The tuberculous pleural effusion

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An up-to-date review of pleural tuberculosis, discussing the unique diagnostic and therapeutic challenges encountered with this disease, and the current evidence-based clinical approach to management https://bit.ly/49BMs62

Abstract

Pleural tuberculosis (TB) is a common entity with similar epidemiological characteristics to pulmonary TB. It represents a spectrum of disease that can variably self-resolve or progress to TB empyema with severe sequelae such as chronic fibrothorax or empyema necessitans. Coexistence of and progression to pulmonary TB is high. Diagnosis is challenging, as pleural TB is paucibacillary in most cases, but every effort should be made to obtain microbiological diagnosis, especially where drug resistance is suspected. Much attention has been focussed on adjunctive investigations to support diagnosis, but clinicians must be aware that apparent diagnostic accuracy is affected both by the underlying TB prevalence in the population, and by the diagnostic standard against which the specified investigation is being evaluated. Pharmacological treatment of pleural TB is similar to that of pulmonary TB, but penetration of the pleural space may be suboptimal in complicated effusions. Evidence for routine drainage is limited, but evacuation of the pleural space is indicated in complicated disease.

Educational aims
- To demonstrate that pleural TB incorporates a wide spectrum of disease, ranging from self-resolving lymphocytic effusions to severe TB empyema with serious sequelae.
- To emphasise the high coexistence of pulmonary TB with pleural TB, and the importance of obtaining sputum for culture (induced if necessary) in all cases.
- To explore the significant diagnostic challenges posed by pleural TB, and consequently the frequent lack of information about drug sensitivity prior to initiating treatment.
- To highlight the influence of underlying TB prevalence in the population on the diagnostic accuracy of adjunctive investigations for the diagnosis of pleural TB.
- To discuss concerns around penetration of anti-TB medications into the pleural space and how this can influence decisions around treatment duration in practice.

Introduction

Tuberculous pleural effusions are a common form of extrapulmonary tuberculosis (TB), varying in incidence from 3% to 30% depending on regional prevalence of TB and on comorbidities such as HIV [1]. Pleural TB (pTB) presents several unique clinical challenges. Paucibacillary by nature, the diagnosis is not always straightforward for the treating clinician, thus consideration of pre-test probability (*i.e.* the likelihood that the patient has pTB, prior to any diagnostic tests, influenced by local TB prevalence, prior TB exposure and immunosuppression) is vitally important in all cases. In practice, histopathological findings or surrogate indicators of infection are commonly relied upon to guide diagnosis, but these approaches fail to provide any information on drug resistance, which is a growing concern worldwide. The natural history of the disease can vary widely, raising questions about optimal treatment regimens, while penetration of the pleural space with antitubercular medications can be challenging. In this review, we discuss the pathogenesis, diagnosis and management of the tuberculous pleural effusion.

Epidemiology and risk factors

In 2021, *Mycobacterium tuberculosis* (Mtb) infection was the second leading infectious disease killer after coronavirus disease 2019 (COVID-19), responsible for 10.6 million cases of active TB disease and killing 1.6 million people worldwide [2]. For the first time in a decade, this figure had risen compared with the previous year, reflecting the negative impact of the COVID-19 pandemic on the hard-won progress made by the World Health Organization's End TB Strategy since the turn of the century.

Extrapulmonary TB, of which pTB is the second-most common form after TB lymphadenitis, accounts for 15–25% of TB cases worldwide and can account for up to 50% of cases in immunocompromised populations [3, 4]. Epidemiological characteristics of pTB resemble that of overall TB, with higher incidence observed in males, the immunosuppressed and socioeconomically deprived populations [4]. Coexistent pulmonary TB is common, with parenchymal disease detected on up to 85% of computed tomography (CT) scans performed in patients with pTB [5, 6], an important consideration both in terms of anticipating the natural history of disease progression and in the pursuit of microbiological diagnosis.

In line with this, significant regional variability in pTB incidence exists depending on the overall prevalence of TB infection [7, 8]. For example, in a study investigating optimal diagnostic approaches involving 51 patients with undiagnosed pleural effusion in South Africa the final diagnosis was pTB in 82% [9]. By contrast, in a review of 147 thoracoscopies performed in Denmark, only 2% of cases represented pTB [10]. Interestingly, the proportion of TB cases presenting with pTB also varies depending on overall TB prevalence in the region. For example, pTB accounts for 4% of all TB cases in the USA [7], 10% in Spain [4] and 20% in South Africa [11]. This may reflect the tendency for pTB to develop in adolescents and younger adults [12–14], meaning that in high-incidence countries where TB disease is seen in the young adult population, the proportion of pTB cases is higher.

