

The hidden epidemic of post-tuberculosis bronchiectasis

In this issue of *AJTCCM*, Titus *et al.*^[1] report on a retrospective cohort of adult patients with non-cystic fibrosis bronchiectasis in the pulmonology unit at Charlotte Maxeke Johannesburg Academic Hospital, South Africa (SA). In doing so, they respond to the paucity of epidemiological data on the disease, particularly in high tuberculosis (TB)/HIV burden settings such as SA. Given the intensity of respiratory insults across the life stages of people in these settings, it is unsurprising that most epidemiological estimates suggest that the true burden of post-infectious bronchiectasis is largely unrecognised. During the two centuries that followed René Laënnec's first reports of the disease in 1819, relatively little attention has been given to bronchiectasis, which has been rising in incidence and prevalence globally and is associated with substantial socioeconomic costs.^[2] The increasing prevalence of bronchiectasis may partly be due to improved imaging technologies, including computed tomography, but is undoubtedly also driven by the increasing cumulative prevalence of its underlying causes.

The noteworthy findings of the report by Titus *et al.* were: (i) the median (interquartile range) age of the cohort was 49 (38 - 60) years; (ii) there was a slight male predominance (51.2%); (iii) chest radiography was used to support the diagnosis of bronchiectasis in 44.6% of the patients; (iv) TB was the most common attributable cause (77.0%); (v) the majority of the patients experienced at least one exacerbation (62.9%); (vi) over half the cohort received inhaled corticosteroids; and (vii) immunomodulatory macrolide therapy was used in only 10.6% of the patients.

The precise prevalence of bronchiectasis in SA is not known – there have been no large population-based prevalence studies, and there is no national registry for the disease. Globally, the prevalence of the disease varies across geographical regions, reflecting regional differences in socioeconomic factors, the epidemiology of contributory or underlying conditions (particularly the relative prevalence of infectious v. non-infectious lung disease), and the demographic profile of the populations. The prevalence of bronchiectasis in the USA, based on historical medical records and claims data, has been estimated to be between 139 and 213 cases per 100 000 persons, and the prevalence in the UK, estimated from a population-based cohort, to be 566 cases per 100 000 women and 485 per 100 000 men.^[3,4] The prevalence of bronchiectasis in these settings is increased in older persons and in women, patterns that are also consistent with data from Germany, Spain and Singapore.^[5-7] The highest prevalence estimates of bronchiectasis are reported in China, where there are 1 200 cases per 100 000 population >40 years of age.^[8] In India, as in other parts of the world where post-infectious bronchiectasis predominates, patients with bronchiectasis were significantly younger and more likely to be male compared with their counterparts in the US and UK, even after accounting for the generally older general population demographics of the latter.^[9,10] The methods used to establish these prevalence figures vary considerably, and population-based studies from Africa are conspicuously lacking.

The finding that post-TB lung disease is a leading cause of bronchiectasis in this Johannesburg cohort is consistent with the conclusion made by a recent systematic review, which identified

post-infectious bronchiectasis as the most common identifiable cause of non-cystic bronchiectasis in adults.^[9] In Asia, for example, more than two-thirds of adult bronchiectasis was attributable to prior TB, consistent with the findings of Titus *et al.* It is now widely accepted that post-TB lung disease is underestimated, underdiagnosed and under-reported. Successful TB treatment is narrowly defined as the achievement of bacteriological cure or the completion of treatment, irrespective of permanent and/or progressive functional deficits resulting from an episode of TB. The large number of people who have survived an episode of TB represent a population vulnerable and susceptible to chronic respiratory disease, and their numbers will continue to increase until TB is eradicated. The current paradigm of perceiving an episode of TB as a discrete life event is challenged by estimates suggesting that an average of 3.6 potential years of life are lost after a fully treated episode of tuberculosis, and that TB survivors bear an excess mortality burden compared with risk-matched controls who have never had TB.^[11-13]

The incidence of bronchiectasis following an episode of TB has been found to range from 16% to 65%, and superimposition by other bacterial infections is a potential risk factor for the development of bronchiectasis.^[14] In a well-characterised cohort from Malawi, bronchiectasis developed in 44% of people who completed TB treatment.^[15] Given that 54 million people have been treated for TB since the year 2000 globally, and that there are an estimated 300 000 new cases of TB in SA each year,^[16] the implications for bronchiectasis are staggering.

The aetiological spectrum of bronchiectasis in SA and other low- and middle-income settings is to be contrasted with that in Europe, North America and Australia, where idiopathic bronchiectasis predominates and post-TB bronchiectasis is exceedingly rare. These differences present major limitations to generalising research findings, care strategies and clinical guidelines across settings, and emphasise the importance of generating local data. Few, if any, of the recommendations in the timely South African Thoracic Society position statement on the management of non-cystic fibrosis bronchiectasis were based on high-quality local or regional evidence.^[17]

The roles of inhaled corticosteroids, bronchodilators, immunomodulators, mucoactive agents, targeted eradication therapy, suppression of colonising pathogens, and airway clearance techniques are particularly difficult to evaluate in post-TB bronchiectasis owing to the pathological heterogeneity of the disease. TB bronchitis, bronchial obstruction by regional lymphadenopathy, and traction bronchiectasis from neighbouring parenchymal fibrosis all contribute to the total burden of post-TB bronchiectasis, but are unlikely to respond uniformly to therapeutic interventions. In contrast to the common use of inhaled corticosteroids in the cohort reported by Titus *et al.*, most guidelines recommend against the use of inhaled steroids for bronchiectasis unless there is coexisting asthma, owing to their association with increased exacerbation frequency, mycobacterial infection and mortality.^[18-20]

The work by Titus *et al.* reminds us that without local epidemiological data, it is difficult to advocate for the resources needed to develop context-specific preventive, diagnostic, therapeutic and care strategies for patients with the disease. In particular, we need a greater focus on

primary and adjunctive treatment options (including host-directed therapies) for tuberculosis aimed at limiting the development of post-TB lung disease in the first instance. For those now living with post-TB bronchiectasis and other forms of post-infectious bronchiectasis, we need therapeutic trials or high-quality cohort data to establish the usefulness of bronchodilators, inhaled corticosteroids, and macrolide therapy. Even the well-intentioned universal application of airway clearance techniques with nebulised saline brings substantial direct and indirect costs to patients and health services, and we should interrogate whether those costs are outweighed by the assumed benefits in our patients, especially those with dry bronchiectasis. In pursuing this work, the authors have issued a call for greater commitment to advancing locally relevant science aimed at informing the care of patients with neglected respiratory diseases in our setting.

Rubeshan Perumal, MB ChB, MMed (Int Med), MPhil, MPH, PhD, FCP (SA), Cert Pulmonology (SA) 

Department of Pulmonology and Critical Care, Division of Internal Medicine, School of Clinical Medicine, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa; Centre for the AIDS Programme of Research in South Africa, Durban, South Africa
perumalr@ukzn.ac.za

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Afr J Thoracic Crit Care Med 2023;29(4):e1728. <https://doi.org/10.7196/AJTCCM.2023.v29i4.1728>