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# The Importance of Chronic Bronchitis in Chronic Obstructive Pulmonary Disease

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## 1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common and important group of conditions characterised by airflow obstruction with related symptoms including cough, shortness of breath, expectoration and wheeze. The widely accepted Global Initiative for Chronic Obstructive Lung Disease (GOLD) has classified COPD as “a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases” (1). The current GOLD definition for airflow limitation is a forced expiratory volume in 1 second ( $FEV_1$ ) / forced vital capacity (FVC) ratio of  $< 70\%$  and disease severity is classified into four physiological stages: stage 1 ( $FEV_1 \geq 80\%$  predicted); stage 2 ( $FEV_1 \geq 50$  to  $< 80\%$  predicted); stage 3 ( $FEV_1 \geq 30$  to  $< 50\%$  predicted); stage 4 ( $FEV_1 < 30$  or  $< 50\%$  predicted in the presence of chronic respiratory failure) (2).

COPD is one of the foremost causes of chronic morbidity and mortality worldwide. Globally, it affected 44 million people in 1990 (3) and recent estimates suggest that COPD affects approximately 210 million people (4) or 10% of all adults (5) with the prevalence continuing to rise. In 2007, COPD accounted for 5% of all deaths (4) but the WHO predicts an increase in COPD-related deaths of more than 30% in the next 10 years, emphasising the continued impact this disease will have internationally (6).

Cigarette smoking remains the most important risk factor for the development of COPD (7) although only approximately 20% of smokers develop clinically significant disease (8). This suggests that a combination of genetic and environmental factors interact to cause COPD, and there has been much research aiming to identify candidate genes that may confer genetic susceptibility. To date, however, only deficiency alleles on the  $\alpha 1AT$  gene have been robustly identified as predisposing to disease (9).

Pathologically, COPD is characterised by widespread inflammation of the peripheral and central airways with destruction of the lung parenchyma. Oedema, fibrosis, smooth muscle hypertrophy and loss of elastic recoil lead to bronchial wall thickening, which affects airflow (10).

COPD, while primarily a lung disease, is associated with increased co-morbidity including cardiovascular disease, type 2 diabetes, osteoporosis and systemic pathology such as muscle wasting and dysfunction. It has been hypothesised that persistent low-grade inflammation may drive the co-morbidity and the systemic effects noted with this disease (11). The systemic manifestations of COPD are important, as they are not only associated with

increased morbidity, but are also predictive of disease outcome, especially Body Mass Index (BMI) which forms part of the BODE index (Body Mass, airflow obstruction, dyspnoea and exercise capacity) and is used to classify the impact of the disease (12).

There is great heterogeneity in COPD, and disease presentation and the underlying pathology seen varies between individuals. Although COPD is defined by airflow obstruction, disease phenotypes include emphysema (defined pathologically as the destruction of alveolar walls and the permanent enlargement of the airspaces distal to the terminal bronchioles); bronchiectasis (defined pathologically as localised, permanently dilated bronchi and characterised by excess mucus production and reduction of mucociliary clearance), bronchiolitis (inflammation of the bronchioles) and chronic bronchitis. Chronic bronchitis is defined clinically as the presence of chronic productive cough for at least 3 months in each of 2 successive years in patients in whom other causes of chronic cough such as tuberculosis, heart failure and carcinoma of the lung, have been excluded (13). It is a feature of approximately 50% of people who smoke (14) and 30% of patients with COPD (15), although air pollution, the inhalation of toxic gases and upper gastrointestinal pathology such as reflux disease have also been associated with the condition (16).

Chronic Bronchitis is thought to be of special significance in COPD, as it is associated with increased inflammation and poorer patient outcomes. This chapter will review the pathology of chronic bronchitis, its' inflammatory basis, associated morbidity and mortality and potential treatments.

## 2. Background

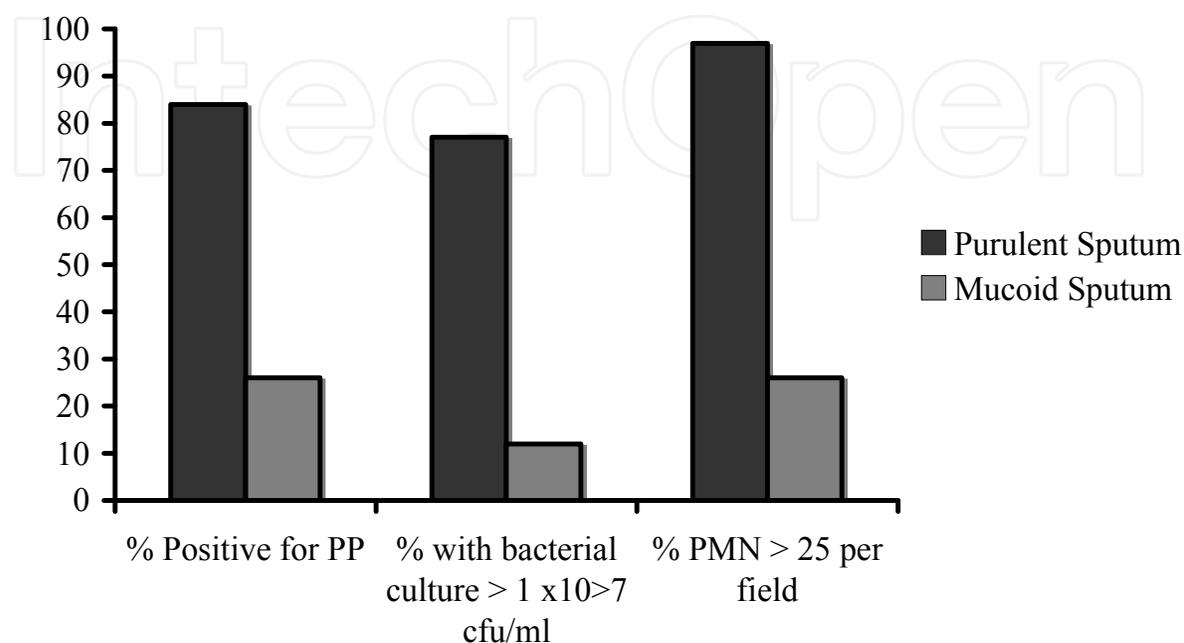
Chronic bronchitis is common, affecting approximately 6 to 12% of adults, over 20 years of age. Cigarette smoke -exposure remains the most important aetiological risk factor for development of both chronic bronchitis and COPD (17-19). There is a six-fold rise in prevalence from 6.3% in non-smokers to 40% in heavy smokers (20), with a linear relationship between cigarette smoke exposure and chronic bronchitis(19). Other risk factors associated independently with chronic bronchitis include poor socioeconomic background, recurrent or severe childhood respiratory illness and exposure to dusty/polluted environments (18, 21).

There is great heterogeneity between patients, and both time of presentation and disease course vary. In a proportion of patients, sputum expectoration occurs without airflow obstruction, while in others, airflow obstruction precedes sputum expectoration (22). There is some debate whether chronic bronchitis is solely a recognised phenotype of COPD, or whether it is an entirely independent disease process. Certainly, while often present in unison, chronic expectoration and airflow obstruction behave largely as independent variables (23). This is perhaps unsurprising as bronchial gland hypertrophy (seen in chronic bronchitis) occurs predominantly in larger bronchioles (24), whereas the dominant site of irreversible airflow obstruction occurs in more peripheral and smaller airways(25).

