INTRODUCTION

The definition of chronic obstructive pulmonary disease (COPD) has shifted with the increased understanding of contributory factors and disease evolution. Previously classified as an irreversible airway obstruction, COPD is now understood to be partially reversible with treatment, as recognised in the most recent GOLD definition: a common preventable and treatable disease, characterised by persistent airflow limitation (post-bronchodilator FEV₁/FVC <0.70).

BURDEN OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CHRONIC BRONCHITIS

Approximately 15 million Americans have been diagnosed with COPD, and data suggest that up to 63% of people with COPD may currently be undiagnosed. Diagnosis may not occur until the disease progresses due to a lack of serious symptoms, poor recognition of clinical symptoms in the early phase, insufficient use of spirometry, or patient reticence in seeking medical assistance.

The epidemiology of COPD may be changing, with younger patients, who are currently...
underdiagnosed, likely to constitute a greater proportion of the patient population in the future. Indeed, the patient population has already altered, with COPD mortality in women eclipsing that in men in the USA at the turn of the 21st century. COPD is the third leading cause of death in the USA and is predicted to be the third leading cause worldwide by 2020, with lower RTIs in fourth position.\textsuperscript{5-7} COPD-related morbidity is a major economic and societal burden: 41% of patients have visited their doctor due to symptoms within the last year and 13% have had hospital or emergency department visits. In addition, shortness of breath is reported to affect quality of life (QoL) in 58% of patients.\textsuperscript{12} In the USA, direct and indirect costs, 75% of which are due to exacerbations, amount to approximately $30 billion and $20 billion per annum, respectively.\textsuperscript{2,4}

Chronic bronchitis (CB) is a common COPD comorbidity. Excessive mucus accumulation is a key diagnostic feature of CB; indeed, pulmonary specialists now talk in terms of excess mucus in COPD rather than CB. Mechanisms contributing to excessive mucus accumulation can be grouped into those that contribute to increased production (inflammatory cells, oxidative stress, and viral or bacterial infection) and those that contribute to decreased elimination (poor ciliary clearance, airway occlusion, reduced peak expiratory flow, and respiratory muscle weakness). The prevalence of CB in adults ranges from 3–22%. In the subpopulation of patients with COPD, prevalence of CB is 27–35%. Smoking remains the major risk factor, with biomass exposure, air pollution, and gastro-oesophageal reflux disease also contributing to the risk of developing the condition.\textsuperscript{8} Historically, CB has been viewed as a relatively benign condition. However, assessment of the disease burden reveals a different clinical reality. In those without COPD, CB is associated with an accelerated decline in lung function (1.7–22.8 mL/year), particularly in women, and an increased risk of developing COPD (1.85 to 2.88-fold increase), particularly in older patients. In patients with COPD, CB is associated with poor health status, increased exacerbations, and hospitalisations (2 to 4-fold increase), and increased respiratory and all-cause mortality.\textsuperscript{9-13}

EXACERBATIONS, INFECTIONS, AND CHRONIC INFLAMMATION

Exacerbations are a diffuse phenomenon broadly defined as “an acute event characterised by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication”.\textsuperscript{1} Other conditions such as pneumonia and congestive heart failure should be excluded before diagnosing an exacerbation.\textsuperscript{14-16}

Exacerbations contribute to increased risk of death, accelerated decline in lung function, and reduced QoL.\textsuperscript{17-19} In addition, exacerbations directly result in frequent visits to physicians’ offices (13 million/year in the USA) and emergency rooms, leading to numerous hospitalisations and absenteeism.\textsuperscript{20} Exacerbations also account for a substantial percentage of COPD treatment costs.\textsuperscript{21} The importance of exacerbations in COPD progression is highlighted by their current prominence as a drug target.

The majority of exacerbations are related to infections (70–80%) from either bacterial (50–60%), viral (30–50%), or atypical (2–5%) organisms. Non-infectious causes account for 10% of exacerbations and 30% have an unknown aetiology.\textsuperscript{22-27} With the increased use of sensitive techniques such as polymerase chain reaction (PCR), it is likely that many exacerbations of unknown aetiology will be reclassified as infectious. Microbes known to have a significant relationship with acute exacerbations include \textit{Haemophilus influenzae} (20–30%), \textit{Streptococcus pneumoniae} (10–15%), and \textit{Moraxella catarrhalis} (10–15%). In more severe disease, \textit{Pseudomonas aeruginosa} (5–10%) is an important driver of exacerbations. Recent work suggests that, despite previous assumptions, \textit{H. haemolyticus} and \textit{H. parainfluenzae} do not have a role in exacerbations. The role of \textit{Enterobacteriaceae} spp. and \textit{Staphylococcus aureus} is currently unclear, although they are known to be important in pneumonia.\textsuperscript{28}

