**Post-tuberculosis lung disease:** Clinical review of an under-recognized global challenge

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ABSTRACT

An estimated 58 million people have survived tuberculosis since 2000, yet many of them will suffer from post-tuberculosis lung disease (PTLD). PTLD results from a complex interplay between organism, host and environmental factors, and affects long-term respiratory health.

PTLD is an overlapping spectrum of disorders that affects large and small airways (bronchiectasis, obstructive lung disease), lung parenchyma, pulmonary vasculature, and pleura, and may be complicated by co-infection and haemoptysis. People affected by PTLD have shortened life-expectancy, increased risk of recurrent tuberculosis, but predictors of long-term outcomes are not known. No data is available on PTLD in children and on impact throughout the life-course. Risk-factors for PTLD include multiple episodes of tuberculosis, drug resistant tuberculosis, delays in diagnosis and possibly smoking.

Due to a lack of controlled trials in this population, no evidence-based recommendations for the investigation and management of PTLD are currently available. Empirical expert opinion advocate pulmonary rehabilitation, smoking cessation and vaccinations (pneumococcal, influenza). Exacerbations in PTLD remain both poorly understood and under-recognised. Among people with PTLD the probability of tuberculosis recurrence must be balanced against other causes of symptom worsening. Unnecessary courses of repeated empiric anti-tuberculosis chemotherapy should be avoided.

PTLD is an important contributor to the global burden of chronic lung disease. Advocacy is needed to increase recognition for PTLD and its associated economic, social and psychological consequences and to better understand how PTLD sequelae could be mitigated. Research is urgently needed to inform policy to guide clinical decision making and preventative strategies for PTLD.

INTRODUCTION

Post-tuberculosis lung disease (PTLD) has been overlooked as a significant cause of chronic lung disease for the last 50 years. In the first half of the last century much was written about post-tuberculosis complications. However, the advent of effective chemotherapeutic agents to treat tuberculosis, the focus of the international tuberculosis research and clinical community shifted towards diagnostics and anti-tuberculosis treatment, with the aim of improving disease survival.

This is now changing: the last decade has seen a renewed focus on the high burden and damaging impact of the long-term sequelae of tuberculosis disease, for individual patients, their households, and their communities.[1] The 1st International Post-tuberculosis Symposium was held in 2019 ([www.post-tuberculosis.com](http://www.post-tuberculosis.com)) to bring together patients, clinicians and researchers working in this area, in order to advocate for patients suffering with post-tuberculosis complications, and to identify existing knowledge and evidence gaps.[2,3] PTLD was an area of particular interest at the symposium, and was defined as “evidence of chronic respiratory abnormality, with or without symptoms, attributable at least in part to previous pulmonary tuberculosis".

In this review, we summarise current thinking around PTLD and highlight research priority areas. However, we caution that PTLD must be viewed as only one of several possible consequences that may occur after tuberculosis. Many other organ systems can be permanently affected by tuberculosis and may result in significant disability, and the importance of economic, social and psychological impacts, including stigmatization, cannot be overstated.

EPIDEMIOLOGY

Last year an estimated 10 million people worldwide suffered from active tuberculosis disease, the vast majority of these cases involved the lung. Among patients who receive anti-mycobacterial treatment, global treatment success rates average 85%, and the World Health Organisation (WHO) estimates some 58 million lives were saved through tuberculosis diagnosis and treatment between 2000 and 2018 alone.[4]

Emerging data suggests a high burden of residual morbidity and mortality amongst tuberculosis survivors, even after treatment completion. Even in high income countries, the observed mortality rates of tuberculosis survivors are significantly higher (three to six times) than those of the general population.[5–7] According to Romanowski et al., cardio-vascular disease is the leading cause of the excess deaths after tuberculosis treatment completion[5], while in contrast, a large Brazilian cohort study found respiratory disease to be the most frequent cause of excess deaths in the first year after tuberculosis diagnosis.[7]