Often, chronic bronchitis is preceded by recurrent episodes of acute bronchitis (26), and the frequency and severity of these acute episodes influences the rate of decline in lung function, patients quality of life and the risk of death (27) (see later).

Symptoms can be restricted to chronic sputum expectoration, or include those related to airflow obstruction, including breathlessness and wheeze. Sputum expectoration varies between and within individuals and in individual patients, in terms of the frequency of cough, the volume and tenacity of sputum produced (which can alter the patients ability to

clear secretions effectively) and sputum purulence. The majority of patients initially describe low-volume, mucoid sputum (clear to grey in colour), but as many as 30% of patients have airways which are colonised with potentially pathogenic bacteria, and this is more likely to be associated with the expectoration of purulent (green) sputum (28). See Figure 1



### Sputum characteristics

Fig. 1. The characteristics of sputum collected from patients with Chronic Bronchitis with either purulent or mucoid sputum.

**Legend.** Sputum samples were collected from clinically stable patients with chronic bronchitis. 87 had purulent sputum and 36 had mucoid sputum. Samples were studied for the presence or absence of putative pathogenic bacteria (PP), bacteria were quantified in colony forming units/ml of sample, and classified as being above or below  $1 \times 10^7$  cfu/ml, and neutrophils (PMN) were counted in a random viewing field on light phase microscopy. Purulent sputum was consistently and significantly associated with the presence of putative pathogens, a higher number of bacterial colonies, and more neutrophils than mucoid sample.

Modified from (29) and (30).

Although standard definitions of chronic bronchitis only include chronic sputum expectoration, early descriptive series of patients found that 70% of patients had bronchospasm, 88% had either sporadic or constant breathlessness and "spells of sickness for several weeks or a few months" with infection thought to be causal in all cases (31). The disease is characterised with periods of stability, interspersed with episodes of worsening symptoms (exacerbations). These will be described later.

Physical examination can be normal, but it can reveal signs consistent with COPD and emphysema (including evidence of hyper-inflated lung fields, peripheral and central cyanosis, cor-pulmonale and hyper-capnia). Radiographic signs in pure chronic bronchitis are poorly documented, as the most frequently quoted studies (for example (32, 33)) did not

exclude patients with emphysema. However, it is likely that chest radiographs in the majority of patients with chronic bronchitis are normal (34), as the bronchial wall thickening which is characteristic of chronic bronchitis is approximately 0.1 – 0.5mm (24, 35) and therefore too small to be noticeable in plain x-rays. Bronchial wall thickening can be seen on high resolution computer tomography scans of the thorax (36). See figure 2.

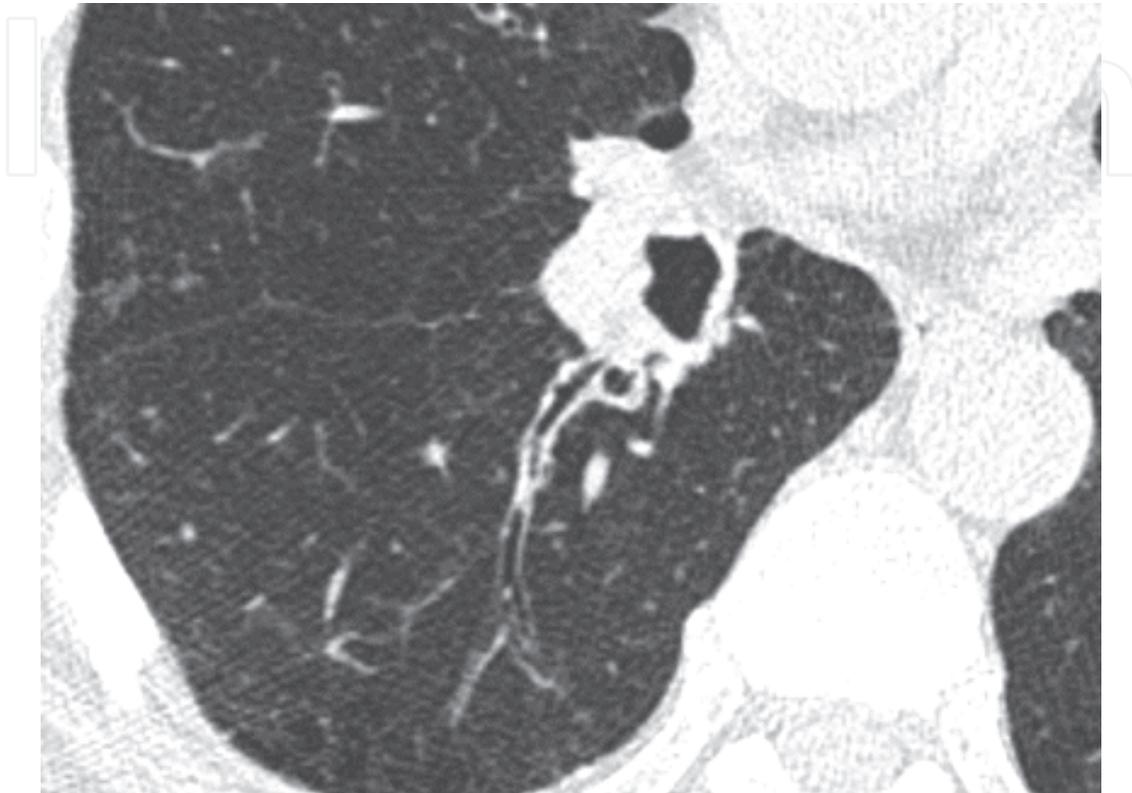


Fig. 2. High resolution CT image showing moderate bronchial wall thickening and mild bronchial dilatation in a patient with chronic bronchitis.

Used with permission from Hochhegger et al, *Imaging*, 2008; 20 (37).

There is a robust series of studies demonstrating that Chronic Bronchitis is associated with increased morbidity and mortality. It is an independent risk factor for all cause mortality both in COPD (38), and in subjects with normal lung function, even when smoking has been accounted for (38-40). The overall ten year mortality following a diagnosis of chronic bronchitis is 50%, with respiratory failure following an acute exacerbation being the most frequent terminal event (41).

Currently there are no clearly identified genetic risk factors for Chronic Bronchitis, however, twin studies have suggested that the heritability estimate for this condition is 40%, with only 14% of genetic influences shared with those related to smoking habits (42). Studies of polymorphisms of the TNF $\alpha$  gene (which reside in the promoter region of the gene, are associated with increased secretion of TNF $\alpha$  in the lung, and an increase in neutrophilic inflammation (43)) have shown a strong association with a chronic bronchitis phenotype in COPD (43, 44). However, this polymorphism has a minor allele frequency of 4 – 6% (43), and hence, other susceptibility factors must exist. There is currently an interest in genome wide association studies, and perhaps these will identify more potential candidate genes (45).

### 3. The pathology of chronic bronchitis

#### 3.1 An overview of the histological changes seen in chronic bronchitis

Chronic bronchitis is characterised pathologically by mucus hyper-secretion with bronchial mucous gland hypertrophy and chronic inflammation of the bronchi and bronchioles, with a subsequent inflammatory cell infiltrate. Inflammation of the bronchial epithelium can produce squamous metaplasia, with a loss of ciliated cells. The metaplastic squamous epithelium can become dysplastic from persistent injury by smoking, and may become malignant (squamous cell carcinoma of the bronchus). Typical changes seen histologically with chronic bronchitis are shown in Figure 3.

