AIMS: To discuss the main clinical challenges associated with acute and chronic infection in patients with chronic obstructive pulmonary disease (COPD).

TARGET AUDIENCE: Clinician, Nurse, Pulmonologist, Physiotherapist

AIMS

- Define the concepts of acute and chronic infection in COPD
- Describe the impact of infection in the natural course of COPD
- Strategies for prevention and treatment of acute infection
- Discuss the treatment options for chronic infection in COPD

SUMMARY

Patients with COPD may present with different clinical characteristics, prognosis and response to treatment (1). This has resulted in increased efforts to identify subgroups of patients with similar clinical characteristics and prognosis, the so-called clinical phenotypes, in order provide more individualized and effective therapy (2,3). One of these phenotypes is the frequent exacerbator and in most cases these exacerbations are caused by bronchial infection.

The concept of chronic bronchial infection in COPD

Subjects with COPD present different forms of impaired immunity, including reduced mucociliary clearance, defective phagocytosis and hyporesponsiveness of alveolar macrophages to bacterial antigens, with a subsequent predisposition to infection (4,5). Among the defense mechanisms, airway mucus plays a leading role; under normal circumstances it protects the epithelial lining by entrapping harmful particles and clearing them from the airway through the mucociliary clearance (4). Cigarette smoke, bacterial infection, cold air, and various irritants and allergens cause mucus secretion by inducing the release of inflammatory mediators or nerve activation (4). The vicious circle of bacterial infection and mucus hypersecretion is further complicated by the fact that a reduction in the numbers of serous and Club cells (caused by globet cell hyperplasia) results in low concentrations of their protective molecules in respiratory secretions and may also explain the increased propensity for bacterial growth in the lower airways of patients with mucus hypersecretion (4,6). Consequently, microbiological cultures of sputum are positive for PPMs in about 40-70% of patients with stable COPD (7).
The PPMs most frequently recovered from respiratory samples in stable COPD include non-typeable *Haemophilus influenza* (NTHi), *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Haemophilus parainfluenzae*. Multibacterial colonization is not uncommon, while *Pseudomonas spp.* is predominately found in patients with more severe functional impairment (7).

The relationship between the isolation of PPMs in bronchial secretions and the evolution of COPD has been demonstrated in a study by Wilkinson et al (8), who observed that patients with higher bronchial bacterial loads and those experiencing changes in colonizing bacterial type over time, presented a faster decline in lung function during a one-year follow-up. These results were confirmed by Marin et al (9) in a series of 79 COPD patients, of which 47 were chronically infected by *H.influenzae*, *P. aeruginosa*, or enterobacteria. These authors found increased neutrophilic inflammation associated with isolation of these microorganisms and a statistically significant relationship with accelerated FEV1 decline. More recently, Bafadhel et al (10) observed that persistence of bacteria in the airways, whether defined by culture, quantitative polymerase chain reaction (qPCR), or both, was associated with lower forced expiratory volume in 1 second (FEV1). Moreover, the increased inflammation associated with the presence of PPMs in the lower airways results in more respiratory symptoms (11) and a significant impairment in health-related quality of life (11,12).

There is therefore sufficient evidence to maintain that PPMs play an important role in the pathogenesis and progression of COPD. The usual term, “colonisation”, suggests passive and harmless coexistence of bacteria on the mucous membranes of an asymptomatic host. However, not only are PPMs far from being passive bystanders, they in fact contribute actively to airway and systemic inflammation, with all the subsequent negative consequences. On the basis of the evidence available, a change in the terminology has been suggested in favour of the term “chronic bronchial infection” to describe the isolation of a significant load of PPMs in the airways in stable COPD patients (13,14). This syndrome can be accompanied by recurrent infective exacerbations, an increase in respiratory symptoms, and a significant impairment to health status, even in the absence of an exacerbation.

Further evidence of the impact of chronic bronchial infection on the natural history of COPD derives from its relationship with increased frequency and severity of exacerbations. Patel et al (15) demonstrated that chronic bronchial infection, mainly from *H.influenzae*, was associated with more frequent exacerbations and more symptoms and increased sputum purulence during exacerbations, compared with patients not infected in a stable state. These results have been confirmed in subsequent studies using molecular techniques to identify microorganisms such as qPCR (10).

In fact, most patients with severe COPD and chronic bronchial infection have significant bronchiectasis when studied by high resolution CT (HRCT) scan. In the study by Martinez-Garcia et al. (16), the isolation of a PPM in the sputum of a patient with stable COPD, together with a FEV1<50% predicted and a history of at least one hospital admission for an exacerbation in the previous year, were associated with a 99% probability of presenting bronchiectasis in an HRCT scan.