The number of PTLD related publications has increased significantly in recent years [1], and includes data from large international population-based studies investigating the global burden of chronic respiratory diseases in low-, middle-income countries (LMICs). Taken together, there is now convincing evidence for the existence of chronic lung disease after pulmonary tuberculosis, that contributes to excess morbidity after treatment completion. Findings from The Burden of Obstructive Lung Disease (BOLD) study and the PLATINO study [8,9], together with other clinical studies and systematic reviews, have consistently demonstrated an association between previous tuberculosis disease and abnormal lung structure and function.[10–13] Several large, prospective cohort studies are under way, evaluating the clinical spectrum, characteristics and severity of PTLD and its evolution over time, with their early data supporting previous findings.[14]

Despite this growing body of data, accurate estimates of the global burden and morbidity associated with PTLD remain limited. Such estimates have been hampered by the diverse clinical spectrum of PTLD presentations (see below), limited correlation between physiological, radiological, symptom and outcome data with different ways of measuring disease, and heterogenous case definitions. Current estimates of residual spirometric abnormalities after tuberculosis vary widely according to the population under study, and range from 34% to 74%, with estimates for obstructive and restrictive physiology ranging from 18.4% to 86%, and 16.1% to 29.7%, respectively.[12–15] Spirometry alone may underestimate post-tuberculosis lung damage when measured against either radiology or extended physiology (e.g. diffusing capacity and plethysmography).[14,16]

Consensus achieved at the 1st International Post-tuberculosis Symposium regarding these patterns and definitions, in conjunction with a number of ongoing prospective cohorts, will hopefully help to clarify these estimates. However, even with improved definitions, post-tuberculosis patients in both high- and low-income settings are frequently exposed to multiple concurrent respiratory exposures, including smoking, cannabis use, indoor biomass fuels, and occupational exposures, such that it may remain challenging to attribute the burden of lung disease due to tuberculosis alone within this group.

PATHOGENESIS

PTLD is a result of the interplay between direct damage caused by the tuberculosis organism in the lower respiratory tract, and the host immune response.[13,17] These processes result in airway distortion, reduced elasticity, destruction of the muscular components of bronchial walls or damage to the lung parenchyma and vasculature, which lead to structural pathology and anatomical distortion on imaging, and abnormal respiratory physiology with abnormal spirometry, altered lung volumes and impaired diffusing capacity.[17] The host-immune relationship in tuberculosis is extremely complex, and beyond the scope of this review. However, the heterogeneity of lung damage observed between pulmonary tuberculosis patients may be explained by variation in the nature and severity of the host immune response, pathogen characteristics, and the host-pathogen interaction.[13] We highlight a few key concepts relevant to the development of PTLD here.

Following inhalation, *Mycobacterium tuberculosis* must evade the innate immune defences of the respiratory tract in order to progress to disease. After negotiating airway epithelial cells, the organism may infect phagocytes such as dendritic cells and alveolar macrophages where it not only survives but replicates.[18] This initiates an anti-inflammatory response that blocks reactive oxygen and nitrogen intermediate production and reduces the acidity of the phagosome, tasked with attempting to contain the bacilli.[19] The alveolar macrophage is subsequently destroyed by the escaping organisms after replication, which in turn attracts other inflammatory cells such as neutrophils. Meanwhile, antigen presenting dendritic cells have travelled to lymph nodes by 6-8 weeks to activate and recruit T lymphocytes that migrate to the site of infection to proliferate and form early granulomas.[20] The heterogeneity of lung damage observed between individuals with (treated) pulmonary tuberculosis may be explained by the host-pathogen interaction and perhaps the variability in gene coding for the complex array of host immune responses.[13] It is important to mention at this point that the prompt initiation of (effective) anti-tuberculosis treatment may mitigate host damage by eradication of the initiating stimulus.[21] Nonetheless, despite appropriate treatment, some patients develop cavitation, bronchiectasis, fibrosis and other irreversible structural changes. Whilst the precise mechanisms are not yet fully understood, there are four important components; 1) the process of granuloma formation and resolution, 2) cytokines production including tumour necrosis factor alpha (TNF), interleukins (IL), 3) transcription factors including hypoxia inducible factor (HIF) and 4) enzymes such as the matrix metalloproteinases (MMP).[13] Granulomas are complex structures containing natural killer (NK) cells, neutrophils, T and B lymphocytes surrounding a necrotic core of infected alveolar macrophages. The granuloma may contain many or few bacilli and rather than being protective to the host, may aid mycobacterial proliferation and lung destruction.[22] Animal studies suggest TNF alpha may perpetuate necrosis however low levels may reduce macrophage activity.[23] The MMP’s are a group of 28 different proteases implicated in lung injury and remodelling through the degradation of extracellular matrix components. Hypoxic conditions have been shown to up-regulate MMP-1 via HIF which may partly explain the greater tissue destruction seen in patients with tuberculosis disease and cavities.[24] A greater understanding of the immuno-pathogenesis and of the underlying genetic factors that regulate genetic factors that regulate these immune responses will lead to improved respiratory outcomes in PTLD, through integration of immune-modulating host directed therapies in the treatment of pulmonary tuberculosis. Finally, environmental and inhaled factors (e.g. smoking), may play an as-yet undetermined modifying role in the host-pathogen interaction, worsening outcomes after treatment completion.

