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Post tuberculosis treatment infectious complications

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Recommended Citation

Hsu, D., Irfan, M., Jabeen, K., Iqbal, N., Hasan, R., Migliori, G. B., Zumla, A., Visca, D., Centis, R., Tiberi, S. (2020). Post tuberculosis treatment infectious complications. *International Journal of Infectious Diseases*, 92(Supplement), S41-S45.

Available at: https://ecommons.aku.edu/pakistan_fhs_mc_pathol_microbiol/1246

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ARTICLE INFO

Article history:

Received 13 January 2020

Received in revised form 14 February 2020

Accepted 14 February 2020

Keywords:

Tuberculosis

Post-treatment complication

Sequelae

Pulmonary rehabilitation

NTM

Bronchiectasis

ABSTRACT

Following greater attention and follow-up of patients with treated pulmonary tuberculosis (TB), it has emerged that infections are more likely to occur in this cohort of patients. This comes as no surprise, as pulmonary TB is a destructive process that leads to cicatrization, alteration of parenchyma, bronchiectasis, and scarring of the lung, with reduction of lung volumes and an impact on pulmonary function. In addition to relapse and re-infection with TB, other pathogens are increasingly recognized in post-TB patients. This paper serves as a summary and guide on how to approach the post-TB patient with new signs and symptoms of pulmonary infection in order to ensure optimal management and rehabilitation.

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Introduction and approach

Patients with pulmonary tuberculosis (TB), even after cure, may develop further respiratory infections and lung disease, which may become chronic, leading to greater morbidity and mortality (Hnizdo et al., 2000). Exacerbations of chronic obstructive pulmonary disease (COPD), bronchiectasis, and pneumonia are more frequent after pulmonary TB (Amaral et al., 2015; Byrne et al., 2015). Lung aging is accelerated, especially in the presence of smoking and atmospheric pollution (Glaser et al., 2015; van Zyl Smit et al., 2010). Colonization and infection with non-tuberculous mycobacteria (NTM) and *Aspergillus fumigatus* are common in individuals with a degree of pre-existing lung destruction (Brode et al., 2014; Pasqualotto and Denning, 2008). In addition to TB recurrence or reinfection, all of these conditions need to be considered in the differential diagnosis when patients present with

symptoms following the treatment of pulmonary TB and/or any evidence of lung function deterioration or TB sequelae is noticed.

Post-TB infections may present with similar clinical features to pulmonary TB, with haemoptysis being a common manifestation. The authors recommend taking a chest X-ray at the end of TB treatment, as this is useful for future comparison. The presence of cavitory disease may prompt the clinician to consider baseline *Aspergillus* serology. Vaccination for influenza virus may be useful in reducing further infectious insults and inflammation (Oei and Nishiura, 2012; Noymer, 2009). Six-monthly respiratory clinic follow-up in the 2 years after TB treatment may be useful in the monitoring and management of possible COPD and bronchiectasis in a subset of patients with chronic lung disease, who might need pulmonary rehabilitation. Clinicians should also be aware of the possibility, and associated higher mortality, of NTM–*Aspergillus* co-infection (Jhun et al., 2017; Naito et al., 2018).

Chronic pulmonary aspergillosis: clinical picture and management

Chronic pulmonary aspergillosis (CPA) encompasses a spectrum of disease patterns, often with considerable overlap. The major subtypes of CPA include chronic cavitory aspergillosis (CCA), chronic fibrosing aspergillosis (CFA), aspergilloma, and *Aspergillus*

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nodules. *A. fumigatus* is the causative species, but *Aspergillus niger* and *Aspergillus flavus* infections have also been reported (Pasqualetto and Denning, 2008; Severo et al., 1997). It has been estimated that patients with residual pulmonary cavities of ≥ 2 cm after TB treatment have a 20% chance of developing aspergillomas (British Thoracic and Tuberculosis Association, 1970). Overall estimates of the mortality rate in CPA where treatment is available range from 20–33% in the short-term to 33–80% over a 5-year period (Camuset et al., 2007; Jewkes et al., 1983; Lowes et al., 2017; Ohba et al., 2012).

