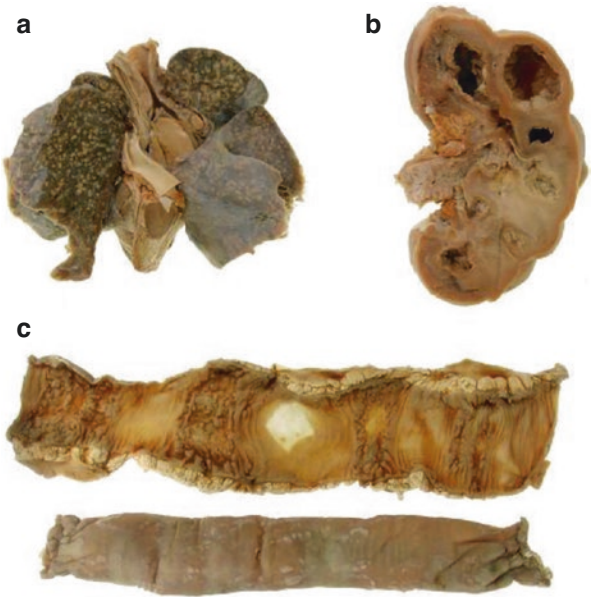

Fig. 1 Gross pathology of miliary and extrapulmonary tuberculosis: (**a**) miliary pulmonary disease, (**b**) renal disease, (**c**) tuberculous enteritis (courtesy of Dr. Tu Vinh Luong, Consultant Histopathologist, Department of Cellular Pathology, Royal Free London NHS Foundation Trust)

Microscopy

M. tuberculosis is a small (2–4 μm in length and 0.2–0.5 μm in width), aerobic, non-motile, non-spore forming bacillus. Its cell wall has a high content of high molecular weight lipids, making the cell surface hydrophobic and resistant to many disinfectants and common laboratory stains [7]. If a Gram stain is performed, *M. tuberculosis* does not retain any dye or will stain as weakly Gram-positive due to the rich lipid cell wall [8]. The distinctive feature of *M. tuberculosis* is the structure of its cell wall, composed of a thick peptidoglycan layer, with no outer membrane but a complex structure of carbohydrates and lipids (60% of the cell wall weight), made from arabinogalactan (D-arabinose and D-galactose), mycolic acids (long chain fatty acids) and free lipids (Fig. 2). Anchored in the plasma membrane are porins, transport proteins and lipoarabinomannan (LAM) which is functionally related to the *O*-antigenic lipopolysaccharides present in other bacteria. This particular structure confers upon mycobacteria resistance to acidic/alkaline substances, detergents, common antibacterials, osmotic lysis and radicals. The same structure is responsible for the unique characteristic of acid-fastness, that is the basis of the commonly used Ziehl-Neelsen (ZN) stain [9]. The term *acid-fast bacilli* is clinically synonymous with mycobacteria, although some other organisms (such as Nocardia and some Corynebacteria) can be acid-fast. In the ZN stain, a fixed smear is covered with carbol-fuchsin, heated, decolorized with alcohol and counterstained with methylene blue or malachite green. Mycobacteria cannot be decolorized with this acid solution and will retain the pink color of the fuchsin, contrasting with the blue

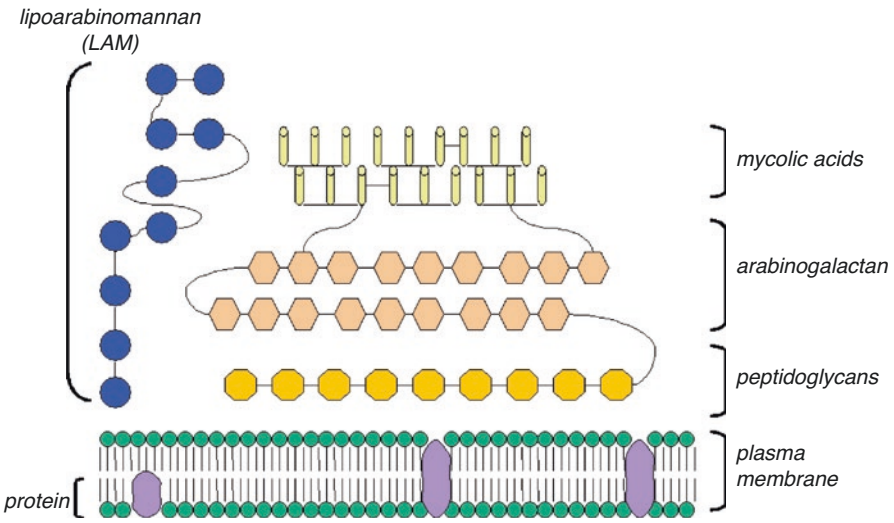

Fig. 2 Graphical representation of the mycobacterial cell wall, with a complex structure of peptidoglycans, arabinogalactan and mycolic acids (created by Dr. Giovanni Satta, PhD thesis, University College London)

background. Among the *Mycobacterium* species, *M. tuberculosis* is strongly acid fast and the bacilli will retain the carbol-fuchsin (Fig. 3). In contrast, *M. leprae* is only weakly acid fast and a decolorizing solution with a reduced content of alcohol and a different decolorizing time are often used for *M. leprae* smears on skin biopsies.

The Auramine-Rhodamine fluorochrome technique (with auramine and potassium permanganate as the counterstain) is an alternative to ZN staining and it is up to ten-fold more sensitive (albeit less specific) compared to ZN [10]. Most modern laboratories use the auramine stain as a screening method, followed by ZN for confirmation. However, it does require a fluorescence microscope and this may be a limiting factor in resource poor settings. It has been calculated that at least 5000–10,000 bacilli per mL are needed for detection of bacteria in stained smears, in contrast to 10–100 organisms needed for a positive culture [11].

Sputum specimens contaminated with normal respiratory flora require a decontamination step before culture to reduce the likelihood of overgrowth by organisms other than mycobacteria. Different decontamination methods have been described but there is no current gold standard [1]. Tissue samples do not usually require any decontamination step and it is generally suggested to also send them for histological examination. Necrotizing granuloma with caseation and giant cells are typical features observed in histological samples. Microscopy should always be performed before the decontamination of samples. It is also recommended that all respiratory samples should be processed in a microbiological safety cabinet in Containment Level 2 conditions with additional precautions to minimize risk of aerosols production and cross contamination of samples. However, considering the high risk of *M. tuberculosis* causing laboratory-acquired infections, full Containment Level 3 conditions should be used, although this may not always be available in some developing countries.

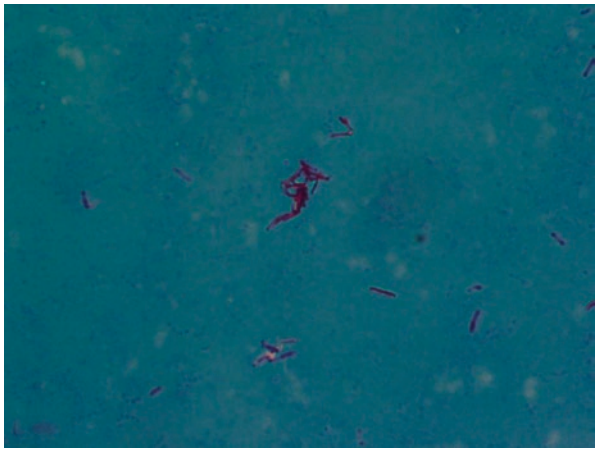

Fig. 3 Example of Ziehl-Neelsen (ZN) stain of *M. tuberculosis*. The bacilli retain the carbol-fuchsin on a background of malachite green (Courtesy of the Microbiology laboratory at North West London Pathology)

Culture and Susceptibility Methods

M. tuberculosis grows slowly with an average generation time of 15–20 h. This is an extremely slow rate compared with other bacteria, which usually divide in less than an hour, and visible growth can take up to 6 weeks on solid media (compared to 12–24 h for other common human pathogens) [7]. The doubling time can go up to 33 h inside human macrophages [12]. This is probably due to the fact that *M. tuberculosis* has only one mechanism to translate mRNA into proteins because of the lack of the *rrn-B* operon. All slowly growing mycobacteria are thought to have either one or two rRNA operons per genome [13].

Culture methods for Mycobacteria use either solid or liquid media. Solid media can be divided into two main types: agar-based (e.g. Middlebrook 7H10) and egg-based (e.g. Lowenstein-Jensen). Liquid media include various agar-based media (e.g. Middlebrook 7H10) and the automated Mycobacteria Growth Indicator Tube (MGIT) system, containing 7H9 broth base and enrichment. The BACTEC MGIT 960 system is produced by Becton Dickinson (New Jersey, USA). The instrument scans the MGIT every 60 min for increased fluorescence. Analysis of the fluorescence is used to determine if viable organisms are growing and a positive tube contains approximately 10^5–10^6 colony-forming units per milliliter (CFU/mL). Culture tubes which remain negative for a minimum of 42 days (up to 56 days) and which show no visible signs of positivity are removed from the instrument as negatives and discarded [14]. Growth in liquid media is faster (average 1–3 weeks) compared to growth on solid media (3–8 weeks) [15]. However, reliance should not be placed on these systems alone for the isolation of all mycobacterial species, particularly when investigating patients who are immunocompromised [16]. The main limitations are their single incubation temperature and the difficulty of providing the growth additives necessary for other fastidious mycobacterial species. When cultured on solid Lowenstein-Jensen media, *M. tuberculosis* colonies have a characteristic appearance, non-pigmented/yellowish and granular (Fig. 4).

Once culture positive (either on solid or automated media), most laboratories refer their isolates for identification and susceptibility testing to the reference laboratories. This is because drug susceptibility testing for antituberculous drugs is a complex procedure and requires an understanding of many issues, including drug resistance mechanisms, potency and stability of drugs during laboratory manipulation and the antimycobacterial activity of compounds when incorporated into different media [17]. The current methods have been developed over several decades and are restricted to specialised reference laboratories, as they are technically demanding, require appropriate isolation facilities and can be difficult to interpret. Three main methods are currently in use and recommended by international guidelines [18]:

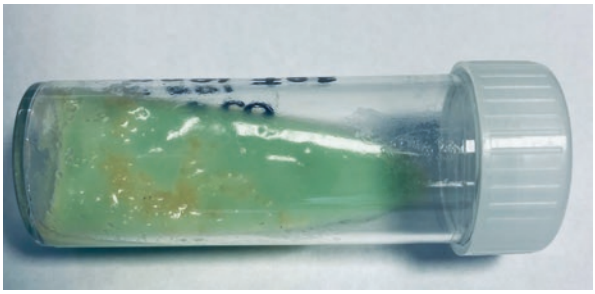

Fig. 4 Growth of *M. tuberculosis* on Lowenstein-Jensen. The colonies appear as non-pigmented/yellowish and granular. The green color of the medium is due to the presence of malachite green which is one of the selective agents to prevent the growth of gram negative and positive bacteria

1. *Absolute concentration*, where the drug is incorporated into solid agar using different dilutions (including Lowenstein–Jensen medium) or in a broth dilution method. Resistance is defined as the lowest concentration of the drug that inhibits its growth (<20 colonies) [18]. Variation is generally due to erroneous drug concentration or inoculum size [19].
2. *Resistance ratio*, where the minimum inhibitory concentration (MIC) for a given isolate is divided by the MIC for a standard susceptible strain (e.g., H37Rv). If the ratio is ≤2 or ≥8, the isolate is fully susceptible or highly resistant respectively. Inoculum size still needs to be standardized to obtain reproducible results [18].
3. *Proportion method*, where a strain is considered susceptible if it contains a proportion of resistant cells below a defined point. The proportion varies with different drugs (e.g., 1% for isoniazid and rifampicin). The introduction of the MGIT BACTEC systems (460 and 960) has allowed semi-automation of this method and lessens concerns regarding the initial inoculum size [20, 21].

Other methods have been developed, mostly colorimetric methods that use redox indicators or nitrate reduction [22, 23]. In particular, the resazurin assay (based on the Alamar Blue fluorescent dye) has been proposed as a simple and inexpensive method for detection of drug resistance in *M. tuberculosis* [24, 25].

Molecular Diagnostics and Whole Genome Sequencing

Considering it generally takes weeks before culture and susceptibilities results may become available, molecular and other point of care assays for rapid identification and detection of drug resistance have been developed. They offer several potential advantages, including lower turnaround times and minimal (or possibly no) initial culture period. The mutations associated with resistance are now well-known for some drugs, and potentially any laboratory could design its own in-house PCR

Table 1 Comparison of molecular assays for detection of MTB and drug-resistance, including next generation sequencing

Product	Approval status	Technology	Advantages	Disadvantages
Xpert® MTB/RIF and Ultra	WHO	Real-time PCR	Rapid results in less than 2 h Requires minimal expertise	Cost (including capital investment and maintenance) Current version only detects rifampicin resistance
Hain's LPA	WHO	Multiplex PCR + reverse hybridization	Can detect both rifampicin and isoniazid resistance Additional version can also detect fluoroquinolones and second line injectable drugs resistance	Cost (including additional machinery required) Multiple steps and complexity of training required Results take at least 5 h
TB-LAMP	WHO	Loop-mediated isothermal amplification	Rapid results in less than 1 h Requires minimal expertise Cost effective	Does not screen for any markers of drug resistance Requires several manual steps
In-house PCR	Not approved	Real-time PCR	Generally reduced cost and rapid results	Not approved by WHO Required local pathology accreditation May not screen for any markers of drug resistance
Whole genome sequencing	Not approved	Next generation sequencing	Oxford Nanopore MinION as point of care technology Possibility of detecting resistance to first- and second-line drugs Identification of MTB and NTMs Epidemiological links and investigations	Very high cost Bioinformatic support needed Culture isolates still required for the majority of samples Limited sensitivity if performed directly from clinical samples

(polymerase chain reaction). In particular, two molecular assays have clinical value: the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, USA) and the Line probe assay (LPA) (Hain Lifescience, Nehren, Germany) [26, 27]. The Xpert® assay is an automated real time-based system with various advantages, including point of care testing, a closed tube system, ease of performance and result availability within hours. It is endorsed by WHO, but its high cost is a disadvantage. A newer version, Xpert® Ultra, is also WHO recommended, and initial data have demonstrated higher sensitivity and lower specificity for TB detection and similar sensitivity and specificity

for rifampicin resistance detection, compared to the older MTB/RIF assay [28]. The LPA technology is suitable for reference laboratories, or laboratories where there is proven capacity to conduct molecular testing, as it requires appropriate laboratory equipment and adequately trained laboratory staff [29]. Other point-of-care diagnostics which the WHO has also endorsed are the loop-mediated isothermal amplification (TB-LAMP) and the lateral flow lipoarabinomannan (LAM) assay. All point-of-care diagnostic tests have their strengths as well as limitations, but the aim is to have rapid diagnostic tests which are affordable at decentralised settings with minimal expertise required [30] (Table 1).

Finally, since 2017 England has become the first country globally to introduce and pioneer the use of whole genome sequencing (WGS) on a national scale for the diagnosis, detection of drug resistance and typing of *M. tuberculosis* [31]. WGS has the potential to revolutionize *M. tuberculosis* susceptibility testing and to provide comprehensive identification of bacterial transmission pathways in hospital and community settings [32]. However, the infrastructure and expertise required may be a limiting factor for its future implementation in other countries, in particular in the developing world.

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Whole Genome Sequencing: Applications and Cluster Investigations

Pretin N. Davda, Hanna Kaur, and E. Grace Smith

Introduction

Whole genome sequencing (WGS) has accelerated the diagnostic workflow for *Mycobacterium tuberculosis complex* (MTBc), improving patient care and streamlining the public health response to new cases of *Mycobacterium tuberculosis* (TB).

TB WGS provides three key results:

1. Identification of MTBc strains
2. Predicting drug susceptibility of MTBc strains
3. Identifying genetically similar MTBc isolates

In England, these results are available from the reference laboratory within 7 working days of receipt of a positive mycobacterial culture [1].

The full impact of WGS is yet to be determined, as it is still in its infancy outside of the research environment, with England being the first country to implement WGS as routine clinical diagnostics in 2017.

We will discuss the applications of each of these results, focussing on TB strains, and its impact on incident and outbreak investigations from both a health protection team and TB nurse perspective.

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Identification of TB Strains and Predicting Drug Susceptibility

Background

Identification of TB strains from a positive mycobacterial culture is available quickly, however phenotypic drug susceptibility testing (DST) is slow, taking weeks after TB is identified (Public Health England, 2017). This delay is likely to contribute to the spread of drug resistant TB, as there is a period of uncertainty about which are the best drugs to prescribe.

Commercial genotypic assays are able to identify drug-resistant TB early; however these assays only screen a few drugs for the common resistance-conferring mutations whilst WGS screens for *all* the known resistance-conferring mutation in all first and second line drugs [2].

The Advancement with WGS

Predictions on drug susceptibility are reported *at the same time* as TB strains are identified by WGS, within 7 working days of a positive culture. This means that drug-resistant strains of TB are identified much earlier than with conventional DST methods.

The availability of these drug susceptibility predictions empower clinicians to treat their patients early with a robust, organism-targeted regimen. This reduces the patients' exposure to inadequate, ineffective and toxic medications, which otherwise may have provided sufficient drug-pressure to induce further drug resistance. Additionally, it will mean patients are isolated appropriately and likely reduce the transmission of drug-resistant TB [3].

These results are generated by a bioinformatics pipeline, which is a software workflow that examines the sequenced genome for the presence of any mutations and analyses them against a mutation catalogue of *all* known mutations, which then provides a drug prediction.

Currently, sensitivity and specificity of WGS to detect resistant-conferring mutation in the first line drugs is >91% and 93.5% respectively. The percentage that a susceptible prediction is correct (Negative predictive value) is 99.7%, and the positive predictive value of a resistant prediction is 87.6% [4].

An international study (CRyPTIC) - Comprehensive Resistance Prediction for Tuberculosis: an International Consortium) is working to strengthen the mutation catalogue and precisely quantify the degree of drug resistance by providing minimum inhibitory concentrations (MIC) for individual genetic mutations [5].

Performing WGS for TB directly on sputum is currently in the research phase [6], which is an exciting concept because if it is successful it will further reduce treatment delays and transmission of TB among contacts and may contribute greatly to WHO's target to end the TB epidemic by 2030 [7].

Identifying Genetically Similar Isolates

In addition to organism identification and drug susceptibly predictions, the bioinformatics pipeline can compare the genetic makeup (fingerprint) of one TB isolate with another and analyse how closely related they are genetically. This is referred to as relatedness and can be applied in several different ways to benefit the patient, public health interventions and laboratories. These include:

1. Patient benefits
   (a) Providing treatment plans for multidrug-resistant (MDR) or extensively drug resistant (XDR) TB cases
   (b) Providing treatment plans for suspected cases of TB who are linked to known cases of TB
2. Public Health Benefits
   (a) Rapidly identify clusters and outbreaks of TB at a greater precision than previous methods
   (b) Focussed patient interviews based on relatedness to rapidly identify transmission networks within clusters to direct contact tracing efforts
   (c) Predict the existence of undiagnosed cases, allowing the health protection teams to actively search for cases
   (d) Increase information on transmission of TB
   (e) Understand the natural evolution of TB
3. Laboratory benefits
   (a) Early identification of false-positive results from laboratory cross-contamination which may highlight problems with laboratory workflows

Background

The TB genome is made up of 4.4 million base pairs from the nucleotides Adenosine (A), Thiamine (T), Guanine (G), Cytosine (C). If one nucleotide is substituted or mutates to another nucleotide (e.g. A substituted by T), then this is known as a single nucleotide polymorphism (SNP).

The natural evolution of TB can be studied by WGS genotyping and has shown that TB is a slow mutating organism when compared to other bacteria, as it mutates at a rate of approximately 1 SNP every 2 years [8].

Patients with TB isolates that are genetically different by more than 12 SNPs can be confidently excluded from having epidemiological links. TB isolates that are different by $\leq$12 SNPs can suggest a common epidemiological source and isolates that are $\leq$5 SNPs apart are more likely to have case-to-case transmission if epidemiological links are established.

Therefore, TB isolates that differ by ≤12 SNPs are said to belong to the same cluster and this information can be visualised on a phylogenetic tree (Fig. 1)[1] and is passed onto health protection teams (HPTs) to investigate for epidemiological links and identify outbreaks of TB. Direction of transmission can be deduced from these trees because backward mutations are rare [8].

Typing Before WGS

Prior to WGS, clusters and outbreaks were detected by MIRU-VNTR genetic typing (mycobacterial interspersed repetitive—unit—variable—number tandem repeat). This technique would amplify repeat sequences of 50–100 base pairs at 24 specific locations on the genome. The number of repeated sequences detected at each locus is calculated and these numbers forms the genetic typing of the TB isolate. Isolates with the same MIRU-VNTR results would be grouped into clusters.

MIRU-VNTR genotyping results would be available 21 days after the initial identification of TB and then made available to HPTs for local cluster investigation [9]. Local and regional HPTs would review clusters periodically to decide if further

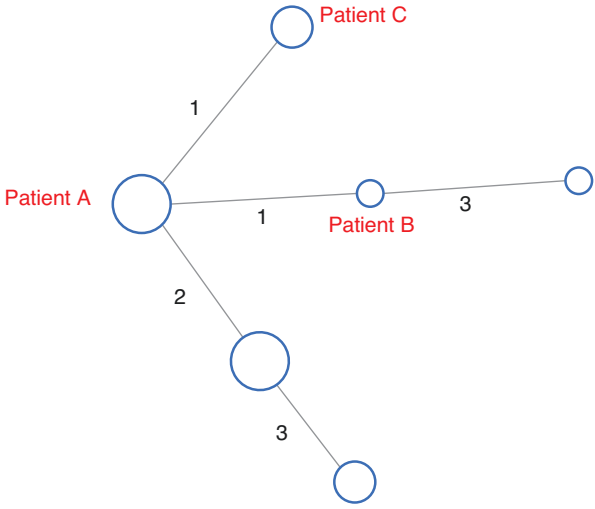

Fig. 1 An example of how WGS relatedness can be visualised as a phylogenetic tree

[1] In Fig 1, each circle/node represents a TB isolate and the size of the circle directly represents the number of TB isolates that are genetically identical (0 SNP difference). The larger the circle, the more isolates that are identical.

The line/branch represents genetic linkage and the number on each branch identifies the number of SNP differences between two isolates.

Patient A is likely to have transmitted to both Patient B and C both of who are 1 SNP away from Patient A, and 2 SNPs away from each other. Because backward mutations are rare, it is unlikely that Patient B would have transmitted to Patient C because the mutational steps would require a backward step from B to A and then a forward step to C.

investigations are required [10]. This could mean that HPTs would be investigating epidemiological links between patients well after they have been established on treatment or even completed treatment, often a time when patients no longer wish to engage or are unable to recall their contacts from over 6 months ago.

Comparative analysis of WGS to MIRU-VNTR has shown that WGS typing provides better resolution and precision of relatedness compared to MIRU-VNTR, which has shown to create false clusters [11–14]. MIRU-VNTR results would cluster 50% of new TB isolates, whilst the increased precision of WGS means that only 25% of new TB isolates are in true clusters (unpublished data).

Patient Benefits from WGS Relatedness

Clinicians treating patients diagnosed with TB, whose isolate is identified as part of cluster, can request for the DST results of closely related/neighbouring isolates. It is likely that both isolates will share a similar phenotypic drug susceptibility pattern if the isolates are closely related and there are no additional mutations present in the newest case [3].

This is particularly helpful when managing drug-resistant TB cases where WGS identifies MDR or XDR TB, based on resistance to the majority of first- and second-line agents. Performing DST on all first, second and third line drugs could take months depending on the viability of the TB organism, so using the already known DST results on neighbouring isolates to create a treatment plan is likely to be successful.

A similar principle can be applied to managing any patient in whom there is a clear epidemiological link with a patient known to have TB (index case). By knowing the drug susceptibility of the index case, a treatment plan can be established for the secondary case. This is particularly helpful when treating children in whom obtaining diagnostic samples is often challenging.

If specimens are obtained and undergo WGS, the transmission chain can be confirmed or refuted depending on whether the isolate from the secondary case is within 12 SNPs of the index case.

Public Health Benefits from WGS Relatedness

The increased resolution and precision WGS relatedness has over MIRU-VNTR typing has prevented unnecessary public health investigation and surveillance of false clusters [8].

The additional benefits relate to whether a new cluster has been identified or whether there have been new cases to established clusters.

The overall benefit to HPTs and TB Nurses is that WGS has been able to prioritise searches for transmission events in clusters where isolates are related by ≤ 5

SNPs rather than broad based transmission event searches that may have occurred through MIRU-VNTR typing.

New Clusters/Incidents

Patients diagnosed with TB are asked questions regarding their occupation and recreational activities to identify risk factors for acquiring TB and establish who may be close and social contacts. This occurs at the initial consultation with TB nurses.

When WGS identifies new clusters, and isolates are related by ≤5 SNPs, these initial assessments are reviewed to ascertain if there are any obvious epidemiological links.

Transmission events may be easily recognisable, for example all members of the cluster are household or workplace contacts, however this is not always the case.

If there are gaps in information or no clear epidemiological links identified, then further interviews are conducted.

Social networking questionnaires are a useful tool to gather epidemiological information and help identify transmission settings that may have been missed before. Figure 2 shows a sample questionnaire, adapted from the TB Case Management Tool [15] more than one sheet may be required or up-to 1 week of logs to identify contacts.

The questionnaire includes a log of daily activities and free space to log social networks. Completion may require prompting and the support of a TB nurse experienced in interviewing patients, or someone who has a good rapport with the patient.

This may not be suitable for all patients because of variations in daily activities and routines, or because patients may feel that they need to give a binary response [16] and in these situations individualised questions may be necessary.

Additionally, not all patients freely disclose their social contacts and these patients who are reluctant or refuse to engage can be difficult and challenging for TB services [8].

If analysis of these social networking questionnaires identifies a possible epidemiological link, for example visits to the same healthcare facility or another congregate setting, then further customised questions may need asking to confirm transmission of TB in this setting.

If transmission is confirmed in a congregate or healthcare setting, then an incident may be declared, allowing HPTs and TB nurses to pool their resources and co-ordinate screening exercises in these congregate settings.

Identifying latent TB infection in contacts can prevent them from developing active TB disease later [15]. This targeting screening programme can also identify cases of active TB and establish them on the correct treatment earlier than through the conventional routes, which will further reduce the transmission of TB [8].

Sometimes, new clusters are made up of patients with isolates that differ by 2–12 SNPs and there may be a missing, undiagnosed patient who is the common source. The bioinformatic analysis is often able to identify if this is the case based on the requirement of a backward mutation to link the two clustered isolates (Fig. 3). In

All questions refer to a three-month period preceding TB diagnosis or evaluation as a contact

1. During the day time (6am to 5pm), where are three places you usually spend time with other people indoors?

Place:	Location: (street address and city/town)	Main activity/purpose:

2. During the evening (5 to 10pm), where are three places you usually spend time with other people indoors?

Place:	Location: (street address and city/town)	Main activity/purpose:

3. During the night (10pm to 6 am), where are three places you usually spend time with other people indoors?

Place:	Location: (street address and city/town)	Main activity/purpose:

Time spent conducting this interview

Date 1:	Time start:	(circle)	am/pm	Time start:	(circle)	am/pm
Date 2:	Time start:	(circle)	am/pm	Time start:	(circle)	am/pm
Date 3:	Time start	(circle)	am/pm	Time start:	(circle)	am/pm

Activity codes:

1 = Eat	6 = Drink
2 = Sleep	7 = Share drugs
3 = Job	8 = Exercise
4 = School	9 = Unknown
5 = Socialise	10= Other (state)

Fig. 2 A sample of a Social Network Questionnaire, adapted from the Royal College of Nursing TB Case Management Tool [15]

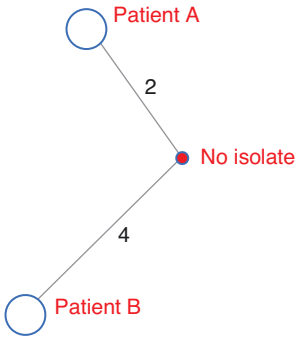

Fig. 3 Phylogenetic tree depicting a missing isolate that would link Patient A and Patient B. The two clustered isolates would require a backward mutation for transmission to have occurred. As this is rare, the bioinformatic analysis hypothesise that there is a missing isolate (patient) who connects the two patients together and may be the index case

these scenarios, active case finding may be implemented by HPTs and TB nurses if there are similarities in patient demographics but no clear epidemiological links (e.g. work in the same establishment but not on the same floor/department/site).

Established Clusters/Outbreaks

In established clusters, often the transmission setting is known (e.g. intravenous drug use, TB within a school or prison, common congregate setting etc.).

If WGS identifies new cases to be related to established clusters, and these patients have epidemiological links to the cluster, but were not identified as contacts of prior cases, then this can suggest an outbreak of uncontrolled TB transmission within the cluster. Public health teams will review the screening already taken place and further screening exercises may be required to prevent the development of further active cases.

HPTs may decide that these endemic cluster require close surveillance to ensure that there is not a rapid expansion of new cases within the cluster. This may require collaboration with TB nurses to confirm treatment compliance, GPs to identify vulnerable patient cohorts, drug and alcohol services if the patient cohort utilise these services, police and local authorities if additional powers are required to isolate an infectious patient to prevent ongoing risk and transmission to the public (Part 2A order Health Protection Order in England).

Transmission and Evolution of TB

Transmission of TB continues to be poorly understood and international guidelines regarding transmission from infectious cases are based on published reports of individual cases and community outbreaks [17, 18].

The increased precision of WGS clusters in collaboration with epidemiological investigations is likely to further enhance the understanding of TB transmission and may pave way to further research into host and virulence factors that facilitate widespread transmission from infectious cases ('super-spreaders') [19] or why transmission may occur between patients with minimal contact with index cases.

As cluster networks enlarge, we will see the natural genetic variation of TB through SNP distances from the original case and this will further our understanding of the natural evolution of TB.

Laboratory Errors

When two genetically identical isolates (0 SNP difference) are identified within a short time frame of each other, this raises the suspicion of a false-positive result, which may have occurred by one specimen being contaminated with TB organisms

from the second specimen, or through mis-labelling of specimens. Both errors can occur at either the initial sending laboratory or the reference laboratory.

Early identification of false-positive results prevents patients from being subject to unnecessary investigations and toxic medications.

Once a false-positive result is suspected, the reference laboratory co-ordinates an investigation with the sending laboratory and health protection teams.

The reference and sending laboratories assess, in parallel, whether these two specimens were processed on the same day for any of the diagnostic steps. If they were, then the culture and WGS is repeated with specimens being processed on different days to confirm the initial TB result was a false-positive result.

The health protection teams inform clinical teams of a possible false-positive result and determine whether the teams suspected TB in both patients. They also request that further specimens are submitted by both patients. Both of these steps provide further evidence to support or reject the hypothesis that a false-positive result was identified.

False-positive results can also be identified by clinical teams directly, if they believe the WGS identification does not match the patient (e.g. TB identified in a patient whose previous cultures identified non-tuberculous mycobacteria (NTM), or in a patient who is not known to TB services with no clear signs or symptoms of active TB). When these queries are raised, the same investigations described above take place to assess if a contamination event took place and if so where.

Investigating false-positive results can identify if there are problems with sample processing or workflow and pinpoint where changes can be implemented to reduce further false positive results.

Conclusion

The speed, sensitivity and increased resolution that WGS provides over conventional TB diagnostics for identification, drug susceptibility and relatedness have many benefits.

WGS allows clinicians to start effective TB treatment earlier and public health teams to target contact tracing exercises and act early when outbreaks are detected.

The full impact that prospective, real-time WGS on TB isolates is yet to be established, however it has the potential to significantly interrupt TB transmission and contribute to the reduction the TB epidemic.

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The Tuberculin Skin Test and the IFN-γ Release Assays

Delia Goletti

Introduction

Tuberculosis (TB) is still a major cause of morbidity and mortality worldwide and is now the most common cause of death from an infectious disease, surpassing HIV/AIDS [1]. In 2019, 10 million new active TB cases and 1.4 million deaths have been estimated [1]. Almost a quarter of the world population, 1.7 billion subjects, is estimated to have latent TB infection (LTBI) [2]. An effective vaccine that prevents infection or disease would be essential for ending TB [3]. However, although promising results have been achieved characterizing the mycobacterial growth inhibition test as a correlate of protective immunity [4], further validations and studies are necessary in order to have reliable immune correlates for an effective TB vaccine.

Mycobacterium tuberculosis (*M. tuberculosis*), the bacterium that causes TB, emerged as a human pathogen 75–150 thousand years ago and spread by clonal expansion among human communities since then, giving rise to seven phylogeographic lineages distinguished as ancient and modern [5–7]. *M. tuberculosis* is an intracellular pathogen transmitted in aerosolized droplets, usually by coughing from a person with active TB disease. Once inhaled, the bacillus (5) primarily infects alveolar macrophages. It then goes to the lung parenchyma where it can infect resident macrophages or other phagocytes, including neutrophils. The replication of *M. tuberculosis* in macrophages is crucial for the pathogenesis of the disease. Recent lineages seem to better replicate within macrophages [8].

Infected macrophages induce cell activation to recruit other immune cells, including monocytes, which differentiate into macrophages and provide additional targets for infection. In parallel, *M. tuberculosis* can be taken up by dendritic cells and transported to the thoracic lymph nodes where T cells are primed against a

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broad range of *M. tuberculosis* antigens (Ags). The primed T cells return then to the lung, to the site of infection, and organize around infected macrophages to form granulomas, the pathologic structure which is closely associated with TB (Fig. 1). Granulomas also function as a reservoir of infection and dissemination for *M. tuberculosis* [9] and several factors contribute to the loss of granuloma integrity thus contributing to disease spread (Fig. 1).