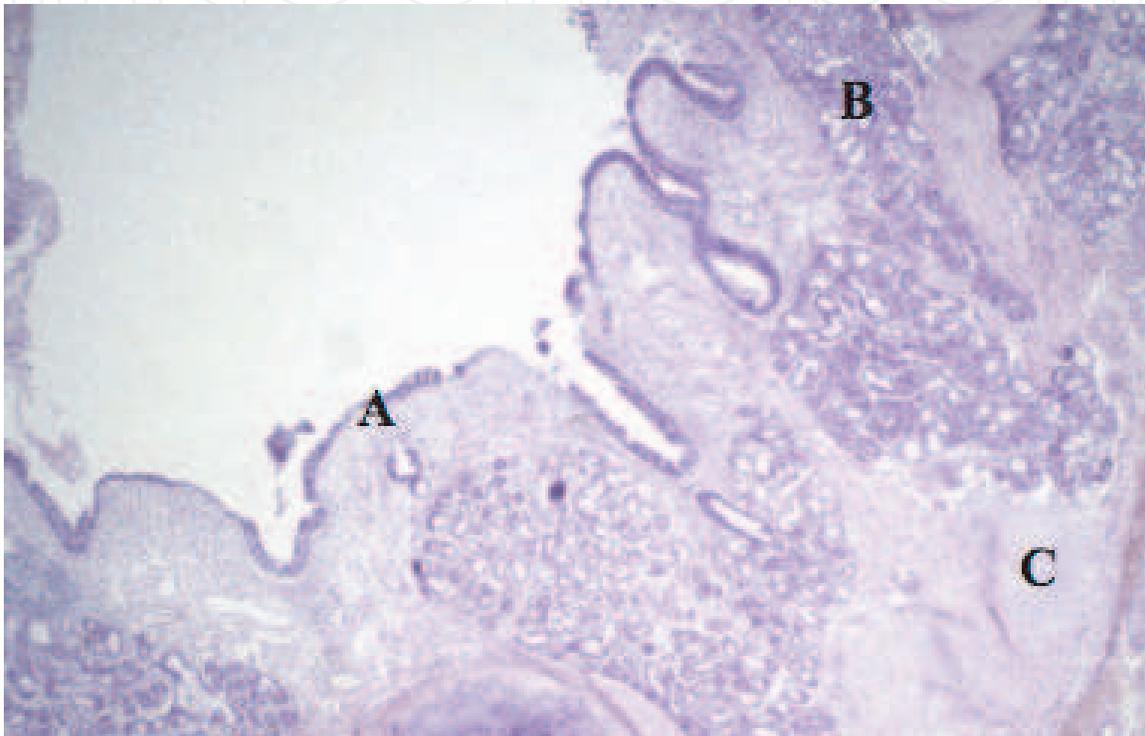


Fig. 3. Histology of Chronic Bronchitis

**Legend.** This figure demonstrates epithelial thickening (A), mucous gland hypertrophy and metaplasia (B) and prominence of airway smooth musculature (C), all of which are typical features in chronic bronchitis.

The earliest abnormality in chronic bronchitis is thought to be a respiratory bronchiolitis, affecting airways of less than 2mm in diameter, in response to chronic cigarette smoke or toxin exposure. Destruction of the airway wall and surrounding parenchymal elastin can lead to mural weakness and this coupled with mucus hyper-secretion predisposes towards bronchiolar obstruction.

The bronchioles are so numerous, that bronchiolar obstruction must be widespread and extensive to give clinical symptoms and studies confirm that pathological changes are seen before the clinical manifestations of disease (46). Squamous metaplasia and increased epithelial thickening is also seen prior to symptomatology and without airflow obstruction, although there is a relationship between epithelial layer thickness and COPD severity (25). However, all of these changes vary between patients, even in those with a similar degree of airflow obstruction (47).

Mucous gland hypertrophy and metaplasia occurs in response to inflammatory signals present in the airways of patients with chronic obstructive pulmonary disease (48) and contribute to airflow obstruction (49). Cigarette smoke-induced chronic airway inflammation also causes constriction and hypertrophy of airway smooth muscle cells (49) which become more prominent in biopsies taken from subjects with chronic bronchitis. In keeping with this observation, some studies have described an increase in airway smooth muscle mass in COPD (50) and have associated this with increases in airway wall thickness, greater luminal narrowing, and increased airflow resistance with poorer clearance of pulmonary secretions (51).

The inflammatory changes seen in chronic bronchitis occur in the mucosa, gland ducts and glands of both the intermediate sized bronchi (with an internal diameter of 2 - 4mm) and smaller bronchi and bronchioles (less than 2mm in internal diameter).

### 3.2 Pulmonary secretions

Airways secretions form an important component of the primary host defence system. In the trachea, there are approximately 4000 submucosal glands which produce both the mucus (52), and important proteins such as antibacterial proteins (including lysozyme (53) and lactoferrin (54)), secretory component necessary for immunoglobulin (Ig) A transport (55), and the antiproteinase, secretory leukoprotease inhibitor (SLPI) (56). Submucosal glands are composed of a central acinus consisting of serous cells, and a tubule lined with mucous cells. Plasma cells (responsible for the production of IgA) are also found in the submucosal glands (57).

The serous and mucous cells of the bronchial glands secrete the majority of the bronchial secretions, although goblet cells, and both the serous and clara cells of the airway epithelium make important contributions. Secretions are further diluted by alveoli surfactant and plasma fluid transudate (58). Bronchial mucus is composed of a continuous watery sol layer which overlays the bronchial epithelium and in which the cilia beat; and a more viscous gel layer, which lies on the tips of the cilia. The sol layer is 5 - 10 $\mu$ m deep, and is derived from the clara cells in the airway epithelium at the bronchiolar level with some contribution from fluid transudation. The sol layer enables the cilia to propel the gel layer over its surface, and is fundamental to mucociliary clearance. The mucus gel layer is derived from several sources including goblet and serous cells in the airway epithelium, clara cells at the bronchiolar level (59) and the submucosal glands (60). The sol phase contains soluble bronchial proteins and serum proteins, whilst the gel phase contains the mucinous glycoproteins, other serum proteins and also proteins bound to mucins (61). Bronchial mucus has many functions. It reduces evaporative loss from the respiratory tract, provides a protective barrier over the bronchial epithelium and removes trapped inhaled particles via ciliary action. The mucus also provides a medium for immunoglobulins and other protective proteins.

In healthy individuals, airway secretions are moved up to the mouth by ciliary action in the mucociliary escalator. Ciliated cells are found primarily in the tracheo-bronchial epithelium, although they are also present in the bronchioles (60, 62). There are approximately 200 - 300 cilia per cell; each is 4 - 6  $\mu$ m long and 0.1 - 0.2  $\mu$ m in diameter. The cilia beat 1000 times per minute, and in health the action of the cilia is co-ordinated, both within a single cell and between adjacent cells (63). The ciliary beat cycle has two components. The first is movement towards the larynx; this is the effective stroke, and is followed by a recovery stroke in the opposite direction where the cilia bend and disengage from the mucus (64).

Microvilli project between the cilia and are believed to regulate the depth of the periciliary fluid level.

