

The Impact of Chronic Bronchial Infection in COPD: A Proposal for Management

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Abstract: Up to 50% of patients with chronic obstructive pulmonary disease (COPD) in stable state may carry potentially pathogenic microorganisms (PPMs) in their airways. The presence of PPMs has been associated with increased symptoms, increased risk and severity of exacerbations, a faster decline in lung function and impairment in quality of life. Although some clinical trials have demonstrated a reduction in exacerbations in patients chronically treated with systemic antibiotics, particularly macrolides, the selection of patients was based on the previous frequency of exacerbations and not on the presence of PPMs in their airways. Therefore, unlike in bronchiectasis, there is a lack of evidence-based recommendations for assessment and treatment of the presence of PPMs in either single or repeated isolations in COPD. In this article, we propose that chronic bronchial infection (CBI) in COPD be defined as the isolation of the same PPM in at least three sputum samples separated by more than one month; we review the impact of CBI on the natural course of COPD and suggest a course of action in patients with a single isolation of a PPM or suspected CBI. Antibiotic treatment in stable COPD should be recommended based on four main criteria: a) the presence of comorbid bronchiectasis, b) the demonstration of a single or multiple isolation of the same PPM, c) the clinical impact of CBI on the patients, and d) the type of PPM, either *Pseudomonas aeruginosa* or non-pseudomonal PPM. These recommendations are derived from evidence generated in patients with bronchiectasis and, until new evidence specifically obtained in COPD is available, they may help in the management of these challenging patients with COPD. Existing evidence suggests that inhaled therapy is insufficient to manage patients with moderate-to-severe COPD, frequent exacerbations, and CBI. New studies must be conducted in this particularly demanding population.

Keywords: exacerbation, colonization, bronchial infection, *Pseudomonas aeruginosa*, bronchiectasis, pathogenic microorganisms

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide, and its prevalence is expected to continue to grow.^{1,2} Tobacco smoke and the inhalation of other toxic gases or fumes are its main known causes, and these external causes mainly act by generating and sustaining bronchial and parenchymal inflammation leading to the development of the characteristic lesions of chronic bronchitis and emphysema.³ These two clinical phenotypes are responsible for the main clinical manifestations of the disease, the symptoms of cough and sputum production, and the progressive exertional dyspnea and airflow limitation.³

The natural course of COPD is punctuated by exacerbations, which are episodes of an acute increase of respiratory symptoms (ie increased cough, sputum production and/or dyspnea) as a consequence of bacterial or viral infection in the majority of cases.⁴⁻⁶ These exacerbations may have different degrees of severity, from mild and self-limiting episodes to severe symptoms that may lead to hospital admission or even death.⁶⁻⁸ Exacerbations may be frequent in some patients with COPD, the so-called frequent exacerbators, and have been associated with more rapid disease progression.^{9,10}

Nowadays, treatment of COPD is basically symptomatic with the use of long-acting bronchodilators that improve airflow limitation and reduce air trapping, thereby relieving dyspnea and improving quality of life.¹¹⁻¹³ Despite the inflammation

present in patients with COPD, no specific anti-inflammatory treatment is available for COPD. Inhaled corticosteroids (ICS) are effective in reducing the risk of exacerbation and improving symptoms in patients with frequent exacerbations and an eosinophilic inflammatory profile, but have very limited efficacy (if any) in infrequent exacerbators without eosinophilic inflammation.^{11–15} Interestingly, COPD patients with frequent exacerbations without an eosinophilic profile usually have potentially pathogenic microorganisms (PPM) in their airways¹⁶ and the use of ICS in these patients may increase the risk of isolation of *Pseudomonas aeruginosa* (PA),^{17,18} bacterial exacerbations or pneumonia.^{19,20} In these cases, oral anti-inflammatory treatment with roflumilast or macrolides can be effective in preventing exacerbations, but the use of these drugs is limited by the frequent appearance of side effects and the possible development of bacterial resistance.²¹

Despite the frequency and importance of the presence of PPM in respiratory secretions of COPD patients in stable state and their relationship with the risk of exacerbations,²² little attention has been given to the assessment and treatment of bacterial infection in stable COPD in clinical practice guidelines. In this article we address the importance of the isolation of PPM in respiratory samples in stable COPD and suggest new lines of research to prevent exacerbations and improve outcomes in patients with COPD.