M. tuberculosis infection is extremely variable in humans. The majority of people control the infection, although they cannot eliminate it. Infected but asymptomatic individuals are classified as having LTBI [10, 11]. Persons with LTBI are characterized as having evidence of infection by an immunologic test [positive tuberculin skin test (TST) or IFN-γ release assay (IGRA)], with no signs or symptoms of TB. The immunological tests are positive within 10–12 weeks from exposure to *M. tuberculosis*. A small proportion (5–15%) of LTBI subjects may progress to active, symptomatic, and transmissible TB within 2 years of infection, likely representing a lack of initial control of infection; this is termed active TB. Active TB can present in a variety of ways, because the bacillus can infect any organ in the body; however pulmonary TB is the commonest localization.

In this chapter, we will review how LTBI is currently defined and diagnosed and to whom testing should be systematically directed. We will report the current role of TST and the IGRA in the LTBI diagnosis, the new experimental tests have been designed to improve on the current IGRA-like approach of detecting circulating *M. tuberculosis*-specific T cells and we will detail the risk groups that need to be tested for LTBI and treated.

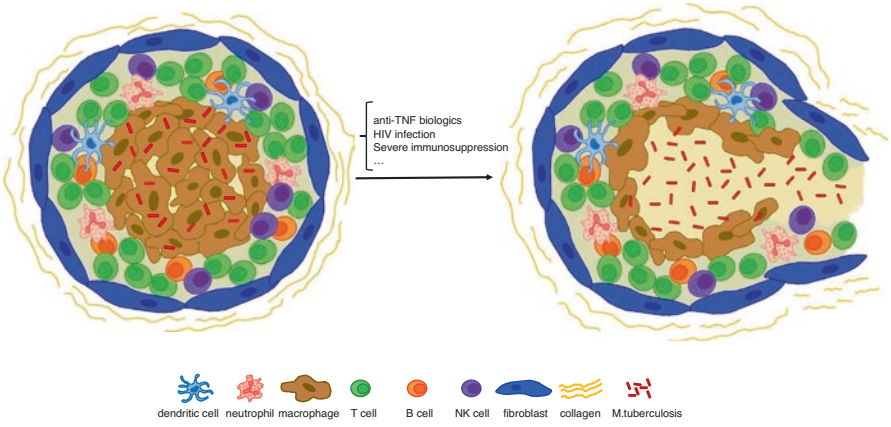

Fig. 1 Modulation of the granuloma integrity by events that generate immune suppression. Granuloma is a complex and well organized cellular structure in which *M. tuberculosis* is contained within a necrotic region surrounded by epithelioid macrophages and a rim of B and T lymphocytes. The TNF-α has been recognized as a key factor for the maintenance of this structure. Similarly, HIV infection and severe immune suppression may lead to the disruption of the granuloma integrity—losing the bacterial containment—and may contribute to active TB reactivation

LTBI Definition and Diagnosis

Based on the World Health Organization (WHO) definition, LTBI is a status characterized by the presence of immune responses to *M. tuberculosis* without clinical evidence of active TB [10]. TST or the IGRA are the assay used to measure LTBI, which are based on the specific recognition of the mycobacterial antigens [12].

In countries in which TB incidence is low, reactivation of LTBI accounts for the majority of the new TB cases [13]. It is not surprising that the LTBI screening of individuals at risk to develop TB and prevention of active TB disease by preventive treatment are crucial components for the WHO End TB Strategy [14].

TST

TST measures the induction of a delayed type hypersensitivity immune response to the intradermal injection of purified protein derivative (PPD) (Fig. 2). PPD is a crude mixture of antigens, many of which are shared by *M. tuberculosis* and other mycobacteria, in particular Bacille Calmette-Guérin (BCG). The absence of the specificity of the antigens used in this assay is the cause of the suboptimal specificity of the test for *M. tuberculosis* infection. This is particular relevant in people coming from high TB endemic countries where BCG vaccination is commonly performed very early in life [15, 16].

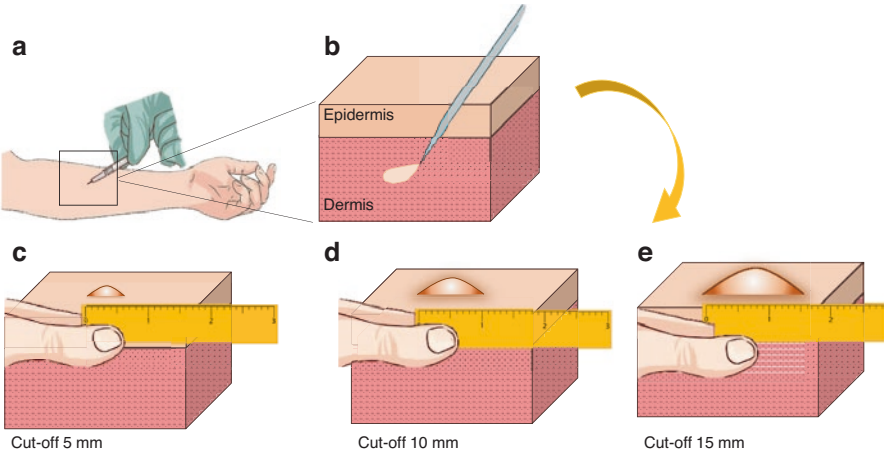

Fig. 2 Administration and interpretation of the tuberculin skin test. (**a**) The injection of protein purified derivative (PPD) is performed 5–10 cm below elbow joint with a short needle syringe. (**b**) The needle must be inserted at an angle of 5–15° to release PPD intradermally, and the needle should be visible just below skin surface. (**c–d**) The results should be read 72 hours after PPD administration. The injection site is visually inspected and the skin induration transverse diameter is measured in mm using a ruler. Differential cut-offs have been used depending on the risk of infection and progression to active disease, as an induration of diameter ≥5 or ≥10 mm or ≥15 mm, as described in the text [18, 19]

Histological studies have suggested that since TST is the result of the classic model of cellular infiltration during a delayed-type hypersensitivity, its response is due to a biphasic cell migration, comprising an initial nonspecific infiltration (neutrophils), Natural Killer cells (NK) that also occurs in non-sensitized subjects, and a second specific peak (mainly CD4 T cells) [17]. The mechanism of this cellular infiltration is not completely clear, but it is likely that early after the injection, pro-inflammatory cytokines such IFN-γ, tumor necrosis factor (TNF)-α, and TNF-β stimulate expression of adhesion molecules (e.g. E-selectin) on the endothelium and increase the permeability of the local blood vessels. Circulating CD4 + CD25 + FoxP3+ Treg cells influence the area of the TST induration [12]. Cutaneous CD4 T cells accumulating after PPD stimulation have a predominant CD45RO memory phenotype [17].

The response is evaluated by measuring the transverse diameter of skin induration (in mm) (Fig. 2). Different cut-off have been identified to define them as positive. The official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention provides recommendations for diagnostic testing for LTBI based upon the likelihood of infection with Mtb and the likelihood of progression to TB disease if infected [18]. Therefore, in those likely to be infected and at high risk of TB progression, an induration is scored positive if ≥5 mm (children <5 years old, HIV infection, immunosuppressive therapy, abnormal chest X-Ray consistent with previous TB, silicosis); in those likely to be infected and at low to intermediate risk of TB progression: an induration is scored positive if ≥10 mm (clinical predisposition, diabetes, chronic renal failure, IV drug abuser); in those unlikely to be infected, an induration is scored positive if >15 mm (no risk factors). In the NICE guidelines if the TST has an induration of ≥5 mm, regardless of BCG history, one should consider performing an IGRA [19]. TST has been broadly used, especially for massive screening in the population all over the years. Large experience has been cumulated for screening recent contacts [20], heath care workers [21], immune suppressed individuals [22], pediatric populations [23, 24]. Therefore, different cut-off sizes that allow an estimation of the risk to develop TB, based on factors such as age, BCG-vaccination, and immune suppression diseases were also considered [25] all over the years. Definitions of conversion and boosting have also been established; conversion is defined as an induration over 10 mm with an increase of at least 6 mm over the previous result [26, 27]. Sensitivity may be reduced by malnutrition, severe active TB disease, and immunodeficiency status, as for HIV infection or therapy with biological drugs inhibiting TNF. Specificity is low in those with BCG-vaccination, although after 10 years or more, the effect of BCG-vaccination on TST reactions is limited if the vaccination was given in infancy [25] (Table 1). Moreover, from a logistic point of view, TST involves two healthcare visits, one for the PPD injection and the other to measure the induration, leading to a loss of reading in around 10% of the cases [28]. Moreover, subjective variability in performing the test or in reading it, is possible.

Table 1 Characteristics of the routinely used immune-based tests for LTBI diagnosis

	TST	QFT-IT[a]/ QFT-P	T-SPOT TB
Laboratory test with internal controls included	No	Yes	Yes
T cell anergy diagnosed	No	Yes	Yes
M. tuberculosis-specific antigen	No	Yes	Yes
Time required for results, hours	48–72	16–20	16–20
Cut-off established depending on age, time of contact, immune suppression	Yes	No	No
BCG status impact on the result	Yes	No	No

Abbreviations: *TST* tuberculin skin test, *QFT-IT* QuantiFERON in tube[a], *QFT-P* QuantiFERON Plus, *TB* tuberculosis, *BCG* Bacillus Calmette–Guérin

New Version of TST

Recently, the C-Tb [29, 30], a new skin test for LTBI detection based on the intradermal administration of recombinant ESAT-6 and CFP-10 has been proposed. This test may have several advantages: low cost and ease of use like the TST and high specificity for LTBI detection similarly to IGRA. It has been shown that C-Tb has similar sensitivity for active TB compared to TST and QuantiFERON-TB-Gold-In-Tube (QFT) in adults [29, 30], in children and in HIV-infected persons [31]. Larger studies are needed to evaluate the routine use of the assay for LTBI detection in fields studies.

IGRA

IGRA are blood laboratory tests and include QuantiFERON Plus (QFT-P; Qiagen, Hilden, Germany) and T-SPOT.TB (Oxford Immunotec, Abingdon, UK) (Fig. 3). The assays involve a negative, a positive control (mitogen stimulus) and a specific *M. tuberculosis* stimulation. IFN-γ production is measured after 16–20 h in whole blood or peripheral blood mononuclear cells (PBMCs), using ELISA or enzyme-linked immunospot (ELISPOT) assay, respectively [12]. The stimulation is performed using *M. tuberculosis*-specific peptides spanning the *M. tuberculosis* antigens ESAT-6, CFP-10 and are restricted to a region of the *M. tuberculosis* genome deleted from *M. bovis* BCG and which is not present in most environmental mycobacteria [32–34] providing the specificity of the test for detection of tuberculosis infection or disease. IGRA are more specific than TST for the diagnosis of TB due to the higher specificity of the antigens used, also for diseases due to the majority of non-tuberculous mycobacteria (NTM) [35] with the exception of exposure to *M. kansasii, M. marinum because* both express ESAT-6 and CFP-10 [36, 37]. An additional important advantage of in vitro testing is that the laboratory test can take

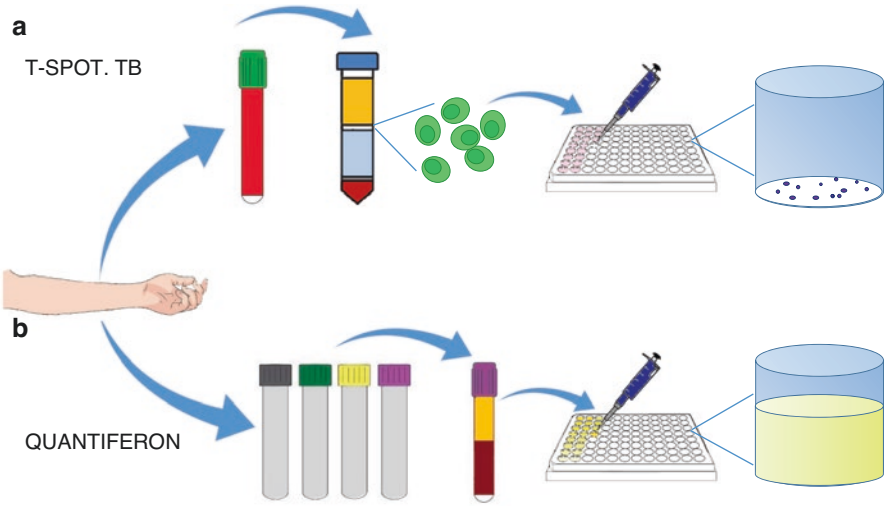

Fig. 3 IGRAs: procedures and principle of the assays. IGRAs are tests for detecting the cell-mediated immune responses to mycobacterial antigens (mainly ESAT-6 and CFP-10). This response involves the secretion of IFN-γ that is measured in IGRAs through the ELISPOT or ELISA methodologies. (**a**) The T-SPOT. *TB* system uses an heparinized blood sample from which PBMCs are isolated. A pre-determined number of PBMCs and *M. tuberculosis* antigens are then added to the wells of a plate with a membrane on the bottom. Cells secreting IFN-γ are enumerated through visualizing the footprint on the membrane. (**b**) The QuantiFERON system uses dedicated blood collection tubes (named NIL, TB1, TB2 and Mitogen). These tubes are incubated for 16 to 24 hours, after which, plasma is harvested and tested for the presence of IFN-γ produced in response to the *M. tuberculosis* antigens by ELISA test

in account background signals or general T cell responsiveness, having the stimulation reactions with negative and positive controls (carried out in parallel) (Table 1). These assays' characteristics are then very important in the setting of immunodeficiency where an impaired mitogen response may additionally be interpreted as a meaningful measure for assessing the overall extent of immunosuppression. Therefore, unlike TST, in vitro tests may be able to discriminate true negative responses from anergy (Table 1).

Based on these characteristics, IGRA are considered in several countries as the new standard of care for diagnosing LTBI. These assays are not recommended for the diagnosis of active TB because they do not have sufficient sensitivity or negative predictive value to rule out a diagnosis of active disease other than in specific scenarios (e.g. in children), with caveats around interpretation of the results and the expertise required [38, 39]. Moreover, both these tests have a low predictive value for active TB prediction, as confirmed in a recent well designed study, the IDEA trial that was performed in UK [40].

QuantiFERON Test: Interpretation of the QFT Values Within the Uncertainty Zone (IFN-γ Values: 0.2–0.7 IU/ml)

No gold standard for detection of LTBI is available. The cut-off at 0.35 IU/ml was chosen in Japan on the basis of data from people with no identified risk for *M. tuberculosis* exposure (in particular, 216 BCG-vaccinated Japanese adults) and sensitivity was estimated on the basis of data from culture-confirmed *M. tuberculosis* (in particular, 118 patients) who had received less than 1 week of treatment. The specificity of the test for the low-risk group was 98.1% and the sensitivity for patients with *M. tuberculosis* infection was 89.0% [41].

To confirm if the QFT assay cut-off at 0.35 IU/ml was optimal in a TB-endemic population, a study in South Africa was performed in which healthy, *M. tuberculosis*-unexposed control subjects from Denmark (50 subjects) and microbiologically confirmed TB cases from South Africa were evaluated. The standard QFT cutoff of 0.35 IU/ml yielded 100% specificity and 91% sensitivity. Because all *M. tuberculosis*-unexposed control subjects had IFN-γ values less than 0.2 IU/ml, the authors evaluated whether a lower QFT cutoff would increase sensitivity. Applying a cut-off at 0.2 IU/ml, which coincides with the lower limit of the uncertainty zone, yielded 96% sensitivity, whereas the specificity remained at 100%. Interestingly, 9% of IFN-γ values from TB cases fell between 0.2 and 0.7 IU/ml, whereas 87% of patients with TB had IFN-γ greater than 0.7 IU/ml [42].

Notably among individuals with IFN-γ values less than 0.2 IU/ml, 0.2–0.34 IU/ml, 0.35–0.7 IU/ml, and greater than 0.7 IU/ml, TST positivity results were 15%, 53%, 66%, and 91% ($P = 0.005$), respectively. Together, these findings suggest that values less than 0.2 IU/ml were true negatives.

Accuracy

Negative Predictive Value

Studies performed in low-incidence countries showed that the negative predictive value for progression to TB within 2 years is high (98–99% for IGRA), whereas it is lower in an intermediate-burden country such as Thailand (88%) [43]. In the few studies in which IGRA and the TST were concomitantly performed to compare the negative predictive value estimates, it was shown that the negative predictive value for the TST was 99.7% compared to 100% for the QFT-Gold in Tube (QFT-GIT) [43] (Table 2).

Recently the UK-PREDICT TB study conducted in UK confirmed the results [44]. The aim was to estimate the predictive values of the TST and two IGRAs for the development of active TB in high-risk groups, i.e., people in recent contact with active TB cases and from high-burden countries. The negative predictive values of each test were 99.4% for QFT-GIT, 99.5% for T-SPOT.TB, 99.6% for TST-5 (5 mm), 99.6% for TST-10 (10 mm), and 99.5% for TST-15 (15 mm).

Table 2 Limits of the routinely used immune-based tests for LTBI diagnosis

	TST	QFT-IT[a]/ QFT-P	T-SPOT TB
Accuracy for active TB from LTBI discrimination	No	No	No
Accuracy to detect those at high risk of developing active TB	Low	Low	Low
Large scale tests for screening	Yes	No	No
Cost	Low	Medium/high	Medium/ high
Infrastructure needed	No	Yes	Yes
Modification of test response after preventive therapy	Usually no	Usually no	Usually no

Abbreviations: *TST* tuberculin skin test, *QFT-IT* QuantiFERON in tube[a], *QFT-P* QuantiFERON Plus, *TB* tuberculosis, *LTBI* latent TB infection

Positive Predictive Value

The strength of the association between positive IGRA results and development of active TB is described as weak to moderate, with relative risks of about 2–3 when considering studies performed in high-prevalence, low- and middle-income settings; the analysis was done using in-house developed and commercial IGRA [45] (Table 2).

Considering individuals from a low-prevalence setting using only commercial IGRA, it was shown that the relative risk was between 8 and 15 [43]. An additional meta-analysis, involving only studies with a definite follow-up for the development of active TB showed relative risks of up to 6.8 for IGRA and 2.4 for the TST [46]. In the recently published UK-PREDICT TB study [44] the positive predictive values for each test were calculated. QFT-GIT had a positive predictive value of 3.3%, T-SPOT.TB had a value of 4.2%, TST-5 had a value of 2.2%, TST-10 had a value of 2.7%, and TST-15 had a value of 3.5%.

Therefore up to now, no available tests for LTBI have been shown to have a high prognostic value. However, in some populations the proportion of IGRA-positive individuals might generally be lower than the proportion of TST-positive individuals. This characteristic of IGRA might be useful in settings in which TST specificity is compromised by cross-reactivity with environmental mycobacteria, BCG-vaccination after infancy, or multiple BCG-vaccinations.

Indeterminate or Borderline Results in IGRAs

Regarding QFT-Plus assay, the results are interpreted by subtracting the IFN-γ value the Nil control well from the IFN-γ value in each of the TB antigen tubes called B1 or TB2, or from mitogen tube (https://www.quantiferon.com/products/quantiferon-tb-gold-plus-qft-plus/package-inserts/). A response is considered positive for an IFN-γ value to either TB antigen tube (TB1 or TB2) that is higher than 0.35 IU/ml

and significantly above the Nil IFN-γ IU/ml value. The plasma sample from the Mitogen tube serves as an IFN-γ positive control for each specimen tested. A low response to Mitogen (<0.5 IU/ml) indicates an indeterminate result when a blood sample also has a negative response to the TB antigens. This pattern may occur with insufficient lymphocytes, reduced lymphocyte activity due to inappropriate specimen handling, incorrect filling/mixing of the Mitogen tube, or failure of the patient's lymphocytes for producing IFN-γ. Elevated levels of IFN-γ in the Nil sample may occur with the presence of heterophile antibodies, or to intrinsic IFN-γ secretion. The Nil tube adjusts for background (e.g., elevated levels of circulating IFN-γ or presence of heterophile antibodies).

Regarding T SPOT TB, the results are interpreted by subtracting the spot count in the Nil control well from the spot count in each of the antigen tubes called "Panel A and Panel B", according to the following algorithm: the test result is considered positive if (Panel A-Nil) and/or (Panel B-Nil) ≥8 spots; the test result is considered negative if both (Panel A-Nil) and (Panel B-Nil) ≤4 spots (https://www.tspot.com/resources/#package-inserts-link). This includes values less than zero; the results where the highest of the Panel A or Panel B spot count is such that the (Panel minus Nil) spot count is 5, 6 or 7 spots should be considered Borderline (equivocal) and retesting by collecting another patient specimen is recommended; if the result is still Borderline (equivocal) on retesting with another specimen, then other diagnostic tests and/or epidemiologic information should be used to help determine the TB infection status of the patient.

Interpretation of Serial QFT Results

Serial IFN-γ Assays

Serial testing for LTBI is performed every 1–2 years in highly exposed groups, such as healthcare workers and prisoners, as well as patients at high risk of disease, such as HIV-infected subjects or subjects with autoimmune diseases who are candidates for biologic agents. Although it has been reported that TST may boost IGRA responses, this effect is not seen if the IGRA is done within 3 days of performing the TST [47, 48]. Unlike the TST, which should only be repeated if previously negative, IGRA tests may be repeated. However, high rates of spontaneous reversions and conversions are found in those untreated with anti-TB drugs, although it is always difficult to know whether conversion is spontaneous or a consequence of real *M. tuberculosis* infection or laboratory inaccuracy [49–52].

QFT-GIT conversion has been reported to be related to higher risk of progression to TB [53], as in children recently are exposed to *M. tuberculosis* [54], or in patients with autoimmune diseases receiving biologic therapies [55, 56]. However, as shown in the section above, the predictive value of IGRA (QFT-GIT) conversion for development of TB disease is low, and fluctuations in IFN-γ responses among serially

tested individuals reported in longitudinal studies remain unexplained and nonspecific.

Notably, spontaneous reversions and conversions are more frequent in subjects with borderline results close to cut-off values and are more likely if scored negative in the TST [53, 56, 57]. A self-clearance of infection has been suggested to explain these cases, but there is not enough evidence to draw such a conclusion [49, 58]. For these reasons, serial testing with IGRA should be considered unreliable and is not recommended, at least until the conversion and reversion phenomena are better understood in both immune-suppressed and immune-competent patients [50, 56]. However, few interesting observations were recently reported, both in evaluating IFN-γ value as a tool for TB development risk [42, 59].

Recently it has been suggested a way to define "stringent QFT-converters" using a large cohort of healthy South Africans adolescents (2432 individuals). Nemes et al. [42] define "uncertain" conversions, when there are at least one value within the uncertainty zone (0.2–0.7 IU/ml). These results were explained by technical assay variability. Individuals who had a change in QFT IFN-γ values from less than 0.2 to greater than 0.7 IU/ml had ten-fold higher tuberculosis incidence rates than those who maintained values less than 0.2 IU/ml over 2 years. By contrast, "uncertain" converters were not at higher risk than non-converters.

Another interesting approach was to evaluate if the use of the IFN-γ level of the QFT test could be used for predicting incident TB [59]. The prospective analyses done in Norway included 50,389 QFT results from 44,875 individuals, of whom 257 developed TB. TB risk increased with the IFN-γ level until a plateau level, above which further increase was not associated with additional prognostic information. The hazard risk (HR) for TB were 8.8, 19.2 and 31.3 times higher with IFN-γ levels of 0.35 to <1.00, 1.00 to <4.00 and >4.00 IU/mL, respectively, compared with negative tests (<0.35 IU/mL).

In conclusions, setting-up particular cut-off, the serial evaluation may improve our ability to evaluate the increased risk of incident TB, suggesting that IFN-γ levels may be used to guide targeted treatment of LTBI [42, 59].

New Experimental Tests

An important limitation of both, TST and IGRA, is the inability to discriminate between active TB and LTBI [11, 60]. Several approaches have been proposed in the literature to increase the accuracy of these tests, as tests based on the response to antigens associated with latency, such as heparin-binding hemagglutinin (HBHA) [61–63] or those regulated by the Dos-Regulon [60, 64, 65], or tests based on the detection of memory response [66, 67]. Moreover, as reported above, the predictive value for TB development of TST and IGRA is low [44, 45]. Several attempts to generate news tests have been developed. A correlating of risk signature consisting of 16 transcripts has been described in a study conducted in South Africa and validated in Gambia; it associates with a discrete accuracy for TB development 6 months

earlier of the disease [68]. Recent studies identified smaller (n = 3 or 4) gene signatures that associate to active TB [69, 70]; some signatures have been also described in HIV-infected subjects [71]. If validated in larger studies, these signatures have the potential to undergo to a clinical routine use. Moreover studies are needed to generate additional tools to predict active TB development [72].

LTBI: Who Does Need to Be Screened?

As mentioned earlier, subjects with LTBI have a 5–10% risk to progress to active TB and this risk is greater in recent contacts, people leaving with HIV, children below 5 years, candidates of biological treatment, immigrants from high TB burden countries, health care workers (Table 3).

Recent contacts

People in contact with a case of transmissible TB (usually smear- and/or culture-positive pulmonary TB) are among the high risk groups for which a LTBI screening and preventive treatment should be considered in case of *M. tuberculosis* infection, as proposed by WHO recommendations [10]. These recommendations are now

Table 3 Risk factors associated to TB development

Risk factors	Risk of developing TB disease compared to those without the risk factor	References
Based on TB exposure		
Close contact with an infectious TB case	16–46	[19]
Recent migration from a high-prevalence setting	15	[78]
Based on comorbidities		
HIV infection	80–110	[83, 84]
Diabetes	2–3	[105]
TNF-α inhibitors	10	[94, 95]
Chronic kidney disease, on dialysis	8	[101]
Organ transplantation	70–300	[102–104]
Stem cell transplant	20	[104]
Age		
Children below 2–3 years	>10	[74]
Work activity		
HCW	3	[107]

Abbreviations: *HCW* Health Care workers, *TB* tuberculosis, *HIV* Human Immunodeficiency Virus, *TNF* tumor necrosis factor

including also individuals from high TB endemic countries. Based on WHO recommendations, LTBI diagnosis can be performed either by TST or IGRA, as indicated by the guidelines of the specific countries. In those diagnosed with LTBI, if at high risk of developing TB, preventive therapy should be recommended.

Children

In 2017, WHO estimated that one million children (<15 years) suffered from TB worldwide, and that more than 170,000 died. Approximately, 1.3 million children [1, 2] aged <5 years were household contacts of bacteriologically confirmed pulmonary TB cases and eligible for TB preventive treatment due to their higher risk of developing TB [1, 2]. Children <1 year of age progress from primary infection to active disease in 30–40% of the cases, whereas those aged 1–5 years show a risk of 24%. The risk of progression declines slowly beyond 5 years and increases again around 10 years of age [1, 73–76]. However, although TB preventive treatment is recommended, only a small fraction (13%) was treated in 2015–2016 [1]. In high burden TB settings childhood LTBI accounts for 13% of the total amount of LTBI, whereas in low TB endemic countries, children LTBI accounts for 2% [1, 2]. Great global efforts are needed to implement preventive treatment in this fragile population.

Migrants

Migration is mainly driven by socio-economic, political, and environmental factors [77]. Western Europe, as well as other high-income settings (e.g., USA, Australia and Canada), are among the favorite global destinations of migrants. They are considered of TB owing to their origin from geographical areas where the circulation of *M. tuberculosis* is high [78]; therefore, it is highly recommended that they undergo LTBI screening and preventive therapy in case of a positive test. Indications for screening are heterogeneous and different policies are in place [79–82].

HIV-Infected Individuals

WHO estimated that almost 820,000 TB cases were associated with HIV infection in 2017, accounting for 9% of all estimated TB cases [1] TB/HIV cases are mainly concentrated in Sub-Saharan Africa and former-Soviet Union countries [1]. HIV-infected individuals with a concomitant *M. tuberculosis* infection are 26-fold more likely to develop active TB disease than HIV-uninfected individuals [1, 83, 84]. Antiretroviral therapy (ART) reduces the probability of TB occurrence improving the quantity and quality of the immune system; the lower the CD4 T cell count, the higher is the ART-associated protection [85]. In HIV-infected individuals, even if the CD4+ T-cell count is within normal range, the risk of developing active TB

disease is still higher than the HIV-uninfected subjects [86]. Therefore preventive therapy is always recommended [84–86].

Subjects Exposed to Biological Therapy

Several treatment options are now available for the inflammatory rheumatic disorders. Around 20 years ago, anti-TNFs infliximab and etanercept were licensed, and over the following years, other anti-TNFs such as adalimumab, golimumab, and certolizumab pegol were approved [87, 88]. These drugs have been associated with an increased risk of TB in LTBI subjects [89–95]. Indeed, the block of TNF-α negatively affects granuloma formation and maintenance, favoring *M. tuberculosis* replication [91, 93, 96, 97]. Screening procedures and preventive treatment has decreased TB incidence in this population group [90, 98, 99]; however, an increased risk of TB reactivation in anti-TNF-exposed patients is still currently observed [91]. During the last 10 years, new treatments targeting new inflammatory pathways sustained by CD20 and CD28 lymphocytes and cytokines other than TNF-α, including IL-6, IL-12, IL-23, and IL-17, have been discovered with the development of new biologics. They have showed a safer profile in LTBI subjects with rheumatic diseases. Indeed, only sporadic cases of active TB, whose frequency is not higher that that recorded in the general population, were reported in tociluzimab (inhibiting IL-6), rituximab (inhibiting CD20), and abatacept (inhibiting CD28)-exposed patients with rheumatoid arthritis, and no cases were associated with stekinumab (targeting IL12/IL-23) and secukinumab (targeting IL-17) in patients with psoriatic arthritis and ankylosing spondylitis [88, 100].

Chronic Kidney Disease, Organ Transplantation, Stem Cell Transplant, Diabetes

Individuals with kidney failure and/or undergoing to dialysis [101] as well those undergoing to transplantation either organ or stem cells [102–104] and individuals with diabetes [105] are at higher TB risk of reactivation (Table 3).

Health Care Workers

HCW are at risk of acquiring TB even in countries at low TB incidence. The average annual risk for developing TB disease has been estimated and is up to threefold higher for HCW compared to the general population. Moreover, HCW are also at higher risk for multidrug-resistant TB (MDR-TB) being up to six times more likely to be hospitalized for MDR-TB than the population they care [106–109]. This is due to a delayed diagnosis, less effective treatment, a longer contact periods with infectious patients that altogether may increase the risk of transmission. Therefore, the

screening procedures of the HCW personnel are crucial for TB control at work place [110].

In conclusion, LTBI screening performed by TST and IGRA is recommended in individuals at high risk for TB. At the moment this strategy is the strongest measure for TB control, especially in low TB endemic countries. New tests are needed to improve the accuracy being able to predict those who develop active TB.

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TB Treatment and Complications

Jamilah Meghji and Onn Min Kon

Abbreviations

ATS	American Thoracic Society
BIS	British Infection Society
CDC	Centres for Disease Control, USA
DILI	Drug induced liver injury
DST	Drug sensitivity testing
EPTB	Extrapulmonary tuberculosis
ETH	Ethambutol
INH	Isoniazid
Lfx	Levofloxacin
M	Moxifloxacin
NICE	National Institute for Health and Care Excellence, UK
PTB	Pulmonary tuberculosis
PZA	Pyrazinamide
RIF	Rifampicin
WHO	World Health Organisation

Introduction

The core aims of the treatment of active tuberculosis disease are (a) to rapidly reduce bacterial load to achieve clinical improvement, (b) to remove slow growing persistor organisms to prevent relapse, and (c) to avoid the emergence of drug

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resistance. These aims have traditionally been achieved by a prolonged course of multi-drug treatment.

The rationale for multi-drug approaches is well described. Replicating *M. tuberculosis* organisms are prone to spontaneous genetic mutations which confer resistance to individual anti-tuberculosis drugs. The use of multi-drug treatment regimens offsets the selection advantage conferred by these mutations by ensuring that other drugs against which the mutant organism has no advantage/a disadvantage (if a 'fitness cost' has been incurred) are present at all times. The probability of incident resistance mutations is high in early treatment when bacillary loads and replication rates are high, hence the need for more drugs in this period. In addition, the drugs employed in TB treatment have different activities, including early bactericidal activity to reduce bacterial load (INH and RIF) and sterilising activities to remove persistor organisms (RIF and PZA), in part related to their ability to penetrate caseating tissue. Combined use allows both early bactericidal activity and sterilisation to be achieved.

An accepted duration of therapy of at least 6-months was established in the 1980s, based on acceptable cure rates of >95%. Subsequent trials have consistently demonstrated higher rates of disease relapse with shorter treatment regimens of 'standard' drugs, and more recently with 4-month fluoroquinolone containing regimens, even with drug sensitive disease.

This chapter will focus on the pharmacological management of drug-sensitive TB disease through multi-drug regimens, as per existing WHO and CDC/ATS guidelines. The essential health system tools required to support patients through their drug treatment, and to deliver a patient-centred approach to care are described elsewhere.

Drug Regimens: Active Disease

Standard Treatment Regimen

First line treatment of drug sensitive tuberculosis includes four drugs: a rifamycin (usually rifampicin), isoniazid, ethambutol and pyrazinamide. Standard treatment is the same for HIV-positive and HIV-negative adults and lasts a minimum of 6-months including:

– 2-month intensive phase (RIF, INH, PZA, ETH)
– 4–10-month continuation phase (RIF and INH).

The WHO Category II regimen, which requires 8-months of treatment and includes streptomycin, was previously used in patients not known to have MDR disease but presenting for re-treatment. This remains controversial, and is no longer recommended by the WHO, with emphasis instead placed on improving access to

drug sensitivity testing (DST) for all retreatment patients and subsequent treatment with either standard drug-sensitive or MDR regimens as required.