Clinical features of CPA are usually non-specific and indolent in onset. Common symptoms include weight loss, chronic productive cough, fatigue, dyspnoea, and haemoptysis (Schweer et al., 2014). A simple aspergilloma without concurrent CCA/CFA often causes few or no symptoms.

Chest imaging remains an important diagnostic modality. A chest X-ray or computed tomography (CT) scan can reveal one or more cavities, typically within the upper lobes, of variable size, with or without the presence of pleural thickening and fibrosis (Desai et al., 2015). Cavities can be thin- or thick-walled, and may or may not contain fungal balls. A simple aspergilloma is usually within a single cavity, with limited inflammation, pleural thickening, and fibrosis (Denning et al., 2003).

The mainstay for diagnosis is the detection of *Aspergillus*-specific IgG in serum (Denning et al., 2018; Denning et al., 2016; Takazono and Izumikawa, 2018). ELISA-based commercial assays are more sensitive and specific than conventional *Aspergillus* precipitin testing (Page et al., 2017). Limitations include false-negative results in patients who fail to mount an antibody response, low sensitivity with non-*fumigatus* species, and false-positive results with non-CPA aspergillosis (Takazono and Izumikawa, 2018). Clinical and radiological correlation is therefore paramount (Denning et al., 2018, 2016; Takazono and Izumikawa, 2018).

The sensitivity of galactomannan in bronchoalveolar lavage (BAL) is far superior to that in serum (Sehgal et al., 2019; Shin et al., 2014). PCR-based detection of *Aspergillus* species for CPA diagnosis has been reported to be more sensitive than culture; however false-positive results may occur (Fraczek et al., 2014; Vergidis et al., 2019; Zhao et al., 2016).

Management depends on the extent and type of disease and whether the patient is a candidate for surgical resection (Denning et al., 2016). The risks and benefits of treatment must be considered in each individual patient. Data on the optimal duration and choice of antifungal agents are limited (Agarwal et al., 2013; Kohno et al., 2010). Voriconazole, isavuconazole, or itraconazole are first-line treatment options for individuals with CCA or CFA (Denning et al., 2016; Maghrabi and Denning, 2017; Patterson et al., 2016). Posaconazole is an alternative. Serum therapeutic drug monitoring is essential to optimize dosing initially (Ullman et al., 2018). Amphotericin B, micafungin, or caspofungin are intravenous alternatives if there is failure, intolerance, or resistance to the above treatment options (Denning et al., 2016; Maghrabi and Denning, 2017). With some centres in Western Europe reporting resistance rates of $>25\%$, relative cross-resistance to multiple azoles is an increasing concern (Bueid et al., 2010; Fuhren et al., 2015).

A minimum treatment duration of 4–6 months is recommended for patients with CCA (Denning et al., 2016). However, individuals with progressive disease, poor response, or ongoing immunosuppression may require a longer duration. Lifelong therapy is required in a subset of patients with progressive disease (Patterson et al., 2016). Radiographic variation in cavity/pleural thickening and reduction/resolution of fungal ball can be used for assessment of the treatment response (Godet et al., 2016).

For individuals with a simple aspergilloma, surgical resection can prevent or treat severe haemoptysis (Patterson et al., 2016). Embolization can be done prior to surgery, or in patients for whom surgery is not possible (Denning et al., 2016).

Bronchiectasis: clinical features, management, and rehabilitation

Bronchiectasis may appear in the course of active TB or develop as a sequela of TB. A systematic review of 27 studies that evaluated patients after recovery from TB based on CT imaging reported bronchiectasis in 35–86% of patients (Meghji et al., 2016).

Bronchial stenosis and scarring in post-TB patients or external compression of bronchi by enlarged lymph nodes can lead to retention of secretions and recurrent infection, further leading to destruction and dilatation of the airways. Fibrosis and destruction of the lung parenchyma can also cause bronchiectasis by parenchymal retraction (Kim et al., 2001).

While bronchiectasis may be localized or diffuse, it most frequently affects the apical and posterior segments of the upper lobes (the most common sites of post primary TB) (Smith, 2017).