Bacterial Isolation in Sputum of Stable COPD. Why is It Important?

Bronchial inflammation caused by tobacco smoke or other toxic inhalations leads to impairment of the antimicrobial defenses of the airways, reducing secretory IgA, a defective bacterial phagocytosis by macrophages, increasing mucus secretion and impairing mucociliary clearance, among other mechanisms, that explain the adhesion of PPMs to bronchial epithelial cells and their proliferation in the airways of patients with COPD.²³ This alteration of bronchial defenses may appear early in the course of the disease, as reflected by changes in the composition of the normal pulmonary microbiota already observed in smokers with normal lung function, but more markedly in those with established COPD.²⁴

As a consequence of the persistence and increased bacterial proliferation in the airways, the isolation of PPMs, basically *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and PA, in stable COPD patients is not uncommon, since they may appear in up to 30–50% of severe cases.^{22,25} This isolation of PPMs in sputum in stable COPD patients has usually been defined as bronchial colonization, similarly to the isolation of bacteria in the skin or the gut. However, several studies have demonstrated that the isolation of PPMs even without the association of increased respiratory symptoms is not innocuous but is associated with enhanced bronchial and systemic inflammation,^{26–29} an increased frequency and severity of exacerbations,^{30,31} accelerated decline in lung function,³² the possible development of bronchiectasis,³³ impaired quality of life,³⁴ an increase in cardiovascular events,³⁵ and even with increased mortality in the case of the isolation of PA.³⁶ Therefore, the presence of PPMs in the lower airways of patients with COPD does not fulfill the criteria of colonization, which does not harm the host, but instead it constitutes a type of bronchial infection.^{37–39}

The Concept of Acute and Chronic Bronchial Infection in COPD

The natural history of COPD is punctuated by episodes of an acute increase of respiratory symptoms, which in most cases are caused by infection.^{5,6,22} These episodes may be caused by the acquisition of a new bacterial strain or by an increase in the bacterial load in the airways^{40,41} and are considered as acute bronchial infection which requires directed antibiotic treatment.^{4,6,42}

In contrast, the persistence of PPMs in the lower airways in patients with stable COPD, not associated with acute symptoms of exacerbation, fulfills the characteristics of a chronic, low intensity infection and has been named chronic bronchial infection (CBI).^{37,39} However, despite its multiple deleterious effects, there is no universally accepted approach to its definition and treatment as yet.

A recent expert consensus proposed a definition of CBI in stable COPD as 3 or more positive sputum cultures by the same PPM over 1 year, separated by at least 1 month.³⁹ This definition derives from the evidence obtained from bronchiectasis studies, which suggest that the clinical consequences of bronchial infection may differ in cases of a single or repeated isolation of the same PPM.^{43,44} This is very likely to also be the case in COPD; a recent study has shown that CBI was associated with an increased risk of pneumonia, especially in patients under ICS treatment and with less than 100 blood eosinophils/ μ L, an effect that was not observed in cases of a single isolation.¹⁹ In another study, CBI was associated with an almost 4-fold increased risk of cardiovascular events (especially coronary events) compared with

patients without PPM isolation or only one isolation during follow-up.³⁵ Moreover, the number of PPM isolations was independently associated with the development or progression of bronchiectasis in COPD.³³ Taken together, these studies suggest that CBI in COPD has a special role in the pathogenesis and progression of COPD, beyond that of a single PPM isolation.^{22,25,37,38}