Duration of Continuation Phase

The standard duration of the continuation phase is 4-months for standard pulmonary tuberculosis (pTB) and extrapulmonary tuberculosis (EPTB) treatment, but should be extended for those with disease in reserved sites, and can be considered for those with likely high mycobacterial load:

- TB meningitis (TBM)
  Concerns regarding the ability of anti-tuberculosis drugs to cross the blood-brain barrier, challenges in monitoring treatment response within the CNS, and the potentially serious implications of disease relapse have led to extension of the continuation phase to 10-months to ensure sterilisation.
  Recommended treatment regimen: 2 HRZE/10HR.
- Ocular TB disease:
  There is no agreed duration of TB treatment required for ocular TB disease including uveitis. However, extension of the continuation phase is suggested due to decreased drug penetration into the eye.
  Recommended treatment regimen: 2 HRZE/7-10HR.
- Extensive baseline disease
  There is some evidence that those with extensive pulmonary disease at diagnosis (cavitation or extensive chest radiograph changes) or who remain smear positive after 2-months of treatment have an increased risk of disease relapse using the standard treatment regimen. Whilst extended durations of treatment are not recommended at the programmatic level by the WHO, CDC/ATS guidelines advise extension of the continuation phase for this group.
  Possible treatment regimen: 2 HRZE/7HR.

Modification of Drug Regimens, According to Drug Sensitivity

If regional/individual drug sensitivity results are not available, clinicians are advised to use the standard TB treatment regimens outlined above. However, where local or individual DST is available, additional adjustments to drug regimens can be used (Table 1).

Table 1 Adjustments to programmatic/individual treatment regimens, according to DST

Context	Adjustment	Potential regimen
Regional DST suggests high prevalence of INH resistance	Programmatic guidelines may be changed to include ETH in the continuation phase, together with INH and RIF, providing appropriate monitoring for ocular toxicity is available	2 RHZE/4 RHE
Individual INH mono-resistance confirmed	A fluoroquinolone (E.g. levofloxacin) should be used instead of INH. At least 6-months of the fluoroquinolone should be completed, and total treatment duration with 6RZE may be >6-months	6 RZE-Lfx
Individual INH and RIF sensitivity confirmed	Ethambutol can be removed from the intensive phase	2 RHZ/4RH

R Rifampicin, *H* Isoniazid, *Z* Pyrazinamide, *E* Ethambutol, *Lfx* Levofloxacin

Adjunctive Treatments

- Pyridoxine
  Concurrent pyridoxine (vitamin B6) should be given to prevent peripheral neuropathy. Doses range from 10 to 50 mg daily, and can be increased for those at high risk (pregnant women, HIV co-infection, diabetes, alcoholism, malnutrition, chronic renal failure, older age).
- Steroids
  TB meningitis: All patients with TB meningitis should receive concurrent steroid with a reducing course over the first 6–8 weeks of TBM treatment, regardless of disease severity at presentation. BIS guidelines recommend that adults >14 years receive dexamethasone 0.3 or 0.4 mg/kg daily (max 24 mg) with a reducing course over 6–8 weeks, whilst children ≤14 years should be given prednisolone 4 mg/kg/24 h (or equivalent dose dexamethasone: 0.6 mg/kg/24 h) for 4 weeks, followed by a reducing course over 4 weeks (See TB meningitis chapter). There is no evidence for concurrent steroid use in those with CNS tuberculomas or spinal cord disease only.

  TB pericarditis: There is no clear evidence of a reduction in the incidence of tamponade/mortality, and only weak evidence of reduction in residual constrictive pericarditis with concurrent steroids use in TB pericarditis. WHO guidelines suggest that steroids may be routinely used, whilst the ATS/CDC guidelines suggest their use only in those with evidence of marked inflammation (large pericardial effusion, high prevalence of inflammatory cells in pericardial fluid, evidence of early constriction seen).

  There is no clear evidence for use of steroids in other forms of TB disease.

Drug Regimens: Latent TB Infection (LTBI)

Six-months of daily INH remains the standard treatment of LTBI in both high and low TB incidence settings. No controlled trials comparing longer courses of INH to this regimen have been completed but modelling suggests a potential incremental benefit with extension of treatment to 9-months.

Alternatives include daily RIF for 4-months (similar efficacy with slightly reduced odds of hepatotoxicity), combined daily RIF and INH for 3–4 months (similar efficacy and safety profile), or once-weekly RPT and INH for 3-months (similar efficacy with reduced hepatotoxicity and higher completion rates when given with DOT).

Rifamycin containing regimens must be used with caution in patients with HIV-coinfection due to drug interactions with antiretroviral treatment (ART), however recent data suggest that daily RPT and INH for 1-month has similar efficacy in preventing incident TB disease amongst HIV-infected adults with latent TB-infection or those living in high TB-prevalence settings as 9-months of INH (Table 2).

Drug Doses and Routes

Standardised drug dosing regimens have historically been used, and are based on clinical trial cost and efficacy data from the 1940s–80s. Pharmacokinetic/pharmacodynamic (PK/PD) evaluation of drugs at this time was incomplete, but subsequent

Table 2 Drug regimens for treatment of active TB disease and latent TB infection

TB pattern	TB disease	Regimen Duration (months) and Drug
Active TB disease	PTB or EPTB	2 HRZE/4 HR[a]
	TB meningitis	2 HRZE/10 HR + reducing course of steroids[a]
	Ocular TB	2 HRZE/7–10 HR
	High mycobacterial load or ongoing clinical concern	2 HRZE/7 HR
	Settings of high INH resistance	2 HRZE/4 HRE
	DST confirmed R and H sensitivity	2 HRZ/4HR
Latent TB disease	Latent TB infection	6 H: daily[a] 9 H: daily 3–4 RH: daily 3–4 R: daily 3 H and RPT: weekly 1 H and RPT: daily (HIV-infected adults)

[a]WHO recommendations as standard of care

R Rifampicin, *H* Isoniazid, *Z* Pyrazinamide, *E* Ethambutol, *RPT* Rifapentine

studies suggest wide variation in plasma levels of individual drugs between individuals, and in drug concentrations between compartments within individuals receiving standard doses. Therapeutic drug concentration monitoring is discussed below, but the standardised dosing regimens here are still advised in uncomplicated cases (Table 3).

Daily dosing is preferred throughout treatment and is especially important in the intensive treatment phase. This is defined as dosing 7 days/week: 5 day/week dosing regimens have been used to facilitate easier DOT, and are thought to have equal efficacy, but have not been evaluated in head to head studies.

Intermittent dosing is not advised, but can be considered during the continuation phase only if daily dosing is not possible/tolerated, the patient is at low a priori risk of treatment failure (HIV-negative, smear negative at baseline, limited burden of disease/no cavitation on CXR, confirmed drug sensitive disease), and supportive DOT is available. If required, three-weekly dosing is preferred over twice-weekly dosing.

Practical Considerations

Drugs should be administered together to maximise and co-ordinate plasma concentrations and for ease of DOT. Absorption of most drugs is better on an empty stomach, except for RPT which is absorbed best with a fatty meal. INH absorption is reduced in the context of glucose/lactose.

Drug doses should be rounded, according to the tablet sizes available. Drug doses should be checked and adjusted for weight, which frequently rises, over the course of treatment. Fixed dose combinations should be used where possible—treatment outcomes are similar, and preparations are convenient for both patients and treatment programmes. However care must be taken in low weight situations when individual components may be underdosed and in these situations, alternate preparations should be considered. Fixed dose combinations are available for both adult (Table 4) and paediatric (Table 5) populations. Adult dosing is recommended for children $\geq$25 kg.

Where patients are unable to take oral medications in the intensive phase, INH, RIF, fluoroquinolones and other injectable agents can be delivered parenterally, whilst PZA and ETH can be administered via nasogastric tube.

Drug Interactions

The rifamycins have numerous drug interactions and these should be looked up for all drugs being taken concurrently with TB treatment. Rifampicin levels are increased by the concurrent use of CYP3A inhibitors (E.g. Ritonavir), and reduced by concurrent use of CYP3A inducers (E.g. Efavirenz/phenytoin). Rifampicin itself is a potent inducer of the cytochrome P450 system and can lead to decreased levels of numerous other important drugs (E.g. anticonvulsants, anticoagulants, corticosteroids). This effect usually peaks 2 weeks after starting rifampicin and resolves

Table 3 Drug dosing, routes of administration, and side effects (available from http://www.tbdrugmonographs.co.uk)

Drugs	Active TB disease	Preparations available	Side effects (SEs)
Rifampicin	<50 kg: 450 mg daily ≥50 kg: 600 mg daily OR <50 kg: 600 mg three times/week ≥50 kg: 900 mg three times/week	Capsules, po—150 mg, 300 mg Syrup—100 mg/5 ml IV solution—600 mg powder for reconstitution	Common SEs: Orange discolouration of body fluids (sputum, urine, sweat, tears) Transient hyperbilirubinaemia Gastrointestinal—nausea, anorexia, abdominal pain Flu like syndrome—more common with intermittent dosing Serious SEs: Hepatotoxicity (rare) Nephrotoxicity (rare) Haematological—agranulocytosis (rare), haemolytic anaemia (rare, usually intermittent dosing), thrombocytopaenia (rare, usually intermittent dosing)
Isoniazid	300 mg daily OR 15 mg/kg three times/week	Tablets, po—50 mg, 100 mg, 300 mg Syrup, po—50 mg/5 ml IV solution—50 mg/2 mL ampoules	Common SEs: Peripheral neuropathy Transient hepatitis Serious SEs: Dermatological—skin reactions (rare) Haematological—agranulocytosis, megaloblastic anaemia, thrombocytopaenia Hepatic—hepatotoxicity (rare) Immunological—drug induced lupus (rare) Musculoskeletal—arthralgia, rhabdomyolysis Neurological—headaches, dysarthria, irritability, seizures, dysphoria, depression, poor concentration (rare)

(continued)

Table 3 (continued)

Drugs	Active TB disease	Preparations available	Side effects (SEs)
Pyrazinamide	<50 kg: 1.5 g daily ≥50 kg: 2 g daily OR <50 kg: 2 g three times/ week ≥50 kg: 2.5 g three times/ week	Tablets, po—500 mg (scored) Liquid available Doses should be rounded to facilitate administration of 500 mg tablets	Common SEs; Asymptomatic hyperuricaemia Arthralgia—non-gout polyarthralgia/ acute gouty arthritis Gastrointestinal—anorexia, nausea, vomiting Hepatic—transient hepatitis Dermatological—rash, photosensitivity Serious SEs: Haematological—anaemia, thrombocytopaenia (rare) Hepatotoxicity
Ethambutol	15 mg/kg daily OR 30 mg/kg three times/ week	Tablets, po—100 mg, 400 mg	Common SEs: Endocrine—hyperuricaemia Gastrointestinal—nausea, vomiting Serious SEs: Ophthalmic: Optic neuritis (1–6%, greatest risk at higher doses or >2 m treatment), red-green colour blindness

Table 4 Examples of fixed dose combinations for use in adults

Drug name	Contents	Dosing
Voractiv	R 150 mg H 75 mg Z 400 mg E 275 mg	30–39 kg—2 tablets 40–54 kg—3 tablets 55–69 kg—4 tablets ≥70 kg—5 tablets
Rifater	R 10 mg H 50 mg Z 300 mg	≤44 kg—4 tablets 45–54 kg—5 tablets ≥55 kg—6 tablets + additional Z if weight >90 kg + E separately
Rifinah	150/100 tablet contains: R 150 mg/H 100 mg 300/150 tablet contains: R 300 mg/H 150 mg	<50 mg—3× 150/100 tablets ≥50 kg—2× 300/150 tablets

<2 weeks of stopping, and drug doses should be adjusted accordingly. Of particular note, rifampicin accelerates the metabolism of oestrogens and progesterones and contraceptive options should be reviewed prior to starting TB treatment. It also reduces plasma levels of key anti-rejection drugs (E.g. sirolimus, tacrolimus, mycophenolate) which require careful adjustment. Lastly, the presence of rifampicin has been known to give false-positive opiate test results.

Isoniazid is an inhibitor of the CYP liver enzyme pathway, and is known to increase levels of other drugs including carbamazepine and aminophylline, and the hepatotoxic side effects of other drugs including paracetamol and sodium valproate.

Table 5 Examples of fixed dose combinations for children <25 kg

	Number of tablets	
Weight	Intensive phase RHZ 75/50/150[a]	Continuation phase RH 75/50
4–7 kg	1	1
8–11 kg	2	2
12–15 kg	3	3
16–24 kg	4	4

[a]Add ethambutol in intensive phase for children with extensive disease, or in settings where the prevalence of HIV co-infection or INH resistance is high

Food interactions with symptoms of histamine toxicity or mono-amine oxidase poisoning have been noted on consumption of foods rich in histamine/tyramine (E.g. cheese, certain fish, some beers/lagers/wine) but are rare and no dietary restrictions are routinely advised.

Monitoring During Treatment

Baseline Assessment

Baseline blood tests should include: Full blood count, liver function tests, renal function and electrolytes, thyroid function tests, HIV, Hepatitis B and C.

All patients starting standard therapy should have baseline visual acuity checked using a Snellen chart, and colour discrimination tests completed. Caution should be exercised in the use of ethambutol if impairment is seen or there is concern about the ability to report any visual changes.

Additional assessments which may be required include: nutritional assessment (low BMI), ECG (quinolone use), audiometry (aminoglycoside use).

Ongoing Monitoring

All patients should be asked about the following side effects on a monthly basis: jaundice, dark urine, nausea, vomiting, abdominal pain, fever, rash, anorexia, malaise, neuropathy, and arthralgias.

Patients receiving standard doses of ethambutol (15 mg/kg) should be asked about visual disturbance on a monthly basis, and referred for formal assessment if any abnormalities are noted. If ethambutol treatment is extended beyond the 2-month intensive treatment phase, patients should have monthly visual acuity and colour discrimination testing.

Liver function tests (LFTs) should be checked at baseline and repeated at 2-weeks. Further monitoring is only required if abnormalities are seen, baseline bloods were abnormal, symptoms consistent with hepatotoxicity develop, or there are other known risk factors for liver disease including: excess alcohol use, concurrent hepatotoxic medications, viral hepatitis or known liver disease, HIV co-infection, older age, malnutrition, pregnancy/<3-months post-partum, or prior drug-induced liver injury. In these patients 4-weekly measurement of transaminases (ALT and AST), bilirubin, and ALP is recommended.

Management of Complications

GI Symptoms (Nausea, Vomiting, Poor Appetite, Abdominal Pain)

Potential drug causes: PZA, RIF.

These are common and frequently mild. Symptoms can usually be managed without stopping therapy. The following approaches can be trialled: nocturnal drug administration (although challenging with DOT), PPI use (may reduce absorption of fluoroquinolones), and if required a small low-fat snack taken together with medication (may reduce biosorption). If unsuccessful, separation administration of individual drugs may be trialled.

Rashes

Potential drug causes: All drugs.

Management depends on the severity and likely aetiology of the rash:

- Simple itchy rash
  Continue medication, with trial of an antihistamine
- Petechial non-blanching rash
  Check platelets, and stop rifamycin if there is evidence of thrombocytopaenia as this may indicate an immune reaction. Rifampicin should not be re-introduced.
- Extensive erythema, fever, or mucous membrane involvement
  This is suggestive of a more severe reaction including Stevens Johnson syndrome, toxic epidermal necrosis, or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome. The full treatment regimen should be stopped and use of systemic steroids considered. Gradual reintroduction of medication with a re-challenge regimen can be considered once the rash has settled but risks should first be discussed with a local dermatology team.

The re-challenge regimen for drug rashes usually involves the reintroduction of a single additional drug every 2–3 days, in the order RIF, INH, ETH, PZA, with incremental dosing. If rash re-occurs the last drug introduced should be stopped. It is commonly the case that the full regimen can be re-introduced without recurrence.

Arthralgias

Potential drug causes: PZA, ETH, INH.

These are common and frequently mild. Symptoms can usually be managed without stopping therapy, and simple non-steroidal analgesia (NSAIDs) should be trialed in the first instance.

Acute gouty arthritis can be caused by PZA/ETH. If an acutely swollen joint develops this should be aspirated to look for urate crystals, and the patient referred for rheumatological assessment. Treatment of the acute episode may require higher doses of NSAIDs, colchicine, or a reducing-course of steroids. Recurrent episodes may persist whilst treatment with PZA/ETH continues, and longer-term use of colchicine may be required.

Peripheral Neuropathy

Potential drug causes: INH.

Peripheral neuropathy presents with a glove-and-stocking distribution of paresthesia (burning, pricking, tingling) in the fingers and toes. Low dose pyridoxine (vitamin B_6) should be used for prevention, especially for those at increased risk, and the dose should be increased to 100–200 mg /day in those who develop symptoms.

Neurotoxicity

Potential drug causes: INH.

Central neurotoxicity is rare in relation to first line anti-TB drugs. If symptoms of central depression or hyper-stimulation occur, the clinical case should first be reviewed for other potential causes.

Potential psychiatric side-effects of first-line drugs include depression or suicidal ideation (INH/ETH), and psychosis (INH/fluoroquinolones). Specialist care should be sought if these occur. Mild depression may be managed with continuation of therapy, supportive care, and antidepressants. Both INH and ETH should be stopped if suicidal ideation develops, and the drugs may be restarted with incremental

dosing only once stability is reached. INH and fluorquinolones should be stopped in patients with psychosis, and high-dose pyridoxine should be given.

Drug induced seizures may occur with INH. In this instance INH should be stopped, and anti-convulsants started. Once the patient is seizure free, INH can be re-introduced together with concurrent high-dose pyridoxine, but anti-convulsant therapy may be required throughout the treatment regimen.

Drug Induced Liver Injury (DILI)

Common drug causes: PZA, INH, RIF.

PZA is the most hepatotoxic drug in the first line regimen—associated hepatotoxicity is often dose-related, but can occur at any level. INH monotherapy leads to asymptomatic elevation of transaminases in 10–20% and enzyme levels can stabilise despite ongoing use of the drug, but INH can also cause a clinical hepatitis particularly when administered together with RIF. RIF can cause a transient hyperbilirubinaemia, or hepatitis with either a cholestatic picture or elevated transaminases.

If deranged LFTs are noted during treatment the patient should be clinically reviewed and both TB drug treatment/other hepatotoxic drugs stopped if ALT or AST levels rise ≥5 times the upper limit of normal (ULN), or ≥3 times the ULN in the presence of symptoms.

Other causes of liver injury should be considered and may include: acute viral hepatitis (hepatitis A, B, and C in all patients; Epstein-Barr virus, cytomegalovirus, and herpes simplex in immunosuppressed patients), alcohol, other hepatotoxic drugs (e.g., acetaminophen, acetaminophen-containing multiagent preparations, lipid-lowering agents, herbal and dietary supplements), and biliary tract disease. A detailed history and ultrasound imaging of the liver may be required, and drug-induced liver injury (DILI) should be diagnosed if no alternative cause is found.

The management of DILI is summarised in Fig. 1. If the patient is non-infectious and clinically stable, all TB drugs should be held. If the patient is unwell as a result of active TB disease, or if they are infectious, a temporary combination of two non-hepatotoxic drugs (E.g. aminoglycosides, fluoroquinalones, ethambutol) should be used to maintain cover after stopping first-line therapy.

First-line drugs can be reintroduced once symptoms resolve and ALT returns to <2 times ULN, or close to baseline levels if LFTs were abnormal prior to treatment initiation. Drugs can either be introduced simultaneously at full dose, sequentially at full dose, or sequentially using step-wise increases in dose (Fig. 1). There is no clear consensus on which approach to use, but although the latter incurs some delay to reintroduction of full standard therapy, it may be preferable in those at high-risk of recurrent hepatotoxicity. Some clinicians choose to omit PZA after an initial DILI.

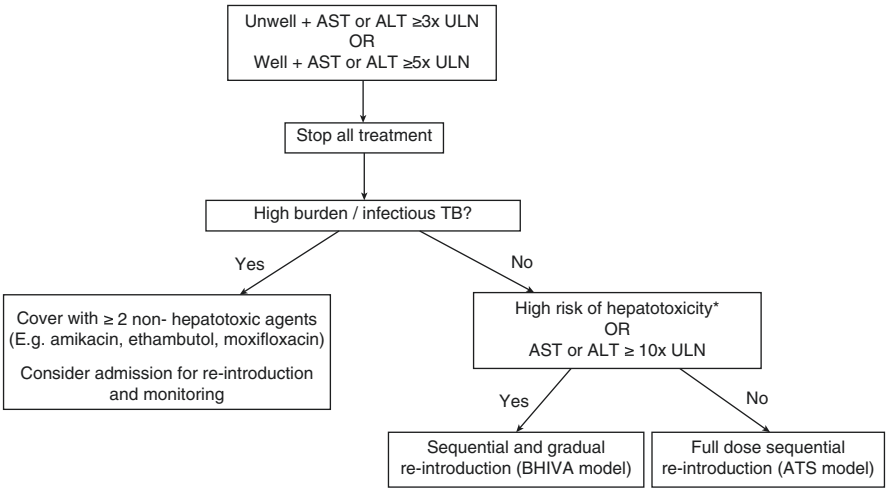

Fig. 1 Suggested approach to management of drug induced liver injury (DILI). *Excess alcohol use, viral hepatitis or known liver disease, HIV co-infection, elderly, malnourished, pregnant or < 3-months post-partum. ULN: Upper limit of normal

Special Groups on First Line Regimen

Pregnancy

There are no high-quality studies of first-line anti-tuberculous drugs in pregnancy. Although most drugs do cross the placenta there are no known teratogenic effects. Similarly, low levels of drug have been detected in breastmilk, but with no known toxic effects. Use of the standard regimen is therefore suggested based on clinical experience, but fluoroquinalones should be avoided in women who are pregnant or breastfeeding.

Renal Failure

Both INH and RIF are metabolised by liver and conventional dosing can therefore be used, but PZA metabolites and ETH are renally excreted and dose adjustments are usually required. Usually this involves increasing the intervals between doses, rather than a dose reduction. Serum drug level monitoring may be required (See Renal disease chapter).

Liver Disease

The risk of drug related liver injury is higher, and monitoring more complex, in those with known liver disease, a previous liver transplant, Hepatitis C co-infection, and deranged transaminases at baseline. Although associated with a risk of hepatitis, INH and RIF form the backbone of TB treatment and should still be used if possible.

Elderly

The risk of drug induced hepatitis increases with age. More frequent monitoring may be required in older individuals.

Alternative Drug Regimens

Alternative drug regimens may be required if drugs are not tolerated due to the complications above (Table 6).

If it is not possible to use RIF, disease should be managed as per multi-drug resistance. Although PZA has limited early bactericidal activity, it plays a key role in killing persistor organisms for long-term cure, and an extended treatment regimen of 9-month is required in the absence of its use.

Management of Treatment Interruptions

There is very little evidence available to guide the management of treatment interruptions, but the timing and duration of interruption are likely key in determining its impact on the clearance of organisms and selection pressure exerted for drug resistance. Interruptions in the intensive phase are more concerning than those during the continuation phase, and management therefore varies accordingly (Fig. 2). Reasons for interruption should be explored in both phases, and increased emphasis placed

Table 6 Alternative drug regimens, in the event of poorly tolerated first line drug

'Failed' drug	Regimen
RIF	Treat as for MDR
PZA	2 RHE/7 RHR
INH or ETH	WHO: 6RZELfx NICE: 2RZE/7-9RE

R Rifampicin, *H* Isoniazid/*Z* Pyrazinamide, *E* Ethambutol, Lfx Levofloxacin, *M* Moxifloxacin

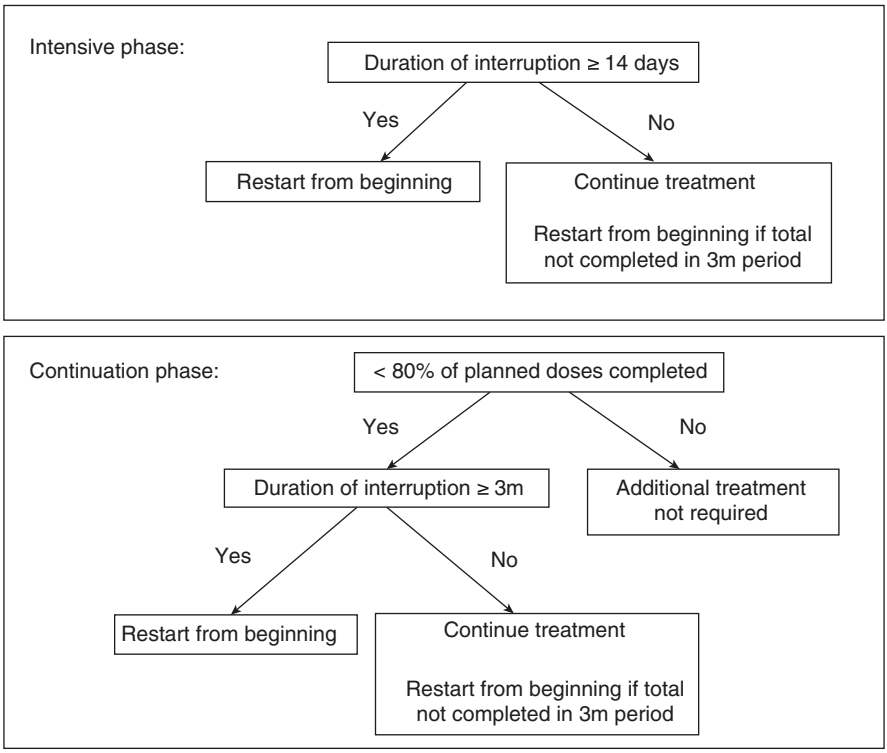

Fig. 2 Management of treatment interruptions

on patient support and the use of DOT to improve the chances of treatment completion.

Priority is placed on the total number of doses received over the course of treatment, rather than the duration of therapy alone, and individuals are still defined as having completed treatment if all doses required during a standard treatment course are taken within a 9-month period (3 m intensive/6 m continuation).

Monitoring of Treatment Response

Monitoring is required over the course of TB treatment to ensure treatment response. Clinical, radiographic, and microbiological parameters can be used.

The latter is key, and monthly sputum samples should be taken from patients with culture positive PTB until two sequential negative culture results are obtained. Average time to culture conversion is 4–5 weeks, and 90–95% of those with drug sensitive disease should be culture negative by 3 months on an INH and RIF

containing regimen. All patients should have DST performed at baseline, but this should be repeated if they remain culture positive at 3-months.

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Multi-drug Resistant Tuberculosis Management

Simon Tiberi, Temi Lampejo, and Alimuddin Zumla

Definitions	
Rifampicin-resistant TB (RR-TB)	is defined as a strain of *Mycobacterium tuberculosis* which is resistant to rifampicin.
Polyresistant TB	is TB that is not susceptible to other drugs excluding rifampicin resistance.
Multi-drug resistant TB (MDR-TB)	is defined as a strain of *Mycobacterium tuberculosis* which is not susceptible to rifampicin and isoniazid.
Pre-extensively drug resistant TB (Pre-XDR)	TB caused by Mycobacterium tuberculosis (M. tuberculosis) strains that fulfil the definition of multidrug resistant and rifampi-

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	cin-resistant TB (MDR/RR-TB) and which are also resistant to any fluoroquinolone.
Extensively drug resistant TB (XDR-TB)	TB caused by Mycobacterium tuberculosis (M. tuberculosis) strains that fulfil the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug
GeneXpert MTB/RIF Assay	is a rapid molecular test that can detect *Mycobacterium tuberculosis* and ascertain whether resistance to the *rpo* gene associated with rifampicin resistance is present or not.

Key Points

1. Multi-drug-resistant tuberculosis (MDR-TB) is a lethal form of tuberculosis (TB) caused by *Mycobacterium tuberculosis* strains which are resistant to rifampicin and isoniazid. It should be suspected in patients who have resided in high MDR-TB areas and/or those who have had previous TB treatment.
2. New rapid molecular based diagnostic tests such as nucleic acid amplification tests e.g. GeneXpert™ MTB/Rif Assay by Cepheid, can provide results of rifampicin resistance operationally within a day and are also useful in diagnosing extra pulmonary TB. An XDR-cartridge from Cepheid is in final evaluation. BD Max and Abbott have similar tests which also add isoniazid susceptibility testing.
3. Whole genome sequencing provides full virtual phenotype drug susceptibility testing providing consistent and more sensitive results with a faster turnaround time than culture and is useful for investigating outbreaks.
4. RR/MDR-TB requires treatment with second-line TB drugs, usually four or more anti-TB drugs for a duration of 18–24 months. In the UK MDR-TB cure rates are above 85%. An all oral longer treatment regimen has been approved by WHO.
5. An oral shorter WHO course has also recently been approved. In addition, under operational research conditions the recently FDA approved bedaquiline, pretomanid and linezolid regimen may be considered. Patients should receive the longer WHO regimen if they do not fulfil the criteria or the conditions required to have the shorter regimens.
6. Surgery for drug resistant TB should be considered if it is indicated (i.e. adequate functional reserve capacity, unilateral lesion which is resectable, poor response to treatment, lack of drugs on drug susceptibility tests, intolerance to medications).
7. Host directed therapy and pulmonary/physical rehabilitation may be useful for patients with an impaired quality of life and/or reduced exercise performance

and is likely to become more important in an elderly patient with comorbidities.
8. Holistic care with a focus on assisting the patient with their social challenges (e.g. homelessness, substance addiction, mental health issues).

Introduction, Background and Epidemiology

Rifampicin-resistant TB (RR-TB) and Multi-drug resistant Tuberculosis (MDR-TB, defined as *Mycobacterium tuberculosis* that is resistant to rifampicin and isoniazid) are harder to treat than those infected with drug-susceptible strains and have worse outcomes. The updated 2021 definition of Extensively drug-resistant TB (XDR-TB) is: TB caused by Mycobacterium tuberculosis (M. tuberculosis) strains that fulfil the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug (Group A drugs are the most potent group of drugs in the ranking of second-line medicines for the treatment of drug-resistant forms of TB using longer treatment regimens and comprise levofloxacin, moxifloxacin, bedaquiline and linezolid). XDR-TB is harder to treat in view of the limited number of active drugs available to treat it and has a high mortality rate. Given the recent changes to the WHO treatment guidelines [1] promoting a full oral longer regimen, WHO have also updated the definitions of pre XDR and XDR-TB [2].

Drug resistance in Tuberculosis is not a new phenomenon and was described during the streptomycin MRC trial in the early 50s, the first ever randomised clinical trial [3]. With the failure of TB programmes through war, political turmoil and aggravated by poverty, drug use and the HIV-TB syndemic there has been an expansion in the number of drug resistant Tuberculosis cases worldwide; currently 1 in 20 cases of TB are RR/MDR-TB. With an estimated 558,000 new cases, RR/MDR/XDR TB is currently posing a global threat to health security [4]. There have however been only 160,684 notified cases (as detection is currently a challenge in many countries especially in sub-Saharan Africa) and 230,000 deaths [4]. Drug resistant TB is delaying and hampering elimination and constitutes a significant burden to healthcare providers through complexity and cost associated with its management.

Treatment success of RR/MDR-TB cases globally increased from 50% in the 2012 cohort to 55% (UK 45 cases, 71%) in 2015, with XDR-TB cases having a successful outcome in 34% (UK 8 cases, 25%) of cases [4]. However unfavourable success rates in some countries appears to be more correlated with lack of drugs rather than just the resistance profile per se. A recent individual-data meta-analysis including 12,030 patients from 25 countries, reported a higher treatment success rate of 65% in MDR-TB, and a success rate of 40% with XDR-TB [5]. Patients however with resistance beyond XDR had a success rate of only 20% (significantly worse than observations prior to the availability of anti TB medications in the middle of the twentieth century) [6, 7]. Seven thousand three hundred and forty six of the 12,030 (61%) patients achieved treatment success, relapse or treatment failure occurred in 1017 (8%) patients and death in 1729 (14%) [5]. The higher treatment success rates are due to the more widespread availability and use of linezolid, later generation fluoroquinolones (moxifloxacin or levofloxacin), bedaquiline,

carbapenems, clofazimine when compared to prior TB cohorts [5]. However a mortality benefit was only associated with the use of linezolid, later generation fluoroquinolones and bedaquiline [5].

Recent evidence from South Africa showed significantly improved treatment success and reduced mortality with bedaquiline use [8, 9], this prompted the South African government to recommend the use of full-oral regimens including bedaquiline for the treatment of MDR-TB [10].

The World Health Organization Europe Region reports that 17% of all new cases of TB are RR/MDR-TB cases, which is the highest proportion of drug resistant cases globally. Of concern the number of MDR-TB cases is increasing [4]. It has been estimated that a third of Tuberculosis cases in Russia could be drug resistant over the next two decades [4, 11]. In the United Kingdom, RR/MDR-TB is relatively uncommon with 55 new annual cases, 1.8% prevalence (PHE 2017), 3 of whom were diagnosed as XDR-TB [12, 13].

Diagnosing a Case of Drug Resistant Tuberculosis

The natural history of infection is identical to that of drug-susceptible TB. Drug resistant TB presents clinically with signs and symptoms in the same way as drug susceptible TB cases. Notably TB in a patient who had prior TB may be more severe and extensive and give a clue of prior disease and drug resistance but it should be remembered that patients may have primary infection with a drug resistant strain.

The patient's history may give important clues as to whether the patient has risk factors for drug resistant infection (see Box 1 risk factors). Patients with social risk factors (alcohol, drug use, homelessness, and prison) have a twofold higher chance of drug resistance compared to susceptible cases. Other risk groups include people from countries with high MDR-TB prevalence and their respective communities.

Box 1 Risk factors for drug resistant tuberculosis
Residence in a country with high incidence and prevalence for MDR-TB
History of prior TB treatment
Non response to TB treatment
Contact with a patient/relative with active drug resistant TB
Psychiatric illness
Alcoholism
Drug addiction
Homelessness
Diabetes mellitus
Life in prison
Healthcare worker

There are two ways of developing a drug resistant TB infection, firstly through acquisition of drug resistant TB and secondly through primary drug resistant TB infection. Acquired drug resistance is whereby a mutant resistant *Mycobacterium tuberculosis* strain is selected; this is more likely to occur with inadequate, partial or dubious quality drug therapy or suboptimal patient compliance with standard anti-TB quadruple therapy. Examples include lack of rifampicin in fixed dose combination tablets [14]. Primary drug resistant TB on the other hand is where infection is with a drug resistant strain of *Mycobacterium tuberculosis.* This is likely to occur in areas where drug-resistant TB is prevalent and where infection control practices are inadequate or have not been implemented.