It is well recognised that people living with HIV (PLHIV) have higher rates of extrapulmonary TB [3, 4, 15]. This is also true for pTB, with one US-based study reporting pleural involvement in 11% of TB patients living with HIV, compared with 6% of TB patients living without HIV [16]. It is worth noting that this study was conducted prior to the widespread use of antiretroviral therapy (ART), thus offers a good representation of the natural history of TB/HIV co-infection. Interestingly, a retrospective review of extrapulmonary TB cases conducted pre- and post-scale-up of ART in rural South Africa found that, although overall incidence of TB fell by 13% following widespread introduction of ART, the proportion of cases involving tuberculous effusion did not change [17]. A caveat of these findings may be an "unmasking" of previously undetected TB infection as part of the ART-associated immune reconstitution inflammatory syndrome.

Pathogenesis

By far the most common tuberculous pleural effusion is TB pleuritis [18]. Although the pathogenesis has historically been debated, current consensus agrees that TB pleuritis represents a delayed hypersensitivity reaction precipitated by the presence of Mtb bacilli in the pleura and the pleural space. It occurs 6–12 weeks after a primary infection or (more commonly in low-TB prevalence countries) due to reactivation of TB [19, 20]. In the absence of overt parenchymal disease, Mtb is believed to access the pleural space following the rupture of a subpleural caseous focus [21]. Animal studies, supported by observations in human populations, suggest early neutrophil and monocyte infiltration, followed by a protracted influx of pre-sensitised T-lymphocytes into the pleural space that give rise to persistent pleural effusion [22–25]. In a purified protein derivative-sensitised guinea pig model, lymphocyte depletion prevented the formation of a pleural effusion following injection of tuberculous protein into the pleural space [23], indicating the centrality of this lymphocytic influx in the pathogenesis of the tuberculous pleural effusion.

The infiltrating lymphocytes seen in most tuberculous effusions are predominantly memory T-helper (Th)1 cells, presumably sensitised at the time of initial host infection, that selectively home to the infected pleural space [26, 27]. In patients with TB pleuritis, pleural fluid memory T-cells express several important homing factors such as CD11a, CCR5 and RANTES [28], and produce higher levels of the pro-inflammatory cytokine interferon (IFN)-γ than their peripheral blood counterparts [27, 29], effectively "compartmentalising" the immune response. Conversely, anti-inflammatory interleukin (IL)-4-producing Th2 cells are reduced in the pleural space compared with peripheral blood of TB patients [27]. Pro-inflammatory cytokines lead to increased capillary permeability, allowing fluid to move into the pleural space, while lymphocytic pleuritis and granuloma formation impairs normal pleural fluid reabsorption [19].

The influx of IFN-γ-producing T-cells generally effects a highly efficient anti-TB response, which may explain the paucibacillary nature of most tuberculous effusions [30, 31]. Thus, of 141 US military

personnel diagnosed with tuberculous effusion in the 1940s, all spontaneously resolved within 2–4 months in the absence of antibiotic therapy [32]. Despite this initial resolution, however, 65% went on to develop active TB in subsequent years, echoing the results of a similar Finnish study [32, 33], albeit both studies were conducted in an era of high TB incidence worldwide, thus reinfection could explain a proportion of these cases. Nonetheless, these observations suggest that while the Th1 hypersensitivity reaction is central to the development and maintenance of the tuberculous effusion, it is likely that true pleural infection is present and persists. The higher pleural fluid smear and culture positivity seen in HIV patients with suppressed $CD4^+$ T-cell counts provides further evidence for the presence of viable mycobacteria in the tuberculous pleural effusion, and the fundamental role of infiltrating lymphocytes in containing these organisms [34]. More recently, a central role for the pleural macrophage in anti-TB responses has been highlighted, with the observation that tuberculous pleural fluid can induce an M2-like immunometabolic phenotype in pleural macrophages that impairs antimicrobial efficacy [35].

While lymphocyte predominance is the most common finding in tuberculous effusions, ~10% of sampled tuberculous effusions in human studies are neutrophil predominant [24, 25], thus a spectrum of immunological responses probably exists. Supporting the model in which early neutrophilic infiltration (precipitated by the presence of the Mtb bacillus) is followed by a chronic lymphocytic influx that helps sterilise the space, a proportion of neutrophil-predominant effusions will yield a lymphocytic effusion upon repeat sampling [24, 25]. Neutrophil-predominant effusions have higher rates of smear and culture positivity [24, 25, 36], are associated with higher circulating markers of inflammation such as C-reactive protein [25] and demonstrate greater loculation [37] (which in turn is associated with higher rates of persistent pleural thickening [38]), again supporting the anti-mycobacterial efficiency of lymphocytic infiltration into the pleura.

On the other end of the spectrum, TB empyema is a rare entity characterised by grossly purulent fluid containing abundant mycobacteria [4, 39], and usually represents progression of a primary tuberculous effusion, although TB empyema can also be caused by spillage of caseous material from a parenchymal focus or bronchopleural fistula, by direct extension from adjacent nodes, by haematogenous spread or following surgical interventions such as pneumonectomy or oleothorax [18]. This chronic infection is associated with a thick, calcified pleural rind and rib thickening visible on imaging (see figure 1), usually leading to severe scarring and fusion of the pleural space causing deformity of the chest cavity, termed a "fibrothorax" [18, 39]. Rarely, TB empyema can present as "empyema necessitans", with purulent fluid extending out of the pleural space and into the neighbouring chest wall and soft tissues, sometimes draining onto the skin *via* fistulae [39].