CLINICAL PATTERNS OF PTLD

Patients after tuberculosis present with a wide range of consequences from completely asymptomatic to severe disability. PTLD is heterogeneous, and includes pathology affecting the airways, parenchyma, pleural and pulmonary vascular compartment. Multiple patterns of pathology can be seen within a single patient, between or within areas of the lung (Table 1). Post-tuberculosis bronchiectasis can range from simple traction to actual disease of the bronchi, and the natural history of this disease may be different from other forms of non-CF bronchiectasis.

Airways pathology

Large population-based studies, systematic reviews, and clinical cohort work suggests that previous tuberculosis-disease is associated with chronic airway obstruction [8,10,11,25–29], reduced lung volumes [8,15,30], and mixed patterns of disease. Few data are available describing the trajectory of spirometry volumes over time from the point of tuberculosis diagnosis, through to treatment completion, and into recovery, but modelling data suggest limited and incomplete recovery over time [31], and this finding is supported by emerging prospective follow up data.[14] A recent study in a small cohort using quantitative computerized tomography (CT) imaging and plethysmography demonstrated an evolution of increased airway gas-trapping, even after treatment completion.[16]

Structural pathology

There are no clinically validated tools for the description or severity scoring of structural pathology on imaging, after pulmonary tuberculosis disease. However, changes seen on chest radiographs (CXR) and CT include residual cavitation, bronchiectasis and fibrotic change, often with anatomical distortion, and destroyed lung tissue [11,14,32,33] (Figures 1 and 2). A high burden of residual inflammatory changes including consolidation, ground glass change, and nodules have been observed at tuberculosis treatment completion, with metabolic activity in these lesions appearing to fluctuate over time on PET-CT imaging – the clinical significance of this ongoing inflammation is not yet clear. [34,35]

Pulmonary vascular disease

The burden of pulmonary vascular disease amongst the post-tuberculosis population remains poorly defined, but is thought to be secondary to lung damage, and may be common in the context of extensive pulmonary disease [36,37], with clinicians in high-burden settings frequently encountering patients with advanced cor pulmonale. More data on the incidence and prognostic implications of pulmonary hypertension amongst tuberculosis survivors is required, to elucidate the pathophysiology, outcomes and potential therapeutic options.

Aspergillus related disease and Haemoptysis

Bronchiectasis and fungal diseases with subsequent haemoptysis are severe, potentially life-threatening complications after successful tuberculosis treatment, and form an important part of the PTLD spectrum. Data on the burden of aspergillus disease amongst tuberculosis survivors in LMICs is limited, with mixed results, largely due to the challenge in containing the imaging, serology, and microbiology required for diagnosis. In a recent cohort of 405 survivors of a successfully treated first episode of pulmonary tuberculosis from Malawi, examined at treatment completion with high resolution computed tomography (HRCT), some form of post-tuberculosis bronchiectasis was found in 170 (44.2%).[14] Moderate to severe cystic bronchiectasis were found in 49 patients (12.7%), with a higher prevalence in HIV negative (18.9%) as compared to HIV positive (8.5%) patients. Mycetoma were present in 5 (1.3%) patients, and Aspergillus IgG were found in 2 (0.8%).[14]