The most common form of drug-resistance is acquired drug resistance frequently caused by the addition of a single active drug to a failing regimen [15]. Natural mutations in *Mycobacterium tuberculosis* resulting in resistance to more than one TB drug can occur but are exceedingly rare. In the United Kingdom, drug-resistance is most likely to occur through migration as primary transmission is unusual due to the low prevalence of drug resistant cases and also the significant contact tracing and infection control measures enforced in the UK.

Globally pulmonary TB is the most common presentation of DR-TB cases, with cases of extra-pulmonary TB generally seen in children, the immunosuppressed or people living with HIV. However, in the UK the majority of TB cases are extrapulmonary (approximately 60%) [12] and there are a significant number of extrapulmonary DR-TB cases reflecting this, hence creating a challenge for the confirmation of the diagnosis of resistance [16].

Diagnosing TB rapidly is important for successful treatment outcomes in the patient and in pulmonary TB cases essential also for minimising the risk of onward transmission. Drug susceptibility testing or whole genome sequencing are also necessary to improve patient management [17].

The first diagnostic tool for the clinician is the suspicion of drug-resistant TB. A chest X-ray is mandatory, further radiological methods and investigations (see Figs. 1 and 2), may localize extrapulmonary disease and associated co-pathology.

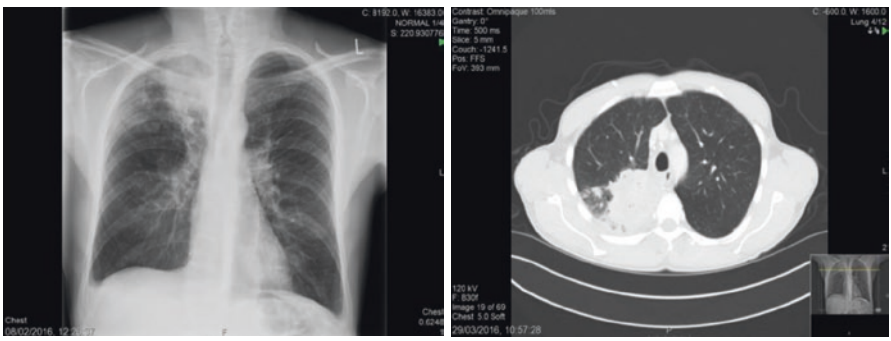

Fig. 1 Chest X-ray and Computer Tomography scan of a 45-year-old man living with HIV presenting with features suggestive of pulmonary TB, mycobacterial sputum cultures isolated *Mycobacterium tuberculosis,* large right sided apical abscess, costophrenic blunting, volume loss and tracheal deviation

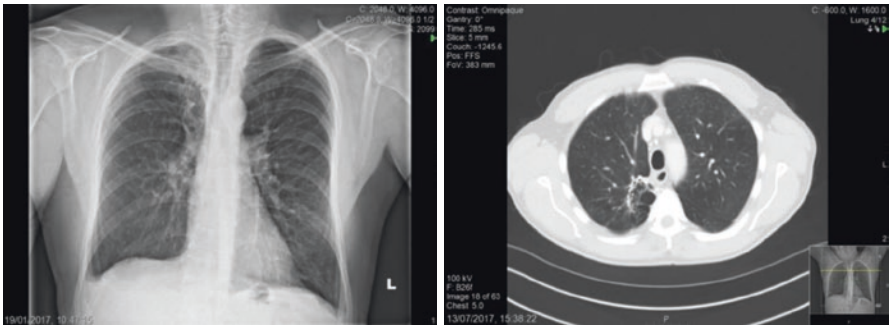

Fig. 2 Chest X-ray and Computer Tomography scan of the 45-year-old man in Fig. 1 a year and 18 months into MDR-TB treatment, note the resolution of the abscess and scarring, mild improvement in right hemi thoracic volume

Imaging can also allow for aspiration, broncho-alveolar lavage or biopsy of pathological material for microbiological, molecular and cyto/histopathological examination. The optimal microbiological or molecular diagnostic method for TB diagnosis will rely on the setting, clinical context and laboratory [1]. Diagnostics of MDR-TB are discussed in chapter "Laboratory Diagnostic Techniques" and whole genome sequencing in chapter "Whole Genome Sequencing: Applications and Cluster Investigation".

Management of DR-TB

The clinical management of RR/MDR/XDR-TB is challenging and often the more drug resistant the more complex the treatment, this may be due to prior failed attempts, complex social challenges with the addition of alcohol misuse, drugs and or HIV co-infection [18]. Drug resistant cases require more resources for treatment, longer duration of treatment and follow up. In some cases some may also require surgery [1, 18]. It is essential to communicate with the patient effectively, using translators if necessary and informing the patient of their diagnosis and offering them the necessary treatment and support to take and complete their treatment. Social issues must never be underestimated and sufficient support and services should be made available. All drug resistant cases moreover should receive a multidisciplinary approach and a discussion with a national consilium (e.g. the British Thoracic Society MDR TB Clinical Advice Service in the UK) [19, 20].

A significant number of patients will develop severe adverse events to drugs in their MDR-TB regimen and it is important that all adverse events be accurately recorded and managed. It is particularly important for the newer drugs as there has been a relative lack of safety data given the accelerated regulatory approvals. Approximately a fifth of patients will develop severe toxicity to linezolid, PAS, amikacin and prothionamide/ethionamide [1, 5].

Due to toxicity and lack of efficacy amikacin, PAS and prothionamide/ethionamide were downgraded in recent years [1]. Linezolid, one of the most toxic drugs,

has been associated with better conversion rates and treatment success and it has been made a priority agent. The ZeNiX study is currently evaluating strategies and alternative dosing schedules to retain the efficacy of linezolid but minimise its toxicity [21].

Firstly, one should ensure that there is no risk of transmission to others and staff, that appropriate protective equipment is utilised and an FFP-2 or 3 masks are used by fit-tested personnel. MDR-TB patients, if hospitalised should be isolated in a negative pressure room with a guaranteed number of air changes per hour (usually above 12 per hour). Infection control policies are necessary in order to enforce appropriate standards and to protect both staff and visitors [22]. The advent of an all oral MR-TB regimen and the lack of acute beds may exert greater pressure on hospitals to discharge sputum smear positive, drug resistant cases earlier; it must be emphasised that appropriate and stringent measures are adopted in the community in order to reduce the possibility of transmission to an absolute minimum and all cases of drug resistant TB should be discussed with the local public health team before discharge. Hospitalization is not always required, especially if not infectious (i.e. extrapulmonary) and ambulatory care should be favored with the caveat that the patient will require more visits at treatment initiation. The patient should receive assistance with adherence and assistance with any social issues identified. Directly observed therapy (DOT) or video observed therapy (VOT) should be considered and arranged.

A recent European Centre for Disease Prevention and Control survey evaluating MDR-TB management, found weaknesses in infection control practices (lack of negative pressure ventilation rooms and lack of infection control plans) [23, 24] A new audit performed in 2017 found improvement on this aspect, however outpatient infection control still required improvement (ref) [25].

The importance of infection control in preventing transmission is stressed in the WHO End TB Strategy (and by the WHO Policy on Infection Control (ref) [22, 26, 27]. WHO has released policy aimed at improving infection control (ref) [28].

The management of drug resistant TB requires administering a drug regimen composed of a minimum of four drugs in combination to reduce further development of resistance and to ensure sufficient bactericidal and sterilising capability.

Box 2 Recommended Adult Dosing (Age 18+ years) (from: http://www.tbdrugmonographs.co.uk/) [20]

- Bedaquiline: 400 mg OD for the first 2 weeks, followed by 200 mg three times per week (oral)
- Moxifloxacin 400 mg OD (oral and IV)
- Levofloxacin 750 mg-1 g OD (oral and IV)
- Linezolid 600 mg OD (oral and IV)
- Delamanid: 100 mg twice daily (oral)
- Amikacin 15 mg/kg OD (max 1 g a day) (IV)
- Streptomycin 15 mg/kg OD (max 1 g a day) (IV)
- Clofazimine 200 mg OD first 2 months then 100 mg OD (oral)
- Amoxicillin/clavulanic acid 625 mg/1.2 g TDS (oral/IV)

- Cycloserine or Terizidone 250 mg BD initially then 500 mg BD (monitor levels) (oral)
- Ethambutol 15 mg/kg OD (oral and IV)
- Imipenem/cilastatin 1 g BD (IV) must give with amoxicillin/clavulanic acid
- Meropenem 1 g TDS (IV) must give with amoxicillin/clavulanic acid
- PAS 150 mg/kg in 2–4 divided doses (oral)
- Prothionamide 15–20 mg/kg (max 1 g a day) (oral)
- Pyrazinamide 25 mg/kg OD (oral)

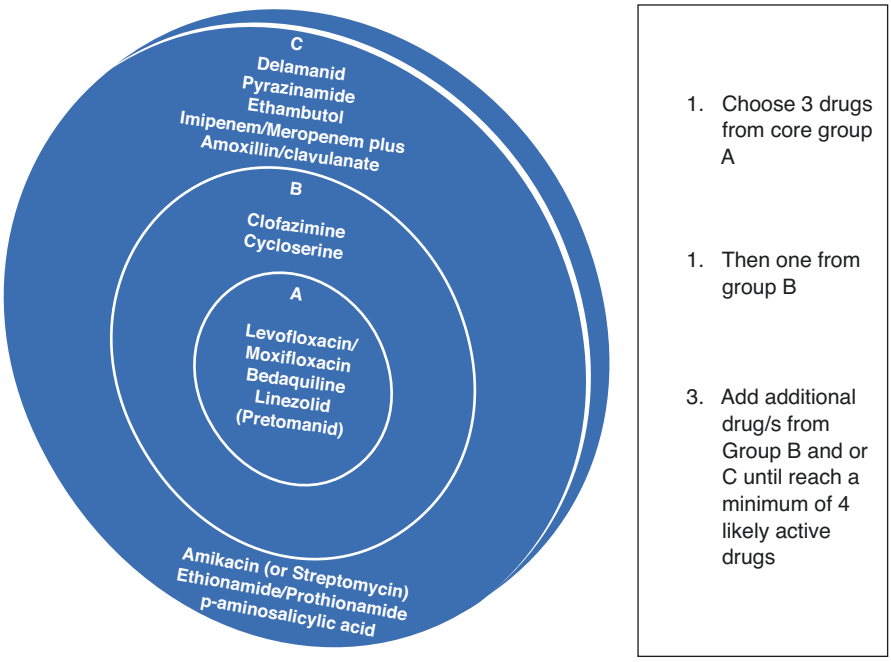

Fig. 3 Recommended drugs to be used in the WHO longer MDR-TB regimen, adapted from the WHO drug classification for MDR-TB regimens: WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019 [1]. A minimum four drug regimen should be offered. The core is comprised of four priority group A drugs, three of which can be chosen. One or two agents can be chosen from Group B. If four drugs cannot be chosen from the core drugs in A + B, then agents from Group C can be used. Group C agents are ranked by decreasing order of preference for use subject to other considerations

The up to date reiteration of the WHO MR-TB drug classification is shown in Fig. 3 [1].

The latest WHO guidelines for the management of MDR-TB have been based in part on a recent individual patient data-metanalysis of 12,030 patients, that reported improved patient outcomes with linezolid, fluoroquinolones, bedaquiline, clofazimine and the B-lactamase inhibitor/carbapenems [5]. The metanalysis also reported greater toxicity and poorer outcomes with prothionamide, amoxicillin/clavulanic acid and second line injectables [5].

The WHO released consolidated guidelines on drug-resistant tuberculosis treatment in 2019 incorporating previous MDR-TB guidance from 2011, 2016 and 2018, as well a prior guidance on bedaquiline and delamanid [1, 16, 18].

The new guideline appraised recent evidence including a new MDR-TB individual data meta-analysis published in 2018 [1], has revolutionised RR/MDR-TB treatment recommending an oral treatment regimen as first line.

The new guideline gives 27 policy recommendations split into seven sections concerning RR-MDR/TB, more will be made available with further advice on their implementation in a revised edition of WHO's "how-to" handbook for the programmatic management of TB.

The seven sections and recommendations are the following (adapted from 2019 WHO guidelines) [1]:

How Should Longer MDR-TB Regimens Be Composed? When designing a longer regimen for RR/MDR-TB patients, all three Group A agents (Bedaquiline, Levofloxacin or Moxifloxacin and Linezolid) and at least one Group B agent (clofazimine or cycloserine) should be included to ensure that treatment starts with at least four TB agents likely to be effective. Bedaquiline is expected to be completed in most patients after 6 months with the three remaining agents continuing for the remainder of the treatment (see Fig. 3). Note that while a drug susceptibility is desirable it is not currently essential for the longer all oral regimen beyond quinolone sensitivity as few have capability to test for bedaquiline and linezolid sensitivity. If only two or just one group A agent can be included, then both Group B agents should be included (unless there are exclusions i.e. resistance or tolerability/toxicity). If the regimen cannot be completed (minimum four agents) then Group C agents should be added, ethambutol is the first choice followed in order of preference (toxicity) followed by delamanid, pyrazinamide, carbapenems, aminoglycosides, ethionamide/prothionamide and the PAS. Bedaquiline may be added to regimens in patients aged 6–17. Evidence on the safety and effectiveness of bedaquiline use beyond 6 months and below the age of 6 years is currently insufficient for review and formulations are currently not available for smaller children. Use of bedaquiline beyond these limits should follow best practices in "off-label" use [29].

Clofazimine, Cycloserine/Terizidone (Group B) may be included in the longer regimen to treat RR/MDR-TB. Ethambutol (Group C) may be included in the longer regimen to treat RR/MDR-TB and visual acuity and Ishihara testing should take place prior to its use. Pyrazinamide (Group C) may be included in the longer regimen to treat RR/MDR-TB, however it is only counted as an effective drug if the DST shows susceptibility. Delamanid (Group C) may be included in the longer regimen to treat RR/MDR-TB and given to children above the age of three and has been so far been demonstrated to be safe and well tolerated. However given the current lack of evidence of efficacy for this has meant it is still in the group C drug list. Imipenem/cilastatin or meropenem (Group C) together with amoxicillin/clavulanate may be included in the longer regimen to treat RR/MDR-TB, their use is most likely reserved for extensively drug resistant patients or patients who cannot tolerate other regimens, however they are injectables and require two, three or four daily dosing which is an important disadvantage. Ertapenem was not considered by the WHO panel and is not currently recommended for intensive phase treatment though it could be considered off label in continuation phase treatment. Amikacin (Group C) may be given to patients >18 years old as part of a longer regimen to treat RR/MDR-TB, but only when susceptibility is demonstrated and adequate measures to monitor for adverse reactions can be ensured (audiometry, renal function tests). If amikacin is unavailable streptomycin may be used but following the same criteria. Kanamycin and Capreomycin following evidence of toxicity and poorer outcomes (twofold higher mortality), should no longer be included in a regimen to treat RR/MDR-TB (see Box 2 for currently recommended dosing schedules and resources) [1].

Ethionamide/Prothionamide may be included in the longer regimen treat RR/MDR-TB, but only when bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible. *P*-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose the regimen are not available. Thyroid function monitoring is important when utilising ethionamide and PAS. Amoxicillin-Clavulanic acid/clavulanate should not be included in the longer regimen to treat RR/MDR-TB without the presence of imipenem/Meropenem, as it's use was associated with negative outcome (Box 3 gives monitoring recommnedations and resources) [1].

The longer WHO MDR-TB regimen which should include a minimum of four likely to be active agents in the first 6 months, after which the regimen can be stepped down to three agents for a total duration (depending on patient response and sputum culture conversion) of about 18–20 months for patients on longer regimens. A treatment duration of 15–17 months following culture conversion is suggested for most patients. In RR/MDR-TB patients on longer regimens receiving amikacin/streptomycin, an intensive phase of 6–7 months is suggested for most patients.

Use of the Standardized, WHO Shorter MDR-TB Regimen

In MDR/RR TB patients without extensive disease or severe extrapulmonary forms, who have not received prior treatment for >1 month with second line agents used in the shorter MDR-TB regimen and who are not resistant to fluoroquinolones may use the WHO shorter 9–12 month regimen instead of the longer regimens [30, 31].

The shorter WHO regimen applies to adults, children, and people living with HIV with rifampicin-resistant TB or MDR-TB, who have not been previously treated with second-line drugs, resistance to fluoroquinolones must be excluded by DST or line probe results. No resistance other than to isoniazid is allowed. Pregnancy and extrapulmonary disease are contraindications. It is an oral modified version of the 'Bangladesh regimen' that has been used programmatically in South Africa.

The new 9–12 month WHO shorter regimen is standardised and composed of 4–6 months of bedaquiline (6 months), moxifloxacin/levofloxacin, clofazimine, pyrazinamide, ethambutol and high dose isoniazid followed by 5 months of moxifloxacin/levofloxacin, clofazimine, pyrazinamide and ethambutol.

There has been consideration of a shorter drug regimen with bedaquiline, pretomanid and linezolid for 6–9 months, based on data from South Africa that has implemented an all oral shorter regimen, together with the NiX TB study and data from the TB Alliance [32–34].

However no further modifications are recommended for the new oral WHO shorter regimen unless through operational research under strict conditions [1, 35]. The main advantage of the WHO shorter regimen is it is standardised for programmatic use and has lower costs estimated at less than a thousand US dollars per patient.

The bedaquiline, pretomanid and linezolid (BPaL) regimen following FDA approval and WHO recommendation may be offered to XDR-TB patients but only under controlled operational research conditions [36].

Monitoring Patient Response to Pulmonary MDR-TB Treatment Using Culture Patients should be monitored for treatment response and sputum microscopy and culture with samples taken at least at monthly intervals (see Box 3).

Start of Antiretroviral Therapy in Patients on Second Line Anti-Tuberculosis Regimens Antiretroviral medication should be started as soon as possible irrespective of CD4 count, and as early as possible (within 2 weeks, if CNS TB within 8 weeks), corticosteroid treatment may help prevent IRIS and improve outcome.

Surgery for Patients on MDR-TB Treatment Adjunctive surgery in the form of elective partial lung resection (lobectomy or wedge resection) may improve the possibility of cure in cases of limited/localized (monolateral) RR/MDR-TB provided that there are no contraindications (bilateral disease, poor lung reserve) [37, 38].

Care and Support for Patients with MDR/RR-TB All patients receiving this treatment should receive comprehensive health education and counselling and understand the importance of treatment adherence. A package of treatment adherence interventions should be offered to patients on TB treatment in conjunction with the selection of the most suitable treatment administration options (daily and non-daily DOT, VOT or if no concerns unsupervised). Video observed treatment (VOT) may replace DOT for a number of patients if sufficient resources are available and can be appropriately organized [39]. Treatment adherence interventions home vis-

its/messages/call and/or digital medication monitor, material support to patient, psychological support and drug and alcohol services may be offered to those on TB treatment. Patients with MDR-TB should ideally be treated using a mainly ambulatory care model and hospitalization discouraged where possible (see Box 4 for common side effects of treatment).

In summary the recent WHO drug resistant tuberculosis guideline has a number of strong recommendations, firstly drug susceptibility testing (DST) is essential for both shorter and longer regimens. There is still low-quality evidence for the group A drugs as phase 3 trial data is not yet available. Amikacin remains a valid option with some caveats, it is still very effective however there are some drugs that are more effective and less toxic, and the guideline reflects upon the results of comparing regimens and AEs and outcomes in IPD meta-analysis. The WHO has now advised against the use of capreomycin or kanamycin based on their lack of efficacy and toxicity. The MDR-TB regimen should have at least four agents with three from group A (linezolid, bedaquiline and fluoroquinolone). Levofloxacin appears to be favoured over moxifloxacin as this drug has a reduced propensity to prolong QT now that regimens include at minimum 2 other QT prolonging agents in the form of bedaquiline and clofazimine. WHO states that bedaquiline may be used beyond 6 months and aDSM should be performed but it should be recognised that there is insufficient data at present to unequivocally support bedaquiline safety beyond >6 months. There are also concerns about the toxicity of linezolid particularly given the duration of use as there are substantive toxicity issues with peripheral/ocular neuropathy and bone marrow suppression.

Drugs are only one component required in the management of drug resistant TB cases and a patient centred approach is needed and adapting care to their needs. This includes providing acceptable and convenient directly observed therapy. Importantly patients require an entire social and holistic provision that cannot be over emphasised.

Box 3 Baseline and Maintenance Monitoring Recommendations

All patients should be monitored routinely for toxicity and adverse events, given the propensity of many MDR-TB drugs to prolong QT, ECG monitoring at baseline and at regular intervals is recommended.

Bedaquiline and delamanid have a mandatory reporting mechanism via the BTS CAS.

Baseline:

Urea and electrolytes, liver function tests, uric acid, full blood count, HIV, hepatitis B and C, G6PD deficiency screen, clotting, ECG, nutritional assessment. Audiometry if amikacin/streptomycin. Visual acuity and colour vision.

Monthly:

FBC, U + E's, LFTs, TFTs (if prothionamide or PAS), lactate.

ECG at a fortnight then monthly (if >60 msec increase or QTc >500 msec stop offending drug/s and monitor closely, correct any electrolyte imbalance)

Consider nerve conduction studies and electromyography if peripheral neuropathy.

Consider Aspergillus antibodies/galactomannan if pulmonary cavities.

Monitoring response: Take sputum weekly if in hospital and monthly in ambulatory care, repeat chest imaging X-ray, consider CT chest scan for all MDR-TB cases at baseline and end of treatment.

Box 4 Common Side Effects Associated with MDR-TB Medications
Linezolid: Peripheral neuropathy, anaemia, thrombocytopenia, ocular toxicity, lactic acidosis, serotonin syndrome.
Bedaquiline: Nausea, arthralgia, headache, QT prolongation, hepatitis
Delamanid: Gastrointestinal intolerance, dizziness, QT prolongation
Prothionamide: LFT rise, peripheral neuropathy, hypothyroidism
PAS: Abdominal discomfort, diarrhoea, hypothyroidism
Amikacin/streptomycin: Ototoxicity, vestibular toxicity nephrotoxicity, hypomagnesemia, hypokalaemia, skin rash
Moxifloxacin/levofloxacin: Tendonitis, QTc prolongation, arthralgia, neurotoxicity, seizures, aortic aneurysm, hepatitis
Cycloserine: Peripheral neuropathy, psychiatric disturbances, seizures
Pyrazinamide: Abdominal discomfort, arthralgia, hepatitis
Clofazimine: Skin pigmentation, QT prolongation, abdominal discomfort and bleeding
Meropenem: LFT rise, rash
Co-amoxiclav: Diarrhoea, colitis, rash, LFT rise.

Conclusion

RR/MDR/XDR-TB is a growing threat to global health security and may in part replace drug susceptible TB cases and challenge global TB elimination efforts. Recently, greater attention to Tuberculosis and lately through the United Nations General Assembly meeting in 2018 has allowed for the development and implementation of rapid diagnostic methods for MDR-TB, these may in turn help increase detection rates and improve access to treatment. New WHO recommendations for use of an all oral, shorter, less toxic treatment regimen provides hope for more patients being enrolled on treatment, however a significant number of detected cases still do not have access to this treatment. It is also important to note that the a significant proportion of MDR-TB patients go undetected and untreated. An important implementation gap between best practice guidelines and programmatic care exists. Scale-up with more funding, education and operational research is required to bridge these. New drug trials evaluating several combinations of drugs and regimens are underway to evaluate less toxic, shorter and more effective treatments.

In low incidence countries, MDR-TB is fortunately a relatively rare phenomenon with iatrogenic MDR-TB being unusual and patients having access to all the recommended drugs and regimens. However despite this challenges remain with respect to the care and support of patients with complex social needs and addiction.

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Therapeutic Drug Monitoring in Tuberculosis

T. G. D. Capstick and M. J. Gilchrist

Introduction

Understanding the pharmacokinetics and pharmacodynamics principles of medicines is a speciality in itself. In its simplest form pharmacokinetics is the study of drug absorption, distribution, metabolism and excretion. Pharmacodynamics examines the relationship between drug concentration at a specific site and the corresponding therapeutic or adverse effect. Clinical pharmacokinetics and pharmacodynamics (PKPD) allows the principles mentioned to be applied to the safe and effective therapeutic management of drugs in a patient.

With PKPD principles inherently interlinked, therapeutic drug monitoring (TDM) may be useful to determine drug concentrations in the plasma and allow interpretation and application of that concentration to drive safe and effective drug regimens. There are no absolute boundaries between therapeutic or adverse concentrations. A grey area can exist in which there are differences in each patient's response. For example there may be patient variations in drug absorption or distribution, differences in patients ability to metabolise and eliminate a drug, altered organ function dysfunction, age or obesity together with drug interactions.

National UK guidelines currently make no recommendations on the role or utility of TDM in the management of tuberculosis. Instead, the standard treatment regimen recommends doses of antituberculosis drugs that are dependent on body weight

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and assumed to be suitable for all patients irrespective of comorbidities or other patient factors [1].

TDM may improve TB treatment success through optimising treatment and preventing under- or over-dosing of antituberculosis drugs [2–4]. Indeed, dosing of antituberculosis drugs is currently based on body weight or stratified dose bands, but there is evidence some drug doses may be too low for many patients [5–7]. Furthermore there is significant variability in drug absorption and subsequent serum drug concentrations between patients, suggesting that a one-size fits all approach to drug dosing may not be appropriate [2, 6].

Pharmacokinetic variability in the serum levels of antituberculosis drugs is dependent on a number of inter- and intra-patient variables including co-morbidities such as diabetes mellitus, HIV co-infection and gastrointestinal disorders where delayed or malabsorption may occur, drug-drug and drug-food interactions and timing of dosing. Under dosing is liable to drive treatment response and increases the risk of the development of drug resistance [2, 3, 6, 8–12].

Pharmacokinetic-pharmacodynamic, and dose-response relationships of antituberculosis drugs have been studied in in vitro hollow fiber system (HFS) and animal models to determine the most important PK/PD parameters for antituberculosis drugs [13]. This includes cumulative drug exposure over time ($AUC_{0–24}$) and peak concentration (C_{max}) relative to the minimum inhibitory concentration (MIC), expressed as the ratios of $AUC_{0–24}$/MIC and C_{max}/MIC [10]. For most antituberculosis drugs, the best predictor of treatment efficacy and preventing the development of drug resistance is the $AUC_{0–24}$/MIC ratio [2–4, 13]. However determining AUC is technically difficult as it requires multiple blood samples to determine cumulative drug exposure [14, 15]. Consequently the ratio of C_{max} to MIC is more commonly used in practice to determine whether adequate doses of antituberculosis drugs are prescribed.

The time to achieve the peak serum concentration (T_{max}) for most antituberculosis drugs is 2 h, with the exception of rifabutin, which achieves this after 3 h. Therefore for most antituberculosis drugs, the most appropriate time to take a drug level is after 2 h (C_{2hr}), as this provides an approximate measure of C_{max}. However in situations where there is delayed or malabsorption of antituberculosis drugs, a 2-h sample will not accurately reflect the true peak serum concentration, and so a 6 h sample (C_{6hr}) can be taken to determine delayed absorption [3, 4].

When Should TDM Be Performed?

In the UK, the range of assays for antituberculosis drugs that are commercially available is relatively limited. Where available, target drug concentrations are listed in Table 1. Standard doses of antituberculosis drugs should achieve these normal target concentrations in many patients, but lower serum concentrations are certainly effective in some patients, but there is no clear guide as to how low a serum

Table 1 Therapeutic drug monitoring available in the UK

Drug	Target level	Timing of sample after oral dose[a]	Frequency
Isoniazid	3–5 mg/mL	2 h post dose	Poor response/suspected malabsorption
Rifampicin	8–24 mg/L	2 h post dose	Poor response/suspected malabsorption
Rifabutin	0.3–0.9 mg/L	3 h post dose	Poor response/suspected malabsorption
Pyrazinamide	20–40 mg/L	2 h post dose	Poor response/suspected malabsorption
Ethambutol	2–6 mg/L	2 h post dose	Poor response/suspected malabsorption
Levofloxacin	8–12 mg/L	2 h post dose	Poor response/suspected malabsorption
Moxifloxacin	3–5 mg/L	2 h post dose	Poor response/suspected malabsorption
Linezolid	12–24 mg/L	2 h post dose	Poor response/suspected malabsorption
Cycloserine	10–20 mg/L 20–35 mg/L	Pre dose 2 h post dose	After 4 days at target dose; Fortnightly for 1 month if stable; Then at least 6-monthly
Drug	**Target level**	**Timing of sample after completion of intravenous dose**	**Frequency**
Amikacin	<5 mg/L	Pre dose	Weekly for 4 weeks, Then fortnightly if stable
	35–45 mg/L	[b]1.5–2 h and 6 h after infusion ends	
Streptomycin	<5 mg/L	Pre dose	Weekly for 4 weeks Then fortnightly if stable
	35–45 mg/L	[b]1.5–2 h and 6 h after infusion ends	

Adapted from TB Drug Monographs [19]

[a]Repeat level for oral meds 6 h post dose if delayed absorption is suspected (7 h for rifabutin)

[b]Preferred method take level at 1.5 and 6 h after infusion ends, plot on semi-logarithmic paper and extrapolate back to time = 0. (In practice, an alternative approach often used is to take 60 mins after infusion ends, but this may under-estimate true level)

concentration can go to remain effective [3]. As the standard regimen has a very good response rate, it is consequently not necessary to perform TDM routinely.

In the absence of high quality randomised controlled trials to determine whether there are positive outcomes from routine use of TDM, it should be restricted to the following scenarios [2, 3, 11, 12, 16–18]:

- Known or suspected delayed or malabsorption (e.g. HIV co-infection, diabetes mellitus, gastrointestinal disorders, and malnutrition)
- Treatment of MDR- or XDR-TB, particularly where the treatment regimen contains few effective drugs
- Potential drug interactions between different antituberculosis drugs (e.g. rifampicin with moxifloxacin or bedaquiline)
- Potential drug interactions with other drug classes (e.g. antifungals, antiretrovirals, antiepileptics)

- Renal impairment (e.g. aminoglycosides, cycloserine, ethambutol)
- Risk of, or actual, drug toxicity (e.g. aminoglycosides, cycloserine)
- Poor response to treatment, or relapse (e.g. those who fail to convert after 1–2 months of treatment)
- Consider for 'High risk' patients (e.g. children, HIV co-infection, CNS TB)

The use of TDM in routine practice increases the cost of TB treatment, but the alternative in slow responders is a watch and wait policy, risking an unnecessarily prolonged infectious period and prolonged exposure to adverse drug reactions [3]. Consequently if used appropriately, TDM may reduce the costs associated with treatment failure, development of resistance, prolonged hospitalisations, and drug toxicity.

In contrast, people who appear to be clinically responding well to treatment in terms of resolution of fever, cough and night sweats, then TDM is unlikely to offer any meaningful data and in these circumstances, low serum drug levels could just be ignored.

Where TDM is performed, it is logical to achieve the target concentration for each drug. Consequently where there continues to be a poor response, delayed or malabsorption can be excluded as the reason and other factors should be considered, such as poor adherence or drug resistance [3].

Interpretation of TDM Data

For most antituberculosis drugs, serum levels should be taken as a 2 h post-dose level to estimate peak concentration (3 h for rifabutin). Where delayed or malabsorption are thought to be a risk, a second level taken as a 6 h post dose level to obtain information on the rate and completeness of absorption (7 h for rifabutin) [2, 3]. A trough drug concentration is often not helpful, as antituberculosis drug trough concentrations are frequently below the limits of detection.

In most cases, the 2 h level will be higher than the 6 h level. Where there is delayed absorption, the 6 h level may be higher than 2 h level, and may even approach the therapeutic range. In cases of malabsorption, both the 2 and 6 h levels will be low [3].

In the case of high drug levels, a dose reduction should be considered; this is particularly important if there are signs of toxicity (e.g. neurotoxicity with cycloserine, hearing loss with aminoglycosides). In cases of low drug levels, a dose increase should be considered, assuming that the patient has been adherent to treatment and taking it on an empty stomach. In such situations, the typical "maximum" doses of drugs can be exceeded if drug levels are low, but they should be increased *cautiously* and monitored closely. If early serum concentrations are low due to malabsorption, this may resolve as the active TB disease is treated, resulting in raised drug concentrations [3].

Toxicity

Adverse drug reactions to antituberculosis drugs are common, and are more common in patients treated for multi-drug resistant TB (MDR-TB) than drug-sensitive TB as second line drugs are generally less effective and more toxic than first line drugs. Common adverse drug reactions resulting from treatment for MDR-TB include nausea and vomiting, diarrhoea, arthralgia, dizziness and hearing disturbances, whilst serious toxicity includes hepatotoxicity, neurotoxicity, psychiatric, ototoxicity, haematological [20, 21]. Whilst very few studies have assessed the risk of toxicity based on serum drug concentrations, dose-dependent toxicity is known to occur with ethambutol induced optic neuropathy, isoniazid induced peripheral neuropathy, pyrazinamide and rifampicin induced hepatotoxicity, fluoroquinolone induced QT-prolongation, cycloserine induced neuropsychiatric toxicity, aminoglycoside induced ototoxicity, linezolid induced haematological toxicity [3, 4, 17, 21, 22]. It is possible that TDM of these drugs may reduce the risk of toxicity requiring treatment changes.