TB is also a common cause of the uncommon cholesterol pleural effusion [18, 40], debatably believed to occur secondary to release of cholesterol and other lipids from degenerating cells within the pleural space in a chronic tuberculous effusion [41]. This so-called "pseudochylothorax" characteristically demonstrates a high cholesterol level >5.18 $mmol·L^{-1}$, and in 50% of cases will have a characteristic milky appearance [40].

FIGURE 1 Computed tomography image of the thorax showing a right-sided tuberculosis empyema, with significant pleural thickening. Lung entrapment was evident following drainage of the effusion; however, the lung slowly re-expanded over several months.

More rarely, obstruction of lymphatic flow secondary to TB disease, for example due to compression of the thoracic duct by an enlarged lymph node, can cause a true chylothorax (see figure 2) [42]. This is characterised by a cholesterol level <5.18 mmol·L^{-1}, with elevated triglycerides and chylomicron levels, and usually a milky fluid appearance [43]. TB-associated lipid effusions usually respond to conservative management with anti-TB medications [18, 42].

Clinical presentation and imaging

In patients with a fully functional immune system, pTB presents as an acute or subacute illness. The most commonly reported symptoms are cough, chest pain and fever, and to a lesser extent, weight loss and night sweats [19, 31, 44–46]. PLHIV with pTB often present later with constitutional symptoms and may have evidence of disseminated disease [11, 34, 47].

TB pleural effusions are unilateral in the vast majority of cases, with no predilection for either the left or right hemithorax [13, 14, 44]. Though size varies, the tuberculous effusion will occupy less than two-thirds of the hemithorax in 80% of cases [13, 14, 44]. Coexistent parenchymal changes evident on chest radiography are uncommon, variably reported as present in 18–50% of cases [13, 14, 31, 44].

Unsurprisingly, the rate of associated parenchymal changes is higher when chest CT is performed [5, 6, 12, 14, 48]. A recent review of 103 cases of pTB found coexistent parenchymal disease was detected on CT in 47.7% [12], while studies from South Korea have suggested CT evidence of coexistent pulmonary disease in 85% of pTB cases [5, 6]. Subpleural and peribronchovascular micronodules and subpleural thickening are the most common parenchymal findings on CT and can help to differentiate TB as a cause of pleural effusion as opposed to other aetiologies [6, 49]. More advanced infection, such as TB empyema,
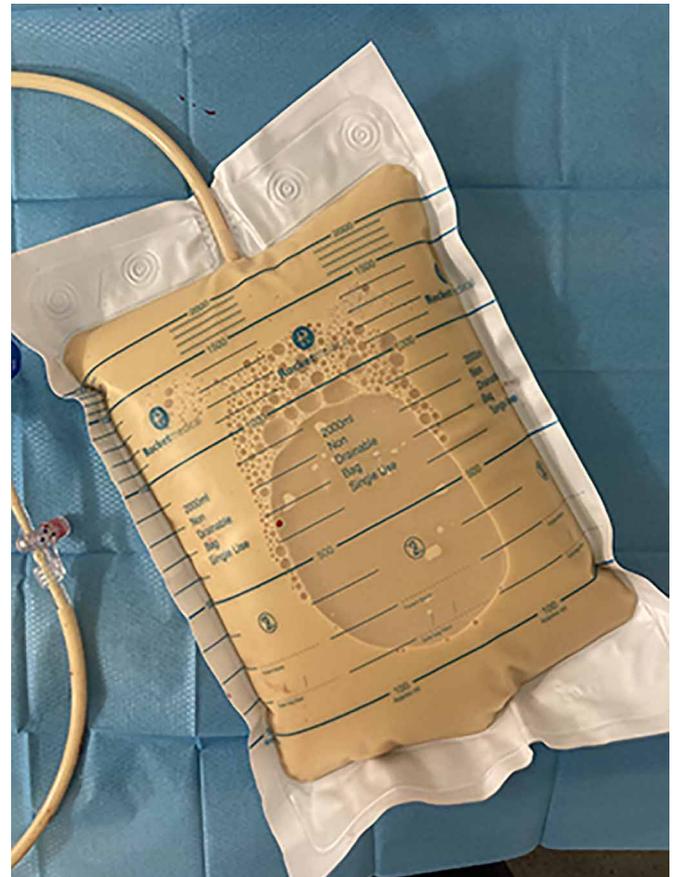

FIGURE 2 Chylous pleural fluid aspirated from a recurrent chylothorax in a pulmonary tuberculosis (TB) patient. This effusion was likely secondary to paradoxical enlargement of crural lymph nodes following initiation of anti-TB therapy, causing impingement of the thoracic duct in the right hemithorax. The effusion was temporarily managed with indwelling pleural catheter, and ultimately resolved with a combination of anti-TB medications to treat pulmonary disease and immunosuppression to treat the paradoxical reaction.

may demonstrate radiological features of empyema such as the "split pleura" sign, diffusely thickened visceral and parietal pleura separated by fluid (see figure 1) [50]. Post-resolution of active infection, radiological features such as pleural thickening, pleural calcification or chronic fibrothorax may persist long term [5, 49, 50].