The clearance of mucus depends on ciliary action (65), cough, mucus volume, and the viscoelasticity and adhesiveness of the mucus to the airway epithelium. Mucus transportation has two phases, a fast phase related to ciliary clearance and cough, which is completed after a few hours in healthy individuals, and a slower phase which represents alveolar clearance and occurs over weeks or months (66, 67).

Mucociliary clearance is impaired in chronic bronchitis. There are many reasons for the impairment, including inhibition of ciliary activity by proteinases such as neutrophil elastase (NE) released from neutrophils recruited to the lungs (68), the presence of bacterial products (69) and epithelial damage. In chronic bronchitis, the inflammatory exudate overwhelms the normal clearance mechanisms, and the excess and accumulated secretions are expectorated in the form of sputum, which is a mixture of bronchial secretions, cells, cellular debris, cleared organisms and saliva, resulting in the chronic productive cough that characterises chronic bronchitis.

Mucinous glycoproteins are synthesised in mucus and goblet cells. Activated transcription factors upregulate expression of *MUC* genes in the nucleus of these cells. New *MUC* transcripts are translated to *MUC* proteins on ribosomes and cotranslationally inserted into the endoplasmic reticulum (ER). Glycosylation of the *MUC* protein backbone is initiated post-translationally in the *cis*-Golgi. Mature (fully glycosylated), mucins are packaged and stored in secretory granules until a mucin secretagogue triggers mucin secretion at the apical surface of the cell (70).

Airway mucins are overproduced by patients with chronic airway diseases like chronic bronchitis/COPD. This sustained mucin secretion, requires increased biosynthesis of mucins to replenish secretory granules, which in turn necessitates upregulation of *MUC* genes. Eight *MUC* genes (*MUC1*, *MUC2*, *MUC4*, *MUC5AC*, *MUC5B*, *MUC7*, *MUC8* and *MUC13*) are expressed in normal respiratory tract tissues (70), and although they are basally active in order to maintain mucin release to promote muco-ciliary clearance, protein transcription can be up-regulated dramatically in inflammation and infection.

In Chronic Bronchitis, a number of factors have been shown to up-regulate *MUC* genes, including neutrophil elastase, a proteolytic enzyme stored within neutrophil granules (see later). Inflammatory mediators have also been implicated, including IL-8 (71) and LTB<sub>4</sub> (72) and oxidative stress (73). It is hypothesized that the on-going inflammation, intermittent infection and viral and bacterial colonization that is present in some patients with chronic bronchitis leads to excessive *MUC* gene activation, mucin production and goblet cell hypertrophy. If these genes were amenable to modulation, they would be a potential therapeutic target in the treatment of this disease.

### 3.3 Immunology and inflammation in chronic bronchitis

The inflammatory response seen in the lungs of patients with chronic bronchitis is complex, involves the innate and acquired immune system and serves as a self-perpetuating stimulus for further immune activation. Cigarette smoke exposure is the most important risk factor for developing chronic bronchitis, but the symptoms, the inflammation and the decline in lung function parameters continue, even after smoking cessation (74, 75).

Chronic Bronchitis is associated with the recruitment of leucocytes into lung tissue, the production of inflammatory mediators and the release of destructive proteins into the milieu, including proteinases. Bronchial biopsies taken from patient with chronic bronchitis

show an increase in inflammatory cells compared with non-smokers and smokers with no symptoms of chronic mucus production (10). The cellular composition varies between individuals, but typically includes neutrophils, macrophages and CD8+ T cells. There are also smaller numbers of CD4+ T cells, but these may be monoclonal (76), and limited to pulmonary follicles (77).

Consistently, research has highlighted the importance of the neutrophil in the pathogenesis of COPD and chronic bronchitis. Patients with chronic bronchitis and COPD have increased numbers of neutrophils in proximal airway secretions (78, 79) and bronchoalveolar lavage fluid (BALF) (80) compared with asymptomatic smokers, and numbers increase with increasing disease (81, 82). Airway neutrophil numbers are also raised in patients with chronic bronchitis without COPD, although less so than when airflow obstruction is present (83). Sputum neutrophilia is associated with a faster decline in FEV<sub>1</sub> compared with those with lower neutrophil counts, losing approximately 1% more than predicted each year (84) and neutrophil counts decline with smoking cessation (85), consistent with the benefits of this intervention.

The neutrophil is the most abundant circulating leukocyte. The average peripheral blood neutrophil count is  $2.5 - 7.5 \times 10^6$  /ml and when inactive, its circulating half life is only 6 - 8 hours, which means that the bone marrow is required to produce and release more than  $5 - 10 \times 10^{10}$  neutrophils daily, with the capacity to increase production further if needed. Exposure to cigarette smoke appears to stimulate neutrophil differentiation and maturation, causing a peripheral leucocytosis (86, 87) which has been found to correlate with the severity of airflow obstruction (88). Fully mature neutrophils leave the bone marrow in a non-activated state and have a half life of 4 to 8 hours before marginating and entering tissue pools (89). Once in tissue, neutrophils are usually removed by apoptosis leading to their recognition and phagocytosis by macrophages in the main and by other neutrophils when the macrophage clearance system is overwhelmed (90). This mechanism prevents cell necrosis and the release of the remaining cellular content of proteinase and other mediators. Neutrophils migrate into the lung in response to soluble pro-migratory stimuli, which include non-chemotactic cytokines (such as TNF $\alpha$  and IL-1 $\beta$ ), chemotactic cytokines (chemokines including Interleukin 8) or chemoattractants (such as Leukotriene B<sub>4</sub>, (LTB<sub>4</sub>) and Complement factor C5a). Neutrophils are present at both the bronchial and alveolar level in chronic bronchitis and COPD, and therefore it is likely that neutrophil migration occurs from both the bronchial and pulmonary circulation.

In the bronchial circulation, neutrophils appear to migrate from vessel to tissue in a step-like process, dictated by the sequential activation of adhesive proteins and their ligands on neutrophils and endothelial cells. Migration begins with the capture of neutrophils from flowing blood, causing the cell to roll along the endothelial surface. Tethering and rolling of the neutrophil along the vessel wall is a normal feature of circulating neutrophils and is due to reversible binding of transmembrane glycoprotein adhesive molecules called "selectins", which are found both on neutrophils and endothelial cells (91). The next step in neutrophil migration is the transition from reversible rolling to firm adhesion with the endothelium. This is achieved by the sequential activation of neutrophil receptors called Integrins (92, 93). The final step of neutrophil recruitment from the bronchial circulation to the lungs is transendothelial migration. This is believed to occur preferentially at tricellular junctions (94), requiring the activation of Platelet endothelial cell adhesion molecule (PECAM1) (95) which is distributed evenly around the neutrophil and at intercellular junctions of endothelial cells. Once through the endothelial cell layer, leukocytes bind to matrix

components such as collagen and laminin via  $\beta 1$  integrins, with VLA-6 and 9 being perhaps the most important in allowing neutrophils to move through venule basement membrane and lung tissue (96-98). See figure 4. After this step, the neutrophil may come in close contact with the sub-mucosal glands and mucus containing epithelial cells. This is associated with mucus emptying from cellular tissues via a proteinase/ epidermal growth factor axis (73).