The isolation of PA in sputum in COPD deserves special attention. Old studies have shown that PA has a role in exacerbations, particularly in more severe COPD patients,⁴⁵ and new evidence suggest that PA may be associated with increased mortality in COPD;^{46,47} all these studies support a role of PA in the progression of the disease. Murphy et al⁴⁸ observed that acquisition of PA was frequently followed by the development of an exacerbation and that approximately one third of PA strains demonstrated persistence, irrespective of the development of an immunological response mediated by antibodies. The clinical impact of the persistence of (or CBI by) PA has only recently been described; one study observed that CBI by PA was associated with increased mortality (hazard ratio 3.06 [1.8–5.2], $p = 0.001$),⁴⁶ but a single isolation of PA was not,^{46,49} and that the risk factors for a first PA isolation and PA persistence were different.⁴⁶

All these results suggest that PA may have increased virulence compared with other PPMs, even when it is isolated only once. This would be particularly true in patients with COPD and associated bronchiectasis, because the single isolation of PA in bronchiectasis has demonstrated to have an impact on the evolution of the disease.⁵⁰ It is also likely that a single isolation of *H. influenzae* may have an impact on the pathogenesis of COPD, since it is associated with increased local and systemic inflammation,^{28,29,51} but evidence about the long-term clinical impact of a single isolation of *H. influenzae* is lacking.

Should We Treat Chronic Bronchial Infection in COPD?

Despite the evidence about the pathogenic effect of the presence of bacteria in the lower airways in stable COPD, there is a lack of evidence-based recommendations for the diagnosis and treatment of CBI in COPD and, therefore, its management remains controversial.^{11,39} It is of note that a significant number of COPD patients with frequent exacerbations and CBI may have bronchiectasis when investigated by computed tomography (CT) scans.^{52,53} In these cases, it is sensible to follow the recommendations of the bronchiectasis guidelines, which establish clear recommendations about the treatment of CBI,^{43,44} but no formal recommendations have been established for COPD patients with CBI without bronchiectasis. Nevertheless, some course of action should be recommended for these particularly challenging and severe COPD patients and based on different recent evidence, it should be possible to reach a consensus on treatment of CBI in COPD while awaiting the results of randomized clinical trials.³⁹

The recommendations for the treatment of CBI should be based on four factors: a) the clinical impact; b) the type of PPM, either PA or non-PA associated CBI; c) the presence of bronchiectasis, and d) whether it is a single isolation or CBI.

A) Clinical impact of CBI: The impact of CBI on COPD has already been extensively described above, but unfortunately, it is only feasible to measure and identify the history and severity of exacerbations in clinical practice. Although CBI may impact other outcomes, such as a decline in lung function or impairment of quality of life, these are not usually quantified and require prolonged follow-up, which make them of little use for demonstrating the clinical impact of CBI in routine clinical practice.

B) PA versus non-PA CBI: Data from bronchiectasis patients and some epidemiological data on COPD suggest that the isolation of PA may be associated with a worse prognosis than the isolation of other PPMs,^{50,54} although it is possible that *H. influenzae* may have a similar impact on the course of COPD.^{28,29,38}

C) Presence of bronchiectasis: The demonstration of bronchiectasis probably indicates a longer evolution of the CBI in COPD, since some studies showed that bronchiectasis in COPD may develop because of repeated exacerbations and the presence of CBI.^{33,53} There are guidelines about the treatment of CBI in patients with bronchiectasis.^{43,44}

D) Single or multiple isolations of the same PPM: Finally, the potential effect on the natural history of COPD of a single isolation of a PPM may be significantly lower than that associated with the CBI. Only the single isolation of PA, but not of other PPMs, in COPD has been associated with worse long-term outcomes.⁴⁶

By combining these four factors, a range of priorities for the treatment of CBI in COPD can be established. The strongest priority for treatment would be the presence of a CBI by PA in a patient with frequent exacerbations and