Septation and loculation, which are not always visible on CT, are frequent features of tuberculous effusions demonstrable on thoracic ultrasound. Naturally the wide spectrum of disease gives rise to a wide range of ultrasonographic features that can be associated with pTB, ranging from free-flowing anechoic effusions to complex effusions with septation and loculation [51, 52]. A recent study from South Korea found the presence of loculation to positively predict likelihood of mycobacterial culture positivity from pleural fluid [37]. Pleural thickening and pleural nodularity are also notable ultrasound features of tuberculous effusions, with a previous study of 20 patients with tuberculous effusions reporting the presence of pleural thickening of <1 cm in 90% of cases, and pleural nodules visible in 20% [51].

Diagnostic tools

The gold standard for definitively diagnosing pTB is detection of Mtb in pleural fluid or pleural tissue, or demonstration of caseating granulomata on pleural biopsy, ideally in the presence of acid-fast bacilli (AFB) [19]. However, achieving this gold standard is a perennial challenge in pTB, due to the paucibacillary nature of the disease. A recent review of 103 pTB cases diagnosed over an 8-year period found that a confirmatory microbiological diagnosis was achieved in only 15.5% [12].

In practice, supportive investigations are commonly relied upon to arrive at the diagnosis. Vital to the interpretation of all investigations supporting a diagnosis of pTB is consideration of pre-test probability, which dramatically influences the diagnostic accuracy of adjunctive diagnostic tests, a fact that must be kept in mind both in the clinical setting and when assessing evidence in the literature. Thus, in high TB endemic areas negative results should be questioned, while in low TB endemic areas positive results should be questioned. Factors that increase pre-test probability include high local prevalence of TB (>120 per 100 000), previous exposure to TB (or a high likelihood of previous exposure, *e.g.* immigrants from high prevalence countries), and immunosuppression [1].

A further consideration when reviewing literature evidence is the "diagnostic standard" against which adjunctive tests are measured. Studies assessing the diagnostic performance of a given test against a suboptimal diagnostic tool such as pleural fluid culture, for example, will invariably overestimate the sensitivity of the test. To improve accuracy, some investigators assess the diagnostic performance of a test against a composite diagnostic standard incorporating several different diagnostic tools (*e.g.* granulomatous inflammation, culture result, radiological diagnosis) to give a more accurate result. Table 1 provides a summary of diagnostic tools used in the diagnosis of pTB.

Obtaining diagnostic material

The approach to obtaining material for culture and histology is very important, as it significantly impacts upon diagnostic yield. In this regard, pleural biopsy is superior to pleural fluid aspiration [53]. Thoracoscopy offers the highest diagnostic accuracy, yielding large samples of pleural tissue that can be used for histological and microbiological analyses, and is reportedly diagnostic in over 90% of cases of pTB [9]. However, the required infrastructure and skillset mean that this is not always accessible. Closed needle biopsy, using either the superior Abrams needle or an alternative biopsy needle, offers a lower diagnostic yield, but it remains somewhere in the region of 60–80% when performed by a skilled operator [9, 54, 55]. It is recommended to obtain at least six samples at the time of pleural biopsy [56]. Thoracocentesis offers a substantially lower diagnostic yield than biopsy, although reported pleural fluid culture sensitivity varies widely in the literature, from 7% to 63% [9, 13, 36, 56]. However, many adjunctive diagnostic tools utilise characteristics of pleural fluid to infer likelihood of tuberculous effusion, thus pleural aspiration still plays an important role in diagnosis of pTB.

Given the high coexistence of pulmonary TB [5, 6, 12], it is imperative to obtain a sputum sample for microscopy and culture in all cases of pTB. In one study of induced sputum in 84 patients with TB pleural effusion, 12% were smear positive and 52% were culture positive [56]. Using a combination of both pleural fluid culture and sputum culture has been shown to increase microbiological diagnosis of pTB by 15% [36].

Histology and cytology

Demonstration of caseating granulomata on pleural biopsy, particularly in the presence of AFB, is considered the gold standard for the diagnosis of pTB [19]. In a Spanish review of 254 patients diagnosed with pTB over a 9-year period, definitive diagnosis was based on pleural tissue histology in 79.9%,

TABLE 1 Summary of investigations used for diagnosis of pleural tuberculosis (pTB)