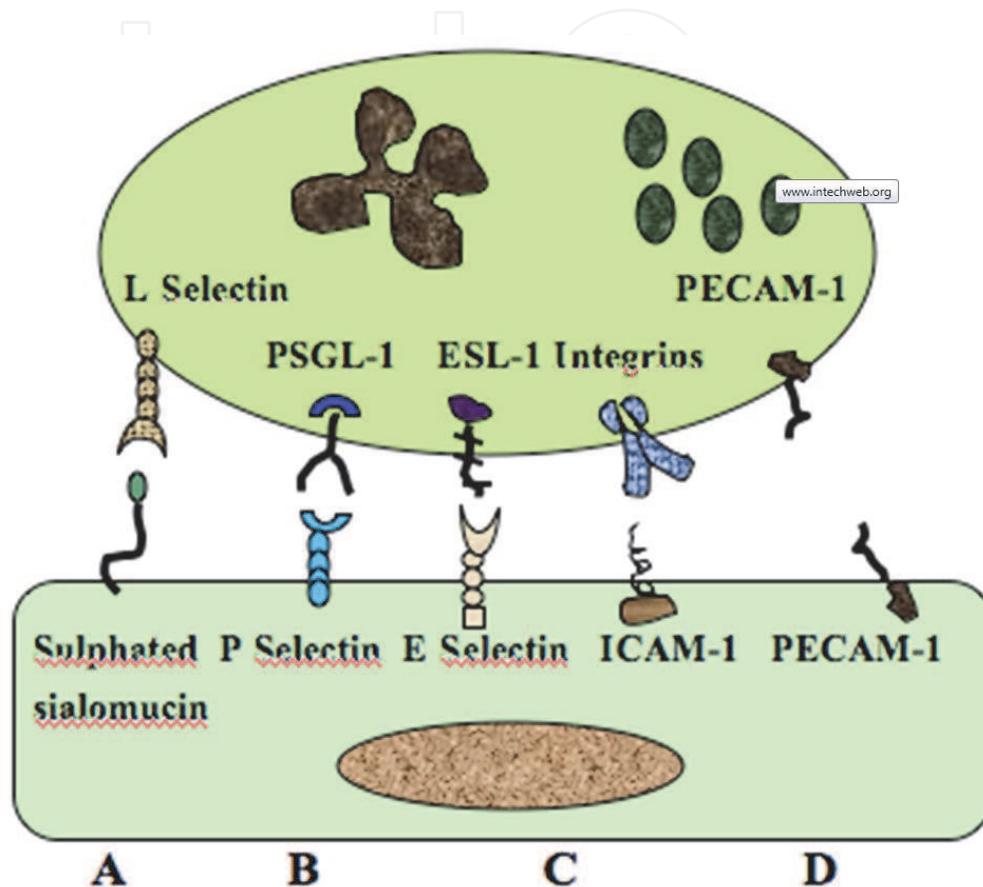


Fig. 4. Schematic summary of Neutrophil and Endothelial Cell Adhesion Molecules and their ligands in neutrophil transendothelial migration.

**Legend.** **A:** Early but short lived binding between L-Selectin and its ligand initiates transient rolling on the endothelium surface. **B:** Interactions between P selectin and PSGL-1 and E-selectin and ESL-1 slows neutrophil rolling and allows transient tethering. **C:** Firm adhesion occurs through integrins and ICAM-1 associations. **D:** PECAM-1 interactions allow homing to intracellular junctions and diapedis via  $\beta 1$  Integrins.

Neutrophils are capable of sensing and migrating to sites of inflammation by sensing chemotactic gradients formed by pro-inflammatory stimuli. Neutrophils migrating within the lung encounter multiple chemoattractants signals in complex spatial and temporal patterns as endothelial, epithelial cells and immune cells respond to infection or injury, releasing a cocktail of cytokines and chemokines. *In vitro* models have demonstrated that neutrophils can migrate up and down chemical gradients, responding to one signal, migrating to its concentration peak and then migrating up a novel, more distant chemoattractant gradient, from endothelium to tissue (99). Thus the size and source of the gradient will influence any affect of neutrophils on mucus production.

Once neutrophils have migrated to the source of inflamed and infected tissue, their role is to kill and remove micro-organisms. The neutrophil achieves this by a process of phagocytosis, the respiratory burst and the release of cytotoxic peptides and proteins. These proteins include proteinases, which are bactericidal. Neutrophil elastase (the most well-studied of the proteinases) can break down the Outer membrane protein A (OmpA) of *E. coli* and other Gram-negative bacteria, and break down *Shigella* virulence factors, by cleaving peptide bonds in target proteins including small, hydrophobic amino acids such as glycine, alanine, and valine (100). Other cytotoxic peptides include the human neutrophil peptides 1 - 4 (collectively known as "the defensins") which account for 50% of the total protein content of azurophil granules and are highly toxic to fungi, enveloped viruses and bacteria (89).

Defensins also enhance mucin production by activating *MUC* gene transcription (101).

Neutrophil proteinases are usually released in a controlled intracellular environment, by fusing phagosomes (lipid membrane enclosed vesicles containing engulfed bacteria) with lysosomes (vesicles containing proteinases and oxidants). However, if proteinases are released from the cell into the extracellular matrix, they have the potential to be extremely destructive. Neutrophil elastase is capable of degrading all components of the extracellular matrix (ECM) by cleaving peptide bonds, including elastin, fibronectin and collagen, causing structural damage to tissue and airways (102).

Neutrophil elastase release is thought to be an important driver of disease pathogenesis in chronic bronchitis (28), and occurs during neutrophil migration, phagocytosis and cell death. Indeed, elastase is the most potent secretagogue studied to date. When neutrophils migrate through the ECM, it is known that a high proportion of neutrophil proteinases are expressed on the neutrophil membrane (103-105), polarising towards the leading edge of the neutrophil (106). A proportion of the proteinase is left behind as the cell moves on (106, 107) and it has been clearly demonstrated that an area of obligate elastase activity (or "collateral damage") always exists following the secretion of free proteinase from activated neutrophils until concentrations have decreased by diffusion to match the concentration of surrounding proteinase inhibitors (108, 109). See Figure 5. Neutrophil proteinases are released during degranulation, and phagocytosis ("sloppy eating"), especially during "frustrated phagocytosis", when cells attempt to ingest large particles (110). In contrast with apoptotic cells, proteinases are released during cell necrosis (111) and finally, proteinases can be released from activated macrophages, which scavenge the proteinases from apoptotic neutrophils via endocytosis and subsequently release them during the first 24 hours of their own inflammatory response (112).

As well as degrading lung tissue, neutrophil proteinases have many other effects in chronic bronchitis and COPD. When released from neutrophils, they damage the respiratory epithelium, reducing ciliary beating (68, 113) and triggering a state of oxidative stress in cells (114). Proteinases can induce apoptosis of epithelial cells (115) and detachment of bronchial epithelial cells from the extra cellular matrix (116), which is thought to be important in COPD and chronic bronchitis (117). Proteinases stimulate the release of other pro-inflammatory signals such as LTB<sub>4</sub> by macrophages (118) and IL-8 from bronchial epithelial cells which enhances more neutrophil migration into the lung. Proteinases also decrease the function of immunoglobulins and activate components of the complement cascade (119, 120) and may also effect wound healing, by effecting transforming growth factor  $\beta$  and the epithelins (121). The inflammatory consequences of neutrophil proteinases on lung tissue and cells relevant to the development of chronic bronchitis and COPD are summarised in table 1.