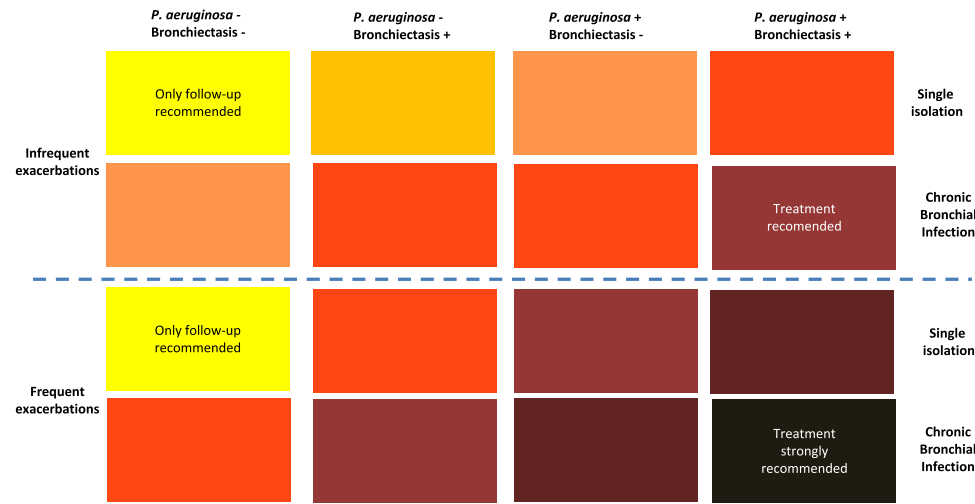


Figure 1 Strength of the recommendation of antimicrobial treatment of CBI in COPD.
Notes: The darker the color, the stronger the recommendation of treatment; from yellow: only follow-up in COPD patients with a single isolation of a PPM, without frequent or severe exacerbations, no bronchiectasis and no PA isolation; to dark grey: strong recommendation of treatment in COPD patients with CBI by PA and bronchiectasis with frequent or severe exacerbations.

bronchiectasis, while the other end of the spectrum; that is, the lowest priority, would be a patient without bronchiectasis, with infrequent exacerbations and a single isolation of a non-PA PPM (Figure 1).

How to Treat Chronic Bronchial Infection in COPD?

There are two main strategies for the treatment of CBI: improve host defenses or eradicate infecting PPMs. A series of candidate treatments for CBI is presented in Table 1. Unfortunately, there are no licensed therapies dedicated to improving host defenses in COPD for the prevention of CBI. Anti-influenza and anti-pneumococcal vaccines are indicated in patients with COPD to prevent influenza, invasive pneumococcal disease and pneumococcal pneumonia, but they have demonstrated a very limited effect in the prevention of exacerbations and it remains to be demonstrated whether they can prevent CBI.^{11,13} On the other hand, oral whole-cell killed nontypeable *H. influenzae* vaccine might provide some protection against CBI by

Table 1 Candidate Treatment Strategies for Chronic Bronchial Infection in COPD

Specific Strategies
Improve mucociliary clearance
Anti- <i>Haemophilus</i> vaccine
Effective and eradicated antimicrobial treatment of exacerbations
Long-term macrolides
Inhaled antibiotics
General Strategies
Quit smoking and avoid exposure to toxic gases or fumes
Immunoglobulin replacement in cases of immunodeficiency
Anti-pneumococcal and anti-influenza vaccination
Long-acting bronchodilators
Pulmonary rehabilitation

this pathogen.⁵⁵ Other strategies include techniques to improve mucus clearance and the investigation of possible immunoglobulin (Ig) deficiencies that have been associated with increased risk of severe exacerbations and death and might be treated with Ig replacement.⁵⁶ In addition, general strategies of management of COPD may help to reduce the risk of CBI, such as the use of long-acting bronchodilators due to their effect in facilitating an adequate bronchomotor tone and the reduction of mucus hypersecretion with anticholinergics.⁵⁷ Similarly, pulmonary rehabilitation has demonstrated to facilitate the mucociliary function and reduce the frequency of exacerbations (Table 1).⁴