Co-morbidities

Certain co-morbidities are known to adversely affect the serum concentration of antituberculosis drugs. In people with HIV co-infection, there are reports that HIV enteropathy or other HIV-related gastrointestinal disease may cause malabsorption of all first-line antituberculosis drugs, as well as second-line drugs such as cycloserine and ethionamide, resulting in lower serum peak concentrations and reduced total drug exposure (AUC) [23–26], although this was not confirmed in one meta-analysis [5]. Whilst there continues to be high response rates to standard regimens in drug sensitive TB, the utility of routine TDM in this population has not been established [27]. However it would appear to be prudent to ensure that TDM is used in the management of TB and HIV in TB-HIV co-infection, particularly due to the potential for multiple drug interactions [3, 5].

Some studies have reported lower serum drug concentrations in people with diabetes mellitus [5], others have not [28]. Malabsorption of antituberculosis drugs in diabetes mellitus is thought to occur as a consequence of experiencing gastrointestinal problems such as gastroparesis [2, 3]. Consequently TDM should be used early in treatment to ensure that the doses of antituberculosis drugs are adequate [3, 5, 28].

People with significant renal failure are at risk of accumulating renal excreted antituberculosis drugs such as ethambutol, pyrazinamide, cycloserine, and aminoglycosides, with risk of drug toxicity [29]. The frequency of dosing should be reduced and TDM used to guide continuing treatment, using 2-h and 6-h serum concentrations to assess the rate or extent of absorption, which may be reduced in this population [3, 29]. People with hepatic dysfunction may also experience malabsorption and reduced clearance of hepatically metabolised antituberculosis drugs, and so TDM may be advisable to guide treatment [3].

The Role of TDM on TB Treatment

A systematic reviews and meta-analysis of 41 studies that reported C_{2hr} levels of first-line antituberculosis drugs found that low levels were common, occurring in 12%–67% of patients. Twelve of these studies also reported outcomes of treatment, and only three reported an association between low levels and unsuccessful treatment (defined as longer time to culture conversion, at least one positive culture at 4, 8, or 24 weeks, or treatment failure and death) [5]. Consequently TDM is unlikely to be beneficial in general populations as the frequency of treatment failure is low [30, 31]. Furthermore, serum levels of antituberculosis drugs were not associated with relapse or the development of drug resistance, which again suggests that the role of routine TDM is limited in most patients [32].

Some studies have reported associations between low serum drug concentrations and poor outcomes. In people with HIV co-infection, low serum isoniazid [33–35], rifabutin [33, 35], rifampicin [33], or pyrazinamide [36] concentrations have been associated with treatment failure and relapses. However, estimations of peak drug concentrations using just 2-h measurement of serum drug level in studies may under-estimate true C_{max}, which could adversely affect data analysis. Furthermore, it should be recognised that serum drug concentration is just one factor that can affect treatment response, with other factors including extent of disease, resistance pattern, and difficult sites of disease with reduced drug penetration (e.g. CNS, abscess and empyema).

A prospective study in 142 patients with tuberculosis reported that poor long-term outcomes were 14 times more likely to occur where patients had a low exposure to at least one antituberculosis drugs (measured using $AUC_{0–24}$), compared to those who achieved adequate AUC. Poor outcomes were particularly predicted by low AUC for pyrazinamide, rifampicin and isoniazid, and low rifampicin and isoniazid peak and AUC concentrations preceded all three cases of acquired drug resistance [6].

Targeting the use of TDM in some groups of TB patients may have a role, such as those who are slow to respond to initial standard treatment regimens, In one study in Virginia, USA, targeting TDM for 42 people with a slow response to tuberculosis treatment found that 52% of patients had sub-therapeutic 2-h post dose (C_{2hr}) serum concentrations of rifampicin, 59% had sub-therapeutic C_{2hr} isoniazid levels, and 33% had sub-therapeutic levels of both drugs. In addition, of the 20 patients tested, all had normal pyrazinamide concentrations, whilst ethambutol concentrations were low in 31% of 26 tested patients. In those patients where the drug doses were increased, 89% and 29% achieved therapeutic drug concentrations with rifampicin and isoniazid respectively. It should be noted that the 2 h serum level is unlikely to have captured all the true peak concentrations, and also as this study did not compare serum drug levels in people with normal responses to treatment, an association between low drug levels and treatment response cannot be made [11].

A similar retrospective study in Montreal, Canada reported on their use of TDM in 20 patients with either a slow response to treatment, or where there were concerns

about correct drug dosing due to drug interactions or other co-morbidities such as HIV co-infection. 87% of these patients had at least one low drug concentration including 87% of isoniazid measurements, 67% of 12 rifampicin measurements and 80% of five rifabutin measurements, but only 15% of 13 pyrazinamide measurements. When compared to the three patients with all normal drug concentrations, sub-therapeutic serum drug concentrations had a trend towards longer time to culture conversion, and were more likely to be seen in patients with comorbid illnesses, smear positivity at baseline, and low serum albumin levels [37]. This suggests that higher antituberculosis drug doses might be needed in patients with these characteristics, but there is no consensus on this within published studies [3].

Some studies have demonstrated a link between dose adjustments resulting from TDM and treatment outcomes. A Canadian retrospective analysis of 52 patients where TDM was performed due to either slow response, positive HIV status, drug resistance or relapse, reported that 48.4% of all drug levels were low and just 2.3% were high. Low initial serum levels were reported for 76.6%, 68.4% and 60.0% of samples taken for isoniazid, rifampicin and ethambutol respectively, compared to just 2.9% of pyrazinamide serum levels. 74 dose adjustments were made, with a median dose increase of 300 mg for rifampicin and 150 mg for isoniazid, but whilst the median serum drug levels increased, there were variable individual responses in drug level, with two people having lower rifampicin drug levels after a dose increase. Of the 47 patients with low drug levels, five subsequently experienced a relapse four acquired drug resistance during treatment. These results indicate the importance and complexities of performing TDM in an attempt to avoid poor outcomes, but highlight that not all patients respond as expected [38].

Similarly in children, there are pharmacokinetic data showing that low C_{max} levels of rifampicin and isoniazid are common both historically, and following revision of the WHO dosing recommendations in children [39], which were made in an attempt to achieve recommended target serum levels. In this prospective study of 127 children, low isoniazid C_{max} levels were achieved in 95.2% and 68.3% of children taking the low and revised isoniazid doses ($p < 0.001$), and low rifampicin C_{max} levels were achieved in 43.5% and 41.3% of those taking low and revised rifampicin doses ($p = 0.8$). Despite an increase in average C_{max} levels following the increase in dosage recommendations, there was no effect on 6 month outcomes [40].

Alternative Drug Monitoring Methods

In areas with limited resources, venous blood sampling can be difficult due to the resources and complexities required for storage, transport, biohazard and consumables required. An alternative method for performing TDM may be appropriate, such as Dried Blood Spot (DBS) sampling. In this method, whole blood sample is obtained using a finger prick to apply a drop on to a sampling paper, which is dried and analysed [3, 4, 10]. Advantages of this method are that it is cheap, simple and quick to obtain a sample, and samples can be stored for longer time periods than a

standard blood sample. However it has not been validated as an analytical method for many antituberculosis drugs [4].

More recently, measuring antituberculosis drug concentrations in hair as a measure of drug exposure over time has shown that low concentrations are associated with clinical outcomes for drug-resistant TB, which could identify where treatment changes are required, but randomised controlled trials are required to determine the utility of monitoring drug levels in hair for the management of drug-resistant TB [41].

For most antituberculosis drugs, the ratio of $AUC_{0–24}$/MIC have been correlated to good treatment outcomes, but it is rarely practical to measure AUC because at least six or seven blood samples are required. Alternatively, a limited sampling strategy can be used to determine which fixed sampling times allow accurate measures of $AUC_{0–24}$ for antituberculosis drugs [3, 42, 43]. However, whilst only two or three blood samples maybe required to estimate exposure, this remains an invasive test for patients, and is not yet well validated for many antituberculosis drugs [4]. These limited sampling strategies require the use of multiple regression analysis to determine the relationship between AUC as the dependent variable and timed concentrations as the independent variables. An alternative approach is to use population estimates with the Bayesian approach, combining both population and individual patient pharmacokinetic data, but this is both time consuming and complex requiring computer software.

Specific Drug Information

The target pharmacokinetic parameters for antituberculosis (C_{max} and T_{max}) are listed in Table 2.

Isoniazid

There is wide variation in peak serum concentration and drug exposure in people taking isoniazid [6], and low serum concentrations have been associated with treatment failure and relapses in patients with TB-HIV co-infection [34, 35]. Drug level monitoring may have a role in TB management in this patient group to ensure successful treatment outcomes.

Table 2 Pharmacokinetic and pharmacodynamic parameters of antituberculosis drugs [2, 3, 16, 19, 44–49]

WHO group	Drug	Adult 70 kg dose	C_{max}	T_{max} (h)	PK/PD[a]
First-line	Isoniazid	300 mg daily	3–5 mg/L	0.75–2	AUC/MIC
	Rifampicin	600 mg daily	8–24 mg/L	2	AUC/MIC
	Rifabutin	300 mg daily	0.3–0.9 mg/L	3–4	n/a
	Pyrazinamide	20–30 mg/kg daily	20–40 mg/L	1–2	AUC/MIC
	Ethambutol	15–25 mg/kg daily	2–6 mg/L	2–3	AUC/MIC
Drugs for longer MDR-TB regimens					
Group A	Levofloxacin	1000 mg daily	8–12 mg/L	1–2	AUC/MIC
	Moxifloxacin	400 mg daily	3–5 mg/L	1–2	AUC/MIC
	Bedaquiline	400 mg daily for 2 weeks, then 200 mg three times per week	2.76 mg/L (week 2) 1.27 mg/L (week 24)	4–6	AUC/MIC
	Linezolid	600 mg daily	12–24 mg/L	1.5	AUC/MIC
Group B	Clofazimine	100 mg daily	0.5–2.0 mg/L	2–7	n/a
	Cycloserine	10–15 mg/kg daily	20–35 mg/L	2–3	AUC/MIC
	Terizidone	10–15 mg/kg daily	20–35 mg/L	0.5–5	AUC/MIC
Group C	Delamanid	100 mg twice daily	228 mg/L (day 14)	4	n/a
	Imipenem-cilastatin	1 g/1 g twice daily	30–40 mg/L	2	T > MIC
	Meropenem	1 g three times daily	20–25 mg/L	0.5–1	T > MIC
	Amikacin	15 mg/kg daily	25–35 mg/L	End of Infusion IV	C_{max}/MIC
	Streptomycin	15 mg/kg daily	25–35 mg/L	End of Infusion IV	C_{max}/MIC
	Ethionamide	15–20 mg/kg daily	1–5 mg/L	2	n/a
	Prothionamide	15–20 mg/kg daily	1–5 mg/L	3–4	n/a
	p-Aminosalicylic acid	8–12 g per day in 2–3 divided doses	20–60 mg/L	6	n/a

Adapted with permission from Alsultan A et Peloquin C. Therapeutic drug monitoring in the treatment of tuberculosis: an update. Drugs 2014; 74:839–854, and Lange C, Abubakar I, Alffenaar J-WC, et al. Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement. Eur Respir J 2014;44:23–63

PK Pharmacokinetic, *PD* Pharmacodynamic, C_{max} maximum/target serum concentration, T_{max} time at which the peak serum concentration is achieved, *MIC* minimum inhibitory concentration, *n/a* no information

[a]The PK/PD parameters indicate the parameters that best correlate with efficacy of the drug

Rifampicin

There have been concerns that the standard 10 mg/kg/day dose of rifampicin (maximum 600 mg daily in patients weighing >50 kg) in the treatment of TB maybe too low for many patients [3]. The rationale for this dose was based on pharmacokinetic, toxicity, and cost considerations, but many studies have demonstrated that this doses commonly produces subtherapeutic serum concentrations [5, 6]. Recent studies of high doses of rifampicin (often twice the standard dose, and also up to 35 mg/kg daily) reported that these were well tolerated and produce greater reductions in bacterial load than standard doses [50–53]. Consequently, there is a rationale that performing TDM to optimise rifampicin dosing may be beneficial for treatment outcomes, particularly in complex cases, but more data are required to confirm this [4].

Rifabutin

Low plasma concentrations have correlated with treatment failure and relapses in one study in people with HIV-TB co-infection [35]. Therefore TDM may have a role to play in optimising treatment in this patient group, especially in the context of potential drug-drug interactions.

Pyrazinamide

Variability in peak serum concentrations and exposure to pyrazinamide have been reported [6], and have been associated with treatment failure and adverse drug reactions [6, 36]. TDM may have a role in ensuring that safe and effective doses are prescribed, but clinical trials of this approach are lacking.

Ethambutol

Ethambutol does not accumulate in fatty tissue, and so doses should be adjusted according to lean body weight to prevent toxicity [54]. TDM may have a role to ensure a therapeutic dose is prescribed whilst avoiding toxicity.

Fluoroquinolones

Fluoroquinolones exert a bactericidal effect against *Mycobacterium tuberculosis*, and studies of early bacterial activity demonstrate that exposure (AUC) to the levofloxacin, gatifloxacin or moxifloxacin correlates with treatment efficacy. However at standard doses, particularly for moxifloxacin, it is likely that drug concentrations may not be sufficient to prevent drug resistance developing despite demonstrable early bactericidal effect [7]. Consequently there is a role for TDM to avoid underdosing of fluoroquinolones such as moxifloxacin [2, 16]. Fluoroquinolones have more recently been used in combination with rifampicin in cases of isoniazid monoresistance, or as an alternative to ethambutol in standard treatment regimens in patients with ocular disease, but rifampicin has been demonstrated to reduce the plasma concentration of moxifloxacin [55]. TDM should be employed to ensure therapeutic moxifloxacin levels. An alternative fluoroquinolone such as levofloxacin may be considered, particularly where moxifloxacin TDM is not available. The evidence base on clinical interactions is an area of interest—attention should be paid to the latest available evidence.

Bedaquiline

TDM is not routinely available in the UK. Bedaquiline is well absorbed and reaches a peak serum concentration after 4–6 h [44]. Where available, a 5-h and 24-h serum concentration have been recommended.

Linezolid

Linezolid has efficacy against *Mycobacterium tuberculosis*, but treatment at a dose of 600 mg twice daily is limited by haematological and neuropathic toxicity in more than half of patients [56]. However lower doses of 600 mg daily, or even 300 mg daily may be effective and well tolerated [22, 56, 57]. TDM is likely to have a significant role to ensure therapeutic serum concentration is achieved to maximise efficacy, whilst reducing the risk of serious toxicity.

Clofazimine

Clofazimine is not licensed for use in the UK, and TDM is not routinely available. There is wide variability in the bioavailability of clofazimine across patients, and due to the long half-life of 70 days, it can take at least 1 month on average before steady state serum concentrations are achieved for TDM to be useful [58].

Cycloserine/Terizidone

Cycloserine is associated with an increased risk of neuropsychiatric toxicity at serum concentrations exceeding 40 mg/L, and consequently serum levels should be routinely measured in all patients to reduce the risk of this occurring [59]. Terizidone is a structural analogue that is a combination of two cycloserine molecules. It is thought to undergo hydrolysis of imine groups in terizidone to cycloserine and paraphthalate. Cycloserine and terizidone are considered to be interchangeable and therapeutically equivalent [45, 60].

Delamanid

TDM is not routinely available in the UK. Peak serum concentrations have been reported to occur between 2 and 8 h in animal studies [61].

Aminoglycosides

A prospective study in 87 adults treated with either daily or three times a week streptomycin, kanamycin or amikacin for TB or non-tuberculous mycobacterial infection, at doses adjusted to achieve a therapeutic target range, demonstrated that the risk of ototoxicity (≥20 db) increases with age, duration of treatment and cumulative dose, but nephrotoxicity could not be predicted [17]. Since aminoglycosides achieve a concentration-dependent killing, treatment efficacy whilst avoiding toxicity is best predicted based on the ratio of C_{max}/MIC [17].

TDM is essential when injectable drugs such as aminoglycosides are prescribed to ensure a therapeutic dose is prescribed and to avoid toxicity. Whilst some guidelines recommend to measure a serum aminoglycoside level 90 min after the first dose to ensure that the dose is not toxic, then a pre- and post-dose serum level after 3–5 days to guide the dose and frequency of dosing [3], others recommend a more complex validated method of back-calculating the serum level to the end of infusion (time zero) [17].

When aminoglycosides are administered by IV infusion, they exhibit a two compartment pharmacokinetic model, whereby in the first phase during and after administration, the serum level appears high whilst the drug distributes into body tissue [62]. Once this is complete (after approximately 90 min), a second phase of renal elimination occurs. Two serum drug levels should be taken during the elimination phase at 2-h and 6-h after the end of the infusion, then use of a logarithmic concentration scale allows back-extrapolation of C_{max} to the end of the infusion (time zero) [17, 62, 63]. If a serum drug level is taken during the distribution phase, this serum level will be artificially inflated and not a true measure of body levels of drug, giving a falsely high clearance of the drug [62] and over-estimating C_{max} when back-extrapolated to the end of the infusion.

Ethionamide/Prothionamide

Ethionamide and prothionamide are not licensed for use in the UK, and TDM is not routinely available. Gastrointestinal adverse drug reactions, particularly nausea and vomiting, are common. Delayed absorption is common, so where an assay is available, a 2-h and 6-h serum concentration should be taken [3].

p-Aminosalicylic Acid

TDM is not routinely available in the UK. The licensed preparation of p-Aminosalicylic acid in the UK, Granupas®, is formulated as enteric coated granules, with a median time to peak serum concentration of 6 h, so where an assay is available, a 6-h post-dose level should be taken [64].

Conclusion/Summary

Therapeutic drug monitoring can be a helpful tool in ensuring patients receive the correct dose to optimise therapeutic effect but to avoid toxicity. It should only be deployed in specific circumstances and matched against the current clinical status of the patient. For more information on antituberculosis drug monitoring please see the UK TB Drug Monographs www.tbdrugmonographs.co.uk [19].

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Anti-tumour Necrosis Alpha Factor Treatment, Immunosuppression and Chemotherapy Prophylaxis

Laura Martin and Georgina Russell

Introduction

The World Health Organisation (WHO) estimates that one quarter of the world's population is infected with LTBI. Five to ten percent of individuals with LTBI will develop active disease during their lifetime [1]. Achieving the WHO's ambitious goal of a reduction in TB related death by 95% by 2035 demands that we address this huge LTBI burden to prevent future active TB cases. The risk of reactivation varies between individuals and the decision to screen for and treat LTBI should focus on groups of individuals who are most likely to benefit or in whom reactivation and development of active disease would cause most harm. Individuals perceive risk differently and so each patient to whom screening is offered and LTBI is identified will have a unique perspective on their risk of reactivation compared to the risks of treatment, and their perspective as well as the experience and views of the responsible clinicians need to be carefully explored. For patients in whom the risk of reactivation is being heightened because of a treatment proposed for another condition (usually immunosuppressive therapy) this risk assessment becomes more complex. The choice to treat LTBI should be reached through shared decision making between the patient and medical professionals.

LTBI is commonly diagnosed by obtaining immunological evidence of prior TB exposure in the form of a positive Interferon Gamma Release Assay (IGRA) and/or tuberculin skin test (TST) result (Table 1). Current tests are not able to distinguish between recent and historical exposure in an individual, although the former confers a higher risk of disease reactivation than the latter. These tests also usually remain positive even after successful latent or active TB treatment.

Immunosuppression increases the likelihood of TB disease (Table 2). Infliximab was introduced in 1999, a revolutionary new treatment for inflammatory bowel

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Table 1 Number of cases of active TB in high risk patients (recent UK arrivals from countries with high TB incidence or TB contacts) associated with results of T-Spot.TB or Quantiferon Interferon Gamma Release Assay or Tuberculin Skin Test (TST) measured at 5, 10 or 15 mm [2]

Test	N TB cases (95% Confidence interval) per 1000 person years
Negative tests	1.2 (0.6–2.0)
T-Spot.TB positive test	13.2 (9.9–17.4)
Quantiferon gold in-tube positive test	10.1 (7.4–13.4)
TST > 15 mm	11.1 (8.3–14.6)
TST > 10 mm	8.5 (6.5–11.0)
TST > 5 mm	6.8 (5.2–8.7)

Table 2 Risk factors that confer increased risk of TB disease and their relative risks

TB risk factor	Relative risk of TB disease (95% Confidence interval where available)	References
Solid organ transplantation	4–30	[3]
Children with haematological malignancy	16.82 (8.81–32.12)	[4]
Leflunomide	11.7 (2.1–65.1)	[5]
Advanced untreated HIV infection	9.9 (8.7–11)	[6]
Glucocorticoid treatment, prednisolone equivalent ≥7.5 mg/day	7.0 (2.9–16.8)	[7]
Close contact with a person with infectious tuberculosis (in 3-year period post exposure)	6.1 (5.5–6.8)	[6]
Radiographic evidence of old healed tuberculosis that was not treated	5.2 (3.4–8.0)	[6]
Chronic renal failure requiring haemodialysis	4.39 (3.6–5.9)[a]	[8]
Cyclosporine	3.8 (0.9–16.6)	[5]
Adults with haematological malignancy	3.53 (1.63–7.64)	[4]
Methotrexate	3.4 (1.8–6.4)	[5]
Diabetes mellitus	3.11 (2.27–4.26)	[9]
Any DMARD	3.0 (1.6–5.8)	[5]
Glucocorticoid treatment, prednisolone equivalent <15 mg/day	2.8 (1.0–7.9)	[7]
Adults with solid cancers	2.61 (2.12–3.22)	[4]
DMARDs[b]	1.6 (0.7–3.6)	[5]
Weight ≥10% below normal	1.6 (1.1–2/2)	[6]
Smoking	1.5 (1.1–2.2)	[6]

[a]Adjusted hazard ratio. [b]Other DMARD include hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, cyclophosphamide, gold compounds, minocycline, or penicillamine

disease that targeted the inflammatory cytokine Tumour Necrosis Factor alpha (TNFα). In 2001 the United States Food and Drug Administration (FDA) modified the drug's labelling to include a boxed warning about infliximab-associated tuberculosis after an analysis identified an excess of reported cases of tuberculosis disease following infliximab infusion. The relatively recent introduction and rapid

expansion of the field of biologics treatment that includes anti-TNFα drugs, as well as non-TNFα targeted drugs, now used for many medical conditions presents a challenge in identifying which patients are at risk.

Individuals at Increased Risk of Tuberculosis Reactivation

Contacts of Patients with Active Tuberculosis

The close contacts of patients with pulmonary TB are at risk of TB infection and these individuals should be screened and treated if evidence of LTBI is identified by immunodiagnostic testing [10]. Only patients with pulmonary or upper airway TB are at risk of infecting contacts but in some settings LTBI screening of the contacts of patients with extrapulmonary tuberculosis may be an effective way of identifying groups who share risks for TB exposure [11]. Individuals who have been previously treated for active or latent TB are likely to have persistently positive IGRA or TST results from prior *Mycobacterium tuberculosis* exposure and repeat testing may not be useful. Instead, a clinical risk assessment that includes infectiousness of the index patient's disease, duration of exposure and host immune status of the contact will guide whether empirical latent TB treatment is warranted. An 8-h index exposure cut off is used to guide identification of those contacts who require screening, [12] however TB transmission is also possible in shorter time periods varies with environmental, host and disease factors. Large scale whole genome sequencing may elucidate this further.

Children under 15 are particularly at risk of TB infection and progression to active disease following exposure to TB. This is addressed in the chapter on paediatric TB.

New Entrant Screening

In countries with a low incidence of TB disease LTBI screening should be offered to recent arrivals from countries with a high incidence of tuberculosis when the benefits of TB prevention outweigh the risks of LTBI treatment [10].

Patients Receiving Biologic Drug Treatment Including Anti-TNFα Agents

The anti TNFα agents confer varying risks of TB reactivation and this should be considered when selecting an appropriate treatment. Table 3 compares relative risk data to illustrate the variability in TB reactivation risk between treatments. The

Table 3 Comparison of TB disease incidence in patients receiving biologic agents, adapted from Souto 2014 [13]

Individual biologic agent	Incidence rate of active TB per 100,000 patients (95% confidence intervals)
Certolizumab	474.2 (350.0–640.0)
Infliximab	347.7 (193.4–539.2)
Adalimumab	184.7 (87.0–318.8)
Golimumab	172.1 (57.6–341.8)
Tofacitinib	169.0 (90.0–300.0)
Tocilizumab	75.6 (36.1–129.5)
Etanercept	65.01 (18.22–136.84)
Abatacept	60.0 (18.2–125.9)
Rituximab	20.0 (0.1–60.0)

consensus is that there is a higher TB risk associated with monoclonal anti-TNFα agents, than the soluble receptor etanercept, and a lower or absent risk for non-anti-TNFα targeted biologics [14].

In recent years the field of targeted monoclonal antibodies to treat chronic inflammatory disease and malignancy as well as rarer conditions has expanded to include many agents with differing molecular targets and mechanisms of actions. It is postulated that the pivotal role that TNFα plays in granuloma integrity infers a significantly greater risk of latent TB reactivation when this is impaired in contrast to the effect on cytokines involved in other inflammatory pathways.

In 2018 the *European Society of Clinical Microbiology and Infectious Disease (ESCMID) produced a consensus document that summarised the evidence to date with respect to screening recommendations for many biologic agents* [14]. Table 4 *summarises these recommendations with respect to TB screening and compares them to the Summary of Product Characteristics advice based on* clinical trial data provided to the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and/or the European Medicines Agency (EMA) [15].

Anti TNFα agents clearly increase TB risk but this is less clear for other agents. For example, a meta-analysis that reviewed the risk of TB reactivation for non-TNFα targeted agents; IL-6 (tocilizumab), CD20 (rituximab), CD28 (abatacept), IL-12/IL-23, and IL-17 (secukinumab) concluded that the risk of TB reactivation was negligible based on clinical trials which did not report an excess of TB cases compared to the country's incidence rate. Many of these studies did not include LTBI screening or treatment in their inclusion protocols. A review of 30 clinical trials of Tocilizumab in 15,485 patients with RA with a clinical observation ranging from 14 weeks to 5 years did not report any active TB cases despite the role of IL-6 in T helper cell differentiation, important for antimycobacterial activity. Only sporadic cases of active TB, not exceeding the frequency of the disease in general population, were reported in rituximab and abatacept exposed patients with rheumatoid arthritis, and no cases were associated with ustekinumab and secukinumab in patients with psoriatic arthritis and ankylosis spondylitis [16].

Table 4 Recommendations for TB Screening for patients receiving targeted biologic agents

Targeted molecule	Named drug examples	ESGIGH Consensus Document: Is LTBI testing recommended?	Summary Product Characteristics. Is LTBI testing recommended?	Notes
TNFα (monoclonal antibody)	Adalimumab, certolizumab pegol, golimumab, infliximab	Yes	Yes	
TNFα (soluble receptor)	Etanercept	Yes	Yes	Likely lowest TB risk in anti TNFα group
IL-1	Anakinra, canakinumab	Yes	Yes	Theoretical increased TB risk only
IL-4	Dupilumab	N/A	No	
IL-5	Mepolizumab, reslizumab	No	No	
IL-6	Tocilizumab, sarilumab	Yes	Yes	Rate of TB cases lower than background TB risk only *
IL-12/23 common p40 subunit	Ustekinumab, guselkuman tildrakizumab, risankizumab	Yes	Yes	No TB cases associated with ustekinumab and secukinumab **
IL-17	Secukinumab, ixekizumab, brodalumab	Yes	Yes	
IgE	Omalizumab	No	No	
Complement factor C5	Eculizumab	No	No	
VEGF	Aflibercept, bevacizumab,	No	No	
VEFGR	Axitinib,cabozantinib, pazopanib,	No	No	
EGFR	Cetuximab, panitumumab	No	No	
ErbB2/HER2	Pertuzumab, trastuzumab,	No	No	
ErbB receptor tyrosine kinases	Afatinib, erlotinib, gefitinib, lapatinib,	No	No	
BCR-ABL tyrosine kinase	Bosutinib, dasatininib, imatinib, nilotiinib,	No	No	
BRAF/MEK kinases	Cobimetinib, dabrafenib, trametinib,	No	No	
Bruton tyrosine kinase	Ibrutinib,	No	No	
PI3K	Idelalisib	No	No	
Bcl-2	Venetoclax	No	No	
Janus kinases	Baricitnib, ruxolitinib, tofacitnib	Yes	Yes	
mTOR	Everolimus, sirolimus, temsirolimus	'May be advisable'	No	TB assessment if additional immunosuppression
CD19	Blinatumomab	No	No	
CD20	Rituximab, ofatumumab, ocrelizumab,	No	No	
CD52	Alemtuzumab	Yes	Yes	
CD22	Epratuzumab, inotuzumab, ozogamicin	No	No	
CD28	Abatacept	Not reviewed	Yes	
CD30	Brentuximab vedotin	No	No	
CD33	Gemtuzumab ozogamicin	No	No	
CD38	Earatumumab,	No	No	
CD319 (SLAMF7)	Elotuzumab	No	No	
CTLA-4	Ipilimumab	If additional i/suppression	No	TB assessment if additional immunosuppression
PD-1 and PD1L	Atezolizumab, nivolumab,	If additional i/suppression	No	TB assessment if additional immunosuppression
a4-Integrins, LFA	Natalizumab	No	No	
a4-Integrins, LFA-1	Vedolizumab	No	Yes	Likely safe in terms of TB risk, but more data needed
Sphingosine 1ephosphate receptor	Fingolimod	No	No	In Multiple Sclerosis [18]
Proteosome	Bortezomib, carfilzomib, ixazomib	No	No	

Shading: red is proven higher risk for TB reactivation, amber moderate risk, green low risk [14, 15]

ESGIGCH European Society of Clinical Microbiology and Infectious Diseases Study Group for Infections in Compromised Hosts, *i/suppression* immunosuppresion. [a]In rheumatoid arthritis. [b]In Psoriatic arthritis and Ankylosing spondylitis, meta-analysis [16]

The risk of TB reactivation is likely to be further increased when combined with other immunosuppression such as methotrexate or azathioprine or serial use of more than one biologic agent [17]. It is recommended that that disease registries and adverse effects reporting systems (e.g. the MHRA 'yellow card' system https://yellowcard.mhra.gov.uk/ in the UK) are used to disseminate new information about drugs which have been in clinical use for a relatively short time. All patients need to have active TB disease excluded as well as a latent TB assessment prior to starting high risk immunosuppression.

Some case series have reported an increased rate of extra pulmonary disease in patients who are diagnosed with active TB on biologic treatment and others an increased rate of TB reactivation in older subjects with Rheumatoid Arthritis, however these rates are highly variable between large case series and so warrant further investigation [18].

Some recommendations recommend annual or repeat screening on biologic treatment but this has unproven efficacy given the unreliability of IGRA testing in this group and may result in unnecessary interruption of clinically important biologic therapy, and so we recommend repeat screening and clinical evaluation only when a new TB exposure is suspected [18].

Other Medical Conditions that Increase TB Reactivation Risk

Patients living with **HIV** are at higher risk of TB reactivation, and this is addressed in an earlier chapter "Radiology of Tuberculosis".

People with **diabetes** are at three times increased risk of developing active tuberculosis compared with people who do not have diabetes [9]. Patients with **renal impairment** are also likely to be at increased risk [8] with those requiring dialysis or transplant being at highest risk with adjusted rate ratios of 3.63 (95%CI 1.79–7.33) and 11.35 (95% 2.97–43.41) respectively [19]. This cohort of patients are also likely to have unreliable immunodiagnostic test results due to chronic immunosuppression [20, 21].

Patients with **silicosis** are at increased risk of TB reactivation [22]. Malnutrition and undernourished states including ileojejunal surgery are also associated with increased risk of TB reactivation [23].

Patients with **immune mediated inflammatory diseases** such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis are at a higher risk of TB reactivation with a peak ranging from 2.0 to 6.4 in rheumatoid arthritis in patients not receiving biologic treatments, lower in ankylosing spondylitis and psoriatic arthritis. This increased rate of reactivation is likely to be related to immunosuppressive drugs used to treat the conditions [18].

Data from a variety of settings demonstrate a higher incidences of active TB in patients with cancer compared to the general population (even when adjusting for age and co-morbidity) with patients with **haematological malignancy, head and neck** and **lung cancer** seemingly at highest risk [4]. Pooled study results in 2017

demonstrate an incidence rate ratio of TB of 2.53 for **solid organ cancers** and for haematological malignancies. The incidence rate ratio in any cancer in children was higher [24]. The UK national guidelines advocates for screening of patients diagnosed with cancer and receiving chemotherapy for LTBI to prevent reactivation [4, 10, 24].

Solid organ transplantation is associated with high levels of immunosuppression and patients are at high risk of TB reactivation. A review of more than 2000 transplantation cases demonstrated TB incidence of 2.6%, significantly higher than the general population and usually occurring in the first year after transplant [25]. Risk increases with lung transplantation, with older age recipients concomitant Hepatitis C, Diabetes, renal failure, higher doses of immunosuppression or lymphocytic depleting antibodies as part of the treatment. Mortality from TB is higher than in the general population (up to 30% in a Spanish cohort) [26]. Active infection can be a result of reactivation from either latent disease in the host (most commonly) or the donor. The American Society of transplantation and the European TBNET consortium recommend screening both host and if possible live donor for LTBI with transplant recipients screened an IGRA, TST and CXR, ideally before receiving immunosuppression. Any positive results require assessment for active TB before commencing LTBI treatment [3, 26]. For patients receiving a stem cell transplant the risk of active TB is appreciably higher (estimates vary from 2 to 40 times) than in the general population [27, 28], with higher mortality associated with the infection and again it is reasonable to assume the majority of that disease is caused by reactivation of latent disease usually in the transplant recipient. TB is a late complication of haemopoetic stem cell transplant and appears to be more likely with significant graft versus host disease. The American and European guidance is allied to the solid organ transplant guidance, proposing assessment for LTBI prior to transplant (ideally prior to immunosuppression) and treatment of LTBI [3, 26], but international agreement is lacking [29].