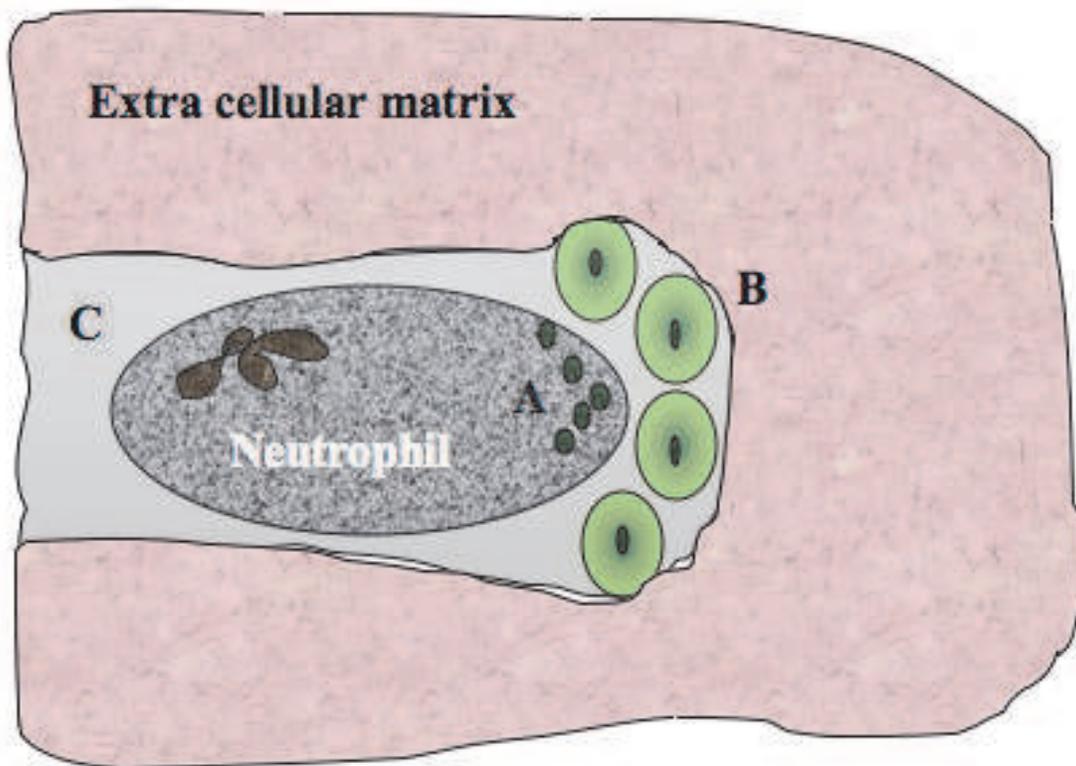


Fig. 5. The potential mechanism for tissue damage during extracellular proteinase release from neutrophils

**Legend.** As neutrophils migrate towards a source of inflammation, granules containing proteinases including neutrophil elastase (NE) are mobilised towards the leading edge of the cell (A). These proteinases are thought to be released during migration through complex media (such as the extracellular matrix (ECM)) to allow a path to be made for the neutrophil. Upon exocytosis, NE has a concentration of 5mM. Alpha-1 anti-trypsin (A1AT) (an anti-proteinase and inhibitor of NE) is thought to be present in the interstitium at concentrations which are 200 times lower than NE when it is first released from a granule, and since the inhibitor inactivates NE on a one molecule to one molecule basis, the proteinase remains active. NE concentrations decrease by diffusion (represented by the dark green to pale green graduated circles) and it is only when concentrations have reduced to approximately 24uM that NE can be fully inhibited by A1AT (B). This leads to an obligate area of proteolysis around the leading edge of the cell, theoretically aiding the cell's transmigration, and potentially leaving damaged ECM behind the cell (C).

Although neutrophils are clearly associated with chronic bronchitis, it is likely that many immune cell populations are involved in the pathogenesis of this disease. Interestingly, there are few differences in the cellular content of bronchial biopsies taken from patients with COPD with and without chronic bronchitis (122) although one study has suggested a predominance of eosinophils in airway secretions when chronic bronchitis is present (123), however this observation has not been replicated. The numbers of CD8<sup>+</sup> lymphocytes in bronchial tissue relate inversely with FEV<sub>1</sub> (122) and have been shown capable of causing lung tissue damage both by their own cytotoxicity and by recruiting macrophages by secreting IFN- $\gamma$ . Macrophages are the most abundant cell recovered in bronchoalveolar

lavage in patients with chronic bronchitis and COPD, and numbers also correlate with disease severity (124, 125). These cells are believed to participate in tissue damage by the release of their own proteinases, such as MMP-12 (although they are less potent than neutrophil elastase) and reactive oxygen species. Whether macrophage proteinases stimulate mucus production and release is unknown. Certainly, more studies are needed to fully understand and identify pivotal inflammatory signals or biomarkers which could differentiate those smokers who are at most risk of chronic bronchitis and COPD, those who are most likely to experience frequent exacerbations of their symptoms and those at risk of bacterial colonisation of their airways, as these disease features are related to worsening clinical outcomes.

Bacterial Killing	Intra-cellular : bactericidal following engulfment of organisms in phagosome Extra cellular: Targeting and cleaving bacterial virulence factors in released granule proteins
Induces Inflammatory Cell migration	NE/alpha 1 antitrypsin complexes are chemotactic for neutrophils Modification of ICAM1 expression enhancing adhesion
Degradation by proteolysis	Degrades all components of Extracellular Matrix Degrades Cystatin C Degrades inhibitors of proteinases Cleaves T Lymphocyte surface antigen
Activation of proteinases by post-transcriptional modifications	Activates proteinases including MMP-2, MMP-3, MMP-9, and Cathepsin B
Modification of inflammatory mediators, enhancing inflammation	Enhances epithelial secretion of IL8 Enhances macrophage secretion of LTB4 Inhibits cellular response to inhibitors of inflammatory mediators, for example, TNFR1 Prolongs the half life of inflammatory mediators including TNF $\alpha$ Increases alpha1-AT expression by monocytes and alveolar macrophages
Enhances Cell Apoptosis	Increases epithelial and endothelial cell apoptosis
Alteration of Cell function	Disruption and detachment of epithelial cells Reduces ciliary beating of columnar epithelium Enhances oxidative stress Increases mucin production Increases bacterial adherence and colonisation on the epithelium

Table 1. An overview of the inflammatory consequences of neutrophil proteinases thought relevant to the development and progression of Chronic Bronchitis and COPD.

**Legend.** References are included in the text.

#### 4. Bacterial colonisation in chronic bronchitis

Approximately 25% of patients with chronic bronchitis have pulmonary secretions from which potentially pathogenic bacteria are cultured, even when they are clinically stable. These patients are deemed to have airways that are colonised with bacteria (126). The most common bacteria cultured in clinically stable patients are *Haemophilus influenzae*, *Streptococcus viridans* and *Streptococcus pneumoniae* (127) although *Neisseria* species and *Proteus mirabilis* have also been isolated. Interestingly, these bacteria have been cultured in lower airway secretions despite the presence of antibodies in serum and sputum against the bacterium (128) and despite courses of appropriate oral antibiotics (129), which suggests that when established, colonisation is difficult to eradicate.