Regarding antimicrobial treatment, there are few studies conducted with systemic antibiotics and these have been inconclusive because their limited efficacy in the prevention of exacerbations must be balanced with the possible side effects related to the prolonged use of systemic antibiotics and the possible selection of resistant strains.⁵⁸ A randomized, double-blind, placebo-controlled trial with moxifloxacin 400 mg daily for 5 days in 40 patients with stable COPD with a previous isolation of PPM in sputum showed a significant difference in eradication (75% versus 30%; $p < 0.01$), but the frequency of acquisition of a new PPM was high and similar in both treatment groups. Consequently, the prevalence of a positive sputum culture for PPM at 8 weeks was also similar between treatment arms.⁵⁹ No difference was found in the number of patients with exacerbations during the 5-month follow-up; however, only the acquisition of a new PPM during follow-up showed a statistically significant relationship with the occurrence of an exacerbation.⁵⁹ Regarding chronic administration of antimicrobials, a sub-analysis of the PULSE study, which analyzed the efficacy and safety of 5 days of moxifloxacin every other month for one year versus placebo, observed a significant reduction of exacerbations of 45% ($p = 0.006$) with moxifloxacin in patients who presented with dark sputum at baseline.⁶⁰ This is relevant because dark sputum is very closely related to the presence of CBI even in patients with stable COPD.⁶¹ Unfortunately, the majority of studies selected patients based on the frequency of exacerbations, and not on the presence of CBI.

Macrolides, which have antibacterial, immunomodulatory and anti-inflammatory activity, have been shown to reduce the number of exacerbations in patients with COPD.⁶² This effect was more pronounced in patients with three or more exacerbations in the previous year and irrespective of the presence of bronchiectasis.⁶³ However, again these studies were not carried out in groups of patients with CBI, and the potential side effects and the development of resistance to these antimicrobials may limit their use in routine clinical practice.²¹

Inhaled antibiotics have been successfully used in patients with bronchiectasis associated or not with cystic fibrosis. These antibiotics can reach high local concentrations without an excess of systemic side effects; however, their efficacy is not yet proven in COPD patients with CBI. A recent large observational study suggested their efficacy in reducing the frequency of exacerbations in severe patients with COPD, but they were not selected for the presence of CBI, and the type of antibiotic and treatment regimens were not standardized.⁶⁴

A final consideration is that effective antimicrobial treatment of bacterial exacerbations may be the first strategy to prevent CBI. The persistence of PPMs, even at low bacterial loads, after the treatment of an exacerbation may be the first step to the development of a CBI.^{41,65,66} The lack of eradication has been associated with increased inflammation and a shorter period until the next exacerbation,^{66,67} therefore, antibiotic treatment of exacerbations must aim at bacterial eradication in addition to clinical improvement.

Conclusions and Future Research

Despite the advances in research about infection in COPD, several unanswered questions about CBI still remain (Box 1). Chronic bronchial infection is frequent in patients with moderate to severe COPD; up to 50% of patients may carry PPMs in their bronchial tree during stable state.^{37,68} The persistence of PPMs in the lungs of patients with COPD may be defined as a CBI due to its impact on symptoms, exacerbations, and the natural history of the disease.³⁸ Due to its deleterious effects, CBI should be considered a treatable trait of COPD.^{13,69,70} Patients with moderate to severe COPD and frequent exacerbations should be investigated for the presence of CBI and bronchiectasis with serial sputum samples and high-resolution CT scan. Until more evidence is available, CBI in COPD should be treated taking into consideration the presence of bronchiectasis, the type of PPM isolated, the clinical impact and the presence of a single or multiple isolates of the same PPM. Patterns of treatment should follow the evidence generated in bronchiectasis with either eradication with systemic antibiotics or long-term treatment with macrolides or inhaled antibiotics.