Risk Assessment for Latent Tuberculosis

Immunological Testing; Interferon Gamma Release Assays and Tuberculin Skin Tests

The most sensitive way to identify all patients with possible latent TB disease is a ‘triple approach’ which includes an Interferon Gamma Release Assay (IGRA) blood test, a tuberculin (Mantoux) skin test and a clinical risk assessment regarding likelihood of prior exposure to tuberculosis infection [30]. The latter is particularly useful for those patients who are already receiving immunosuppression during assessment and are at high risk of false negative IGRA or TST outcomes [31, 32]. Currently, the most commonly available IGRA tests in the UK are the Quantiferon-TB Gold In-Tube and T-Spot.TB tests (see chapter “TB Treatment and Complications”).

Both have been demonstrated to predict progression from latent to active TB disease. The T-Spot.TB test may be more sensitive in the immunosuppressed patient group but there are no good head to head studies of this compared to the latest version of the Quantiferon test (QFT Plus) which incorporates CD8 reactivity [32]. Neither test can discriminate between latent and active disease or identify those who are more at risk of TB reactivation. Table 1 presents the number of patients who are not on biologics treatment but have been recently exposed to TB and progress to active disease dependent on their immunodiagnostic test result [2].

Clinical Risk Assessment for Tuberculosis Exposure

Figure 1 outlines a assessment strategy for LTBI infection. Patients who are already immunosuppressed prior to immunological testing, have a high risk of false negative test results [31, 32]. Table 5 lists conditions and treatments that signify an individual should be considered immunosuppressed at the point of testing for LTBI. In this group a clinical and epidemiological risk assessment based on likelihood of TB exposure is likely to be helpful. The risk assessment consists of identifying epidemiological factors that put the patients at risk of TB exposure (Table 6) alongside co-morbidities and treatments that will also increase TB risk (Table 1). When considering TB treatment, the cumulative risk of disease over a lifetime will vary according to the patients age. The online TST/IGRA Interpreter https://www.tstin3d.com provides useful risk estimates based on age and exposure risks that can be used as a basis for discussions between patients and the medical professionals treating them [34]. These treatment risk estimates can then be balanced against the risks associated with LTBI treatment.

Treatment of Latent Tuberculosis

Since the 1950s when a trial of isoniazid for people with radiographic evidence of previous TB treatment was endorsed by the union of TB and lung disease, treatment has been offered to reduce the risk of TB reactivation [35]. When the index case is likely to be infected with a drug susceptible strain, treatment is composed of regimens of rifamycin and/or isoniazid antibiotics. Proposed adult regimens are as follows (see chapter “HIV and TB” for paediatric and chapter “Multi-Drug Resistant Tuberculosis Management” for adult regimens):

1. Isoniazid 300 mg once daily for 6 months
2. Rifampicin 600 mg (≥50 kg) or 450 mg (<50 kg) plus isoniazid 300 mg once daily for 6 months
3. Rifampicin 600 mg (≥50 kg) or 450 mg (<50 kg) once daily for 4 months
4. Rifapentine 900 mg plus isoniazid 900 mg once weekly for 3 months

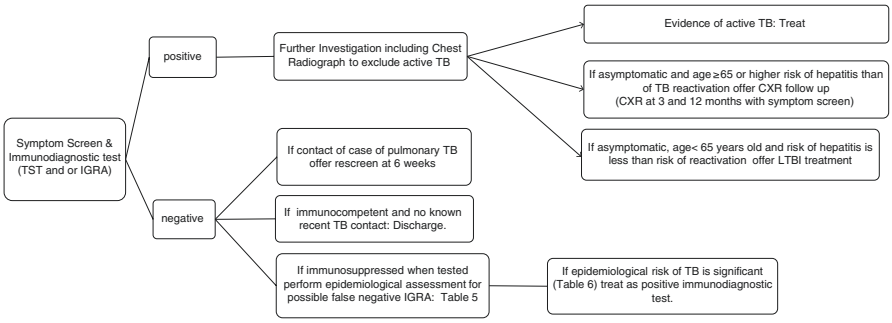

Fig. 1 Suggested algorithm for LTBI assessment and treatment

Table 5 Patients who can regarded as immunosuppressed and at risk of false negative immunological testing for LTBI. Table modified been from Public Health England's guidance regarding suitability for live vaccination [33]

Patients who are receiving or have received in the past **3 months**: • >1 week of high-dose corticosteroids i.e. >40 mg prednisolone per day or 2 mg/kg/day in children <20 kg) • >2 weeks of lower dose corticosteroids i.e. >20 mg prednisolone per day or 1 mg/kg/day in children <20 kg) • Non-biological oral immune modulating drugs e.g. methotrexate >25 mg per week, azathioprine >3.0 mg/kg/day or 6-mercaptopurine >1.5 mg/kg/day
Patients who are receiving, or have received in the past **6 months**: • Immunosuppressive chemotherapy or radiotherapy for malignant disease or non-malignant disorders • Immunosuppressive therapy for a solid organ transplant (with exceptions, depending upon the type of transplant and the immune status of the patient)
Patients who are receiving or have received in the past **12 months**: • Immunosuppressive biological therapy

Table 6 Significant epidemiological risk factors for tuberculosis exposure and LTBI when immunodiagnostic testing may be falsely negative

Prior TB, inadequately treated
Individuals living in close contact with persons with suspected or active TB
Individuals born in high TB incidence countries
Travellers who visit areas with a high prevalence of active TB, frequently and/or for a prolonged time e.g. >3–6 months
Individuals who work in close contact with subjects at increased risk of active TB such as those medically underserved, low-income populations, drug or alcohol abusers, and infants

In the case of rifampicin or isoniazid monoresistant index cases a preventative regimen containing only the drug to which the index strain was susceptible should be used.

Pyrazinamide containing regimens have been used historically (particularly in patients who are co-infected with HIV) but are longer recommended due to drug intolerance and hepatotoxicity. A weekly rifapentine regimen is an addition to the effective options available for latent tuberculosis and may be more acceptable to patients in terms of tablet burden [36]. A systematic review of factors that increase adherence to LTBI treatment noted that shorter regimes are more likely to be completed [37]. A clinical trial of just 1 month of treatment for patients who are co-infected with HIV (Rifapentine 300 mg (>35 mg) 450 mg (35–40 kg) 600 mg (>45 kg) plus isoniazid 300 mg daily for 1 month (HIV positive patients only) demonstrated to achieve completion rates of 97% and non-inferior to 9 months of INH alone [38]. Drug interactions should be considered when selecting an appropriate regimen and the interaction between the rifamycins and corticosteroids as well as hormonal contraceptive treatments and antiretroviral drugs makes isoniazid monotherapy regimens preferable in these groups of patients.

In the case of exposure to multidrug resistant tuberculosis, the WHO recommend 2 years of close follow up. Fluoroquinolone containing regimens have been used in TB contacts, including those where the index case has multidrug resistant disease, and preliminary results suggest they may be effective, with only pyrazinamide containing regimens being less well tolerated, results of further clinical trials are awaited [39]. See chapter "Contact Investigation" for more details on the process of contact tracing.

Adverse Reactions to LTBI Treatment and Hepatotoxicity

A decision regarding whether to treat or observe LTBI requires accurate information regarding the risks and benefits of therapy to be provided to both healthcare professionals and their patients. The commonest side effects from treatment are nausea, itching and vomiting, and these are usually self-limiting. Polyneuropathy during LTBI chemoprophylaxis is usually caused by isoniazid, it occurs due to inactivation of pyridoxine metabolites and inhibition of the enzyme pyridoxine phosphokinase which is a necessary enzyme to convert pyridoxine to its active form of pyridoxal 5′ phosphate. Seizures and psychosis are rare but important side effects associated with isoniazid, because of depletion of gamma-aminobutyric acid (GABA) which is a pyridoxine dependent pathway. Another rare but important side effect is neutropenia secondary to rifampicin.

Hepatotoxicity is a potentially serious side effect associated with isoniazid, rifamycins and pyrazinamide. Up to 10% of patients taking isoniazid may have an asymptomatic rise in liver function enzymes. The incidence of hepatotoxicity varies widely in different studies with rates from 0.1 to 4% for isoniazid with a death rate from hepatitis of 23.2 per 100,000 in the early studies that guided the American

Thoracic Society guidelines on hepatotoxicity [35, 40]. The British Thoracic Society anti-TNFα guidelines reviewed LTBI isoniazid only studies from 1996 to 2002 and calculated a weighted average risk of hepatotoxicity with 6 months of isoniazid of 278 per 100,000 treated patients. Similar methodology calculated a risk of 1766 per 100,000 with the combined 3 month isoniazid and rifampicin regime [41]. This fits with estimates from earlier studies where isoniazid in combination was demonstrated to have a higher incidence of toxicity than isoniazid alone [42].

A recent network analysis has attempted to quantify the risk of hepatotoxicity compared to no treatment in the existing efficacious regimes. Pyrazinamide containing regimes have the highest risk of hepatotoxicity and there was no significant difference in toxicity in single or dual drug regimes, with rates of hepatotoxicity being lower in dual regimes when compared to longer duration (>12 months) isoniazid differing from prior studies that indicated single agent isoniazid was safer [43].

The risk of hepatotoxicity is also dependent on host and treatment factors. There is good evidence that although most hepatotoxicity occurs in the first 16 weeks of TB treatment (for active TB and with isoniazid monotherapy) the duration of treatment affects the risk of hepatotoxicity with higher rates seen in longer regimes [44]. Other well recognised risk factors for hepatotoxicity with LTBI treatment (data mostly taken from isoniazid monotherapy regimes) include alcohol consumption, HIV co-infection, malnutrition, female gender and viral hepatitis infection. Unless preventative treatment is time critical we would advocate treatment and control of viral hepatitis infections prior to starting LTBI treatment. A significant factor relating to the risk of hepatotoxicity is increasing age [44, 45] with the rates in patients over 50 being 2.3 per 1000 treated cases. The UK NICE guidelines recommend LTBI treatment only in those patients under 65 years of age, and only under 35 years of age for new entrant screening where the risk of TB reactivation is likely to be lower because the time since exposure is less certain.

In all patients contemplating LTBI treatment there should be a thorough assessment for risk factors to heighten awareness of hepatotoxicity and education of all patients taking medication will be required, verbal and written information in the patients preferred language [46].

Timing of Starting Immunosuppression and Biologics Treatment

Wherever possible LTBI treatment should begin prior to biologic treatment. In the first reported series of 70 patients receiving infliximab with tuberculosis, 48 of them developed tuberculosis after three or fewer infusions, suggesting that early reactivation is possible [47]. There is insufficient high quality evidence to guide the interval between LTBI treatment and immunosuppression, but expert consensus suggests a

4 week interval between starting LTBI treatment and biologic immunosuppression [48, 49]. A risk: benefit decision will guide whether this interval can be shortened in the case of treatment for severe disease.

Biologic Treatment with Active TB Disease

Biologic treatment should be withdrawn in the case of active disease and guidelines vary regarding when it can be safely restarted, most agreeing that treatment re-start should be defer until TB treatment is successfully completed, with the suggestion that if inflammatory disease is severe and the biologic is low risk they can be restarted after the first 2 months of TB intensive therapy [41, 50].

Adherence and Treatment Support for Patients Taking Latent TB Treatment

The efficacy of treatment LTBI depends on adherence to treatment and all patients should be counselled regarding what to expect when starting treatment, strategies to enhance their adherence and the rationale for treatment [37]. Those patients with risk factors for non-adherence may require enhanced support to complete their LTBI treatment including directly observed treatment [10]. It is useful to explain that the test that confirmed the diagnosis of latent TB infection (the IGRA or TST) will remain positive, particularly in the case of healthcare professionals who may be subject to repeated testing. Asymptomatic patients with LTBI are not unwell or infectious and this should always be explained to patients and their healthcare professionals for clarity.

Successful LTBI assessment and treatment requires collaboration between all relevant heath care professionals. We advocate a patient centred approach that acknowledges a difference in acceptance of risk between individuals.

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Further Reading

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Contact Investigation

Marie O'Donoghue and Hanna Kaur

Introduction

The importance of tuberculosis (TB) as a global health concern is well established. In conjunction with other elements of a successful programme contact investigation (CI) is a central component to achieving TB elimination. If countries are to achieve the WHO target to eliminate TB by 2050 [1] then an increased focus on active case finding is required.

Contact investigation is a systematic approach to identifying and assessing people exposed to a person with infectious TB. It is undertaken to (a) intercept the cycle of transmission through the prompt identification of undiagnosed cases of active TB (b) detect those with latent infection (c) treat those at risk of progressing to active disease and (d) offer BCG vaccination if applicable to the country public health strategy. The process is more commonly undertaken in low incidence high resource settings. Its implementation in low-middle income countries is variable and inconsistent therefore the impact on global TB control is uncertain [2]. The yield of previously undiagnosed active TB at the time of CI varies from 1–2% [3] up to 5% [4, 5] and a further 5% of newly infected contacts will develop active TB within 2 years following exposure [6].

There are several guideline documents from low incidence high resource settings but the increased focus on the contribution of CI to TB control has seen the publication of recommendations by WHO for investigating contacts in low- and

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middle-income countries [7]. There are no EU/EEA CI guidelines however, several EU/EEA Member States have national guidelines [8]. The UK guidelines [9] recommend testing contacts of people with pulmonary and laryngeal TB regardless of smear and culture status. US [10] and Canadian [11] guidelines generally recommend investigation of contacts with microbiological evidence, and WHO [7] recommend investigation of contacts age <5 years and those with HIV infection.

Decision to Initiate Contact Investigation

Assessing the Index Case

The contact investigation process (See Table 1) is triggered by evidence of active disease or the decision to treat a person for active TB. Although the assessment is usually undertaken by a nurse or trained field worker it requires a multidisciplinary approach and information from a variety of sources that were used to make the diagnosis or inform the decision to treat. It should not be delayed pending test results, although subsequent results may impact on the scope of the investigation, whether to proceed with testing, and the timing.

It is necessary to collate information to estimate the degree of infectivity, the infectious period, the proximity of exposure and susceptibility of those exposed. The sources include the referral and clinical notes for the symptom history, and all investigation reports: microbiology, histology and radiology. The information should be collated in chronological order and analysed to form a clear and comprehensive version of events that led to the referral and presentation to healthcare for investigations and diagnosis. If there are conflicting or vague symptom history

Table 1 Contact investigation summary

1. Decision to initiate contact investigation
• Assessing the index case
• Estimate the degree of infectivity
• Estimate the infectious period
• Proximity
• Susceptibility of contacts
• Source case investigation
2. Undertaking a contact investigation interview
• Compile information
• Schedule a CI focused meeting within 1–2 days and at least one more CI focused meeting within 1–2 weeks
• Establish a therapeutic rapport
• Select an interview framework or questionnaire
• Prioritise contacts
3. Make recommendations and arrangements to test contacts
4. Analyse attendance and results
5. Consider whether to expand

records these can be clarified with the index case. Caution and sensitivity are required if a detailed symptom history is later denied by the patient following diagnosis as this may represent an attempt to curtail CI. The timeline can vary from a short and linear pathway to one that is several months duration if there is a delay to diagnosis, and complicated by investigation involving multiple clinical teams in different organisations.

Assessing the risk to others is based on the principles of disease transmission. It is a systematic process that involves a focused CI discussion with the index case and most likely follow up discussions to collate comprehensive information on their location and activities during the infectious period. This might also involve proxy discussions to gather or validate the information regarding the duration and frequency of time spent at each location, identifying all those exposed, assessing the risk of transmission, and if this occurs, the likelihood of others developing disease as a result. This is a complex process based on cooperation from the index case, anyone involved in their care during the infectious period prior to diagnosis, and the contacts.

Estimate the Degree of Infectivity

The degree of infectiousness is the core factor dictating the extent of CI [11]. Index cases with extra pulmonary TB are not infectious but it is important to confirm there is no evidence of concomitant pulmonary disease. Although TB affecting the pleura is not infectious, there are recommendations that pleural disease should be considered infectious because there are reports of up to 50% culture positivity on induced sputum in those with no evidence of pulmonary disease on plain chest radiology [12]. Laryngeal TB is rare, with an incidence of around 1% in patients with pulmonary TB [13] and it is highly infectious due to the extent of concurrent extensive pulmonary disease [14].

Pulmonary TB has varying degrees of infectivity along the spectrum of subclinical to overt disease. The longer the delay to diagnosis and initiation of effective treatment, the more likely the patient will experience manifestations of more extensive disease. Factors associated with transmission are extensive lung involvement, the presence of high levels of tubercle bacilli in sputum and frequency of cough [14, 15]. The number of bacilli in solid nodules range between 10^2 and 10^4 but this increases to 10^7–10^9 in cavitary lesions [16]. High grades of positivity on smear samples is strongly linked to increased levels of transmission and active disease among contacts [17] and cough frequency has been shown to increase transmission among household contacts [18]. These features are usually interdependent and frequently occur in combination thereby compounding the cumulative effect on the degree of infectivity. The detection of tubercle bacilli on smear from respiratory samples i.e. sputum, bronchoalveolar lavage and gastric washings should be considered as evidence of infectiousness with potential to transmit infection to others. Some country guidelines do not recommend testing of contacts of pulmonary cases if there is no microbiological evidence of infectiousness and radiological features do not include cavitation.

Infectious Period

The infectious period start date should be estimated using a combination of sources; symptom history and patient report regarding onset of cough, investigation dates and reports: microbiology, histology and radiology and analysed in conjunction with the multidisciplinary team if required. There are variations in parameters for estimating the infectious period from onset of cough [16] to 3 months before onset of respiratory symptoms [10]. Index cases that smoke or have an underlying respiratory condition might report cough for several years. It is important to establish a clear history regarding changes in cough and radiological features in conjunction with the multidisciplinary team. If patients are asymptomatic or onset of cough is unreliable go back 3 months from date of diagnosis. This is important because patient recall regarding symptoms might be inaccurate due the slow and insidious onset of TB disease or concern regarding the implications of testing contacts. The infectious period end date is when the contact with the index case ceased or when the index case is assessed as no longer infectious.

Proximity

The volume of air, circulation and exchange rate influence how dilute or concentrate the air is with droplet nuclei. Transmission is more likely to occur in confined and poorly ventilated spaces. Assessing the environment in which the exposure occurred is an important element but may be difficult if it is based on a description by the index case. Ideally, staff should visit the locations used by the index case during the infectious period but this is a retrospective proxy observation which will limit the accuracy of any estimates and a visit is not always practical.

Evidence from airline investigations showed that those passengers seated near the index case on a flight for ≥8 h were more likely to have evidence of infection than passengers seated in other rows [19, 20] however whole genome sequencing (WGS) has demonstrated apparent transmission after seemingly short periods. Transmission of TB outdoors is considered unlikely due to the infinite dilution of air [21] however, there is no exposure time or proximity that is without risk.

Susceptibility of Contacts

The risk of transmission is determined in part by features related to the index case but also those exposed as the 'host'. The risk and consequences of developing active disease following exposure guides identification of individuals, their priority for testing and management recommendations. Those at increased risk of developing active TB following exposure include children age <5 years and

immunosuppression due to illness or medication e.g. HIV infection, chemotherapy, steroids, anti TNF. There is high morbidity and mortality associated with active disease in children. Individuals with immunosuppression are less likely to mount an immune response to eliminate or contain even low levels of infection during brief episodes of exposure. Active TB in those with immunosuppression is often serious and complicated to treat due to dissemination of disease, interactions with concomitant medication and may necessitate interruptions to treatment for comorbid illnesses. These individuals should be assessed in the priority category following even brief episodes of exposure.

Source Case Investigation

Source case investigation is the identification and testing of adults in the child's settings to identify the source case following the diagnosis of active disease (any site) in a child if one has not been identified in the household or family. This is based on the presumption that it represents recent infection from an undiagnosed infectious case in the child's surroundings and others may be at risk. Children <10 years are rarely infectious however if a child has features of adult type pulmonary TB such as cough, sputum smear positive or cavitation on chest X-ray [5], this should trigger both source case and CI.

The recommendations vary from source case investigation in pre-school and childcare settings for children <5 years but not schools for older children unless there is evidence that warrants this focus [10, 11] to locating all adults during the previous year of a child <16 years or at minimum the household contacts for children <18 years [22]. Although the yield from source investigation is low [10, 23] this is undertaken in low prevalence high resource settings where the programme is meeting the objectives for effective TB control and is progressing towards TB elimination.

Challenges

The principles of CI are positive public health interventions with the potential to enhance the health of individuals, families and communities affected by TB. However, TB is associated with considerable stigma and myths in many of the most affected communities. In less affected communities or those with knowledge of the disease from a historical perspective, it can prompt fear and exaggerated perception of the risk. This can drive public health inventions such as extensive testing beyond those at risk to allay anxiety; it can reinforce negative messages and make interpretation of the CI results difficult. However, it is possible to mitigate the challenges and optimise the contact investigation process (See Table 2).

Table 2 Recommendations to optimise contact investigation

• Contact investigation and interview technique training for staff
• Advanced communications skills
• Sensitive empathic approach
• Awareness of language e.g. identify 'people at risk' rather than 'contacts they infected'
• Focused CI interview, allow sufficient time and schedule at least one follow up CI focused interview
• Conduct the initial CI interview in the index case's usual place of residence and within 1–2 working days of the diagnosis
• Avoid CI as part of the index case appointment to commence treatment. If the initial interview took place in a hospital setting, at least one follow up interview should be done in the index case's usual place of residence
• Compile all clinical and social risk factor information in advance of the CI interview
• Use a high quality interview questionnaire with a variety of open and focused questions about the patient's activities and people exposed
• Location based contact investigation
• Use of priority categories rather than site based categories
• Provide information about TB, CI, confidentiality, and access to public funded healthcare for all those tested and treated for TB regardless of immigration status
• Information to assess congregate settings e.g. workplace, college should be obtained from a person with authority to assist the assessment and release details of others at risk
• Provide contact cards for the index case to give to contacts if preferred
• Discuss the perceived impact of the CI process with the index case. Loss of employment or accommodation risks should be discussed with the public health department
• Evaluation of contact attendance and test results as they occur
• Contact investigation process to remain a priority for evaluation by the multidisciplinary team in tandem with clinical response throughout the treatment episode

Successful CI requires the cooperation of the index case and those exposed. Reactions driven by stigma and fear can limit cooperation which can manifest in reports of few or no contacts, or low uptake for testing among contacts. While the provision of information might fill a knowledge gap, it is often ineffective to address cultural attitudes and stigma. It is essential that the multidisciplinary team is empathic to the impact of the process on the index case and those exposed and that the CI process remains a priority for evaluation in tandem with clinical response throughout the treatment episode.

It is important to explore with the patient the variety of reactions people have about TB exposure and the reasons. This is not to reinforce stigma or imply blame, it is to support and engage with the patient to manage this proactively. For example, informing colleagues and or a manager about one's diagnosis before an assessment of the risk, the provision of clear information and plan to test those at risk is undertaken is likely to have negative consequences for all involved. Accurate information delivered in a transparent manner with access to a TB nurse or public health person with knowledge to answer questions can help prevent reactions and behaviours driven by stigma and fear. Knowledge does not always change behaviour. When behaviours driven by stigma persist despite knowledge, the person with TB might experience loss of their home or job.

Contacts' consent to provide details for CI or attend for testing might be influenced by multiple factors. This includes immigration status, fear of registration with a government authority if they are undocumented, accessing public funded health care if there is an immigration application in progress, experience of healthcare in their home country, or concern about the implications on their job or ability to get employment if they are tested positive. Contacts that have ostracised the person with TB might be reluctant to attend for testing when they have information about their personal risk factors for remote infection and testing positive does not necessarily mean they acquired the infection from the person recently diagnosed with active TB. Low uptake of TB testing, barriers or concerns can be addressed by follow up telephone call, e-mail and home visits. Routine re-appointment systems should be avoided as this does not address the individual's reason for non-attendance.

Contagion and disease can be associated with guilt, blame and reinforce stigma. The language healthcare professionals use can contribute to this by asking patients to list people they infected rather than people at risk [24]. The person with TB might feel guilty that they have unknowingly put others at risk and having TB infectious to others was their fault. Sometimes contacts decline CI to demonstrate their support for the index case. Giving details for CI and accepting testing can be interpreted as disloyal and acknowledgement they think the person gave them TB.

Healthcare staff often rely on the person with TB to inform their close contacts about their diagnosis and the recommendation for testing. In effect, this requires the index case to disclose their personal health information to other people. All those we share the same air and that are close contacts are not necessarily people we would wish to disclose our private information. We are asking people who are unwell with a significant health issue to disclose their private information and expose themselves to what are often unpleasant reactions at a time when they need support to recover. We can supply leaflets to supplement the information but in reality, we do not know whether the index case informs their contacts about the diagnosis, the recommendation for testing or passes the leaflets. This situation can often manifest in radical changes to symptom history and lifestyle to limit CI from a cough for months to a cough that started recently or after they stopped work and socialising due to other symptoms.

Contact investigation is subject to bias, memory recall, and exposure generally does not occur in fixed or controlled environments. It is not possible to say what is a safe exposure time because many factors will be unknown about the environment, ventilation will change, and most aspects of the assessment are subjective and estimations e.g. estimation of proximity, length of time, ventilation. In the UK there is a recommended target for the number of contacts tested per patient. While this might help motivate staff to have follow up discussions with patients to identify people exposed, the focus on a target figure could miss identification of contacts above the target figure or conversely identify those with less exposure but whom the person is comfortable to declare. It is important to identify all the right contacts.

Patients are often concerned about their confidentiality and this represents a significant challenge and barrier to effective CI. It is important to have a shared understanding of confidentiality in the context of CI and the limitations. For some patients,

their understanding is that no-one will find out they are the person with TB. Healthcare staff are bound by the principles of confidentiality outlined by their professional bodies and employer. Information is disclosed on a need to know basis [25] but this might conflict with the index case's understanding. For example, in order to undertake a workplace assessment and identify those exposed, it will be necessary to disclose the index case details to the individual that can authorise the assessment and release of staff details for testing. This might involve discussion with a senior manager rather than a supervisor. Information should be released only after confirming they have the authority to assist the assessment and release staff data. It should be explained that the name of the individual is confidential and disclosed to them on a need to know basis, and should not be shared with other staff.

It is important to be realistic about the limitations of confidentiality and the likelihood that no-one will know the person with TB. For example, if colleagues, class or house mates know the person has been unwell they may guess the identity of the individual. Staff should never confirm this and maintain a standard response that this is confidential. If a group of individuals or a household is identified for CI, the index case should also be included in the correspondence and appointments so that the person's confidentiality is not breached by being the only person in a defined group not invited for testing. This can result in considerable anxiety for the person with TB and they will almost certainly require additional support to respond to contacts that suspect they are the index case. For some patients, this is too stressful and they prefer to disclose their diagnosis, and some make the decision to leave their employment or accommodation. It is important to support the patient to plan and manage the situation where possible so that they have uninterrupted access to somewhere to stay, income support, medication and clinical appointments.

There are laws to prevent the transmission of disease and protect the public but there is no law that requires an individual to declare their contacts. In some jurisdictions there are legal measures to ensure the assessment and follow up of contacts [10]. Public health interventions to address stigma, access to information and testing is preferable to a legislative response to these issues that manifest in nondisclosure of contacts and low uptake of CI tests.

Testing for an infection and disease in people without symptoms is a challenging concept for some communities and can increase stigma. This is further complicated when we inform contacts that we cannot disclose who they were exposed to; there is no test to diagnose latent infection, the test is an immune based test that does not distinguish between latent and active TB, or recent or remote exposure. If the test is positive and the individual completes a course of medication, it will reduce, not eliminate, the risk of active TB and the test will not revert to negative. People that received the BCG vaccination often assume they are protected and are not aware of its variable efficacy.

The public is increasingly aware of the importance of keeping their personal data safe, and not sharing data belonging to others without permission. This is frequently cited as a reason not to provide details of contacts. Contact investigation and access to testing needs to be made available through self-referral and the use of contact cards from the index case in the same way that sexual health services offer notification and voluntary confidential access to testing.

The timing and location of the assessment, and the approach are fundamental elements of successful CI. The assessment often takes places at the same appointment the index case is informed of their diagnosis. The patient is processing the diagnosis, the implications of a long course of treatment, the potential side effects and adjusting their life to attend follow up appointments. Responding to the patient's immediate concerns about potential transmission to others and arrangements for testing should be addressed as required by the patient. However, this is usually not the ideal time to develop the trust and rapport required to undertake a detailed assessment. Common pitfalls due to time pressure include focusing on obtaining a specified number of contacts and giving the patient a form to complete details of their contacts in lieu of an assessment. Patient led contact identification without an assessment often results in the identification of household but no close non household contacts, those that are aware of the patient's investigations, omitting contacts or the wrong contacts. Consideration should be given to arranging a dedicated time to undertake the assessment and identification of people exposed. If possible, the assessment and testing of household contacts should take place in the home environment. It is at this point that use the of a form to add locations or individuals is useful with at least one follow up contact identification meeting to review the assessment and collate additional locations and contacts. Gathering information in collaboration with the patient is important to understand all the locations and individuals exposed, and for the nurse or field worker to prioritise contacts for testing.

Staff training to undertake assessments is variable. Some programmes have specific TB training materials (CDC) to support competencies to undertake CI while countries like the UK have none and training occurs on the job. Contact investigation practice is guided by a framework if used, or varies considerably according to the skill and experience of individual staff.

Undertaking a Contact Investigation Interview

Compile Information

Compiling all the information required (See Table 3) is a key requirement that will increase the patient's confidence in the process, help develop trust and rapport, and increase the likelihood of a successful contact identification.

Table 3 Information required in preparation for contact investigation assessment

Site(s) of disease
Symptoms including cough
Date of symptom and cough onset
Microscopy investigation dates and results
Chest radiographic dates and results
Other imaging dates and results
Comorbidities
Social risk factors
Estimate infectious period (start and end dates)

Schedule a Contact Investigation Focused Meeting

Schedule a specific CI focused face to face meeting and allow sufficient time. This should take place within the timeframe directed in local public health guidelines but preferably no longer than five working days from the diagnosis. CDC [10] recommend a minimum of two CI meetings, the second 1–2 weeks later when the patient has had time to further adjust to the diagnosis and think about additional locations and contacts.

Establishing a Rapport

The complexity of successful CI cannot be under estimated. It requires considerable TB knowledge, training to develop skillful interviewing techniques and experience.

Ideally this should take place in the home environment taking account of outreach health and safety protocols. Staff should be trained and understand their role as a visitor in the patient's home and demonstrating respect for social and cultural etiquette. Be aware the patient has the same rights to privacy and confidentiality in their home especially if there are others present or asking questions. Contact investigation in the home environment can enhance our understanding of the patient's psychosocial needs and support the development of a caring relationship built on trust with the patient and family. Reducing the patient's vulnerability and balancing the power in the relationship can increase collaboration and this is fundamental to a successful CI and supporting treatment adherence.

Framework for Identifying Contacts

In addition to the information provided by the patient, staff should be cognisant of the opportunity to identify other contacts in the home and observe for evidence of contacts not already declared e.g. shoes and coats belonging to other people, toys etc.

There are different approaches to collating contacts. Traditionally, close household contacts were prioritised for CI but this is no longer applicable to how many communities live and has similar limitations to the name-based approach.

The 'stone in the pond' or 'concentric circle' approach is a systematic method to organise and prioritise contacts according the intensity of exposure and the risk of acquiring infection [11, 16]. Those in the household or with contact equivalent to a household contact are tested as high priority. Testing is extended in a stepwise manner if there is evidence of transmission until the infection rate detected reaches the background rate for the community [11]. Although the theory of this approach is that first circle should include those with close prolonged exposure regardless of whether this is in a household, work or social venue, in practice those prioritised are

usually confined to the household. This might be due to the varying interpretations of close and casual contact and a generalisation that the household exposure equates with close contact and co-workers are usually casual contacts [9] or that screening close non household contacts is required only if there are certain features indicating higher levels of infectiousness [16]. The approach can preclude the identification of non-household contacts that might have more intense exposure or people with less intense exposure but that are at increased risk of disease if infected. Also, many people have more intense prolonged exposure with co-workers than their household, and conversely those that live in multi-occupancy households might share a kitchen but not at the same time. It also yields few or no contacts for those that live alone or in small households and this provides an insufficient number of results to assess the need to expand to the next circle. The assessment lacks information on contacts in the second and third circles and should the results from the tests of those in the first circle make it necessary to expand CI, it can be difficult to obtain this information later. This might be due to lack of engagement from the patient or inaccurate recall of activities due to the length of time that passed while the first circle were tested. This approach is no longer recommended.

The name-based approach, asking the patient to provide names of people they had close prolonged contact, has similar limitations to those above due to the loosely structured approach. It is also subject to bias and more likely to include only those contacts the patient is comfortable to disclose their diagnosis. It provides no information regarding locations at risk if the patient is unwilling or does not have the details to name contacts. More importantly, it will not identify high priority contacts with less frequent contact but at high risk of progression to disease if infected.

The location-based approach may be more useful and all patients should be asked about locations where they spend time [11]. This can improve recall and prompt identification of contacts at risk but without close family or social relationships.

The aim of the assessment is to identify individuals with all levels of intensity and frequency of exposure, and those at high risk of progression to active disease if infected. Services should develop a high quality interview questionnaire with a variety of open and focused questions about the patient's activities and people exposed. A comprehensive CI questionnaire should include a typical Monday to Sunday diary of activities and locations before and after onset of symptoms. This should be supplemented with prompts such as those listed below (See Table 4). This will allow staff to make recommendations for testing high and medium priority contacts, or low priority contacts at a later date if there is evidence of transmission.