Diagnostic tool	Comment	Reference(s)
Thoracoscopy	Yields large samples of pleural tissue that can be used for histological and microbiological analyses Diagnostic accuracy of >90%	[9]
Closed needle pleural biopsy	Lower diagnostic yield than thoracoscopy Diagnostic in 60–80% of cases when performed by a skilled operator Recommended to obtain at least six samples at the time of pleural biopsy	[9, 53, 55]
Thoracentesis and pleural fluid culture	Lower diagnostic yield than pleural biopsy Liquid culture outperforms solid culture Fluid culture sensitivity varies widely (7–75%)	[9, 36, 53–55, 60, 61]
Sputum	Essential to obtain sputum culture in cases of suspected pTB (spontaneous or induced) Sputum culture positive in up to 52% of pTB	[12, 36]
Combined pleural fluid and sputum culture	Increases microbiological diagnosis by 15%	[36]
NAAT on pleural fluid (Xpert)	Highly specific for detection of Mtb in pleural fluid; however, sensitivity is poor Sensitivity 50.9%, specificity 99.2% when compared with standard culture Sensitivity 18.4%, specificity 98.2% when compared with composite reference standard (presence of caseating granulomas ± positive culture)	[62]
NAAT on pleural fluid (Xpert Ultra)	Xpert Ultra, a more sensitive version of Xpert MTB/RIF, with improved sensitivity compared with both culture (68%) and composite reference standard (47%) Specificity is slightly lower than Xpert (97%)	[64–66]
Pleural fluid ADA	Elevated pleural ADA in the context of high pre-test probability can help diagnose pTB Levels above 40 U·L^{-1} have shown sensitivity of 92% and specificity of 90%	[68–70]
Pleural fluid lymphocyte:neutrophil ratio >0.75 and elevated pleural fluid ADA	Pleural fluid ADA should not be used in isolation to diagnose pTB A combined pleural fluid lymphocyte:neutrophil ratio >0.75 and elevated pleural fluid ADA has shown sensitivity of 88% and specificity of 95% in diagnosing pTB	[57]
Pleural fluid unstimulated IFN-γ	Elevated pleural fluid unstimulated IFN-γ has shown a pooled sensitivity of 93% and specificity of 96% in diagnosing pTB Optimum cut-off not yet established PPV 100% when combined with high pre-test probability and elevated ADA	[76]
IGRA	IGRA performs poorly in the diagnosis of pTB, a pooled sensitivity and specificity for pleural fluid assays of 72% and 78%	[80]
Pleural fluid IL-27	When used to differentiate between TB effusion and malignant effusion: sensitivity 93% and specificity 97%	[84, 85]
Mtb HspX ALISA	Shows promise as a potential biomarker for diagnosis of pTB Sensitivity 93% and specificity 98% as compared to composite reference standard in one study	[89]

NAAT: nucleic acid amplification test; ADA: adenosine deaminase; IFN: interferon; IGRA: interferon-γ release assay; IL: interleukin; Mtb: *Mycobacterium tuberculosis*; ALISA: aptamer-linked immobilised sorbent assay; PPV: positive predictive value.

compared with 11.7% based on pleural tissue culture [13], emphasising the centrality of histopathological examination. Similarly, diagnostic yield of pleural tissue histological examination was reported as 74% in a retrospective review of 382 pTB patients in Taiwan [36]. However, it is important to keep in mind that diagnosis based upon histological appearances alone cannot offer information on drug resistance, which is an increasingly serious concern worldwide.

While early stage pTB effusions may be predominantly neutrophilic, ~90% of pTB effusions will contain >50% lymphocytes [9, 13]. Thus, in the absence of diagnostic pleural tissue, cytological analyses of pleural fluid demonstrating a lymphocyte-predominant exudate can be highly supportive in high prevalence settings [19]. A high lymphocyte-to-neutrophil ratio (>0.75) in combination with elevated adenosine deaminase (ADA) offers a sensitivity of 88% and specificity of 95% for the identification of pTB [57]. However, caution must be exercised to ensure malignant effusions are not misdiagnosed, as these can also present as lymphocyte-predominant exudates with variable ADA level.

Pleural fluid biochemistry
TB pleural effusions are typically straw-coloured exudates [31]. Fluid lactate dehydrogenase (LDH) and protein are elevated in over 75% of cases, and fluid glucose may be low compared with serum [31, 44].

Culture positive TB effusions are associated with higher protein level, higher LDH level, lower lymphocyte count and higher neutrophil count [36]. Similarly, in an uncomplicated TB pleural effusion the pH is usually above 7.3; however, as an empyema develops the pH will classically reduce [19, 58].

Mycobacterial stain and culture

In keeping with the paucibacillary nature of pTB, the yield of direct microscopy is inherently low, except in the setting of TB empyema [59]. Although in PLHIV, where mycobacterial load is often higher due to an impaired local lymphocytic immune response, AFB are visualised in ~20% of cases [53, 59].

Similarly, PLHIV are more likely to have culture positive tuberculous effusions [36, 54, 60]. Liquid culture consistently outperforms solid culture methods in the diagnosis of pTB, both in HIV positive and HIV negative individuals [36, 54, 61]. A 2001 study in Uganda found BACTEC liquid culture media yielded 75% pleural fluid culture positivity in tuberculous effusions compared with 45% positivity in Löwenstein–Jensen solid culture media [54]. Liquid culture is also associated with a shorter time to positivity [54, 61]. Transfer of pleural fluid directly into culture bottles at the time of sampling may increase positivity of fluid culture and reduce time to positivity [54, 61]; however, the volume of pleural fluid inoculated does not appear to increase diagnostic yield [60].