The mechanism of bacterial exacerbations in COPD is complex. Previous theories were based around a change in bacterial load overwhelming the immune system. However, evidence suggests that exacerbations are in fact driven by the acquisition of new strains of bacteria from the environment. Inflammatory defence mechanisms then cause the increased symptoms that characterise an exacerbation. The next stage is the development of strain-specific adaptive immunity, which eliminates the infecting strain but does not protect against subsequent acquisition of new bacterial strains, leaving the door open to subsequent infection and acute exacerbation events.\textsuperscript{15,28-33}
The related ‘Goldilocks hypothesis’ postulates that dysregulation in the adaptive immune response to exacerbations is key to driving progression. Dysregulation may result in either too little a response, failing to clear the infection resulting in prolonged symptoms, or too great a response, resulting in prolonged or excessive inflammation.34

Acute infections and subsequent exacerbations are not isolated disease processes in COPD, rather acute infection acts as a comorbidity in COPD. Key to this concept is an understanding that comorbid conditions, rather than merely existing simultaneously, have a synergistic relationship with one another. Acute infection as a comorbid condition increases inflammation and obstruction, while chronic inflammation increases susceptibility to infection and the severity of the subsequent consequences.35 Hence, acute exacerbations and chronic processes in COPD act as two intersecting cycles, at the centre of which is impaired lung defence (Figure 1). Much of this impaired defence is due to dysfunction in the innate immune system, making this a central target for therapies that can improve both the chronic and acute processes driving progressive loss of function in COPD.36

### COLONISATION VERSUS CHRONIC INFECTION

In addition to acute bacterial infection driving exacerbations and the acute cycle in COPD, bacteria also play a key role in the chronic inflammatory cycle of COPD (Figure 1). New molecular techniques, principally 16S rRNA amplification, have led to the identification of a complex microbial ecosystem colonising the lungs of healthy individuals (the lung microbiome). The lungs of COPD patients exhibit decreased diversity, with significant heterogeneity in species at different lung locations.37 Following the culturing of bacteria from a sputum sample, a differential diagnosis between bacterial colonisation and an acute infection was traditionally made on the basis of the presence or absence of symptoms. However, the true difference between colonisation and infection is the absence of both an immune response and damage to the host by colonising bacteria.38

Several lines of evidence suggest that some bacteria present in stable COPD may represent infection rather than colonisation. Firstly, using bronchoalveolar lavage and traditional culture techniques, a greater proportion of ex-smokers with COPD (35%) had ≥10^5/mL potentially pathogenic microorganisms (PPMs) than ex-smokers without COPD (0%) and healthy non-smokers (6.7%) (p=0.003). Those COPD patients with PPMs showed increased indices of airway inflammation, including higher numbers of neutrophils, increased levels of interleukin (IL)-8, and an increased level of MMP-9, a metalloproteinase involved in extracellular matrix degradation. These data suggest that both an immune response and cell damage are occurring, which is indicative of infection. Furthermore, similar but larger increases in neutrophils, IL-8, and MMPs are found during exacerbations.37 Another line of evidence for infection over colonisation is immune system reorganisation. This includes the formation of germinal centres and lymphoid follicles, which are increased in number and dimension in severe COPD. This is likely to occur as a response to infection, although autoimmunity may also have a role.39

Further data supporting the key role of bacteria in COPD comes from studies conducted in mice. Exposure to tobacco smoke alone resulted in an emphysema-like phenotype, while exposure in combination with H. influenzae resulted in a COPD-like phenotype with lymphoid follicles, mucus hypersecretion, and airway changes.40-41 In addition, bronchiectasis, bronchial, and bronchiolar dilation related to infection appears to be common in patients with moderate-to-severe COPD (58%), and patients with bronchiectasis have more severe COPD, higher concentrations of PPMs, and a greater likelihood of being hospitalised.42,43 These data suggest that bronchiectasis may be a diagnostic feature of patients with COPD strongly driven by chronic infection.

A recently published prospective cohort study (N=41) collected symptoms daily using the Breathlessness, Cough, and Sputum Scale (BCSS) for 4 years and plotted symptom scores against colonisation, determined by biweekly culturing and PCR.44,45 As expected, exacerbations were associated with higher BCSS scores; however, colonisation was also associated with a significantly higher BCSS score compared with no colonisation. The difference was 0.7, indicative of a moderate and clinically significant effect. In the same study, inflammation measured by sputum IL-8 followed the same pattern, peaking during exacerbations with elevated levels during colonisation.45 These data further illustrate that chronic infection in COPD patients increases both vulnerability to exacerbations and also daily symptoms.
To summarise, evidence of immune system activation, increased inflammatory cytokines, and increased symptoms associated with the presence of an increased number of bacteria in stable COPD suggests that these bacteria represent an infection rather than a colonisation in a subset of COPD patients. The presence of chronic infection and associated inflammation is likely to drive the progression of COPD as previously indicated (Figure 1).