Prioritising Contacts

Each contact should be prioritised (See Table 5) as high, medium or low priority at each site [26] e.g. household, workplace, restaurant, college. It is preferable to use priority categories and not the site as this will help avoid delays testing high priority

Table 4 Prompts to supplement a contact investigation diary

Can you tell me more about: • Who lives here? Who visits? • Who do you see every day, weekly, monthly? • Who did you see in the last week and for how long? • Who takes the children to school and after school activities? • How do you get around/commute?
Depending on the information, it might prompt further discussion about a particular activity e.g. attendance at college, coffee shop
Prompts related to current diagnosis, comorbidities and social risk factors e.g. hospital and GP visits, who do you drink alcohol with?
Do you travel to other towns in the UK or abroad?
Do you have visitors from other towns or abroad?
Have you attended any events, celebrations, family or community gatherings?
Do you know anyone having treatment for a serious illness such as cancer? Can you tell me about when you last spent time with them?
Do you know any children under 5 years? Can you tell me about when you last spent time with them?
Do you know anyone that is experiencing symptoms that could be related to TB?

Table 5 Framework for prioritising contacts

Priority	Examples	Contacts
High	Contacts with suspected TB symptoms Contacts at high risk of progression with any exposure during the infectious period Single household sharing breathing space >8 h cumulative exposure during the infectious period Congregate setting contact with >8 h cumulative talking distance exposure Cumulative exposure sharing breathing space in a confined space >8 h e.g. at work, visiting the household Talking distance exposure and shared air <8 h in an environment with poor ventilation e.g. car, room Exposure to a particularly high concentration of bacilli during aerosol producing procedures e.g. sputum induction, bronchoscopy, dental examination, resuscitation	Name …….. Contact details …….. Name …….. Contact details …….. Name …….. Contact details …….. Name …….. Contact details …….. Name …….. Contact details ……..
Medium	Multi occupancy household living in own room with shared use of facilities at the same time or within 2 h Non household contact with >8 h cumulative talking distance exposure	Name …….. Contact details …….. Name …….. Contact details ……..
Low	Share multi occupancy household living in own room shared use of kitchen facilities at different times and <8 h cumulative talking distance exposure Non household contact with <8 h cumulative talking distance exposure Colleagues with contact >8 h cumulative talking distance exposure non confined spaces	Name …….. Contact details …….. Name …….. Contact details …….. Name …….. Contact details ……..
Low	Sporadic contact in the same college, sports club, workplace	Name …….. Contact details …….. Name …….. Contact details ……..

contacts. Lack of evidence of transmission in one location e.g. household, should not prevent or delay testing high priority contacts at another location e.g. workplace [26]. Contacts are prioritised according to the risk of acquiring infection and if infected, the likelihood of developing of disease.

Recommendations and Arrangements to Test Contacts

Recommendations and arrangements to test contacts should be made according to public health protocols. It is important to test those exposed and at risk of progression as well as sufficient numbers to assess evidence for transmission. In the US the average number of close contacts is six per case [3, 27].

All contacts should have a symptom and medical history assessment. There are a variety of testing protocols that include single or combination of immune based tests (Tuberculin Mantoux skin test and Interferon Gamma Release Assay) and chest radiograph.

Some countries recommend testing for close contacts of pulmonary and laryngeal TB regardless of smear or culture status [9]. Others recommend initial testing for high and medium priority contacts of smear positive cases and single testing 8 weeks after exposure for most non household contacts [11]. CDC does not prioritise testing contacts of smear negative cases [10] however the proportion share of transmission attributable to smear-negative cases is estimated to be between 17% and 41% [28, 29].

High priority contacts should be recommended testing as soon as possible. Contacts with symptoms should have an urgent medical assessment to assess for active disease regardless of their priority. If this is ruled out, they should complete the recommended testing for latent infection. Contacts at high risk for progression to active disease if infected should be considered for medical assessment particularly if they have comorbidities that are known to reduce the sensitivity of immune based tests. If immune testing occurs less than 6–8 weeks post exposure and the results are negative, the immune test should be repeated to assess for conversion.

In situations where the recommendations and arrangements to test contacts increases the index case or contact's social risk factors for developing TB and loss to follow up e.g. resulting in loss of employment or accommodation, this should be discussed with the public health department to analyse the individual and public health risks.

Analyse Attendance and Results

Attendance and test results for contacts should be reported to the case manager and interpreted as they are completed. This allows timely review of uptake of TB testing and expansion of CI if there is evidence of transmission in the high and medium priority contacts.

Complete follow up telephone calls, e-mail and home visits to contacts that did not attend. Multidisciplinary review and special efforts should be made for contacts at high risk of progression to active disease. Routine re-appointment systems should be avoided as this does not address the individual's reason for non-attendance.

Consider Whether to Expand

Contact investigation should be expanded if there is evidence of transmission:

- active disease in a contact
- TST or IGRA conversion
- latent infection rates above the background rate in the community
- clusters of cases with identical whole genome sequencing

Special Circumstances

TB nurses are often faced with special circumstances, where CI requires a multi-agency approach and expertise. This is due to complexity of the disease, where the index case may be diagnosed with drug resistant TB, or the case is involved in an institution, and the CI requires broader public health intervention.

Multidrug Resistant-TB (MDR-TB) and Extensive Drug Resistant-TB (XDR-TB)

Contact investigation for MDR or XDR-TB cases is undertaken with similar measures irrespective of the mycobacterium strain or resistance pattern. This is assuming that MDR-TB and XDR-TB strains are equally infectious or transmissible as drug-susceptible strains. Therefore, routine CI procedures can be used [30]. However, MDR-TB and XDR-TB are serious forms of TB, with considerable implications for the index case and contacts. They require a lengthy treatment period in addition to costly drugs with severe side-effects [31, 32]. Some persons are more vulnerable, such as immunocompromised persons and children under the age of 5 years are more susceptible to infection and have an increased risk of disease progression, therefore extra efforts should be made to test these groups if they are identified as contacts [16].

Contacts suspected of having active disease, symptomatic individuals or those who have had conversion results of TST or IGRA should be referred to a physician with experience in managing MDR and XDR-TB. Contacts identified with latent TB should also be referred to a physician with experience in managing these

conditions. Children in contact with cases of MDR or XDR-TB, who are either symptomatic and who have been identified with latent TB should be clinically managed by a paediatrician with experience managing TB.

A full clinical assessment is crucial for contacts of MDR TB or XDR TB cases. This should include:

- Full medical history including medication
- TB history: if previously tested for TB, previous latent or active TB, previous treatment history and adherence
- Risk factors for development of TB disease e.g. children and immunocompromised persons
- If indicated, based on local protocol testing should be performed (this may include Tuberculin Skin Test, Interferon Gamma Release, chest radiograph [30].

Contacts that are asymptomatic, not immunocompromised and have negative test results including repeat tests that do not show evidence of conversion, do not usually require further routine evaluation. However, they should receive information about the signs and symptoms of TB, and how to seek urgent medical advice if they occur.

There are two options for management of those identified with latent TB; treatment to decrease the possibility of progression to active TB [33] or observation to promptly identify progression to active disease. There is limited efficacy data for latent treatment for contacts of MDR-TB. Therefore, it is recommended that patients on therapy should be clinically reviewed every 3–6 months for a minimum of 2 years after the TB infection, including those who have completed preventative therapy. Immunocompromised persons should be reviewed every 3 months, as they have a greater risk of developing active TB [34].

The observation option requires clinical evaluation for a minimum of 2 years. It is also important to educate contacts who are infected about the signs and symptoms of TB, and that they must seek urgent medical advice if they occur. Clinical reviews should include symptom check, chest radiology and sputum sample examination where indicated [34].

Air Travel

Patients who have infectious TB, and plan to travel by air during the infectious period, should be advised against the plan unless a clinical assessment confirms that there has been an improvement in their condition and they have had adequate treatment of 2 weeks or more and that there is evidence of treatment adherence [31].

If a TB case travelled by air during the infectious period, a CI risk assessment is required. The approach is similar to routine CI and includes gathering information about the index case to estimate infectiousness and if possible, an assessment of the susceptibility of the exposed passengers. All such incidents must be reported to the public health authority.

The risk assessment should include:

- Confirmation that the index case had infectious pulmonary or laryngeal TB during air travel; or clinical information if the person travelled in the 3 months prior to starting treatment or being diagnosed
- Evidence of transmission (to assess infectiousness), this includes information of results for contacts already tested (high and medium priority)
- Whether the air travel took place during the period when the index case was infectious
- Duration of flights 8 h or more
- Seating arrangements on board the flight

During a flight, air supply to the aircraft cabin is drawn from the engines and conditioned before it enters the passengers' cabin. It is filtered and dispersed evenly throughout the cabin through channels and overhead outlets. Airflows in a circular pattern and airflow in forwards and backwards directions is minimal. Most aircraft recirculate the cabin air [35]. If CI is required, the initial step is to screen passengers who were seated in the same row as the patient, two rows ahead and two rows back [35]. Extra efforts should be made to screen groups at increased risk of progression if they are identified in the group of contacts [35]. Cabin crew have minimum exposure, but they should still be assessed based on a risk assessment by the airline protocol, which should include susceptibility and risk factors [31].

If the index case is diagnosed with MDR or XDR-TB, then the same principles should be followed. There is no evidence that patients who have drug resistance TB are more infectious than patients with drug sensitive TB [31].

These criteria apply to long distance flights, where large jets are used. Index cases that have travelled on smaller aircraft for shorter durations should also be reported and risk assessed on a case by case basis [36].

Contact Investigation Following Contact with Bovine TB and Animals/Pets Infected with TB

Mycobacterium bovis causes TB in cattle, but can also be found in pets. Humans can be infected by the organism, although the risk is very low, especially in countries where TB control programmes exist and where it is routine or mandatory to pasteurise cow's milk. Transmission usually occurs through inhalation of the bacteria, through consumption of unpasteurised milk or by direct contact with mucous membranes and skin abrasions [37].

The principles of CI and symptoms are similar to those of *Mycobacterium tuberculosis* as is the treatment for most cases of bovine TB. This includes if the contact has been with a domestic pet. Based on local systems the local public authorities should be informed in case any further action is required to be undertaken.

As in any CI, detailed information should be taken during assessment. This to include:

- type of contact with the infected animal (domestic, work, visit)
- proximity of contact
- duration of contact
- whether contact was outdoors or in enclosed environment

Contacts who are either symptomatic, or at increased risk of progression to active disease or have latent TB should be referred to a TB physician for further assessment.

Congregate Settings

Congregate settings can be referred to educational, sports clubs, prisons, workplaces etc. Whether an index case belongs to a congregate setting should be identified at the earliest possible opportunity. Although this is often known, especially if the index case is a child and attends educational establishment or the index case is currently held in a correctional facility. It is often the TB physician or nurse who identifies this information and further information is gathered through follow up interviews directly with the index case or by proxy. Contact investigation takes place in a congregate setting following a decision from a risk assessment, in partnership with the local public health authority [16].

Homelessness

Homelessness is an important risk factor for TB [33]. Homeless persons are identified as contacts from congregate settings. The information is dependent on the index case divulging potential contacts [16]. This also makes identifying and follow-up for evaluation of contacts challenging [38].

Other challenges for CI in homeless persons include:

- The index case is part of extended and complex social networks.
- The identified contacts are difficult to locate and motivate to attend for screening [16].

An alternative approach is active case finding on possible sites or locations where there could have been exposure, such as homeless hostels and shelters [16]. In the UK screening homeless people for active pulmonary TB using digital chest radiography is recommended [9], however this will not detect latent TB infection. It is also important to provide symptom and service access information to those working with the homeless should there be concerns of someone having symptoms [16].

Social Network Analysis and Whole Genome Sequencing

Index cases who do not disclose their contacts or are reluctant to provide information can be a difficult and challenging task for TB nurses [39]. Social networking interviews or questionnaires can aid information gathering, by identifying links or an unidentified setting. It is important that the person interviewing the patient is experienced in interviewing and skilled to use various interviewing methods.

Where it is suspected that new contacts or an unknown setting will be identified, the index case is required to log their activities [16]. A questionnaire may include a log of daily activities or social network groups with free space for detailed information on locality and timing. The index case completes this as a diary e.g. their daily plan in the morning, afternoon, evening and so on. Support from a TB nurse or someone who has a good rapport with the patient may be required or it can be completed through an interview. Interviews are best held in the patient's chosen environment and face-to-face. Some questions require prompts for more detailed information. For example, if it is logged that the patient attends a drug rehabilitation centre daily, then details of time frame will be required e.g.

- time spent at the centre
- location of the setting
- how long has the patient been attending (important for onset of symptoms)
- any other centre attended or other congregated areas

In practice it can be difficult to encourage patients to provide details, from the time of onset of symptoms, or entering this in to a diary, especially when they are already reluctant and there is the issue of recalling information. Therefore, where this is the case, then asking them to log daily from starting treatment can help with obtaining information by prompts e.g. if they have stated they attended a public house, the prompts could be *how long have you been attending the public house? How often do you attend?*

Whole genome sequencing is an additional tool which can be used in combination with the questionnaires. WGS provides data that supports targeted CI investigation and wider public health investigation e.g. where there is strong evidence of TB transmission. Thereby TB services can employ efforts where there is a previously unknown link identified rather than using resources in needless investigations [39] (See Whole Genome Sequencing chapter "Whole Genome Sequencing: Applications and Cluster Investigations"). For example where two cases have been linked through WGS, and no initial connection was made, by re-interviewing the patients may provide an association with the unidentified setting and confirm the time scales of transmission as identified through WGS. This can lead to a targeted screening programme.

Conclusion

Contact investigation is a key component of successful TB control programmes that requires considerable skill and sensitivity. It is a complex and challenging process for the index case, contacts and staff. The complexity is increased in special circumstances. The process is constrained by stigma and can also drive behaviours that further increase stigma. There is no exposure without risk but pragmatically the process is focused to identify those most likely to have acquired the infection and those at most risk of developing disease if they have latent TB. Recommendations are based on estimates derived from a systematic approach to the assessments, intervention and analysis of outcome data. The process should be evaluated in tandem with the clinical response until completion of treatment. Social network analysis and whole genome sequencing data can enhance assessment data and improve the efficacy of contact investigation.

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Approaches to New Entrant Screening and Occupational Health Screening

Dominik Zenner

Background

Globally, and despite a modest (2%) decline, Tuberculosis (TB) remains a major public health problem and the world's deadliest infectious disease. In 2017, an estimated 10 million people fell ill with TB causing an estimated 1.6 million deaths, of which 1.3 million were among HIV-negative individuals [1]. Much more effort is needed to make progress to achieve the ambitious World Health Organization (WHO) End TB Strategy targets [2].

At the beginning of the twentieth century, mass, often radiographic screening for Tuberculosis (TB), had been commonplace [3]. However, many countries experienced rapidly decreasing incidence, whilst in other countries with ongoing high incidence but with poorer TB control mechanisms, there was uncertainty about the ethics and cost-effectiveness of promoting such screening, if more basic TB control mechanisms and treatment support could not be guaranteed. These considerations rendered a mass-screening approach obsolete by the latter part of the century, prompting the World Health Organization (WHO) to advise against "indiscriminate" screening by 1973 [4]. Efforts were focussed on ensuring early detection and adequate treatment of cases such as through the WHO Directly Observed Treatment (DOT) Strategy, however this was supported by targeted screening in groups at particular risk, either because of underlying co-morbidities (such as HIV) or because they are at high risk of infection (such as close contacts) [5]. There are only few notable exceptions during this period, such as large population based efforts to screen and treat latent TB infection (LTBI) amongst native Alaskans [6, 7].

However, this has changed with the advent of the WHO End-TB strategy, which aims for a reduction of TB deaths by 95%, a reduction of TB incidence by 90% and

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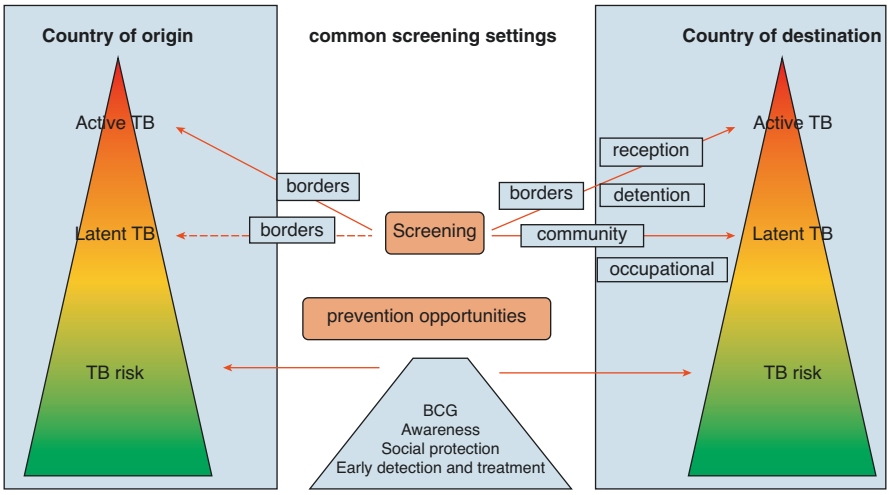

Fig. 1 Overview of setting and types of TB prevention opportunities, including screening for active and latent TB. Adapted from Pareek M, Greenaway C, Noori T, Munoz J, Zenner D. The impact of migration on tuberculosis epidemiology and control in high-income countries: a review. BMC Medicine. 2016;14:48

the absence of catastrophic costs by 2035 [2], and with the Sustainable Development Goals (SDGs) aiming to "end the epidemic of …TB" by 2030 (SDG 3.3). Whilst an acceleration of TB drug and vaccine development may be urgently needed, modelling demonstrates that more is needed [8] and these ambitious goals have sparked a renewed interest in TB screening, particularly LTBI screening as means to achieve these.

This chapter is written from a low incidence country perspective and will present a review of different approaches to screening, their evidence of effectiveness and cost-effectiveness, covering both active and latent TB (Fig. 1), focussed on their use in two discreet settings—screening of newly arrived migrants from high incidence areas and the use of screening in an occupational health context.

Latent TB Screening

What Is LTBI?

TB has a fairly complex natural history determined through a wide range of immunological reactions between *Mycobacterium tuberculosis* and the human host, which ultimately allow the pathogen to be controlled by the host immune system in a majority of cases of infection, albeit the pathogen frequently remains alive [9]. Latent TB infection (LTBI) is such a state, where a fully controlled small-area infection with live bacteria persists, often for long periods of time. The person will

remain entirely asymptomatic, unless there are changes in this immunological balance between host and pathogen, in which case infection can become disseminated, leading to (active) TB disease.

Whilst there is increasing evidence and agreement on the general mechanism of LTBI and reactivation, it is likely that not in all cases, Mycobacteria will remain alive and viable, and there is no clarity to the exact extent to which LTBI reactivation can explain new cases [10]. All current tests for LTBI are indirect (based on in vivo or in vitro immune diagnostics) and there are no tests for direct pathogen detection in LTBI to date. This means that positive results could be influenced by cross-reactivity (environmental mycobacteria or BCG), or the result of previous, now cleared TB infection or disease. For further details also see chapter "Bacillus Calmette–Guérin (BCG) Vaccine".

Nevertheless, it is estimated that globally about one quarter of the population have LTBI, creating a reservoir from which new cases can potentially arise [11] and therefore hampering efforts to achieving the goals of the WHO End TB strategy or SDGs [2, 12]. The role of tackling LTBI to achieve these goals has therefore been well acknowledged [13]. In low incidence countries such as within the EU/ EEA, a majority of TB cases arise among persons born abroad [14], and it is likely that most of these cases arise as a result of reactivation. Re-infection within low incidence countries plays only a minor role.

Notwithstanding the importance of tackling LTBI, particularly in the context of TB elimination in low incidence countries, and the consensus that such screening should be offered on a voluntary basis, there is ongoing debate about how to best test for it, how to manage it, how to select the most appropriate population for identification and management and how to support individuals through the pathway of testing and treatment. Ultimately the approach in LTBI testing and treatment of migrants comes down to choices within these parameters, balancing effectiveness, cost effectiveness, acceptability and practicality. These choices, which include the test, the population, the LTBI management and the programmatic support are discussed in turn below.

Choice of the LTBI Test

All three currently commercially available LTBI tests are based on the detection of cellular immune response to *Mycobacterium tuberculosis*, therefore indirect. The Tuberculin Skin Test (TST) is the only in vivo test—based on intradermal injection of a small amount (0.1 ml) of purified protein derivative (PPD), usually on the volar side of the patient's forearm. PPD is a culture filtrate of around 200 tubercle bacilli antigens, and causes a delayed hypersensitivity reaction, which is measured as skin induration about 48–72 h after injection. Side effects are rare and mostly local [15] and TST preparations tend to be inexpensive. The test has been validated extensively in high and low incidence settings, has a high sensitivity and a good concordance with interferon gamma release assays (IGRAs). However, it is based on a

relatively unspecific hypersensitivity reaction, and cross-reactions with environmental mycobacteria and BCG vaccination have been well described and are key reasons for the relatively low specificity [16]. Expected hypersensitivity reactions in populations with lesser environmental mycobacteria or lower BCG vaccination rates tend to be reduced [17], a phenomenon acknowledged in several guidelines, which recommend different thresholds for reading depending on the type of population [15] or BCG vaccination status [18]. Hypersensitivity reactions also vary with the concentrate of PPD. Whilst a standardised 5 tuberculin units (TU) preparation is the most common, 2TU and 10TU preparations are also available influencing the size of induration on reading [19]. In addition, the test is heavily operator-dependent, including its application, which requires a strictly intradermal injection of the correct volume in the correct fashion (creating a small wheal through upward pointing of the needle bevel), as well as correct measurement of the induration later. Minimising undesirable variability therefore requires specialised operator skills, which together with the need for a second (reading) visit are important practical considerations informing the choice of approach in LTBI testing. Finally, another factor which adds complexity to the interpretation of TST is the booster effect. This occurs, when in serial testing a person who initially tested negative becomes positive without any apparent exposure or new infection [20]. This effect is thought to be caused by waning of the TST immune reaction, e.g. through remote infection or immunosuppression, which is 'boosted' through repeated TST [21]. Guidance exists on how to tackle this [15], but test interpretation and treatment decision are more complex.

Two systems of in vitro LTBI tests are currently commercially available. Both are whole blood tests, based on the detection of antigen-specific memory T cell release of gamma interferons ("Interferon Gamma Release Assays", IGRAs). These antigens (Early-secreted antigenic target 6, ESAT-6 and culture-filtrate protein 10, CFP-10) are coded in the mycobacterial region of difference 1 (RD1) and fairly specific for M. tuberculosis, thus increasing the specificity of these tests compared with TST [22]. The two tests primarily differ in the mechanics of their reading: QuantiFERON (QFT) is based on the quantitative measurement of the Interferon Gamma concentration through an enzyme-linked immunosorbent assay (ELISA), whereas T-SPOT.TB is based on the count of activated T cells through an Elispot test. Newer developments have improved the practicalities and the specificity of both tests further, for example by adding additional antigens or reducing the number of required blood tubes. The main advantages of IGRAs compared with TST are the test properties and the practicalities including decreased operator and patient dependency, obviating the need for specialised training and second (reading) consultation, making them attractive for programmatic testing, particularly in larger and less accessible populations. The main concerns with IGRAs have centred around the relatively high price compared with TST with the latter sometimes preferred based on cost-effectiveness considerations [23]. At the time of writing, costs for both IGRAs differed significantly even in the same countries, depending on

local arrangements, and having a systematic approach on the latter may have contractual advantages [24]. See chapter "TB Treatment and Complications" for further details.

TST and IGRA can be used either alone or in combination. Broadly speaking there are two different scenarios, where sequential testing would be of interest. In the first scenario, a positive test with lower specificity (e.g. TST) is followed up by a test of higher specificity (e.g. IGRAs), and LTBI treatment would be reserved for those who test positive on the follow up test. Since the sensitivity of all tests is comparable, the key advantage of such an approach is in cost-saving. This has to be balanced against the risk of loss to follow up and may not be ideal for migrant screening. The second scenario arises, when there are concerns around sensitivity which can be mitigated by using sequential or concurrent testing and any positive test is regarded as indication for preventive treatment. Such situations may typically occur, when test confidence is lower, for example with immunosuppressed patients and such testing appears to be the recommended action for this specific group of patients [25].

The test properties of LTBI tests, unlike other clinical tests, cannot be directly compared a gold standard. Most commonly, test properties have been successfully assessed using active TB as a surrogate marker, but the complex natural history and immunology of TB limits the ability to directly translate this into test properties for reactivation (the outcome of interest) from this. Notwithstanding that, many of the direct comparisons between test properties used this approach [22]. Another approach is to measure the ratio of odds ratios (ROR), which is based on comparing LTBI positivity along an exposure gradient across different groups, considering correlations between factors such as place of birth, ethnicity and country prevalence and test positivity. This has been done in smaller studies, which do not provide conclusive evidence for either TST or IGRAs [26–28].

Until recently, most studies on reactivation were small-scale [29, 30], making firm conclusions and meta-analysis difficult, although pooled incidence rate ratios appear to favour IGRAs, albeit not significantly [31]. However, a very large cohort study has recently reported TB re-activation rates and analysed test properties for T-Spot.TB, QuantiFERON Gold in-Tube and TST with three different reading cut-offs (5 mm, 10 mm and 15 mm) based on a sample of almost 10,000 patients [32]. It found that whilst the negative predictive value was similar across all three tests, a positive T-Spot.TB was the most predictive for reactivation, and that both IGRAs and BCG-adjusted TST-15 were all significantly better predictors than TST-10 or TST-5.

Both tests are generally regarded as valid approaches in the context of new-entrant screening, and at the time of writing key guidance documents contend that there is insufficient evidence to prefer any of the tests above the other [25, 33]. Current guidance recommends to adapt context-specific approaches. Therefore, acknowledging practicalities and acceptability, a single IGRA could be recommended for programmatic screening of larger groups of migrants [25].

Choice of LTBI Management

Classically, LTBI treatment required a course of 6–9 months of isoniazid (INH) [34], however a number of recent systematic reviews have established that other regimens are at least equivalent, potentially less toxic, shorter and reduce the number of daily pills [35–37]. This new evidence has particularly emphasised the role of rifamycins. Globally recognised and recommended regimens include a 3 months regimen of isoniazid with rifampicin, a 4 months regimen of rifampicin monotherapy, in addition to a 6 months isoniazid regimen [25, 33]. A new 3 months regimen of a once-weekly isoniazid rifapentine combination looks hopeful to address adherence issues [25, 36]. Whilst a number of different side effects have been noted, the primary concern is around hepatotoxicity, which appears lower with rifamycin based regimens. See chapter "TB Treatment and Complications" for further details.

Choice of Eligible Population

All current tests are imperfect to predict re-activation; therefore the choice of eligible population is key to any successful programme. Rational choices require careful consideration of a number of different trade-offs. Approaches can either emphasise the individual benefits, therefore limiting LTBI testing to individuals at very high risk or emphasise a broader, population-based approach. The benefits for each individual will decrease proportional to broadening the approach, but to make an impact at population level, moderate risk groups may need to be included in screening efforts [38].

Common parameters utilised to determine an eligible population, include force of infection, the length of time since infection, the immune status of the host, and other factors, such as age. Unfortunately, many of these are not measurable, or information is often not available. It is therefore common to use proxies. For migrants the force of infection is considered as TB incidence in the country of origin, the time since infection as the time since entry to a low incidence country, and the immune status as consideration of co-morbidities, such as HIV. Getting these parameters right—i.e. the pre-test probability, would allow restricting the population very efficiently. Historically, highly effective preventative treatment programmes had been carried out by adhering to similar principles, even before LTBI testing was available [7].

LTBI prevalence is thought to broadly correspond to active TB incidence and prevalence globally [39] and it is common to restrict eligibility for LTBI screening to high incidence countries, although there is no consensus about these thresholds and insufficient evidence to establish one [40]. Current examples of TB incidence thresholds include 30/100,000 (Canada), 40/100,000 or 200/100,000 depending on migrant typology (Norway), 50/100,000 (Netherlands), 100/100,000 (Sweden) or

150/100,000 (England) [41]. Determining this incidence threshold therefore is a health system choice, which tries to balance detecting the highest proportion of individuals with LTBI (thus preventing the majority of cases), whilst maximising cost-effectiveness. England based her decision for the LTBI screening threshold of 150 per 100,000 on the observation that at this threshold, 92% of LTBI cases could be treated an incremental cost effectiveness ratio (ICER) or just over £20,000 per prevented case [42]. Ultimately this will come down to a choice of the size of population at moderate to high risk, with implications on the public purse on the one hand and population impact in TB incidence reduction on the other.

It is also common to restrict eligibility to recent migrants. LTBI re-activation rates are thought to vary with time since infection, however this is usually not measurable unless there is a clearly documented transmission. However, studies demonstrate that cases notifications in a given cohort also vary with time since entry to a low incidence country with a peak around 2–3 years post entry [43], and this variable is therefore commonly used as proxy. Based on these observations, defining new entrants as those who arrived within the last 5 years appears reasonable [44], although the long tail in the distribution suggests that trade-offs exist, similar to TB incidence thresholds.

Co-morbidities can increase the susceptibility of TB, or the risk of re-activation because of immunosuppression. LTBI testing and treatment has been recommended for a number of groups, particularly those with underlying lung disease or those with immunosuppression. Recommendations are usually patient-based, often independent of whether the person is native to the country and in the domain of the attending physician. Recommendations for patients with defined co-morbidities, such as those with severe immunosuppression (including through medications), pre-existing silicosis or those living with HIV have been issued internationally [25, 33], and nationally [45]. Although other co-morbidities, such as diabetes or smoking can be associated with a higher risk of TB [46], evidence has not been found sufficient to include them into guidelines [25, 33].

Age is an important consideration for an LTBI programme and programmes have been limited to young adults, as cases in this group usually represent the highest disease burden. Although age-stratified TB rates and therefore the overall TB burden is lower in children, severe disease and adverse outcomes can be more common, particularly in very young age groups [47], making children are a particularly important target group for contact tracing exercises. Children therefore are often included in programmatic screening, although this requires a range of pragmatic considerations, including the most appropriate test and pathway [23]. Older age groups are often not included in programmatic screening, as evidence suggest that isoniazid—related hepatoxicity increases with age [48], although this seems a more gradual increase rather than a binary cut-off. As treatment regimens change and the ability to manage side effect increases, new guidelines have suggested to initiate LTBI treatment up to the age of 65 years [23], although good population data on safety are still scarce and programmes are often limited to younger groups (e.g. up to 35 years [44]).

New evidence regarding preventative treatment in the context of MDR-TB contacts is emerging, but evidence on effectiveness and particularly toxicity is still scarce. Current WHO guidance recommends that potential preventative therapy should be tailored the individual patient (including weighing the risks and benefits and drug sensitivity profile of the index patient) and carefully monitored [33]. Such individualised regimens are neither practical nor advised for population-based screening programmes.

It is important to consider all such choices carefully, and a number of online tools have been developed to aide decision making in this context [49, 50].

Programmatic Issues and Pathway Support

In addition to uptake of LTBI testing, the initiation and completion of LTBI treatment are necessary to prevent future TB disease. The LTBI care cascade has been well described, and in the absence of programmatic support, patient drop-outs can quickly add up, so that only a minority of eligible patients benefit from TB prevention [51]. It is worth noting that non-completion of pathway is widely variable within studies, and depends on the context as well as on the target population [52]. Patients with co-morbidities tend to have higher screening [53], and LTBI initiation and completion rates [52], perhaps because they are already embedded in the healthcare system. There is some evidence that LTBI treatment initiation is improved when using IGRA compared to TST, albeit in the healthcare worker context [54]. Initiation and completion can be worse in persons with social risk factors, such as alcohol or substance abuse or homeless persons, although high heterogeneity between studies makes it difficult to come to firm conclusions [52, 55]. Treatment uptake can also be provider dependent [53]. Shorter (for example rifamycin-based) treatment regimens are associated with better completion rates [52, 55].

It is therefore well recognised that programmatic and pathway support is essential to a successful LTBI programme, as ultimately the effectiveness, cost-effectiveness and impact will also depend on the proportion of persons who successfully complete the pathway (see Fig. 2). Unfortunately, the evidence for specific interventions is scarce. A recent systematic review found an association between improved LTBI treatment completion and shorter treatment regimens. There was also an improvement of treatment completion with social interventions, such as adherence coaching, counselling, including self-esteem counselling cultural interventions and peer-based interventions [55]. Despite the scarce evidence, the importance of pathway based interventions has been well recognised and expressed in a dedicated chapter of the recent ECDC LTBI guidance [25].

This guidance recognised the importance of accessible health services, but also the contextuality of support measures, such as target groups, setting and resource availability as well as incentives and enablers to the initiation and completion of treatment. Whilst there is scarce evidence for a number of interventions, these measures can be particularly important for vulnerable patients and those with

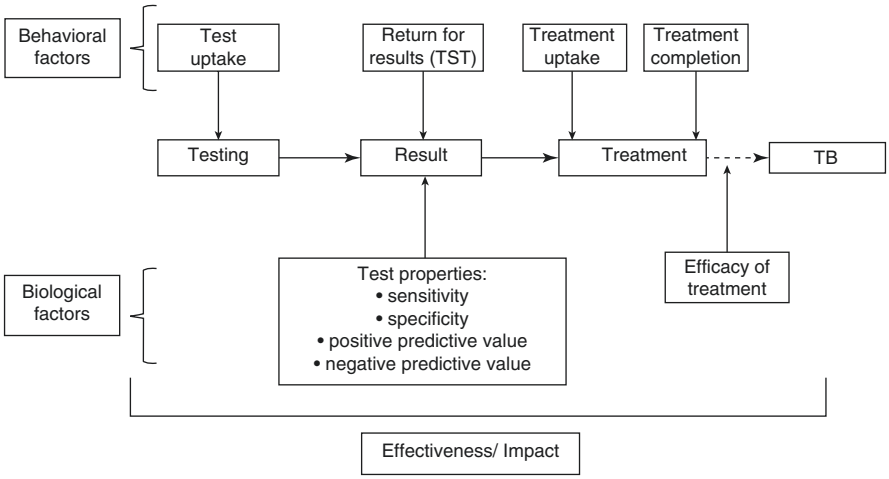

Fig. 2 Conceptional model of factors influencing effectiveness and cost-effectiveness of screening. Figure reprinted with permission from: Zenner D, Hafezi H, Potter J, Capone S, Matteelli A. Effectiveness and cost-effectiveness of screening migrants for active tuberculosis and latent tuberculous infection. Int J Tuberc Lung Dis. 2017 Sep 1;21(9):965–76

socioeconomic risk factors. Social interventions is an umbrella term, reflecting the reality that multiple interventions are often implemented simultaneously, making it difficult to measure the exact effect of each. Training and education for healthcare workers and patient counselling and education can be important to improve adherence. Lastly, the importance of surveillance and monitoring of programmatic LTBI screening was emphasised [25]. A number of these important considerations are further elaborated below: getting the setting right, awareness and de-stigmatisation, support for providers and support for patients.