PCR-based techniques

Nucleic acid amplification tests (NAATs) can rapidly detect Mtb-specific nucleic acid sequences in clinical specimens. The Xpert MTB/RIF (Cepheid) is one such commercially available PCR-based test that can detect Mtb DNA, as well as offering information on the presence of the rpoB mutation responsible for 95% of rifampicin resistance [62].

Although Xpert MTB/RIF is highly specific for detection of Mtb in pleural fluid, its sensitivity is poor. A large meta-analysis (n=4207) including people from regions of both high and low TB prevalence assessed the performance of Xpert MTB/RIF against standard culture for the diagnosis of extrapulmonary TB [62]. Xpert MTB/RIF demonstrated a pooled sensitivity of 50.9% for diagnosis of pTB when compared with fluid culture, or just 18.4% when compared to a composite reference standard (*i.e.* granulomatous inflammation and/or positive culture), although specificity remained high at 99.2% or 98.2%, respectively [62]. Interestingly, Xpert MTB/RIF sensitivity was lowest in pleural fluid compared with all extrapulmonary specimens assessed in this meta-analysis [62]. PCR inhibitors have not been detected in pleural fluid, thus it is likely that the paucibacillary nature of pTB results in an absolute quantity of genetic material that is below the level of detection using this technique [63].

A more sensitive version of Xpert MTB/RIF exists, the Xpert MTB/RIF Ultra. Xpert MTB/RIF Ultra has a larger PCR chamber, includes two additional genetic targets and reduces the level of detection from 130 to 20 organisms per mL [64]. A recent meta-analysis compared performance of Xpert MTB/RIF *versus* Xpert MTB/RIF Ultra on pleural fluid in the diagnosis of pTB, including 64 studies assessing Xpert MTB/RIF alone, five studies assessing Xpert MTB/RIF Ultra alone, and five studies comparing Xpert MTB/RIF with Xpert MTB/RIF Ultra [65]. Overall, pooled sensitivity of Xpert MTB/RIF Ultra was 68% relative to a culture-based reference standard and 47% relative to a composite reference standard, a substantial improvement on the performance of standard Xpert MTB/RIF (where sensitivities were 52% and 21%, respectively, in this meta-analysis). It is worth noting, that specificity of Xpert MTB/RIF Ultra is slightly lower (97%) compared with that of standard Xpert MTB/RIF (99%) [65], so clinicians should be aware that false positive results are possible, particularly in the setting of previous TB infection [66].

Excitingly, GAO *et al.* [67] have recently reported that, when applied to pleural biopsy tissue, the Xpert MTB/RIF Ultra has a similar diagnostic accuracy to that of histopathological examination. This is significant from the point of view of potentially increasing diagnostic yield of the current "gold standard", but also in terms of providing (albeit limited) information on drug resistance, which histopathological diagnosis alone cannot. With the imminent launch of newer second-line drug resistance PCR platforms, more extensive information around drug resistance may be more readily available to guide treatment of pTB in the future [66].

Pleural fluid ADA

ADA is a purine-degrading enzyme present in abundance in TB pleural effusions and can be measured *via* a rapid, inexpensive assay. A pleural fluid ADA level above 40 $U·L^{-1}$ is frequently used as the diagnostic cut-off for pTB, and appears to be unaffected by HIV status, even at low CD4 count [68]. A 2019 meta-analysis including 174 publications with 27 009 patients reported a high pooled sensitivity (92%) and specificity (90%) for pleural fluid ADA in diagnosing pTB [69], reaffirming results of a previous

meta-analysis in 2008 [70], although the authors acknowledged that all included studies showed a risk of bias, and significant inter-study variability in terms of geographic region and ADA cut-off thresholds limit application of these results in the clinical setting. Crucial to the interpretation of pleural fluid ADA level in practice is consideration of the pre-test probability. For example, although a lymphocytic effusion with fluid ADA level >40 U·L^{-1} in an area with a high TB burden has a very high positive predictive value (PPV) [71, 72], this value declines in areas of low TB prevalence.

Pleural fluid ADA levels should not be interpreted in isolation, as elevated levels are not exclusive to TB [45, 59, 71]. In fact, very high levels (>250 U·L^{-1}) are unusual in TB, and should prompt consideration of an alternative diagnosis such as bacterial empyema or lymphoma [73]. In a retrospective study comparing 72 tuberculous effusions to 47 parapneumonic effusions in a high TB endemic area, a pleural LDH/ADA ratio of <16.2 was found to reliably identify tuberculous effusions, with a sensitivity and specificity of 93.6% and 93.1%, respectively [74].

Assays that detect ADA2, the ADA isoenzyme that accounts for the elevated ADA levels observed in TB effusions, have increased specificity in diagnosing pTB [24, 75]. However, the assay is not routinely available at present, and is not thought to add much value beyond existing ADA assays [75].