After inhalation of Aspergillus species, early innate immune reaction activates alveolar macrophages and epithelial cells to trigger neutrophil recruitment and reduce fungal burden.[38] In pre-existing structural lung damage, e.g. persistent cavitary lesions after healed tuberculosis, chronic necrotizing pulmonary aspergillosis with slowly progressing invasive fungal pneumonia and inflammatory necrosis are a classical sequelae.[38,39] On a world-wide scale, it has been recognized that previous tuberculosis is by far the most common risk factor for chronic pulmonary aspergillosis (CPA), with some researchers estimating 5-year prevalence rate of 18% after tuberculosis treatment [40], however estimates vary widely, and evolution over time may be an important factor.[14,41,42] In cases of CPA, chronic inflammation leading to increased vascularization with bronchial arteries and the feared complication of profound haemoptysis and asphyxia may result. Diagnostic criteria for CPA include the presence of respiratory or constitutional symptoms for at least 3 months, suggestive radiological findings and serological or microbiological evidence of aspergillus.[43]

CHILDHOOD POST–TUBERCULOSIS LUNG DISEASE AND LUNG DEVELOPMENT

An estimated 1.1 million children <15 years develop tuberculosis each year, with paediatric disease accounting for an estimated 10% of the total tuberculosis disease burden in LMICs. [4] Children <5 years have a high risk of disease progression following infection, with risk declining in children of primary school age (5 to <10 years) and rising again during puberty, [44,45] such that almost 60% of all paediatric cases of tuberculosis disease occurred in children <5 years of age.[46] These young children and especially those <2 years of age, also have high risk of severe and disseminated disease.[47,48] Despite the high burden, there are currently no data available on the impact of tuberculosis on long-term child lung health.

Lung development starts in utero, and continues through early adulthood, when lung growth plateaus.[49,50] Data suggest that alveoli continue to increase in number, size and complexity into early adulthood [51] and early lung insults have been shown to lead to alterations in lung growth and development, and potentially permanent loss of lung function.[49,52] The extent to which insults to the developing lung are associated with increased risk of chronic respiratory illnesses in later life depends on the underlying cause, timing and significance of such insults. [53] Numerous cohort studies have shown that there is an association between lung function in childhood and adulthood [54,55], and lower respiratory tract infections (LRTIs) during infancy have been shown to reduce lung function in childhood [56,57]. A longitudinal study by Githinji and colleagues [58] in HIV infected adolescents recently found that prior history of tuberculosis or severe LRTIs were independently associated with consistent lower lung function trajectories. This finding suggest tuberculosis has an impact on lung function, however prospective and more detailed data about type and severity of tuberculosis episode and its impact on lung health is required.

The pathophysiology of paediatric pulmonary tuberculosis is different from adult type tuberculosis disease, with less destructive cavitary disease as seen in adults and adolescents. Nevertheless, paediatric pulmonary tuberculosis represents a wide disease spectrum, both in terms of severity and typical patterns, which is often related to age at disease presentation. Children may present with uncomplicated lymph node disease, complicated lymph node disease with airway compression and lobar collapse, bronchopneumonia, miliary tuberculosis, adult-type cavitary disease, pleural effusion or a peripheral opacity with associated lymphnode enlargement.[59,60] Young infants are particularly at risk for severe intrathoracic and disseminated tuberculosis associated with increased morbidity and mortality [47,48], while adolescents present in a manner similar to adults, with destructive pulmonary disease. The variability in disease presentation in the different age groups and the developing lung, combined with the intricacies of lung function assessment in young children causes challenges in investigating long-term respiratory outcomes in children. Overall, tuberculosis in childhood likely has an effect on an individuals’ attained lung function (i.e. lower trajectory) and potentially the rate of decline later in life (Figure 3). This potential impact may be subclinical throughout childhood, but may result in a symptomatic respiratory morbidity threshold being crossed at an early adult age. [49,61] Paediatric data is urgently needed to establish the burden of PTLD in children and this should include lung function measurements regardless of symptoms and social determinants for lung health.