One of the major complications of bronchiectasis is frequent exacerbations of disease due to recurrent infections, progressively deteriorating lung function and reducing exercise tolerance and quality of life (QoL) (Spruit, 2014; Spruit et al., 2013). This recurring cycle of infection is due to the interplay between structural lung damage, persistent inflammation, bacterial and fungal colonization of the respiratory tract, and mucociliary insufficiency. Frequent infectious exacerbations in bronchiectasis patients are associated with higher rates of hospitalization and increased mortality, as well as incremental costs for the health system (Finch et al., 2015; Spruit, 2014; Spruit et al., 2013). Clinical manifestations of disease include a productive cough – often associated with haemoptysis. Pleuritic chest pain, dyspnoea, fever, fatigue, and weight loss are common clinical features (Smith, 2017).

Microbiology of recurrent infections exclusively in post-TB non-cystic fibrosis (CF) bronchiectatic patients is limited. However, data can be extrapolated from studies on all non-CF bronchiectasis patients, especially from settings with high TB endemicity. Commonly associated microorganisms in infectious exacerbations include *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus* (Dhar et al., 2019). *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, and other members of the *Pseudomonadaceae* family are increasingly recognized as causative organisms (Tunney et al., 2013; Kenna et al., 2017). This change has been attributed to advances in microbial diagnosis, enhanced sputum surveillance, and long-term suppressive antibiotic treatment (Green and Jones, 2015). NTM are also commonly isolated in bronchiectasis patients with infectious exacerbations (Chandrasekaran et al., 2018).

Medical management includes pulmonary rehabilitation (airway clearance through chest physiotherapy, inhaled hypertonic saline, and exercise if indicated) aimed at reducing the frequency and severity of recurrent infections, improving exercise tolerance and QoL (Spruit, 2014; Spruit et al., 2013).

Long-term antibiotics are given to prevent recurrent exacerbation and break this vicious cycle. Several trials have demonstrated a significant reduction in exacerbation frequency using long-term macrolide therapy (either 6 or 12 months) compared to placebo (Altenburg et al., 2013; Serisier et al., 2013). However, this practice may lead to selecting macrolide-resistant microorganisms including NTM. Inhaled antibiotics are also used to reduce the bacterial burden and typically have fewer side effects compared to oral antibiotics. However, tolerability and availability can be an issue with inhaled antibiotics. Occasionally surgical

resection of the involved segment or lobe may be indicated when there is failure of medical management of localized disease (Watanabe et al., 2006).

Non-tuberculous mycobacterial infection

Evidence suggests that the global burden of NTM infection is increasing (Brode et al., 2014). The most frequently isolated NTM from pulmonary samples is *Mycobacterium avium*–*intracellulare* complex (MAC) (Shah et al., 2016). *Mycobacterium kansasii* is another important cause of progressive pulmonary disease. Patients with pre-existing structural lung disease – including bronchiectasis and prior TB – are at risk of developing NTM lung disease (Fowler et al., 2006). NTM co-isolation occurs in 7–11% of patients with pulmonary TB (Damaraju et al., 2013; Hsing et al., 2013).

Clinical features of MAC lung disease are variable and non-specific and include cough, fatigue, dyspnoea, chest discomfort, haemoptysis, weight loss, and fever. *M. kansasii* presents more acutely. Radiological findings for both include parenchymal infiltration, nodules, and cavitation (Christensen et al., 1978; Swensen et al., 1994). Diagnostic criteria include compatible clinical/radiological features with either one or two positive microbiological results from bronchial lavage or sputum samples, respectively, or with suggestive histopathological features on biopsy (Griffith et al., 2007). The advent of accessible whole genome sequencing may change the diagnostic context for differentiation between infection and colonization.