Interferon-γ

IFN-γ is a cytokine released by activated CD4$^+$ T-cells [1, 8]. Assays that directly quantify the amount of IFN-γ in pleural fluid ("unstimulated IFN-γ") have shown a high diagnostic accuracy, with a pooled sensitivity of 93% and specificity of 96% reported in a recent meta-analysis of 67 studies and 7153 patients [76]. Unstimulated IFN-γ may even outperform ADA in terms of diagnosing pTB [77, 78], although the historical reliability of ADA and its affordability mean it remains the preferred test at present. Combining these strategies may also offer some advantage, as a recent study in a high TB prevalence area reported a PPV of 100% for a combined elevation of pleural fluid unstimulated IFN-γ, ADA and unstimulated IP-10 (also known as IFN-γ-inducible protein of 10 kDa) [79]. Optimum cut-off values for IFN-γ concentration have not yet been established [76]; however, preliminary data from trials of an affordable immunosuspension assay (IRISA-TB; Antrum Biotech and University of Cape Town, Cape Town, South Africa) suggest that a cut-off value of 20.5 pg·mL^{-1} IFN-γ offers a sensitivity and specificity of 89.9% and 96.4%, respectively [64].

IFN-γ release assays (IGRA), such as the commercially available QuantiFERON-TB Gold (QIAGEN, Hilden, Germany) and T-SPOT.TB (Oxford Immunotec, Oxford, UK), use Mtb-derived antigen to stimulate the release of IFN-γ from T-lymphocytes in a sample, which is then quantified [1]. In contrast to "unstimulated IFN-γ", IGRA has performed poorly in the diagnosis of pTB, with a pooled sensitivity and specificity for pleural fluid assays of 72% and 78%, respectively [80], possibly because T-lymphocytes within the pleural space are already maximally stimulated at baseline in pTB [81–83].

Pleural fluid IL-27

IL-27 is a cytokine which facilitates the production of IFN-γ and Th1 responses and has emerged as a potential biomarker for pTB [84]. When used to differentiate between TB effusion and malignant effusion it achieves a sensitivity and specificity at or above 93% and 97%, respectively [84, 85], although some controversy exists around its potential superiority to ADA [86, 87]. However, a combination of pleural fluid IL-27 and ADA measurement may improve diagnostic accuracy above either approach alone [86, 88], and has been suggested as a useful "rule-out" test even in areas of high TB prevalence [88].

Novel aptamer-based test against Mtb HspX protein

A novel aptamer-linked immobilised sorbent assay (ALISA) targeting Mtb HspX protein has the potential to bridge the gap in the diagnosis of pTB [89]. HspX has been established as a TB biomarker, its significance lying in its *in vivo* expression and its detectability through antibodies in sera obtained from active TB patients [90, 91]. Having already demonstrated diagnostic utility in TB meningitis [92, 93], interest has recently been directed towards its application to pTB [89]. Mtb HspX ALISA achieved a sensitivity of 93%, using a cut-off value to provide a specificity ⩾98%, when compared with a composite reference standard in a study including 106 patients with pleural effusion in New Delhi [89]. Further research with larger numbers of patients and among a variety of ethnic groups is required, but this is a promising avenue for future development.

Other biomarkers

Other less well explored pleural fluid biomarkers postulated as potential adjuncts for the diagnosis of pTB include lysozyme [94, 95], hyaluronic acid [96], neopterin [96], leptin [96], fibronectin [96], combined

measurement of decoy receptor 3 (DcR3) and soluble tumour necrosis factor receptor 1 (TNF-sR1) [97], and combined measurement of tumour necrosis factor and ADA [98].

Management

Infection control measures

The high coexistence of parenchymal disease in pTB patients recommends that the same infection control measures be employed for pTB as for pulmonary TB during initiation of therapy [5, 6, 12, 18, 30]. Similarly, given evidence for the presence of Mtb bacillus in tuberculous pleural fluid [34], appropriate infection control measures should be in place during any procedures which could potentially expose this fluid to the air, such as insertion of an intercostal drain [18].

Anti-TB medications

While many cases of pTB are self-limiting, over half of untreated patients will go on to develop active disease [45]. With sparse data available on penetration and activity of anti-TB drugs in the pleural space, and with knowledge of the high coexistence of and risk of progression to parenchymal disease, recommended drug regimens are the same as those for pulmonary TB [18, 99]. A standard 6-month regimen is commonly used for drug-sensitive disease, with use of directly observed therapy where concern exists around potential compliance [18, 100]. Given the paucibacillary nature of pTB, some studies have explored the use of shorter regimens with fewer drugs [101–103].

Longer regimens are commonly employed in complicated, loculated tuberculous effusions and in TB empyema, however, where penetration of anti-TB drugs across the thickened or calcified pleural rind may be limited. Reduced maximal concentration and slower time to achieve maximal concentration compared with serum has been reported for anti-TB drugs in TB empyema, causing concern around evolving drug resistance during the course of treatment [104–106]. Suggested strategies to counter this poor penetration include high-end dosing of anti-TB medications [39] and monitoring of therapeutic drug levels in the pleural fluid [105], as well as direct administration of anti-TB medications into the pleural space [107], but evacuation of the infected space, either by drainage or surgically, is usually the central tenet of management in these cases. Extended treatment durations have also been suggested for subgroups of patients such as those receiving empiric therapy (as can frequently be the case in pTB) or PLHIV, although data supporting this strategy are limited [18, 19, 108].