CLINICAL OUTCOMES ASSOCIATED WITH PTLD

Prospective data on the long-term outcomes of PTLD remain limited, and no validated prognostic scores are yet available. However, cross sectional data from tuberculosis survivors suggest a high prevalence of chronic respiratory symptoms some years after treatment completion, including breathlessness and chronic cough. [62,63] These symptoms can be stigmatizing and lead to repeated investigation or perhaps empirical re-treatment for suspected recurrent tuberculosis disease. [64,65] The frequency and severity of respiratory exacerbations amongst those with residual structural and physiological abnormalities is poorly described, but many face reduced quality of life and impaired functional capacity,[66] and those with extensive PTLD and destroyed lung tissue experience high rates of hospitalization and respiratory-related mortality.[67]

Adults previously treated for tuberculosis in high tuberculosis-burden settings have an increased risk of developing incident tuberculosis, compared to those who are tuberculosis naïve, including both disease relapse and recurrence.[68] The extent to which this is driven by underlying impaired immune function in damaged lung tissue, or underlying socioeconomic risk factors and sustained increased exposure also remains unclear.[69] Although population level data suggest increased mortality amongst tuberculosis survivors compared to tuberculosis naive adults,[5–7] the extent to which PTLD contributes to this excess mortality remains unclear.

RISK FACTORS FOR PTLD

As described above, reasons for the heterogeneity of pattern and severity of PTLD between tuberculosis patients are not known, but likely involve host, pathogen and environmental factors.[13] Investigation of these risk factors is ongoing. Human immunodeficiency virus (HIV) co-infection is anticipated as a key effect-modifier in the relationship between tuberculosis disease and residual lung damage, and the extent of PTLD in HIV co-infected patients likely reflects a balance of the protective effect of low CD4 counts and impaired immune responses to mycobacterial infection at tuberculosis diagnosis [70–72], with the impact of immune reconstitution for those initiated on anti-retroviral therapy concurrently with tuberculosis treatment.[13] Preliminary findings suggest that HIV co-infection may be associated with reduced severity of PTLD,[14,73] but these data are limited and require confirmation in further studies.

More severe lung damage is observed in the context of multi-drug resistant tuberculosis (MDRTB) [74,75], with recurrent episodes of disease [72], and where tuberculosis diagnosis is delayed.[70,71,76] The influence of concurrent respiratory exposures is less clear. Tobacco smoking has been shown to have a positive association with PTLD in few studies.[72,77] Environmental factors such as indoor air pollution or occupational risks and their distribution in the respective populations may worsen PTLD and/or may lead to concurrent lung damage, thereby explaining the severity, heterogeneity and inconsistency of respiratory outcome data which were observed in specific sub-groups such as females [71,73] or miners.[72,76]

MANAGEMENT

The lack of clinical intervention studies in this patient population mean that there are currently no evidence based international guidelines for the management of PTLD.[1] This represents a challenge for both treating clinicians and patients who experience persistent and disabling respiratory symptoms despite mycobacteriological cure. Whilst evidence-driven guidelines are urgently needed, expert opinions must be sought to bridge the management gap. We discuss below some of the treatment options available and identify the (many) gaps in the published literature to date.

Tuberculosis disease prevention

Undoubtedly, the most important step in the management of PTLD should be its prevention. Where possible, providing prophylactic tuberculosis treatment to those people with latent infection at high risk of progression to disease including household contacts and people living with HIV [78] has potential benefits for population lung health as well as tuberculosis control. The upstream social determinants of tuberculosis disease must also be addressed. Studies evaluating the impact of such interventions should evaluate impact on residual lung pathology, as well as their effect on reducing TB related mortality.