The relationship between chronic and acute bronchial infection in COPD

The balance between microorganisms and their host may be altered by several factors that determine an uncontrolled increase in bacterial load and associated inflammation, giving rise to the symptoms of an exacerbation. This is suggested by the observation that PPMs are more frequently isolated and have higher loads during exacerbations when compared to the stable state, both in traditional cultures and in qPCR (7). All these findings, and the fact that the severity of bronchial inflammation is directly correlated with bacterial load, support the “fall and rise” or quantitative hypothesis of bacterial exacerbations of COPD (17). According to this hypothesis, symptoms of exacerbation appear when the inflammatory reaction caused by the increasing bacterial load in the airways exceeds a certain threshold. Furthermore, findings based on molecular typing of bacterial isolates have demonstrated that the
acquisition of new strains of bacteria or antigenic change in pre-existing strains play a crucial role in the pathogenesis of bacterial exacerbations, and that a change in the bacterial load, with a subsequent increase in inflammation, is merely a secondary phenomenon (18). It has been suggested that after a new strain is acquired, due to the absence of an effective host immune response, bacteria may proliferate in the airways, resulting in a greater bacterial load, more severe local and systemic inflammation, and the development of symptoms of exacerbation (18). There is also the possibility that a viral infection could trigger an increase in bacterial load and a bacterial exacerbation.

**Antibiotic therapy for chronic bronchial infection**

There are several studies of long-term macrolide therapy in COPD with the objective to prevent exacerbations. Recently, in a large pivotal study, Albert et al (19) reported the use of 12-month treatment with daily azithromycin. In this study, the addition of azithromycin to standard therapy was associated with a 27% decrease in the frequency of exacerbations and an increased in the median time to exacerbation (266 days vs. 174 days, respectively; p<0.001). In addition, patients treated with azithromycin showed a significant reduction. In another 12-month retrospective study, azithromycin was also shown to reduce exacerbations, hospitalizations, and length of hospital stay (20).

The risk of increasing bacterial resistance with long-term use of macrolides is a concern. In view of the large patient population affected by COPD, widespread use of macrolides, particularly azithromycin, has the potential to substantially influence antimicrobial resistance rates of a range of respiratory microorganisms (21). Another concern is the possible superinfection by non-tuberculous mycobacteria that has been observed in some cases of patients with bronchiectasis treated with macrolides long-term. There is also the possibility of hearing loss associated with long-term use of macrolides, this effect may have been related to the high dose used in the study by Albert et al (19) (250 mg/day for one year).

Intermittent, pulsed fluoroquinolone antibiotic therapy in COPD patients was reported by Sethi et al (22) In this study, moxifloxacin was given once daily for 5 days, and the treatment was repeated every 8 weeks for a total of six courses. Pulsed therapy with moxifloxacin reduced the odds of an exacerbation by 25% in the primary population for efficacy analysis (per protocol population as pre-specified in the protocol) in patients with moderate-to-severe COPD, while in a post hoc analysis, this reduction was 45% in patients with purulent or mucopurulent sputum at baseline. As with macrolides, the use of quinolones has also been associated with a prolonged QTc interval, and the same concerns about the prolongation of the QTc interval are valid.

The use of prophylactic antibiotics in COPD is a clear example of a decision that has to be made based on a careful evaluation of a risk-benefit analysis. There is no doubt that antibiotic prophylaxis reduces exacerbation frequency in selected populations of COPD patients, but it is also clear that long-term use of antibiotics is associated with potentially serious adverse events and increased risk of bacterial resistance; therefore, both pros and cons must be evaluated in a case by case indication.

The clinical data suggest that a small population of COPD patients may benefit from the use of long-term antibiotics. The real challenge is to provide this treatment to the right patient and prevent the excessive use of long-term antibiotics in the community. Most guidelines do not recommend the use of long-term antibiotics based on a limited benefit and potential harm, but they fail to consider the selected population in which may benefit (23). The recent Spanish COPD guidelines suggest that long-term treatment with macrolides can be considered in patients with severe COPD and frequent exacerbations or hospital admissions, despite optimal pharmacologic and non pharmacologic treatment and always with an accurate clinical and bacteriological control (24).
REFERENCES


FACULTY DISCLOSURE

Dr Marc Miravitlles has received speaker fees from AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Grifols, Menarini, Gebro and Teva. He has also received consulting fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Grifols, Gebro, Teva and Cipla

EVALUATION

1. Which of the following is not correct regarding infection in COPD
   a. Bacteria can be found in sputum in up to 50% of patients with exacerbations
   b. Viruses are also frequent pathogens in exacerbations of COPD
   c. Bacteria and viruses can not be found simultaneously in exacerbated patients
   d. Bacterial etiology is associated with a darker colour of sputum

2. Which of the following is not correct regarding macrolide treatment in COPD
   a. Macrolides have antibacterial and anti-inflammatory effects in COPD
   b. Macrolides can eradicate Pseudomonas aeruginosa en colonized patients with COPD
   c. Macrolides may cause hearing problems when used long-term
   d. The use of long-term macrolides is associated with increases risk of development of bacterial resistance

3. Which of the following bacteria is not a common cause of bronchial infection in COPD?
   a. Serratia marcescens
   b. Pseudomonas aeruginosa
   c. Haemophilus influenza
   d. Moraxella catarrhalis

4. Which of the following criteria is useful for the identification of exacerbations that require an antibiotic?
   a. FEV1
   b. Blood eosinophilia
   c. Color or sputum
   d. Peak flow

5. Which of the following is not a consequence of the chronic bronchial infection in COPD?
   a. Faster decline in FEV1
   b. Reduced response to bronchodilators
   c. Increased bronchial inflammation
   d. Impaired quality of life