

Bacterial Lung Disease and COPD

Sanjay S. Gautam and Ronan F. O'Toole*

Breathe Well NHMRC Centre of Research Excellence, School of Medicine, University of Tasmania, Hobart, Australia

Abstract

Pneumonia is the single largest infectious cause of death in young children worldwide and a major cause of mortality in the elderly. Tuberculosis (TB) is the leading cause of mortality due to respiratory infection worldwide, killing approximately 1.5 million people each year. It is perhaps not surprising that the bulk of applied research on these high burden diseases has focussed on the development of new vaccines, diagnostic tools, and therapeutic interventions. However, in recent years, it has become apparent that both transmissible diseases contribute to the development of a major non-communicable disease, namely, chronic obstructive pulmonary disease (COPD). The latter chronic illness is emerging as the third largest cause of human mortality worldwide after heart disease and stroke and hence, there is increasing interest in understanding its genesis and development. In this review, we examine the evidence that previous lower respiratory tract infectious disease is a contributory factor in the development of COPD. Based on the available data, there is an apparent epidemiological association between pneumonia, TB and COPD in later life. In addition, elements of COPD treatment place patients at a higher risk of presenting with pneumonia or TB. There is now a need to generate a deeper understanding of the interactions between bacterial lung disease and COPD from which new, complementary preventive and co-management strategies can be designed.

Keywords: Lower respiratory tract infection; Chronic airway obstruction; Corticosteroid

Early History of Communicable Lung Disease

The progenitor of *Mycobacterium tuberculosis* has been reported to exist as early as 3 million years ago among our hominid ancestors living in East Africa [1]. Morphological and molecular analyses of bone samples obtained from human remains at the now-submerged site of Atlit-Yam in the Eastern Mediterranean have confirmed the existence of human tuberculosis (TB) dating back to 9250-8160 years ago [2]. Though there are many historical records of individuals presenting with tuberculosis like symptoms, it was not until 24 March 1882 that the etiological agent responsible for the disease was reported by Robert Koch in his presentation to the Berlin Physiological Society [3]. Today, we know that tuberculosis in humans is not caused by a single species, but instead by a complex of species including *Mycobacterium tuberculosis*, *M. africanum*, *M. bovis*, and *M. canetti* which originated from a common African ancestral strain 35,000-15,000 years ago [4]. To date, seven distinct phylogenetic lineages have been identified for the species *M. tuberculosis* and *M. africanum*, based on genomic polymorphisms [5,6], which differ with respect to global distribution, and in some cases infectivity and drug-resistance [7-10]. Compared to 1.2 million global deaths due to HIV/AIDS virus in 2014, TB has now emerged as the most common cause of human mortalities due to infectious disease with the toll reaching 1.5 million in same year [11].

Pneumonia is an acute infection of the parenchyma of the lung caused by viruses, bacteria, fungi or other pathogens which is contracted primarily via inhalation or aspiration of infectious droplets or other particles [12]. It is ranked as the single largest cause of infectious death in children aged under five years with an estimated 922,000 mortalities in 2015 [13], and it is also a major cause of morbidity and mortality in the elderly [14,15]. Primarily bacterial in origin, community-acquired pneumonia (CAP) is evidenced by radiological and/or clinical observation of consolidation in one or both lungs [16]. The major cause of CAP, is *Streptococcus pneumoniae*, described by Louis Pasteur in 1881 [17,18]. To date, over 90 different serotypes of *S. pneumoniae* have been identified based on polysaccharide capsule antigens [19]. Besides *S. pneumoniae*, there are several other etiologies of bacterial pneumonia that include *Haemophilus influenzae*, *Staphylococcus aureus*, *Legionella pneumophila*, and *Moraxella catarrhalis* [20], in addition to viral agents such as influenza viruses, coronaviruses, respiratory syncytial virus,

and rhinovirus [21].