Testing and treatment for LTBI can take place in a number of settings, including reception centres, primary and secondary care. The setting is a key consideration, and whilst LTBI [56] screening is often performed in secondary care, close ties to the community are important, and links with the non-statutory sector may have advantages, when reaching out to patients. There is evidence that migrants may prefer screening and treatment at convenient places, perhaps closer to home and at times which may work with their daily life. In England, programmatic LTBI testing is performed in primary care, whilst treatment is done in secondary care [44]. This required rapid upskilling of GP practices and use of IGRA tests, but allows more accessible services. In addition, primary care-based treatment has been piloted in East London [53] and is currently formally evaluated through the cluster randomised CATAPULT trial [57]. Whilst final results are outstanding, it appears that more community-based settings and bringing treatment closer to home may have advantages for the pathway.

For the success of the programme there is also a need to raise awareness and to train healthcare workers, both on the subject matter as well as on practicalities,

including pathway and recording issues. This is particularly needed for non-specialist healthcare workers, such as in primary care [58] and the impact of provider knowledge and attitudes on treatment uptake has been documented [53]. Successful programmes have utilised a range of different methods, including face-to-face teaching, e-learning [59] and written materials [60].

In conclusion with the advent of the WHO End TB strategy, LTBI screening has recently gained considerable importance for TB control. In the absence of an ideal test, the benefits and costs of migrant LTBI programmes heavily depend on the ability to optimise the target screening cohort and provide strong programmatic support. More sensitive and specific tests as well as shorter treatment regimen are important milestones that can make screening for LTBI more feasible in further contexts in the future.

Screening for Active TB

There is a long history of screening for active TB, including for migrants, much of it administered at or around international borders, dating back at least to the early part of the twentieth century, where screening was integrated into quarantine arrangements and administered by port health departments [61]. Screening for active TB is usually aimed at point-prevalent pulmonary TB and usually carried out for public health reasons—that is to prevent airborne transmission. Given the complex natural history of TB, only a small proportion of cases can be detected as prevalent at any given moment, therefore minimising the population impact of such screening programmes. A recent study quantified the impact of the UK pre-entry screening programme as 11.4% of the total reduction of TB incidence in the UK [62].

In addition, there is also some evidence that screening for active TB can also detect Chest X-Ray abnormalities, which do not represent active TB but have a higher likelihood for re-activation later in life [43], and this information is used in some settings to inform enhanced follow up procedures [63] for migrants although this approach is not always systematically used. Screening programmes for active TB differ by the population screened, the setting of screening and the test utilised.

Population Screened

In keeping with its public health rationale, and in the context of its close link to borders and with cost-effectiveness considerations, almost all screening programmes for active TB apply a risk stratification to determine the eligible population for screening. The result is often a compromise, triangulating scientific considerations (public health and cost to the receiving country healthcare system) and pragmatic considerations (border and visa requirements). Current practice is

highly variable, dependent on the practicalities in relation to the specificities of programme and Alvarez found in 2011 that "no two countries [surveyed] had the same approach to TB screening among migrants" [64], a situation that had gradually improved in 2017, where still major variations persist [41]. A lot of policy decisions are context specific—programmes based in reception centres for example may focus on asylum seekers, whilst other programmes may be linked to visa procedures and may capture other migrant typologies, such as students or labour migrants [65]. Public Health considerations are usually risk-based. It is common to stratify by TB incidence at the country of origin, migrant typology or length of stay in the receiving country.

There is no consensus and the evidence is not conclusive about setting TB incidence thresholds [66] and applied policies are therefore variable, including an incidence threshold of 40 per 100,000 for the UK programme, 50 per 100,000 for the Dutch programme or 100 per 100,000 for the Swedish programme [41]. There is evidence that TB risk increases with the estimated incidence in the country of origin, and setting a screening threshold involves a compromise between costs and benefits and it is possible, that the desire to maximise risk reduction may lead to lower incidence thresholds than would be the case if based purely on effectiveness and cost effectiveness considerations [67]. In addition, TB transmission appears to follow networks of family and friends, making transmission events between migrants and the host population overall a rare event [43].

There is evidence that TB risk varies by migrant typology, and labour migrants or students could on average have a lower risk compared with those on family reunion or resettlement visas [65]. Asylum seekers and other persons who experienced forced migration have been recognised as a relatively high-risk group for TB. A number of programmes are therefore focussed on screening asylum seekers and/or refugees [68]. Some authors have summarised target groups in different countries and different screening programmes [41, 69].

TB screening programmes, which are closely linked to border arrangements, may also limit requirements and/or offer of screening only to those who apply for longer stay visas (e.g. visas for more than 6 months [65]. The limited contact time and therefore limited transmission opportunities to the receiving country population are too low to warrant systematic screening of short-stay tourists, and the short time window and insurance coverage restrictions may also make it less likely that care is sought during their stay, thus unlikely to cause cost pressures to the receiving country healthcare system. Screening millions of short-stay visitors is therefore a costly, and highly unlikely cost-effective exercise.

Setting

Active TB screening programmes are often related to border requirements. It is therefore possible to distinguish on-entry, pre-entry and post-entry programmes. Although there is tentative evidence that TB detection yields may be slightly higher

in pre-entry programmes and that there could be higher uptake [70], this is likely confounded by other important factors, such as whether programmes are mandatory (like most pre-entry programmes) [71] or voluntary, such as a number of post-entry programmes [72].

Practical considerations are important, when choosing a setting. In the context of large resettlement movements, such as in the US-bound refugee programme, pre-entry screening seems the most effective choice [71], whereas in settings with unstructured arrivals, such as seen in Italy—post arrival screening for example in reception centres are preferred [73]. Linkage to care considerations are vital and the setting can play a role. Referral difficulties and loss to follow up have been well documented for some screening schemes and played a role in considerations for redesigning screening [74].

Screening Test

In the classic screening approach, a highly sensitive test will be followed by a highly specific confirmatory test. Screening is usually for active pulmonary TB and several tests and combinations are possible, but most commonly Chest X-Ray and symptom checks are used either alone or in combination as initial screening test. It is worth noting that predictive values vary with TB prevalence and many screening tools are observer-dependent, leading to inter and intra-observer variability for example in Chest X-Ray interpretation. In addition, countries may choose highly sensitive X-ray reading guidance to avoid missed cases [75]. Commonly given sensitivities (to detect microbiologically confirmed TB) are between 82% and 99% for digital Chest X-Rays [76], but lower for standardised symptom checks with sensitivities of 65–90% [77, 78]. The gold standard confirmatory test is of course TB culture, but the long time period to obtain culture results raises practical issues. The Xpert© MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) may be an alternative, although sensitivity and specificity are lower than culture and test properties are also significantly affected by the setting [79]. The low sensitivities and specificities clearly render smears with the Ziehl-Neelsen or Auramine stain to be an inadequate substitute for culture confirmation, and many programmes therefore require culture as confirmatory test [75].

The combination of Chest X-Ray with either sputum culture (if possible) or the Xpert© appears to have the highest positive predictive value and lowest number needed to screen [80]. New tools are becoming available, and there may be advantages of utilising the new Xpert© Ultra, which has a higher sensitivity than the classic Xpert©, albeit a slightly lower specificity [81]. Owing to the higher sensitivity it may be feasible to use it as initial screening test, although evidence is still scarce. None of the currently available tests are ideal, and country policies are highly variable [41], but it seems that the combination of digital Chest X-Ray with standardised symptom enquiry with a highly specific sputum test (Xpert© or culture) appears the most effective algorithm.

In summary, screening for active TB, often using Chest X-Ray and symptom screening followed by sputum culture confirmation can be an important intervention to make progress toward the Global TB control. Often such migrant screening occurs at borders, and WHO and ECDC guidelines emphasise that all such screening programmes should be non-discriminatory and be beneficial for the health and wellbeing of the person screened, including ensuring appropriate follow up for those with abnormalities detected.

Occupational Health

It is common practice to carry out occupational health examinations for new or returning employees in a number of areas, particularly in healthcare, laboratory or veterinary professions. TB prevention amongst employees has two main objectives: protecting the individual and protecting the patient. Three interventions are common: active and latent TB screening, as well as BCG vaccination for BCG-naïve and TB free.

As with migrant screening, the TB risk and therefore any screening benefits vary by potential previous or future exposures. The already discussed TB risk factors such as a country of origin or time since infection are therefore applicable for healthcare workers as well. Occupational setting can be an additional risk factor, but its relevance depends on the context. For example, healthcare workers (HCW) in large institutional settings, such as hospital wards or prisons of high incidence settings can be at particular risk and are in need of specific protection measures, including TB screening and treatment. The same applies for specific laboratory staff, for example in specialised TB laboratories. However, such settings are rare in low incidence countries, such as in Europe or in North America, where the risk of TB in HCW approximates the one determined by individual risk factors without taking occupation consideration. One could therefore argue, that the same principles of risk stratification as applied to the general population should apply to a low incidence setting HCW cohort also.

Whilst transmission events between healthcare workers and patients in low incidence settings tend to be very rare [82], there is an ethical imperative to protect patients from risk of transmission. In addition, any eventual incidents require significant public health workup and may involve legal proceedings. Most occupational health guidance on TB screening therefore adopt a highly precautionary approach. Current guidance varies significantly by country and sometimes the employer, but usually includes screening for active TB and ensuring BCG vaccination and can include LTBI screening [23, 83].

In summary, TB screening interventions in occupational health tend to follow the general principles of risk stratification followed for other types of screening albeit taking a much more precautionary approach to protect both healthcare workers as well as the patients.

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Incident Management and Mass Contact Screening

Deepti Kumar

Only those tuberculous patients comprise an important danger to the people around them, who suffer from laryngeal or pulmonary tuberculosis and have sputum which contains bacilli. This type of tuberculosis is designated "open" as opposed to "closed", in which no tubercle bacilli are discharged into the environment.

Robert Koch, Nobel Prize Lecture, 12 December 1905.

Introduction

Contact investigation for tuberculosis (TB) is undertaken to identify cases of active or latent TB infection when transmission is likely to have occurred. Breaking the transmission cycle of any infectious disease underpins its control strategy. A robust understanding of the aetiology, pathogenesis, risk of infection acquisition and risk of progression to disease is essential for any public health risk assessment. Only contacts of cases with *Mycobaterium tuberculosis* require investigation from a public health perspective. Environmental mycobacteria have very low infectivity and therefore do not warrant contact investigation or public health follow up.

Any case of TB which requires public health input over and above routine management is an 'incident'. The most frequent TB incidents are those involving an infectious TB case in a community setting where a number of contacts have been exposed to the index case and therefore require follow up. Examples of these settings include educational institutions, such as nurseries, schools, colleges, universities; care homes; hospitals; prisons; any work place; and on board long-haul flights.

In the UK, public health professionals lead the risk assessment for follow up of mass contact screening with support from local TB services. The objectives for underlying mass contact screening in the community are:

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1. To identify anyone who may have acquired the infection from the index case and who requires treatment for active disease or latent TB infection
2. To identify the source case
3. To identify anyone who may benefit from BCG vaccination
4. To provide information on TB to contacts who have been exposed

The ultimate aim of mass contact screening is to control TB by preventing further infection transmission.

Risk Assessment for Contact Investigation

Various factors need to be considered when undertaking a risk assessment prior to a mass screening exercise. These factors include:

1. The clinical features of the index case
2. The susceptibility of contacts
3. The duration of contact and the proximity of the contact
4. Environmental factors

A decision to conduct contact screening should be based on the probability of transmission, which is directly affected by each of the above factors. These factors are also taken into consideration to influence the timing of contact investigations and to identify priority groups for screening.

Clinical Features of the Index Case

The infectiousness of an individual with TB depends on host and bacterial factors. Those with smear-positive pulmonary TB are highly infectious and the degree of infectiousness is thought to increase with the degree of smear positivity. Compared to smear-negative index cases, smear positive index cases are associated with a higher risk of infection among household contacts, regardless of the age of the household contacts [1]. However, it should be noted that those with smear-negative tuberculosis cases may also still transmit TB [2].

Clinical features of the index case associated with high risk of transmission include:

1. Sputum smear positive disease
2. Extent of pulmonary disease; presence of cavitation in the lung
3. Presence of cough
4. Laryngeal involvement

Public health action is generally needed only if the case is infectious; that is, the patient has a productive cough and acid-fast bacilli (AFB) can be seen in the sputum

or bronchoalveolar lavage (BAL) sample. However, if there is a case of non-infectious TB in a young child with no evidence of a possible source within the household, contact tracing should be undertaken to identify a possible source within the wider social network, nursery or school, as appropriate.

According to the British Thoracic Society (BTS), people whose bronchial washings are smear positive should be managed as non-infectious unless: (i) their sputum is also smear positive or becomes so after bronchoscopy; (ii) they are on a ward with immunocompromised patients; or (iii) they are known to have or are suspected of having multidrug resistant (MDR) TB [3].

In general, adults are more infectious than children, as adults have a higher bacterial load and more effective cough. Adults are more likely to infect a child than vice versa. However, all close contacts need to be screened regardless of age. Casual contacts of cases who are smear negative and culture positive do not normally need to be screened. The provision of information is sufficient unless the contact is deemed to be at high risk of contracting TB, e.g. due to being immunocompromised.

Susceptibility of Contacts

Contacts of TB cases should be reviewed to assess their risk of acquiring infection and progression to disease. Close contacts of infectious TB cases are susceptible to becoming infected and subsequently progressing to TB disease, particularly within the first year following exposure [4]. Children less than 5 years of age and those who have human immunodeficiency virus (HIV) infection have the greatest risk of developing TB. Immunosuppression, extremes of age and co-morbidities increase the risk of early progression from acquisition to development of active disease. An immunosuppressed individual who has a brief contact with a case of sputum smear TB has a high risk of acquiring infection and progression to disease. Antiretroviral therapy reduces the risk of TB among people with HIV infection by 67% [5].

Duration and Proximity of Contact

There is no safe exposure time to *M. tuberculosis* infection and even a brief contact presents a risk of transmission to a susceptible contact. However, contact investigation must focus on those at highest risk of becoming infected [6].

Those who have the longest and closest contact are the most at risk. Transmission of TB among household contacts is well documented [1, 7]. Transmission of TB to household contacts is most likely to occur when the index case is smear positive and the household contacts are under 15 years of age [1, 8].

In the UK, 8 hours of cumulative close contact with a case of infectious TB is usually used as a cut off for identifying close contacts. However, transmission through casual exposure to high risk contacts has been documented [9].

Environmental Factors

The environment where the exposure has taken place is an important consideration. Poor ventilation increases the risk of transmission of all airborne infections, including TB. Droplet nuclei containing *M. tuberculosis* bacilli can remain suspended in the air for longer in the absence of good ventilation. In areas of high TB prevalence, high rates of transmission have been documented in households of smear-positive TB patients [10]. Overcrowding in households significantly increases the risk of TB transmission [11].

Duration on Infectiousness

The period of infectiousness is determined by the onset of cough. Hence contact investigation should date back to all contacts exposed to the index case whilst they had a cough. If the duration of cough is unknown, contact investigation should be extended back to 3 months from the time of diagnosis.

Categorising Contacts

The next step is to allocate contacts into categories according to whether they are at high or low risk of infection. Household members and those who have shared accommodation with the index case while they were infectious are the top priority and should be screened in the first instance. Contacts in workplace, institutional settings, such as educational institutes, nurseries and care homes etc. may also have the same risk of exposure as the household contacts, depending on the duration and proximity of contact, the physical environment and the infectiousness of the index case. When there are a large number of exposed contacts in community settings, such nurseries, schools, colleges or work places, a risk stratification approach is helpful, as described below.

Stone in the Pond Principle: Guiding Principle for Mass Contact Tracing
The stone in the pond principle is a risk stratification approach to categorize contacts according to their risk of acquiring TB infection and progression to disease thereafter [12]. It refers to extending contact screening using a concentric ring approach for identifying contacts for screening. Those who have the most extensive

Fig. 1 Stone in the pond principle

exposure to the index case are at highest risk of acquiring infection and those with the highest risk of progression to active disease, such as children and immunocompromised individuals are identified for screening in the first instance. Depending on the outcome of this, screening is extended to the next tier (Fig. 1) [12].

By following the stone in the pond principle, the extent of contact investigation can be limited. The infectiousness of the index case can be assessed by evaluating contacts at higher risk of TB infection and disease. This information can be used to guide and extend screening to the next tier in the concentric circle.

The extent of screening can be limited by adopting the following principles:
Screen the highest risk contacts first.

1. If there is no evidence of recent transmission of infection in this group, do not extend the investigation.
2. If there is evidence of recent infection in the higher-risk group, extend the screening to progressively lower-risk contacts. It is generally accepted that if more than 10% in the highest risk group are positive, screening should be extended to the next tier. Continue extending the screening until the levels of infection detected equals the level of infection in the local community.

Contact Identified with Infectious TB

If the screening identifies a contact with infectious TB, further risk assessment should be undertaken to identify additional contacts of the infectious case.

Timing of Contact Tracing

Investigation of household contacts can be initiated soon after diagnosis of the index case. Timing for contact investigation and screening of individuals outside the household setting, such as those in educational institutes and work places, should be determined by the risk assessment. If the contacts are not highly susceptible and the index case is not highly infectious, as determined by the screening of the household or high-risk contacts, then screening should be undertaken at around 8 weeks following the last exposure to the index case.

Assessment of Contacts

Contacts are assessed to investigate if they have latent or active TB disease (Fig. 2).

Prior to conducting any screening test contacts should be assessed for:

- Any clinical symptoms of TB disease
- BCG vaccination status

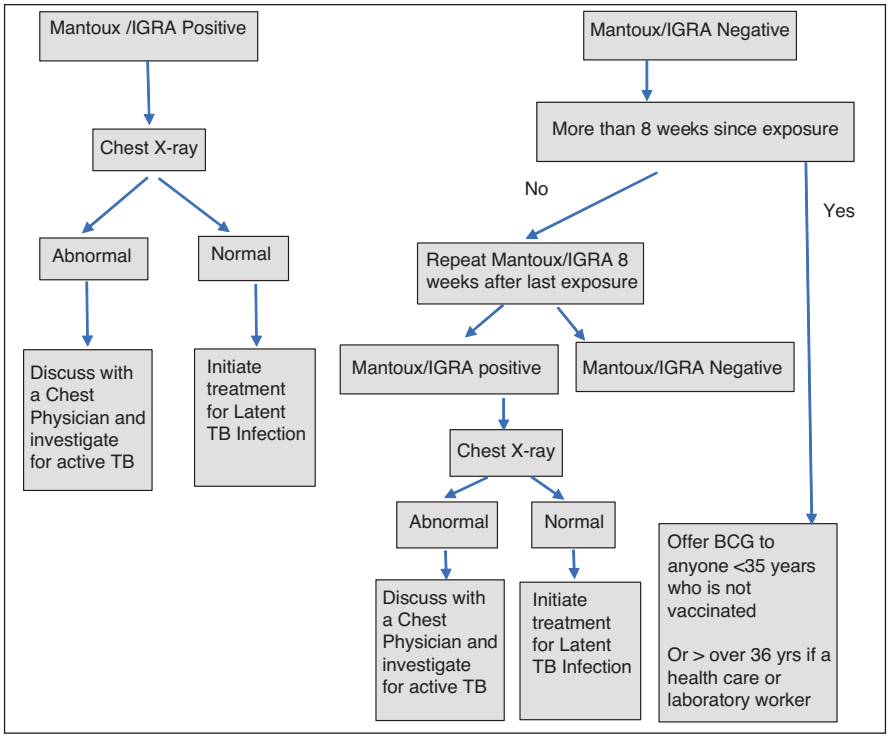

Fig. 2 Contact investigation flow chart

- Previous Mantoux or interferon gamma release assay (IGRA) testing
- Country of birth
- Previous history of TB.

Screening Tests

In the UK, the National Institute for Health and Care Excellence (NICE) recommends that contacts over the age of 65 years have a chest X-ray to rule out active disease [9]. Treatment for latent TB infection is not recommended in this age group as the risk of hepatic toxicity outweighs the benefit of treatment.

Mantoux and IGRA are the two tests available for screening contacts. NICE recommends the use of Mantoux as the screening test. An induration of 5 mm, regardless of BCG status, is considered positive. Anyone with a positive Mantoux should be offered IGRA and if either are positive they should be offered a chest X-ray and assessed for active TB.

NICE recommends that IGRA alone should be used only when Mantoux is not available or if a large number of contacts need to be screened.

Children Under 5 Years

Children under the age of 5 years have a high risk of developing TB disease following infection, which can be as quick as within weeks [13]. The risk of developing active disease in infancy following infection is as high as 40% [14].

Children aged between 4 weeks and 2 years who have had contact with a case of pulmonary or laryngeal TB who has not had at least 2 weeks of treatment should be assessed for active TB in the first instance.

Treatment for presumed latent TB infection should be initiated and a Mantoux test should be carried out [15]. If the Mantoux is inconclusive they should be assessed by a paediatric TB specialist. If the Mantoux test is positive, i.e., 5 mm or more, regardless of BCG history, reassessment for active TB should be undertaken. If active disease is ruled out, treatment for latent TB infections should be instituted. If the Mantoux test is negative, treatment for latent TB infection should be continued and a reassessment for active TB disease should be undertaken after 6 weeks by repeating the Mantoux test.

If the Mantoux test is negative, an IGRA should be considered. If the IGRA is negative, treatment for latent TB should be stopped and BCG should be administered if not vaccinated already. If either the Mantoux or the IGRA are positive, reassessment for active TB should be undertaken; if this assessment is negative, treatment for latent TB infection should be completed.

Pregnancy

A Mantoux test can be carried out in pregnancy. If the Mantoux or IGRA are positive, contacts should be referred to their antenatal care provider.

Chest X-ray

Contacts should be offered a chest X-ray if: (1) they are symptomatic; (2) they have a positive Mantoux or IGRA; (3) they are above 65 years of age; (4) prior to starting treatment in a child under the age of 5 years, irrespective of the Mantoux result, if the index case has pulmonary TB [9].

Contact Investigation of MDR TB Cases

There is no consensus on the follow up of contacts of MDR TB cases. While some may advocate following up MDR TB contacts in the same manner as following up contacts of drug-sensitive TB (i.e. offering a Mantoux or IGRA), others opt for regular clinical review with a chest X-ray every 6 months for 2 years, while some opt for providing information only on symptoms of TB to contacts. A pragmatic approach would be to follow-up those who are IGRA positive with symptom review and CXR for 2 years. There is also little consensus on the treatment regime offered to those who are tested and are either Mantoux or IGRA positive. The latent TB treatment offered varies from the standard regimen for latent TB infection (assuming some may have drug sensitive LTBI) to chemoprophylaxis treatment with drugs to which the strain of TB in the index case is sensitive.

Contacts Who Decline Investigations or Treatment

In the UK, if a contact of a confirmed, symptomatic case of TB declines investigations, they can be assessed by applying for the Health Protection Regulations 2010 legislation [16]. The Proper Officer for Health of the local authority where the contact is resident should be contacted to apply for this.

Contacts who screen positive for latent TB infection and either decline treatment or are not offered treatment should be provided with information on signs and symptoms of TB and monitored clinically with a chest X-ray every 6 months for 1 to 2 years.

Contact Investigations in Special Settings

Educational Settings

Contact investigation in a nursery, school, college or university merits careful risk assessment, investigation and management due to the potential for spread, levels of associated anxiety and potential political ramifications.

The risk assessment in these settings should be carried out using the "stone in the pond" principle. If the index case is a smear positive staff member, consideration should be given to screening all pupils who have been in the class since the staff member became symptomatic. If their symptom onset history is unclear, all those who have been in contact with the staff member in the 3 months prior to their diagnosis should be screened.

If the index case is a pupil who is smear negative, household contact screening should be carried out and if a source is not identified within the household setting, screening at the nursery, school or college should be considered. If the index case is a smear positive child and there is evidence of transmission within the household or to social contacts, then consideration should be given to screening all pupils in the class or year group. If there is no source/index case in the household setting and the contacts are less than 11 years old, it may be necessary to screen the nursery or school in an attempt to identify the index case. If the contacts are older than 11 years old, screening should be extended to wider social groups prior to extending the screening at the nursery or school (Fig. 3).

Prisons and Detention Centres

Prisons present a unique challenge for contact investigation. There is very close contact between inmates and the environment in prisons is conducive to transmission of TB. Furthermore, prisoners are frequently moved between prisons and if they have been in shared cells, the contact information may not be easily available.

As with other TB incidents, the risk assessment is led by public health in discussion with prison staff [17]. Inmates with the longest duration of contact should be screened in the first instance and screening extended if there is evidence of transmission. Once again, the "stone in the pond principle" should be applied for extending the screening.

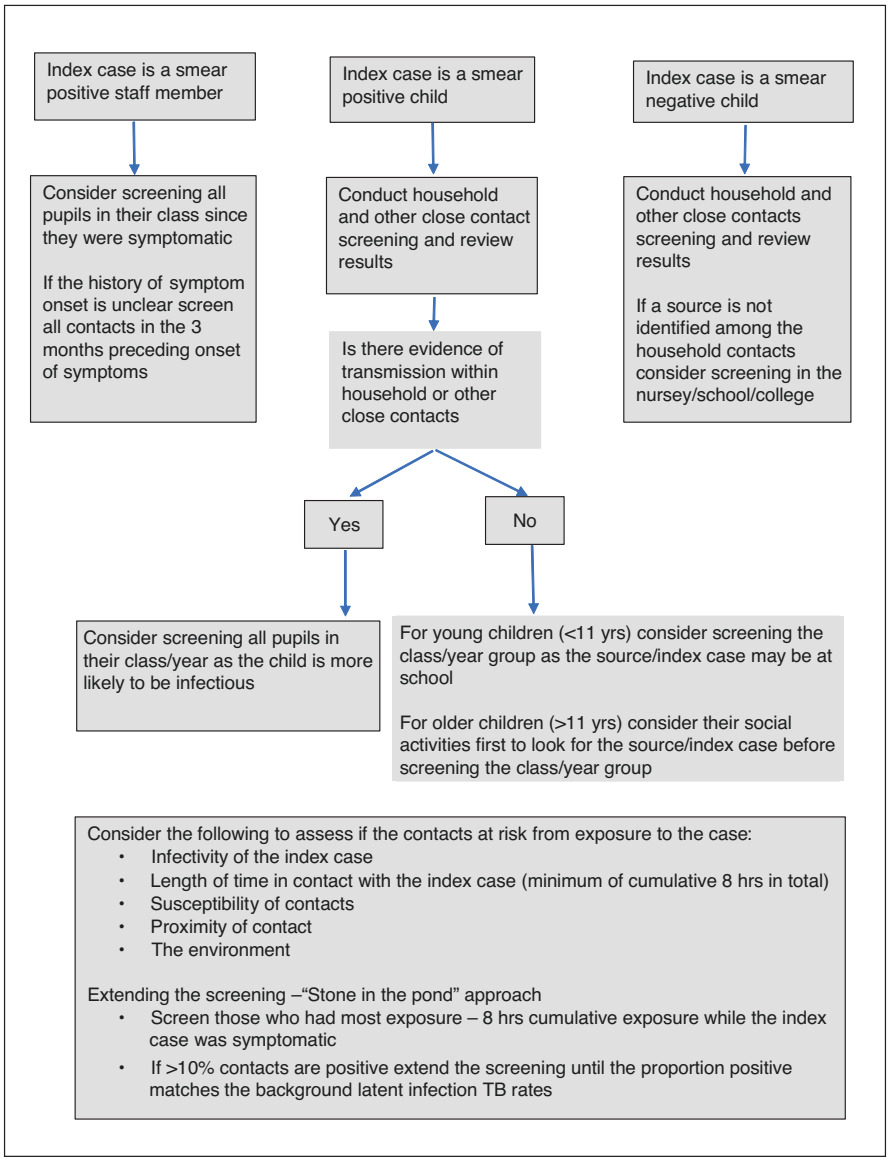

Fig. 3 Contact investigation in nursery/school/college

Exposure on an Aircraft

Transmission of TB has been documented in long-haul flights [18]. The risk of transmission in aircraft is now considered to be very low. Aircraft cabin air quality is well controlled with 20–30 air changes per hour and 50% of the air is recirculated

after passing through high efficiency particulate air (HEPA) filters.

However, increase in air travel and emergence of drug-resistant TB merit ongoing vigilance. Transmission of TB can occur between passengers who are seated close together. Contact investigation of co-passengers is recommended if the case meets the following criteria [19, 20]:

- The case is infectious, i.e., evidence of sputum smear positive pulmonary or laryngeal TB
- The case has travelled on a long-haul flight (8 hours or longer) in the last 3 months

Passengers on the flight sitting in the same row, two rows in front and two rows behind should be invited for screening. Public Health officials contact the airline to obtain this information and refer the individuals for screening.

TB Clusters and Outbreaks

Two or more TB cases linked by epidemiology, strain typing or whole genome sequencing (WGS) constitute an outbreak. When a TB cluster or outbreak is identified, further detailed investigations are warranted to identify further undiagnosed cases and a possible source or index case.

Practical Aspects of Contact Investigation

Management of TB incidents should be led by public health physicians. An Incident Management Team (IMT) should be convened when appropriate, particularly when large number of contacts may need to be screened in the community. The IMT should include a lead public health consultant, TB physician, TB nurse, press officer and other team members depending on the nature of the incident. The IMT takes responsibility for the risk assessment, timing of screening, tests to be used for screening, follow up arrangements and communication with the media and public (Fig. 4).

If a mass contact investigation is planned, information should be sent out to all those invited for screening, and in the case of children and adults with learning disabilities, consent should be obtained from parents or legal guardians. If there is a high level of anxiety surrounding the confirmed TB case, a public meeting should be offered prior to the screening where matters pertaining to health protection can be discussed with the wider public.

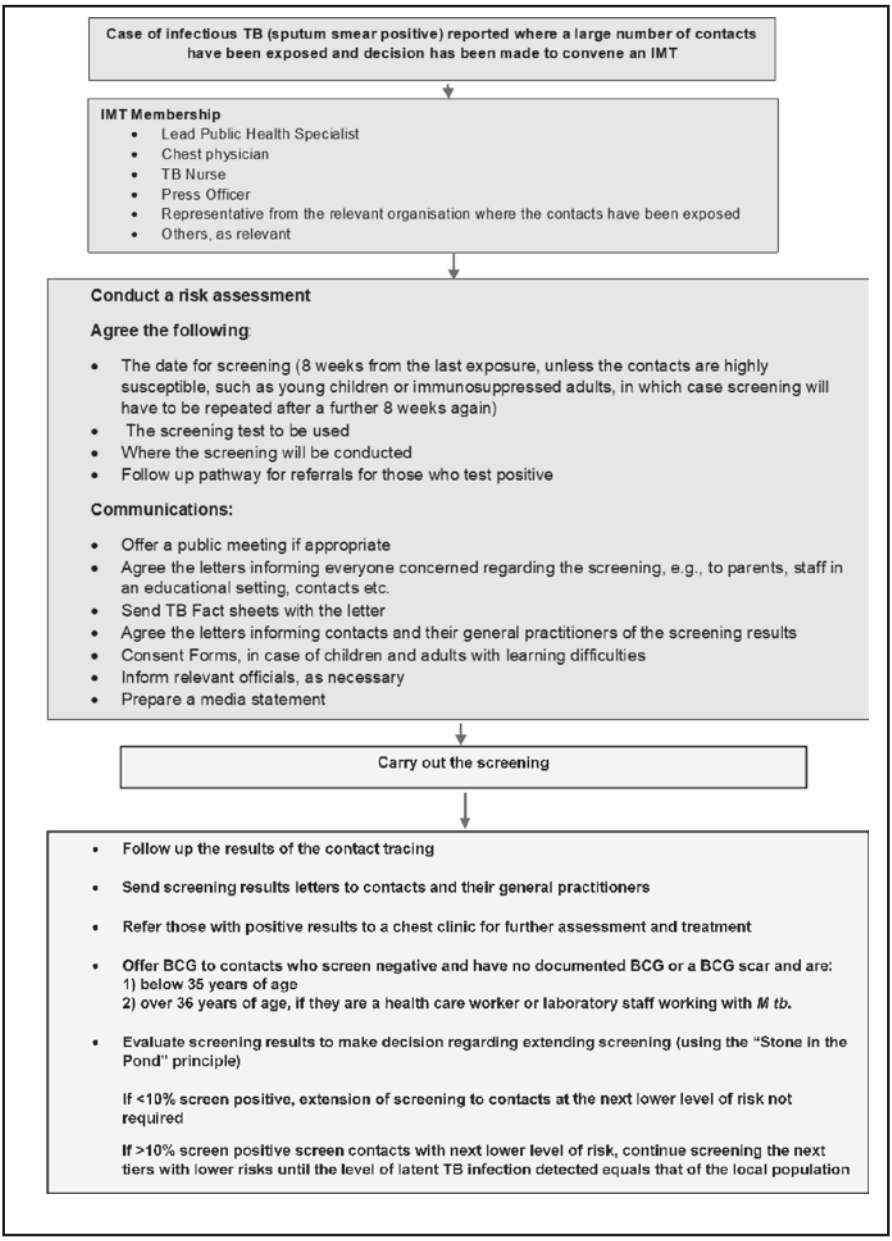

Fig. 4 TB contact investigation incident management team

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