Minimising tuberculosis related lung damage

Once tuberculosis disease is established, early diagnosis and effective treatment is crucial for limiting the lung damage caused.[21] Delayed diagnosis and longer disease durations in MDRTB are likely important factors in the observed greater pulmonary function impairment in drug resistant, compared to drug susceptible tuberculosis.[79]

Smoking cessation interventions have proven efficacy for asthma and COPD. In a non-randomized study from Malaysia, tuberculosis patients that received smoking cessation advise and nicotine replacement therapy had earlier sputum smear conversion and better quit rates and treatment outcomes at 6 months.[80] Even though no specific study for the PTLD population exists, smoking cessation should be an integral part in the management of PTLD.

Because excessive inflammation may contribute to lung damage, corticosteroids during tuberculosis treatment have been hypothesized to reduce lung function loss. However, among 118 patients with pulmonary tuberculosis given systemic corticosteroids in addition to tuberculosis treatment, there was no change to airflow obstruction at 1 year follow up, compared to tuberculosis treatment alone.[81] Thus, corticosteroids cannot be advocated for. Given the broad immunosuppressive action of steroids and their adverse metabolic and cardiovascular effects, a more precise method of immunomodulation may still hold promise. Preliminary studies show that metformin use among patients on tuberculosis treatment resulted in a reduction to the levels of MMP 1,2,3,9, and 12, which correlate to the degree of pulmonary involvement and degree of cavity formation.[82] To date, there are no randomized trials that assess lung function outcomes following the use of metformin among patients with pulmonary tuberculosis, however other host-directed therapies are underway.

Managing established PTLD

For those with established PTLD, treatments that are widely used for other chronic lung diseases such as COPD, bronchiectasis, asthma and pulmonary fibrosis may be of benefit, however, specific evidence in PTLD remains lacking.

Outpatient pulmonary rehabilitation has been shown to be widely accepted by patients and results in improved symptom scores and health-related quality of life in tuberculosis survivors.[83]

Inhaled bronchodilators may be useful in the management of PTLD in patients with airflow obstruction to reduce symptoms of breathlessness and improve (or prevent) a decline in lung function. However, there are no long-term randomised trials to inform efficacy, effect size, or medication choice. A single randomized trial of PTLD patients with moderately severe disease found that daily use of the long acting beta agonist (LABA) inhaler, indacaterol (dose 150mcg), resulted in a significant improvement in lung function (trough FEV1) and dyspnoea score at 8 weeks compared to placebo, but no improvement in quality of life was achieved.[84] A smaller, non-randomized study demonstrated significant improvements in lung function from baseline among tuberculosis survivors with destroyed lung and FEV1 <80% that received the long acting muscarinic antagonists (LAMA) 18mcg tiotropium for 2 months, but no quality of life measure was studied.[85] Thus, there is currently no sufficient evidence to generally recommend bronchodilators in PTLD.

Inhaled corticosteroids may be associated with an increased risk of mycobacterial disease when used amongst tuberculosis survivors (including re-infection or relapse).[86–88] Inhaled steroids may also alter the respiratory microbiome and increase the risk of non-tuberculous infections and the rate of “exacerbations”.[89] Currently, there is insufficient data to support their use, and they should probably be avoided until evidence emerges.

Clinical challenges in the management of post-tuberculosis bronchiectasis include prophylaxis and treatment of bacterial and fungal infectious complications. Since management strategies specifically for post-tuberculosis bronchiectasis do not exist, recommendations developed for non-CF bronchiectasis [90] may be applied. The mainstay of therapy in the context of structural lung disease is to avoid the vicious cycle of impaired mucociliary clearance, chronic infection and inflammation, leading to further structural lung damage.[90] The presence or absence of infection with pseudomonas aeruginosa determines if – after exclusion of additional non-tuberculous mycobacterial infection - long term macrolide treatment or long-term inhaled antibiotic treatment is preferred. If pseudomonas aeruginosa is isolated for the first time, eradication treatment should be given. However, evidence for anti-pseudomonal strategies in PTLD and LMICs remains unclear and may be challenging due to inherent resource limitation. Short or long acting bronchodilators, mucolytic (hypertonic saline) and regular airway clearance are beneficial in non-CF bronchiectasis, especially if patients have difficulty with sputum expectoration and airway clearance.