Pathogenesis of Bacterial Pneumonia

Lung inflammation in pneumonia begins with the invasion of microorganisms either by inhalation of droplets from an infected contact or environmental source, or by micro-aspiration of potential pathogens that normally colonize the upper respiratory tract such as the nasopharynx [22]. Five major pathogenic steps of pneumococcal pneumonia have been identified in a murine model. The first step during the first 4 hours of infection was characterized by partial but poor bacterial elimination by alveolar macrophages, and activation of cytokines (TNF and IL-6 in broncho-alveolar lavage (BAL) fluid; TNF, IL-6, and IL-1 in lung tissues; IL-6 in serum) and transient nitric oxide (NO) release in BAL fluid [22]. At between 4 and 24 hours, there was an increase in bacterial numbers, neutrophil counts and in the levels of TNF, IL-6, IL-1 and leukotriene B₄ (LTB₄) at the infected site together with a transient rise in serum IL-1 levels. At 24 to 48 hours post infection, the level of pro-inflammatory cytokines (TNF and IL-1) in BAL fluid and lung tissue decreased, while tissue injury and bacterial invasion of the blood was observed. At 48 to 72 hours, there was sharp decline in blood leukocytes and a gradual increase in monocytes and lymphocytes in BAL fluid. Activation of TNF and IL-6 together with decreased numbers of platelets were associated with bacteraemia. Finally, in the fifth stage, between 72 and 96 hours, lung histopathology revealed severe airspace disorganization, absence of alveolar architecture accompanied by a loss in body weight and an increased rate of mortality [23].

Resolution of chest radiographic abnormalities due to pneumococcal pneumonia (4.1% at day 10 and 56% at day 28) is slower than those with other causes of pneumonia (31.9% at day 10 and 69.4%

*Corresponding author: Ronan F. O'Toole, Breathe Well NHMRC Centre of Research Excellence, School of Medicine, Faculty of Health, University of Tasmania, Medical Science 1, 17 Liverpool Street, Hobart, TAS 7000, Australia, Tel: +61-3-6226 6974; E-mail: ronan.otoole@utas.edu.au

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at day 28). Reports indicate that childhood pneumonia is followed by long term sequel, the major (restrictive lung disease, obstructive lung disease, and bronchiectasis) and the minor (chronic bronchitis, asthma, other abnormal pulmonary function, other respiratory disease) [24]. After controlling for age, sex, height, smoking, type of spirometer, and other illnesses, pneumonia before 2 years of age has been linked to decreased lung function in adults where difference in mean forced expiratory volume in 1 second (FEV₁) of -0.39 litres (95% CI: -0.67-0.11) and mean forced vital capacity (FVC) of -0.60 litres (95% CI: -0.92-0.28) have been reported [25].

Pathogenesis of Tuberculosis

Tuberculosis is an aerosol-borne communicable disease caused by *Mycobacterium tuberculosis* complex (MTBC) [26]. It primarily affects the lungs but can manifest as extra-pulmonary disease at other sites [11]. The chronological events in the pathogenesis of tuberculosis have been derived from Lurie's studies using in-bred rabbits [27]. The first event entails inhalation of tubercle bacilli and uptake by alveolar macrophages. Elimination of the bacteria at this stage principally depends on capacity of host phagocytic cells to overcome mycobacterial intracellular survival strategies. Surviving mycobacteria multiply resulting in their release from infected macrophages. The second stage commences with migration of inflammatory cells and monocytes towards the focal site of bacilli release. This results in accumulation of macrophages around the mycobacteria which continue to replicate. The macrophages release proteolytic enzymes which cause collateral damage to the lung tissue. Cell mediated immunity ensues approximately 2-3 weeks after infection where antigen-specific T cells reach the infected site, multiply within early tuberculosis lesions and activate macrophages to kill intracellular mycobacteria. The third stage of the disease is characterised by a pause in mycobacterial growth within solid necrotic tissue. A poor host immune response at this point may exaggerate primary infection resulting in liquefied caseous foci and cavitation which facilitates bacillary spread to extra pulmonary sites [28].