Identified risk factors for colonisation include behavioural factors such as current smoking (127, 130), and repeated bacterial infections in the form of exacerbations (see later). Cigarette smoke exposure is known to effect lower airway mucociliary clearance by reducing ciliary beat frequency (131) and the neutrophilic inflammation present in chronic bronchitis has been shown to be conducive to bacterial colonisation (132). Colonisation is associated with increased sputum concentrations of inflammatory mediators including IL-8, LTB<sub>4</sub> as well as neutrophil elastase (30). Lower airway bacterial colonisation in the stable state appears to increase the frequency and alter the character of COPD exacerbations (with patients with Chronic Bronchitis experiencing more exacerbations) (133). Exacerbation frequency relates to subsequent decline in lung function (134) and health status (135); suggesting that colonisation may be important in disease progression, although it does not directly relate to decline in FEV<sub>1</sub> (127).

The numbers of bacteria present may also alter immune cellular responses which could impact on subsequent inflammation, as patients with sputum bacterial loads of > 10<sup>6</sup> cfu/ml have been shown to have a more robust inflammatory response than those with bacterial loads that are lower (30). In animal models, bacterial loads of less than 10<sup>5</sup> organisms can be eradicated by macrophages and other components of the innate host defence without inducing much inflammation. In patients with chronic bronchitis, a load of this magnitude can co-exist without secondary inflammation perhaps because a balance between bacterial killing and replication controls the situation. However, greater bacterial loads require neutrophil recruitment and the involvement of the secondary acquired immune response (136). Macrophages and dendritic cells facilitate bacterial clearance in a variety of ways. They are able to migrate to the bronchial lymph nodes, particularly to the T cell paracortical areas (137) where the antigen they carry is available for primary stimulation of the T cell clones. T cell derived cytokines then amplify the effector function of macrophages by enhancing their phagocytic and anti-microbial capacity (138).

#### 5. Exacerbations of chronic bronchitis

Chronic Bronchitis is characterised by periods of disease stability punctuated by exacerbations. Several different definitions of exacerbations exist (for example (139, 140)) but a common definition is a subjective increase from baseline of one or more chronic symptoms including cough frequency, sputum production or sputum purulence and breathlessness (27). The episodes can be defined by severity or aetiology (bacterial, viral, environmental or unknown). Approximately 30% of exacerbations are thought to be caused by viral infections (141) with 30% of these being caused by influenza, 25% by parainfluenza, 20% by rhinovirus and 15% by coronavirus (27). In exacerbations requiring ventilatory support, only 15% of cases were

associated with positive identification of a viral pathogen, and half of these were also associated with a concomitant bacterial infection, suggesting that viruses are less important in more severe exacerbations (142).

Pathogenic bacterial organisms are found in 50 – 80% of patients during exacerbations (143, 144), with the most common organisms being *Streptococcus pneumoniae*, nontypable *Haemophilus influenzae* and *Moraxella catarrhalis* (19, 145). Less frequently, gram negative organisms are isolated, including *Pseudomonas aeruginosa* (146). Previously there was controversy as to whether bacteria isolated from sputum during exacerbation were truly causative, or whether they represented colonization. However, recent studies have demonstrated that mean bacteria colony forming units per ml of sample (counted during quantitative sputum culture) are at least a log higher in exacerbations compared with those seen in the stable state (27). Further more, bacterial exacerbations such as these are characterized by a significant increase in pulmonary inflammation including neutrophil recruitment and can be identified by the presence of purulent sputum (147) which resolves with resolution of symptoms (148).

Examination of sputum purulence is a simple and accurate way to differentiate between bacterial and non-bacterial exacerbations of chronic bronchitis (29), and can be used to rationalize antibiotic therapy to target those patients likely to benefit, and to protect others from unnecessary antibiotic exposure and potential side effects.

Exacerbation frequency appears to increase with decreasing FEV<sub>1</sub> and the presence of chronic bronchitis, but in patients with moderate to severe disease, the median exacerbation frequency is 2 -3 per annum and patients with more frequent exacerbations experience a faster decline in FEV<sub>1</sub> (134). There is also a correlation with the degree of airflow obstruction and the type of bacteria isolated from sputum during acute exacerbations of Chronic Bronchitis and COPD, with *Pseudomonas* species and *Enterobacteriaceae* being predominant in patients with an FEV<sub>1</sub> ≤ 35% of the predicted value (149) although it is difficult to ascertain whether the bacteria are the cause or a consequence of reduced lung function.

Exacerbations are a significant cause of morbidity and mortality, with increasing exacerbation frequency being related to worsening patient outcomes, reduced exercise capacity and a reduced quality of life (150). Exacerbations remain the commonest precipitant of death and even after an exacerbation resolves, respiratory, physical, social and emotional impairment may persist for prolonged time (150). The decline in health status is thought to be the result of prolonged periods of heightened pulmonary inflammation, with more immune cell recruitment to the lungs, more proteinase release, and more tissue damage (151). Preventing exacerbations and treating them expeditiously is a priority in order to slow disease progression.

## 6. Established and emerging therapies in chronic bronchitis

Treatments for chronic bronchitis have focused upon improving or reducing sputum clearance and treating airflow obstruction, when present. Airflow obstruction is treated in accordance with guidelines for the treatment of COPD, and these will not be covered here.

### 6.1 The treatment of exacerbations of chronic bronchitis

During clinical exacerbations of chronic bronchitis and COPD, studies have demonstrated that oral prednisolone (continued for 10 days) is efficacious, improving dyspnoea, increasing improvements in FEV<sub>1</sub> and increasing the time until the next exacerbation (152).

Results from trials of antibiotic treatment during exacerbations have been more confusing, as they have often not proved clinically effective (for example, (153, 154)). However, these trials have often been limited in their design, as they have not differentiated between bacterial exacerbations (where one would expect an improvement in clinical outcomes following appropriate treatment) and non-bacterial exacerbations (where antibiotics should not effect outcomes). Antibiotics are an appropriate therapy for suspected bacterial exacerbations, and should be reserved for patients with symptoms and signs consistent with infection, in the presence of purulent sputum (30, 147). Given the bacteria isolated from sputum during exacerbations (see earlier), an appropriate choice of antibiotic includes broad spectrum penicillins such as amoxicillin (155), tetracyclines such as doxycycline (156) and quinolones and macrolides where allergies and bacterial resistance are important determinants of anti-bacterial choice. International guidelines for treatment choice have not altered in the past ten years and the majority of guidelines suggest that an initial sputum culture is only required prior to treatment initiation when resistance is suspected.

Salbutamol and ipratropium have been shown to improve symptoms of breathlessness and wheeze during exacerbations of chronic bronchitis and COPD, and increase FEV<sub>1</sub> (157), and these therapies are routinely used where these symptoms predominate. Both appear equally efficacious and while only a select group of patients benefit from both therapies in unison, side effects are minimal, supporting their use (158). Delivery device (nebulised or via an inhaler) does not effect outcome (159). It is less clear if they are beneficial in the absence of chronic airflow obstruction, as studies have shown mixed results (160). There are currently no published studies which support the use of long acting Beta<sub>2</sub> agonists or anti-muscurinic medicants during acute exacerbations of chronic bronchitis.

A meta-analysis of 23 trials suggested that mucolytics also reduce symptom scores, days of illness and increase time until next exacerbation in chronic bronchitis (161) supporting their use in patients with frequent exacerbations.