Exacerbations of PTLD are a priority area for research. Little data exists to inform management, or policy decisions, yet exacerbations are likely to both identify individuals at increased risk, and those who disproportionally access medical care. As noted above, patients previously treated for tuberculosis are at increased risk of recurrence, and this should be actively excluded with exacerbations. However, exacerbations of PTLD are frequently and erroneously re-treated with empiric treatment for “recurrent tuberculosis” without microbiological evidence, exposing patients to harm.[65] Adding complexity, Xpert nucleic amplification tests yield a 14% (one-in-seven) false positive rate in retreatment cases, and may remain positive for years after successful tuberculosis treatment completion.[91] Thus decisions on initiating tuberculosis retreatment can be difficult, and should be made in conjunction with a careful history, physical examination and sputum microscopy and culture (if possible), with planned review at 4 to 6 weeks.

Fungal disease and haemoptysis are characterized by nonspecific clinical presentation, and the diagnosis may be delayed. In chest CT, an early pulmonary nodule, a “halo sign”, defined by a ground-glass opacity around a nodule, or fungal balls in a pre-existing cavity are classical presentations of CPA. The diagnosis is supported by fungal elements in bronchoalveolar lavage or by the presence of galactomannan or beta-D-glycan. Serum aspergillus precipitins are more sensitive and appear to correlate with disease activity.[92] CPA is associated with a high morbidity and mortality [41], and it has been recognized that the presence of aspergillus Ig-G and Ig-M antibodies predispose for haemoptysis complications.[93] Unfortunately, availability of diagnostic tests can be challenging in LMICs, where the highest prevalence is anticipated. The recommended first-line treatment of choice for invasive CPA is voriconazole with therapeutic drug monitoring.[38,39] Antifungal therapy leads to improvement in symptoms and radiological findings, but relapses after several months of treatment are common, and life-long therapy may be necessary.[41] Other recommended antifungal agents include itraconazole and posaconazole, while intravenous liposomal amphotericin B and caspofungin are less effective and more complicated to apply, and fluconazole has no anti-aspergillus activity. Surgery with resection of cavity and aspergilloma offers a chance for cure in operable patients with a solitary lesion. Symptomatic patients with a simple aspergilloma can be managed with surgery alone, but in more complex cases, pre- and postoperative antifungal therapy is recommended for at least 2 months. Surgery also is a last-line therapy in CPA-associated major haemoptysis.[41] However, in daily practice in LMIC’s with a high PTLD burden, many of these therapeutic and surgical options are either unavailable or unaffordable, limiting clinician’s choices.

Major haemoptysis, defined by a loss of 300-600 ml of blood within 24 hours and/or blood causing airway obstruction is a major life-threatening emergency.[94] It is not only a well-known and feared complication of active pulmonary tuberculosis and of chronic bronchiectasis of any cause, but often the presenting syndrome of an unrecognized CPA. Under these circumstances, clinicians frequently use bronchial artery embolization to address active bleeding, although recurrence is common. [95,96] Other interventional or complex surgical options have also been applied with good results.[97,98] Unfortunately for many patients with PTLD associated haemoptysis, surgical resection is not an option due to either the overwhelming extent of disease, or poor physiological reserve.

For now, it seems reasonable that, as in other forms of chronic lung diseases, smoking cessation, vaccination and pulmonary rehabilitation should be considered in a PTLD management plan. However, well designed randomized trials are urgently required to identify feasible and scalable interventions to improve the outcomes of PTLD patients. In order for these trials to move forward, consensus is needed on how patterns and severity of PTLD are defined, how disease is measured, and outcomes to be evaluated over time.