Chronic deficits in lung function as estimated by FEV₁ (<80% of predicted) relate to the extent of tuberculosis disease whereby functional decreases of 18.4%, 27.1% and 35.2% are associated with one, two and three or more episodes of tuberculosis, respectively [24]. The Korean National Health and Nutrition Examination Survey 2008-2012 identified that a prior history of pulmonary TB (OR of 2.314, 95% CI: 1.922-2.785), and also an inactive TB lesion on chest X-ray (OR of 2.300, 95% CI: 1.606-3.294), were predictors for the subsequent development of obstructive airway disease [25]. Development of airflow obstruction and restrictive loss of pulmonary function can manifest even in TB patients who have successfully completed treatment [29]. Furthermore, patients with multi-drug resistant (MDR) TB exhibited significantly lower levels of lung function in terms of FVC (43.58 ± 16.03% versus 72.06 ± 14.95% predicted) and FEV₁ (33.08 ± 15.64% versus 66.13 ± 19.87% predicted) compared to patients who had non-MDR TB [30].

Pneumonia and Tuberculosis as Potential Precursors to COPD

The association between childhood pneumonia and COPD in adulthood is being increasingly recognised. Hayden and colleagues in recent study of 10,192 adult current and former smokers, concluded that development of adult respiratory disease is influenced by childhood respiratory infections whereby childhood pneumonia was identified as a predictor of COPD (OR 1.40, 95% CI: 1.17-1.66) [31]. Similarly, a reduction of lung function by 0.17 litre (0.02 to 0.32) and higher mortality due to COPD in adults was observed in adults who

had bronchitis or pneumonia in infancy [32]. This apparent association of childhood pneumonia in COPD development and severe COPD exacerbations [31] may relate to possible reduction in lung growth due to pneumonia [32] and also to inadequate treatment of pneumonia [33]. Regarding acute exacerbations of COPD, a study involving 1,114 subjects over 40 years of age from Korea identified that the exacerbation rate was many times higher (18-fold, $p < 0.001$) in COPD patients who had a previous history of pneumonia compared to patients who were not affected by pneumonia [34].

Tuberculosis is also emerging as a potential important cause of obstructive disease. A systematic review reported in 2015 a significant association between a previous history of TB and the presence of COPD in patients aged over 40 years adjusted for known COPD risk factors such as cigarette smoking and age [35]. Furthermore, a large Burden of Obstructive Lung Disease (BOLD) study based on 14,050 participants from 18 countries recently determined that a self-reported history of TB was significantly associated with both airflow obstruction (adjusted OR of 2.51 [95% CI: 1.83-3.42]) and spirometric restriction (adjusted OR of 2.13 [95% CI: 1.42-3.19]) [36]. It was concluded that a history of TB should be regarded as a potentially important cause of obstructive lung disease, in particular, in regions where TB is endemic [36].

While impaired lung function, due to previous pneumonia or TB, may in itself contribute to an elevated risk of subsequent COPD, a lower patient immune status may also link pneumonia and TB with COPD. Iatrogenic use of corticosteroids in COPD treatment can increase the risk of pneumonia and TB (discussed below), but other forms of host immune suppression could potentially play a role. For example, the incidence rate of community-acquired pneumonia is higher in patients with HIV/AIDS compared to HIV-negative subjects (adjusted OR of 2.48 [95% CI: 1.34-4.58]) [37,38] while HIV/AIDS is well established as a risk factor for TB, including multi-drug resistant TB [39,40]. In regard to COPD, it has previously reported that prior to the use of combination antiretroviral therapy, HIV-infected persons were found to exhibit "an accelerated form of COPD" [41]. A number of possible factors have been suggested which include increased susceptibility to chronic sub-clinical infections, a dysfunctional inflammatory response, and the effects of antiretroviral therapy on the immune system, but to date, the exact mechanism remains to be established.

Chronic Airway Disease as a Risk Factor for the Development of Tuberculosis and Pneumonia

Patients with COPD have been found to exhibit a higher risk of developing tuberculosis [42]. A population-based study conducted in Sweden on 115,867 in-patients aged ≥40 years, found that the relative risk of developing active TB was 3-fold higher in individuals with a hospital discharge diagnosis of COPD compared to controls (multivariate hazard ratio, HR, of 3.14 [95% confidence interval: 2.42-4.08]) [42]. Furthermore, COPD patients who developed active TB had a 2-fold increased risk of death from all causes during the first year after TB diagnosis compared to general population controls with TB (odds ratio, OR of 2.2 [95% CI: 1.3-3.9] when adjusted for age at time of TB diagnosis) [42]. A study from Taiwan involving 23,594 COPD patients also found that COPD was an independent risk factor for the development of TB with a hazard ratio of 2.468 [95% CI: 2.205-2.762] compared to 47,188 non-COPD control subjects who were matched for age and gender [43].