The treatment of drug-resistant pTB should follow international guidelines for the treatment of drug-resistant pulmonary TB and should be undertaken in an experienced centre. Where clinical suspicion of drug-resistant pTB is high, every effort should be made to attain an accurate microbiological diagnosis and drug sensitivity profile, including performing bronchoscopy or thoracoscopy if necessary [1].

Corticosteroids

There is no definitive evidence that steroids are beneficial in the management of pTB, and their routine use is not recommended [109]. A Cochrane review suggested a possible reduction in the risk of residual pleural effusions, pleural adhesions and pleural thickening; however, there is a coinciding increased risk of adverse health effects associated with steroid administration, including Kaposi sarcoma in PLHIV [110, 111].

Pleural fluid drainage and intrapleural fibrinolytics

TB pleural effusions causing dyspnoea should be drained to provide symptomatic relief [18]. There is also a role for drainage of TB empyema as source control and to reduce the infectious burden [18]. Aside from these scenarios, the evidence regarding the potential benefits of routine drainage of TB pleural effusions is limited and inconsistent [30]. Some studies have shown that early drainage leads to minor improvements in residual pleural thickening and pulmonary function tests compared with standard treatment alone [30, 112], while other studies did not reflect these benefits from early intervention [113].

Drainage facilitated by the instillation of intrapleural fibrinolytics such as urokinase has been shown to reduce residual pleural thickening, improve pulmonary function results and accelerate resolution of the effusion compared with drainage alone in both free-flowing and loculated TB pleural effusions [114–120]. However, the optimal regimen has not yet been established.

Surgery

In a select number of cases, medical thoracoscopy for removal of adhesions in loculated TB pleural effusions may be an effective option [121]. However, surgical intervention with decortication and/or pleurectomy may be required in cases of pleural thickening causing encasement of the lung or TB empyema to control infection, relieve symptoms and prevent progression to fibrothorax. Video-assisted thoracoscopic surgery

techniques have shown comparable results to open thoracotomy and decortication [122]. Studies have shown no increased risk of mortality but do report morbidity reaching 33%, most commonly due to persistent air leak [123, 124]. Complications appear to be more common amongst patients with chronic empyema as compared with acute, suggesting a potential role for earlier intervention [124].

Conclusion

pTB is a common entity but presents unique clinical challenges, particularly around diagnosis and drug sensitivity testing of this often paucibacillary disease. Progress is ongoing in finding new biomarkers to aid diagnosis, and increasingly sensitive PCR-based testing has the potential to improve diagnosis and provide crucial information on drug resistance profiles in the future.

Key points
- pTB is common, but presents unique challenges in terms of diagnosis and management.
- pTB refers to a wide spectrum of disease, including simple effusions that can spontaneously resolve, purulent TB empyema that can evolve into severe chronic sequelae, and TB-associated lipid effusions.
- The gold standard for diagnosis of pTB is based on pleural microbiology and/or histopathology, but adjunctive diagnostic investigations can aid diagnosis in practice.
- Treatment of pTB is similar to that of pulmonary TB, but penetration of the pleural space may be suboptimal in complicated effusions, and drainage may be indicated.

Self-evaluation questions
1. What is the postulated aetiology of TB pleuritis?
2. What is the gold standard for the diagnosis of pTB, and what is the best method of obtaining specimens to achieve this?
3. If a diagnostic investigation has a high PPV for diagnosis of pTB in a region with a high TB prevalence, is it likely that it will have a higher or lower PPV in a region with a low TB prevalence?
4. What is the recommended duration of treatment for pTB?

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Suggested answers

1. TB pleuritis is caused by a delayed hypersensitivity reaction precipitated by the presence of Mtb bacilli in the pleura and the pleural space. Mtb accesses the pleural space either by direct extension from overt parenchymal disease, or by rupture of a subpleural caseous focus. Early neutrophilic infiltration is followed by a prolonged infiltration of sensitised T-lymphocytes that mount a highly efficient anti-TB response, giving rise to the paucibacillary nature of TB pleuritis.

2. Detection of Mtb in pleural fluid or pleural tissue, and/or demonstration of caseating granulomata on pleural biopsy, ideally in the presence of AFB. Medical thoracoscopy to obtain pleural biopsies for histology and culture offers the highest diagnostic yield.

3. Lower. As the number of cases within the population increases, the PPV of a diagnostic test will increase while the negative predictive value (NPV) will decrease. As the number of cases within the population decreases, the PPV will decrease and the NPV will increase.

4. A standard 6-month regimen is recommended for drug-sensitive pTB, but longer regimens are commonly employed in complicated, loculated tuberculous effusions and in TB empyema.