**HIGH-RISK PATIENT PHENOTYPES AND UNMET NEED**

There is currently significant unmet need in exacerbation management. Standard management of exacerbations involves treatment with bronchodilators and steroids, as well as antibiotics in cases of increased sputum volume and purulence. In a study of prednisone added to antibiotics, the relapse rate was 26% within 1 month in the steroid-treated group. Similarly, in a study from the Netherlands in patients treated with doxycycline and corticosteroids, the treatment failure rate at 1 month was approximately 50%, with a quarter of patients going on to relapse. Even in a specialised tertiary care population in which close to 80% of patients were treated with long-acting bronchodilators and inhaled steroids, approximately 47% of GOLD 4 patients had ≥2 exacerbations/year, with 33% of GOLD 3 and 22% of GOLD 2 patients also having frequent exacerbations.

The frequent-exacerbator phenotype (≥2 exacerbations/year) has been suggested as a patient group that should be targeted for prophylaxis. In addition, patients who have experienced ≥1 hospitalisation due to exacerbation (7%, 18%, and 33% of GOLD 2, 3, and 4 patients, respectively) may also represent a viable COPD phenotype for prophylaxis. However, given the high costs of even a single hospitalisation, earlier preventative therapy may be desirable.

Prevention strategies can be split into those that are infection-specific and those that are not. Non-specific strategies include: smoking cessation (prophylactic after 10 years); anti-inflammatory drugs, including inhaled steroids and phosphodiesterase 4 inhibitors; bronchodilators; mucolytics/anti-oxidants; specific anti-inflammatory drugs, which are in development but yet to show efficacy (anti-IL-1 receptor and Nrf2 agonists); and pulmonary rehabilitation, which has shown efficacy in reducing exacerbations. Infection-specific strategies include: vaccines; oral bacterial lysates; and prophylactic antibiotics.
INFECTION-SPECIFIC PROPHYLACTIC STRATEGIES FOR COPD AND CHRONIC BRONCHITIS: A FOCUS ON VACCINES AND IMMUNOMODULATORS

Different stages of the immune response appear to be important at different stages of COPD. The innate immune response is important in the very early stages of COPD (formerly GOLD 0 and GOLD 1) and continues to play a role throughout the pathological process. Remodelling of the lung immune tissue begins in GOLD 2, with the adaptive immune response becoming important in the later stages (GOLD 3 and 4). Both immune dysregulation and infections are key drivers of exacerbations in COPD, making treatment with both immunomodulators and vaccines useful prophylactic strategies. The efficacy of influenza vaccines in reducing serious COPD-related illness is noted in the most recent GOLD guidelines, and the pneumococcal polysaccharide vaccine is now recommended for COPD patients ≥65 years of age and for COPD patients <65 years of age with FEV\textsubscript{1} <40% of predicted. OM-85 is currently the most studied immunomodulator for the prevention of COPD exacerbations and recurrent respiratory infections. OM-85 is a lysate of 21 strains of respiratory bacteria, encompassing the main strains involved in respiratory infections. As noted above, dysfunction in the innate immune system has a major role in the impaired lung defence at the heart of the vicious cycle of COPD. OM-85 has been shown to stimulate monocyte and macrophage activity, promote dendritic cell (DC) maturation and activity, and stimulate the activity of neutrophils and natural killer cells. OM-85 has been shown to elicit a mild and dose-dependent activation of DCs from healthy donors and those with COPD in vitro, with the highest doses resulting in a similar response to that caused by lipopolysaccharide. The activation of DCs by OM-85 produces a pre-alert phenotype, essentially creating a primed immune system with barriers raised against infection. OM-85 has been shown to increase the release of the protective cytokine IL-10 from the DCs of both healthy donors and COPD patients (Figure 2).

![Figure 2: Release of IL-10 from peripheral blood mononuclear cells in COPD patients and healthy donors following treatment with OM-85.\textsuperscript{54}](image)

*p<0.05, COPD patients versus similarly treated healthy donors. COPD: chronic obstructive pulmonary disease; IFN\textsubscript{γ}: interferon gamma; IL-10: interleukin 10; TNF\textsubscript{α}: tumour necrosis factor alpha; Ut: untreated.
IL-10 release was more pronounced under inflammatory experimental conditions (addition of interferon gamma [IFN\(\gamma\]) and tumour necrosis factor alpha [TNF\(\alpha\]), and COPD patients showed a more pronounced OM-85-induced release of IL-10 than healthy donors under all conditions. Therefore, OM-85 may reduce inflammation-related tissue damage in patients with COPD.