The combined use of an inhaled corticosteroid (ICS) and a long-acting beta2-adrenoceptor agonist (LABA) is recommended in the treatment of patients with severe COPD with FEV₁ <50% predicted and ≥2 exacerbations

in 12 months [44] but there is concern that certain COPD treatments may be a contributing factor in the COPD-related risk of developing TB. For example, in the above Taiwanese study, COPD patients who presented with TB had been administered higher daily doses of oral corticosteroids (OCS) and oral β -agonists compared to COPD patients who did not succumb to TB [43]. Earlier work found that when 554 COPD patients were stratified for dosage of the inhaled corticosteroid (ICS) fluticasone, development of pulmonary TB was associated with the highest dose of fluticasone treatment (>500 $\mu\text{g}/\text{day}$) compared to low or no ICS use [45]. In a study of 427,648 subjects in Canada, including 564 TB patients, it was reported that current users of ICS, who are not taking OCS therapy, were at an increased risk of developing TB (rate ratio, RR of 1.33 [95% CI: 1.04-1.71]) [46]. Similarly, in a study conducted in Korea with 4,139 TB cases and 20,583 controls, ICS use was linked to a dose-dependent increased rate of TB diagnosis in non-OCS users (adjusted OR of 1.20 [95% CI: 1.08-1.34]) [47]. Further studies are required to establish whether the increased risk of TB in COPD patients is due primarily to the use of corticosteroids and other therapeutics in the treatment of COPD, or whether there are additional factors at play which increase susceptibility to *Mycobacterium tuberculosis* infection and progression to active TB disease.

The use of immunosuppressant corticosteroid based therapy in COPD patients has also been linked to pneumonia development [48]. A meta-analysis found that ICS therapy is associated with an increased risk of serious pneumonia in COPD patients when compared with placebo (RR of 1.81 [95% CI: 1.44-2.29]) [49]. In a study conducted in Quebec on 163,514 patients with COPD, current use of ICS was associated with a 69% increase in the rate of a serious pneumonia event during a 5.4 year follow-up period (RR of 1.69 [95% CI: 1.63-1.75]) [48]. The risk was maintained with long-term use but declined following cessation of ICS use and eventually disappeared after 6 months (RR of 1.08 [95% CI: 0.99-1.17]) [48]. A study performed in the USA on 145,586 newly-diagnosed COPD patients found that subjects on ICS treatment were 1.38 [95% CI: 1.31-1.45] times more likely to have a hospitalization for pneumonia than non-ICS users [50]. Similar to TB risk, the risk of pneumonia in COPD patients also relates to the dosage of ICS. While lower doses of fluticasone/salmeterol (500 $\mu\text{g}/\text{day}$) pose a risk of pneumonia [51], Ernst and co-workers reported that an increased RR of hospitalization for pneumonia correlated with higher ICS doses i.e., fluticasone at 1,000 $\mu\text{g}/\text{day}$ or more (RR of 2.25 [95% CI: 2.07-2.44]) [52]. The risk of pneumonia development connected with inhaled corticosteroid-containing medicines used in COPD treatment has recently been confirmed by the European Medicines Agency but the agency did not find conclusive evidence of differences in risk between distinct classes of ICS drugs [53].

It is becoming apparent that COPD patients are at higher risk of developing of TB and pneumonia. Our understanding of the effect of corticosteroid-based COPD therapies on the pulmonary immune defence against lower respiratory tract bacterial pathogens is derived from a relatively small number of experimental studies. Therefore, investigations are required to elucidate the mechanisms underlying the association between COPD therapy and bacterial lung disease, and other potential causative factors that place COPD patients at greater risk of developing TB or pneumonia.