Box I Ten Unanswered Questions in Relation to Chronic Bronchial Infection in COPD

1. What is the definition of CBI in COPD?
2. Do all PPMs have the same impact on the natural history of COPD?
3. Is there an infective phenotype of COPD?
4. How often must sputum samples be analyzed? In which type of patients?
5. Must all CBIs be treated? Only in frequent exacerbators?
6. How can we evaluate the success of treatment of CBI? How should bacterial eradication be defined?
7. Should bronchiectasis be ruled out in all patients with CBI?
8. Which is the treatment of choice in patients with COPD and CBI?
9. Should patients with CBI and bronchiectasis be treated differently to those without bronchiectasis?
10. Should ICS be avoided in patients with CBI?

Abbreviations: CBI, chronic bronchial infection; COPD, chronic obstructive pulmonary disease.

Treatment of severe COPD should go beyond the usual inhalers and, in particular in frequent exacerbators, the infective component of the disease should be investigated and treated. However, future studies must clarify several aspects of the diagnosis, impact and treatment of CBI. First, an international consensus should be established to define the different microbiological issues arising in COPD patients: the differentiation between bronchial colonization (if it really exists) and CBI; the definition and consequences of an initial, intermittent, or CBI; and the definition of the eradication of a given PPM from the airways, either spontaneously or after treatment. Second, the relevance, frequency and processing methods of sputum sampling in patients with stable COPD should be established. Microbiological monitoring of sputum is essential for these purposes, and it should be carried out at each clinical visit in COPD patients with frequent exacerbations able to expectorate.³⁹ Third, the relevance of using molecular methods such as polymerase chain reaction or sequencing to complement the culture of respiratory samples should be determined.⁷¹ Fourth, the importance of performing a CT scan for the diagnosis of associated bronchiectasis due to the clinical, prognostic and therapeutic repercussions of the combination of the two diseases must be demonstrated.^{52,72} Fifth, trials aimed at the study of the safety and efficacy of treatments for CBI in patients with COPD and frequent exacerbations must be designed.

Furthermore, some key aspects remain to be clarified, with at least three of these being of special importance, and thus appropriate topics for future studies. 1. Is COPD with CBI a differentiated clinical phenotype of COPD? Although scientific evidence is still lacking in this regard, according to the definition of the clinical phenotype of COPD described by Han et al,⁷³ this is very likely the case. These patients present a different clinical, prognostic and therapeutic profile, especially if they have bronchiectasis. It is possible that there is an “infectious” phenotype of COPD³⁷ in patients genetically predisposed to bronchial infection and exposed to certain environmental factors that should be treated early to avoid the disease progressing towards an irreversible alteration of the lung parenchyma and airways; 2. Should patients with COPD and CBI be treated with ICS? There is no clear answer to this question, although it is likely that the most sensible decision might be to minimize their use and dosage, especially bearing in mind the frequent presence of bronchiectasis in these patients (a disease in which ICS are not indicated⁷⁴) and the marked and well-known immunosuppressant properties of this treatment.^{75–77} Future studies are needed to investigate the impact of ICS treatment on patients with COPD and CBI, as well as interaction with blood eosinophil concentrations.^{19,78,79} As an example, a recent study showed that COPD patients with CBI treated with ICS had a higher risk of future pneumonia only if they had less than 100 blood eosinophils/ μ L.¹⁹

Conclusions

There is evidence of the impact of the presence of PPMs in bronchial secretions of patients with COPD. Nonetheless, there is very limited information about the management strategy for patients with COPD and CBI. It is clear that the usual inhaled therapy is insufficient to manage patients with moderate-to-severe COPD, frequent exacerbations, and CBI.

Therefore, it is necessary to conduct clinical trials in patients with COPD and CBI to shed light on their prognosis and on the role of different treatments such as ICS, macrolides, or different systemic and inhaled antibiotics. In the latter respect, an analysis of the efficacy of the different inhaled antibiotics currently on the market would be very relevant.

Abbreviations

CBI, Chronic bronchial infection; COPD, Chronic obstructive pulmonary disease; CT, Computed tomography; ICS, Inhaled corticosteroid; Ig, Immunoglobulin; IgA, Immunoglobulin A; PA, *Pseudomonas aeruginosa*; PPM, Potentially pathogenic microorganism.

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