The adaptive immune system drives exacerbations and has a major role in advanced stages of COPD, and OM-85 has been shown to modulate adaptive immunity. Treatment with OM-85 preferentially increases serum IgA and increases levels of serum IgG and IgM. Secretory IgA, which is the main immunoglobulin involved in the adaptive response to respiratory infection, is also stimulated by OM-85. Furthermore, OM-85 boosts T and B cell activity: key cellular constituents of the adaptive immune response.\(^{52,53,56-61}\)

Multiple studies have demonstrated the therapeutic potential of OM-85 in patients with COPD and CB.\(^{62-66}\) In a 6-month placebo-controlled study in patients with CB or COPD, OM-85 was prescribed for 30 days, followed by three 10-day courses during Months 3, 4, and 5. Acute exacerbations were reduced by 29% at the end of treatment (\(p<0.05\)).\(^{65}\)

A 12-month placebo-controlled study in CB and COPD used a different (standard) dosing frequency of 10 days for each of the first 3 months. The number, severity, and duration of exacerbations and the duration of antibiotic use in patients receiving OM-85 was significantly reduced (\(p<0.01\)) over the study period compared with the previous year and compared with untreated patients. Cough, sputum, and dyspnoea scores were all significantly lower in patients treated with OM-85 versus placebo (Figure 3).\(^{64}\)

High-risk patients are an important target population for prophylaxis and OM-85 has been shown to reduce hospitalisation in patients with severe COPD (\(p<0.05\)), who are prone to frequent exacerbations.\(^{68,63}\) In the elderly population with CB, a vulnerable and understudied group, OM-85 reduced the number of RTIs by 28% and exacerbations by 40%.\(^{62}\)

In a recent double-blind, placebo-controlled trial (N=428), patients with COPD received standard OM-85 treatment. The primary endpoint of a

**Figure 3:** Number (A), duration (B), and severity (C) of acute infections, and total days of antibiotic treatment (D) in OM-85-treated and placebo-treated patients.\(^{64}\)

\(*p<0.01\) versus placebo; \(*p<0.01\) versus before treatment.

This figure is based on a study first published in *Chin Med J.* 2004;117(6):828-34.
reduced proportion of patients with ≥2 acute exacerbations during the 3-month treatment period was met in both the full analysis population and the per-protocol population (23.4% versus 33.3%, p<0.05 and 17.0% versus 31.2%, p<0.05; respectively). The prevalence of recurrent exacerbations was numerically lower in those treated with OM-85 versus placebo (32.8% versus 38.0%; p=0.277), but the difference was significantly in favour of OM-85 only in the per-protocol population (26.3% versus 36.1%; p=0.038). Tolerability was good, with similar rates of adverse events in both groups.66

The clinical findings from placebo-controlled trials provide evidence that OM-85 has a preventative effect as an adjuvant medication in the management of COPD and/or CB, thereby reducing the number, duration, and severity of recurrent exacerbations and also the use of antibiotics in this patient population.

**COST-EFFECTIVENESS**

From the perspective of healthcare providers, cost-effectiveness is a key factor in evaluating which drugs should be prescribed. In 2001, Collet and colleagues67 carried out a pharmacoeconomic analysis of their 1997 double-blind, placebo-controlled trial. In total, 381 patients with moderate-to-severe COPD participated in the trial. Direct costs included treatment, visits, tests and diagnostic procedures, and hospitalisation. Indirect costs included absenteeism and care costs. OM-85 achieved a 44% (p=0.02) reduction in mean cost of respiratory-related hospitalisation per patient, a 42% (p=0.02) reduction in all-cause hospitalisation per patient, and there was a trend towards a reduction in indirect costs. In a similar Italian study on the cost-effectiveness of OM-85 for the treatment of CB, the cost of treating exacerbations was reduced by 36% in patients treated with OM-85 compared with those who were not.68

**CONCLUSION**

In summary, most COPD exacerbations are the consequence of infectious events, which in turn are the consequence of immune dysregulation. The above data from both clinical and basic studies indicate that these defences can be positively modulated using treatments such as OM-85. This immune modulation leads to the prevention of COPD exacerbations, reducing both symptoms and the number and severity of exacerbations, thus reducing costs and potentially modifying the natural course of the disease.

**REFERENCES**