Bacterial Infection as a Trigger for Acute Exacerbations of COPD

Until recently, the lower respiratory tract was considered to be devoid of microorganisms in healthy individuals. This doctrine shifted with the advent of culture-independent techniques for identifying microbes from patient specimens. The lungs contain a normal

airway microbiome which is dominated by the phyla Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria [54]. The risk of mortality and morbidity from COPD escalates when infections cause acute exacerbations (AE) which result in a further decline in lung function [55]. Bacteria have been implicated in up to 50% of COPD exacerbations [56], and 72% of severe exacerbations requiring ventilatory support [57]. Of the many bacterial genera that inhabit the human respiratory tract, it is primarily the two species, *H. influenzae* and *S. pneumoniae* that are involved in COPD exacerbations [59]. Hence, there is a degree of overlap in the bacterial species which drive AECOPD and pneumonia.

Changes in the relative abundance of different phyla in the lung have been reported for chronic lung disorders COPD and asthma due to the outgrowth of individual bacterial genera [54]. However, in relation to COPD, we do not yet know if any of these observed microbial community changes are a "cause or consequence" of COPD, and therefore, whether they are of clinical relevance. It has previously been found that the "isolation of a new strain of *H. influenzae*, *M. catarrhalis*, or *S. pneumoniae* was associated with a significantly increased risk of an exacerbation" of COPD [60]. This indicates that the appearance of specific bacterial strains may play a greater role in the manifestation of chronic lung disease than the total relative abundance of different genera. In support of this finding, strains of *H. influenzae* isolated from patients with COPD exacerbations have been shown to induce more airway inflammation in mice and in human tracheobronchial epithelial cells than non-COPD isolates, independently of bacterial inoculum size [61]. Understanding the events leading to colonisation by *H. influenzae* and *S. pneumoniae* of the lower respiratory tract of COPD patients and to subsequent increased local and systemic inflammation would greatly enhance our understanding of AECOPD.

While not the focus of this review, viral agents are also a major cause of AECOPD. In a study of 220 subjects, a respiratory virus was detected in sputum and nasal/throat swabs in 37% of patients with exacerbations of COPD compared to 12% of stable COPD patients and 12% of non-obstructed smokers ($p < 0.0001$) [62]. A subsequent systematic review found that the most commonly detected virus in AECOPD cases was picornavirus (including rhinovirus) followed by Influenza, and Respiratory Syncytial Virus (RSV) [63].

Positive filamentous fungal culture is a common feature of COPD with the majority of isolates being *Aspergillus fumigatus* [64]. A study in 2014 reported that the prevalence of *Aspergillus* spp. in a cohort of severe COPD patients requiring hospitalisation for an acute exacerbation was 16.6% upon admission, and 14.1% at a one-year follow-up [54]. A significant number of cases of fatal invasive pulmonary aspergillosis have been reported in COPD patients [66] and patients with severe COPD who are receiving corticosteroid therapy are now regarded as an important risk group for pulmonary aspergillosis [67].

Conclusions and Future Perspectives

An epidemiological association has emerged between infectious respiratory disease and non-communicable COPD. A patient history of TB or pneumonia significantly increases the likelihood of subsequent COPD development. Investigations are now needed to define the specific immunopathological events that occur during episodes of TB and pneumonia that culminate in irreversible lung damage and increased COPD susceptibility. An enhanced understanding of the associations between COPD and bacterial respiratory illness may lead to interventions that better detect or prevent disease. Although the benefit of a universal spirometric screening programme of asymptomatic individuals for COPD is not supported by the available evidence [68],

studies are needed on whether targeted screening of individuals with a confirmed history of TB or pneumonia could detect signs of COPD or other airway disease earlier. Regarding treatment, investigations are needed into COPD therapeutics which avert a heightened susceptibility to TB or pneumonia which is believed to be caused by an immune suppressant effect. Although COPD is a chronic lung disease, an examination of the contribution that acute communicable illnesses make to the overall burden of COPD morbidity and mortality is warranted. Research is now needed to raise our level of understanding of the associated epidemiologies of TB, pneumonia and COPD, and to enable the design of new interventions for their prevention or co-management. In the meantime, continued emphasis is needed on existing COPD preventive strategies, as recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), which include tobacco-control policies, smoking cessation through counselling or nicotine replacement therapy, and reduction of occupation or domestic exposure to biomass fuel smoke or other air pollutants [69].

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