ECONOMIC, SOCIAL AND PSYCHOLOGICAL IMPACT

It is well known that tuberculosis is driven by poverty and is associated with a catastrophic financial burden on affected, mostly low-income, households.[99] High patient costs not only worsen the financial situation of households, but also negatively influence tuberculosis treatment outcomes.[100] The need to mitigate catastrophic costs associated with tuberculosis disease has been prioritized within The End TB agenda. People cured of tuberculosis may find themselves with long-term socio-psychological consequences of the acute disease episode and PTLD may result in ongoing economic, social and psychological distress. However, data on these impacts of tuberculosis, beyond treatment completion remain limited and their impact on long-term wellbeing is poorly defined.

There are currently no recommendations for the evaluation on mental or health-related quality of life (HR-QoL) in people beyond tuberculosis treatment. There is limited evidence that people who are microbiologically cured of tuberculosis have substantially lower HR-QoL compared to those with similar pulmonary risk factors or healthy controls.[30,100–103] Preliminary modelling data suggest that inclusion of post-tuberculosis morbidity and mortality may increase estimates of disability adjusted life years (DALYs) by at least 54% (and potentially as much as 174%), when permanent disability and early mortality is also considered.[69] Further, social stressors such as discrimination and stigma are common among people with tuberculosis, and increasingly recognized as factors that compromise mental health, quality of life and tuberculosis treatment outcomes long-term.[2,3,104] There is an urgent need for robust epidemiological and large multi-country cohort studies on the economic and psychosocial impact beyond tuberculosis cure.

FUTURE AND CONCLUSION

It is true to say that currently we have more questions than answers around PTLD, its determinants, natural history and management. Yet in recent years, there has been an expansion of interest in this complex condition, with the realization that the high prevalence of PTLD in LMICs, where 80% of the world’s population resides, may in fact make it an extremely important form of chronic lung disease and respiratory impairment worldwide.

Several priority research areas have been identified. Firstly, epidemiological research is needed to better define the risk factors and predictors for PTLD, as well as long-term functional outcomes, and most importantly causes and predictors of the observed premature mortality in tuberculosis survivors. This includes the burden and nature of PTLD in children, and its long-term effects on the individual’s lung health thought life. Secondly, a better understanding of the immunological drivers of PTLD is needed, combined with prevention and host-directed strategies during treatment to avoid or minimize damage during tuberculosis disease. Thirdly, research into effective treatment of the various PTLD phenotypes is urgently needed, for those with established PTLD in whom primary prevention is too late. Finally, it must be remembered that PTLD is only one of many complications after tuberculosis, which significantly effects the economic, social and psychological wellbeing of individuals, families and societies. This broader impact needs to be defined with a view to designing effective intervention strategies to minimise this impact.

In conclusion, PTLD, for many decades forgotten, is now being recognised as an important cause of chronic lung disease globally, particularly in LMICs. Whilst there is an emerging literature on PTLD, collaborative research is urgently needed to inform our understanding of the natural history, prevention and treatment of PTLD and to allow for the development of much needed evidence-based management guidelines.

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Figure Legends

Figure 1.

Two patients with post-tuberculosis lung disease, exhibiting bronchiectasis predominantly in the right lower lobe with residual nodularity bilaterally (Panel A); and bronchiectasis predominantly in the left upper lobe, lingula (Panel B).

Figure 2.

Post-tuberculosis lung disease in four individuals demonstrating: residual cavitation and bronchiectasis in the right lung, with volume loss (Panel A); complete left lung destruction with relatively preserved left lung volume (Panel B); Mosaicism, residual nodularity and lobar destruction /collapse (Panel C), and complete collapse of the left lung with compensatory hyperinflation (Panel D).

Figure 3.

Lungs develop throughout childhood until they reach a plateau a plateau around the age of 20 years. Alveoli appear from week 29 of gestation and continue to form until 2-4 years after birth. After that alveoli continue to increase in number, size, and complexity until early adulthood. It is known that lung function tracks throughout life, meaning that it remains in similar percentile over time. Early life insults can cause de-tracking of lung function. We hypothesize that tuberculosis disease early in life might cause de-tracking of lung function which might remain diminished throughout childhood. This could mean that these individuals will be prone to symptomatic respiratory disease earlier in life. FEV1=forced expiratory volume in 1.