The decision to start treatment for patients who meet diagnostic criteria is influenced by the severity of disease, the risk of progression, the presence of comorbidities, the tolerability of treatment, and the goals of treatment. The presence of fibrocavitary disease is associated with more rapid progression and calls for rapid start of treatment (Griffith et al., 2007). The treatment regimen depends on susceptibility to macrolides. Most guidelines suggest a three-drug regimen comprising rifampicin, ethambutol, and azithromycin or clarithromycin (Griffith et al., 2007; Haworth et al., 2017). Antibiotics can be administered three times a week for individuals with mild to moderate severity and with no evidence of fibrocavitary disease. Patients with severe disease or fibrocavitary disease require daily dosing of rifampicin, ethambutol, and azithromycin or clarithromycin, with consideration of a fourth agent in the form of either intravenous or nebulized amikacin (Haworth et al., 2017). The treatment duration is a minimum of 12 months after sputum culture conversion (Haworth et al., 2017). Therapeutic drug monitoring should be performed routinely for aminoglycosides, and should be considered for other drugs in individuals where there is a concern about malabsorption, drug–drug interactions, or suboptimal adherence (Haworth et al., 2017). There remains an urgent need for research into novel drugs or new combinations of existing drugs for NTM infections.

Prevention and vaccination

Mathematical modelling of epidemiological data suggests that there is an increase in frequency and severity of influenza-associated disease during pandemics and seasonal epidemics in individuals with pulmonary TB compared to healthy individuals (Oei and Nishiura, 2012; Noymer, 2009; Zürcher et al., 2016). Influenza and TB co-infection can impair host immune responses leading to increased susceptibility to secondary bacterial infections (Ballinger and Standiford, 2010; Small et al., 2010). The resultant increased risk of severe outcomes can potentially be

mitigated by timely empirical antiviral therapy in individuals with possible influenza infection. Seasonal influenza vaccination is recommended for patients with chronic pulmonary conditions in most international guidelines (Public Health England, 2019; European Centre for Disease Prevention and Control, 2008). As the severity and chronicity of lung disease differs between individuals with treated pulmonary TB, influenza vaccination should be considered particularly for those with established chronic respiratory disease.

Cigarette smoking is a risk factor for pulmonary infections, as well as a co-factor contributing to rapid lung function deterioration, reduced exercise tolerance, and impaired QoL (Muñoz-Torrico et al., 2016; Spruit, 2014; Spruit et al., 2013). A number of studies have demonstrated a reduction in frequency and severity of exacerbations in individuals with established chronic lung disease (Willemse et al., 2004; Au et al., 2009). Additionally, population-based studies have demonstrated correlations between smoking and the development of adverse outcomes, relapse, and development of drug-resistant TB (Zhang et al., 2016). A comprehensive smoking cessation and pulmonary rehabilitation programme (Chalmers et al., 2015) is likely to be an important strategy in reducing infective exacerbations in patients with established lung disease.

Conclusions and summary

Awareness of post-TB lung health is increasingly important and gaining more attention. It is increasingly recognized that patients completing TB treatment should be followed up in time, especially if there are significant lung changes or cavities. Patients with evidence of COPD/bronchiectasis are particularly likely to experience further infectious insults and decline in lung function, with hampering of quality of life. The authors consider end of treatment spirometry, sputum for acid-fast bacilli, screening for *Aspergillus*, and a chest X-ray to be helpful when assessing a post-TB patient presenting subsequently with potential relapse of TB, non-specific infection, neoplasia, or other sequelae. Smoking cessation, vaccination, preventive antibiotics, and pulmonary rehabilitation may help curb exacerbations, reduce lung function decline, and improve quality of life.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

Approval was not required

Conflict of interest

No competing interest declared.

Acknowledgements

This article is part of the activities of the Global Tuberculosis Network (GTN; Committees on TB Treatment, Working Group on Pulmonary Rehabilitation and Global TB Consilium) and of the WHO Collaborating Centre for Tuberculosis and Lung Diseases, Trondheim, ITA-80, 2017–2020–GBM/RC/LDA. This article is part of a supplement entitled *Commemorating World Tuberculosis Day March 24th, 2020: "IT'S TIME TO FIND, TREAT ALL and END TUBERCULOSIS!"*

published with support from an unrestricted educational grant from QIAGEN Sciences Inc.

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