Not all patients respond to therapy, and a poorer response (with increased risk of death) is more commonly seen in patients aged over 65 years, those with significant co-morbidities, significant airflow obstruction (FEV<sub>1</sub> < 50% predicted) and more than 4 exacerbations per year (139). Patients fulfilling these criteria should be assessed carefully to ensure that treatment, where needed, is started promptly. In order to facilitate this, many patients are now being managed in the community with prophylactic antibiotics and oral corticosteroids, as it has been shown that early intervention is associated with better clinical outcomes (162).

## 6.2 Treatments for stable disease

Most studies of potential treatments used in chronic bronchitis have not differentiated between chronic bronchitis and COPD, and therefore results should be interpreted with caution. Certainly, patients with mild symptoms and infrequent exacerbations may not necessitate regular pharmacotherapy and no treatments (apart from smoking cessation) have been shown to reduce symptoms and alter progression or the development of airflow obstruction. In light of this, all patients should be encouraged and supported with appropriate pharmacotherapy to stop smoking, as this has clear health benefits and has been shown to reduce disease progression.

Inhaled corticosteroids are a common treatment in COPD, and recommended for patients with a FEV<sub>1</sub> less than 50% predicted or in patients who experience frequent exacerbations. Studies of inhaled corticosteroids in chronic bronchitis without airflow obstruction are

limited, and contradictory. Llewellyn-Jones et al, saw a reduction in the chemotactic activity of lung secretions with reduced neutrophil activity in sputum from patients with chronic bronchitis and emphysema (163), however, other authors have not shown a similar response in short term trials (164). Furthermore, a three year trial of inhaled budesonide in mild and moderate COPD did not show any benefit in lung function decline, symptom scores or exacerbation rates, questioning the role for inhaled steroids in the absence of severe airflow obstruction (165). Similarly, there is no clinical evidence to support the use of bronchodilators in chronic bronchitis in the absence of airflow obstruction, however, long acting  $\beta_2$  agonists have been shown to increase ciliary beat frequency, which could enhance sputum clearance (166).

Phosphodiesterase 4 (PDE4) inhibitors are effective anti-inflammatory agents in animal models and have been shown to reduce inflammation in COPD and chronic bronchitis (167). PDE4 hydrolyzes cyclic adenosine monophosphate (cAMP) to inactive adenosine monophosphate (AMP). Inhibition of PDE4 blocks hydrolysis of cAMP thereby increasing levels of cAMP within cells. Increases in the intracellular levels of cyclic AMP can reduce the activation of a wide range of inflammatory and lung resident cells (168).

There have been trials of PDE4 inhibitors in COPD (169-171), that have confirmed a modest but significant improvement in spirometry in COPD, and quality of life scores and a reduction in the number of exacerbations experienced. There is evidence that Roflumilast may be particularly beneficial in patients with COPD and chronic bronchitis (172), but it is unclear if this drug is effective in chronic bronchitis without airflow obstruction, and further trials are awaited. PDE4 inhibitors appear to reduce the number of neutrophils recruited to the airways, with a reduction of between 30 - 50%, which could explain their clinical efficacy (168).

N-acetylcysteine is both a mucolytic and an anti-inflammatory and antioxidant drug (173, 174). It is widely prescribed for the treatment of chronic bronchitis in mainland Europe (175) and studies have confirmed that it is effective in reducing the risk of exacerbations and improves symptoms of chronic bronchitis (reducing sputum volume) (176). The use of other mucolytics including carbocysteine, have been reviewed in a recent Cochrane publication (177) of 28 trials. This review surmised that regular use of mucolytics reduced exacerbation frequency and days of disability during exacerbations in patients with chronic bronchitis, however, this benefit was not seen in patients taking regular inhaled corticosteroids. The authors suggest that oral mucolytics are a potentially useful treatment in patients with frequent exacerbations who are not on inhaled corticosteroids(177).

Prophylactic antibiotics have been used in patients with stable chronic bronchitis in an attempt to treat bacterial colonisation, and reduce associated inflammation. There have been few trials examining the efficacy of this, however a meta-analysis of 9 trials suggested that antibiotics reduced the days of illness experienced due to exacerbations of chronic bronchitis, without reducing actual exacerbation frequency (178). Erythromycin has been shown to reduce exacerbation frequency in patients with chronic bronchitis and COPD (179) and clarithromycin has been shown to reduce the development of emphysema in smoke-exposed mice (180). These actions are thought to be mediated via the macrolides effect on matrix metalloproteinase 9 secretion (a proteinase) and are separate from the anti-microbial properties of the drugs (181). Further trials are needed to assess the longterm impact of macrolide therapy in chronic bronchitis.

If chronic bronchitis is caused and perpetuated by neutrophilic inflammation, one would expect that therapies which decrease the inflammatory response would improve clinical outcomes. Unfortunately, neutrophilic inflammation (as seen in COPD and chronic

bronchitis) is, in the main, resistant to the generic inflammatory treatments employed in other respiratory conditions, such as asthma and new therapeutic strategies are urgently required. It may be that there is no single treatment that is effective in all patients with chronic bronchitis, and perhaps as more is learned about its genetic and environmental drivers, more specific treatments for subsets of patients will be developed (practicing pharmacogenetics). Until that point, there are no clear therapeutic options for patients with stable disease without airflow obstruction, and no treatments that prevent the decline in FEV<sub>1</sub> in patients with airflow obstruction. Current best practice includes the prompt treatment of exacerbations, coupled with smoking cessation support.

## 7. Conclusion

Chronic bronchitis is a common and debilitating feature of COPD, which affects between 8 and 12 % of adults globally and despite improvements in air quality in developed countries, its prevalence has not fallen. The main risk factor for developing chronic bronchitis is now chronic cigarette smoke exposure, but environmental air quality remains an important contributing factor in the developing world.

Chronic bronchitis is associated with bronchial inflammation, and although the neutrophil and its products have been shown to cause all of the pathological features of disease *in vitro*, many other cell types have been implicated in its pathogenesis.

In COPD, the presence of chronic sputum expectoration is associated with worse clinical outcomes than those without. The inflammatory burden is higher in patients with chronic bronchitis compared with matched patients without (182) and chronic mucus hypersecretion is consistently associated with both an excess FEV<sub>1</sub> decline, an increased risk of subsequent hospitalization (183) and death from respiratory infections (184).

Despite its importance in terms of prevalence, morbidity and mortality, chronic bronchitis remains under-investigated and poorly treated. No medicants have been shown to robustly improve symptoms, decline in FEV<sub>1</sub> or exacerbation frequency. The mainstay of treatment remains smoking cessation and prompt treatment of exacerbations. New therapeutic strategies are urgently required.

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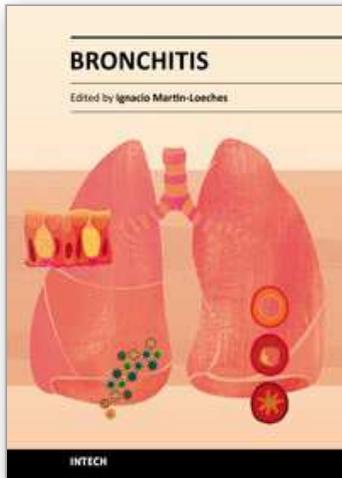
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Lung parenchyma has been extensively investigated. Nevertheless, the study of bronchial small airways is much less common. In addition, bronchitis represents, in some occasions, an intermediate process that easily explains the damage in the lung parenchyma. The main target of this book is to provide a bronchial small airways original research from different experts in the field.

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