Exacerbations of chronic obstructive pulmonary disease: when are bacteria important?

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Exacerbations of chronic obstructive pulmonary disease: when are bacteria important? M. Miravitlles. ©ERS Journals Ltd 2002.
ABSTRACT: The progressive course of chronic obstructive pulmonary disease (COPD) is often aggravated by exacerbations, the majority of them produced by bronchial infection. Frequent exacerbations have been demonstrated to have a negative impact on quality of life and pulmonary function in patients with COPD, particularly in active smokers. Furthermore, acute exacerbations are the most frequent cause of medical visits, hospital admissions and death among patients with chronic lung disease.

Evidence indicates that the number of patients with pathogenic bacteria in respiratory secretions and the bronchial bacterial load increase during exacerbations. Furthermore, the local inflammatory response of the host parallels the increase in bacterial load. From these observations, it can be speculated that, for symptoms of acute exacerbation to appear, there must be a minimum bacterial load in the airways, *i.e.* a threshold above which the inflammatory reaction is severe enough to elicit clinical symptoms of exacerbation. This threshold may vary from patient to patient owing to different modifying factors. Some of these factors may be the recognised risk factors for relapse, such as increasing age, impairment of lung function, comorbid conditions or frequent exacerbations in the past.

Relapse rates after ambulatory treatment of acute exacerbation of COPD may be as high as 20–25% of cases. Relapses are associated with significant mordibity and increased costs.

A number of unanswered questions remain regarding exacerbations of chronic obstructive pulmonary disease. These include the role of viral infection, the importance of residual bacterial colonisation and the impact of new antibiotics on the treatment of exacerbations.
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Chronic obstructive pulmonary disease (COPD) is one of the most prevalent diseases in developed countries. Furthermore, the number of individuals affected has grown since the 1980s [1]. In Spain, the prevalence of COPD is 9% in adults aged 40–70 yrs, although only 22% of these are diagnosed [2]. Tobacco smoking is the main aetiological factor for COPD. In a population-based study in Spain, 25% of the population aged 40–70 yrs were smokers and another 25% former smokers [3]. Only 15–20% of smokers will develop COPD, and smokers with COPD exhibit higher tobacco consumption and greater dependence on nicotine than smokers who do not have COPD, and more than one-third have never tried to stop smoking [3]. These figures indicate that the problem of COPD in most developed countries will continue to increase in the near future.

The chronic and progressive course of COPD is often aggravated by short periods of increasing symptoms, particularly increasing cough, dyspnoea and production of sputum which can become purulent. The majority of these exacerbations are caused by bronchial infection, and, if frequent, have been demonstrated to have a negative impact on quality of life in patients with COPD [4]. Furthermore, acute exacerbations are the most frequent cause of medical visits, hospital admissions and death among patients with chronic lung disease [5]. Persistence of bacteria in the lower airway has been associated with increased inflammation, which may potentially cause damage to the lungs.

Some of the existing evidence of the role of bacteria in acute exacerbations and the significance of bronchial colonisation in patients with COPD are reviewed in the present article.

Aetiology of chronic obstructive pulmonary disease exacerbations

Patients with COPD show significant impairment of their lung defence mechanisms. The effects of tobacco smoking on the ciliated bronchial epithelium and excessive production of mucus hamper normal drainage of secretions. In addition, impairment of the phagocytic function of macrophages and neutrophils exists, which makes it difficult to eliminate microorganisms that may reach the lower airways [6]. For

all of these reasons, the bronchial secretions of some patients with stable COPD carry potentially pathogenic microorganisms (PPMs) in significant concentrations; therefore, the isolation of such microorganisms during exacerbations should not be interpreted as a definite demonstration of their pathogenic role. However, studies performed using specific invasive techniques have shown that both the number of patients with pathogenic bacteria in their respiratory secretions and the number of colony-forming units (cfu) of such bacteria increase during exacerbations [7]. Furthermore, the local inflammatory response of the host increases with increasing airway bacterial load [8]. Current knowledge indicates that the presence of green (purulent) as opposed to white (mucoid) sputum is one of the best and easiest methods of predicting a high bacterial load in respiratory tract secretions and the need for antibiotic therapy [9]. The production of green sputum is a surrogate marker for exaggerated bronchial inflammation associated with the presence of bacterial pathogens in increasing concentrations [10]. Based on these findings, two types of exacerbations can be distinguished, with therapeutic implications as presented in table 1.

Despite the importance of bacterial infection, other factors may provoke exacerbations. In a cohort of 1,016 severe COPD patients, infection was the cause of 51% of exacerbations, whereas heart failure was the second commonest cause with 26% of cases; however, in as much as 30% of cases, the cause was unknown [13]. Among these cases of unrecognised cause, the importance of environmental factors such as low temperature [14] and air pollution [15] must be stressed. However, the most "plausible" explanation might be that most of the so-called "exacerbations of unknown aetiology" are in fact due to bronchial infection not detected with the diagnostic techniques currently used

in medical practice or research. Similarly, up to 60% of cases of community-acquired pneumonia are classified as being caused by an unidentified pathogen, even with the aid of invasive diagnostic techniques, but no doubt is raised as to the infectious origin. These results serve only to highlight the enormous difficulties involved in obtaining a definite microbiological diagnosis in respiratory infections in general. In favour of this argument, a recent study demonstrated the presence of intracellular *Haemophilus influenzae* in 87% of bronchial biopsy samples from acutely ill patients with chronic bronchitis compared with the no bacteria found in healthy controls and 33% of stable chronic bronchitis patients [16], which emphasises the importance of infection in the aetiology of exacerbations. However, *H. influenzae* was recovered from the lower airways in only 7% of the same acutely ill patients using the usual microbiological sampling methods.

Published evidence indicates that respiratory infection may be responsible for 50–70% of exacerbations [17], with *H. influenzae* being the most frequent bacterium isolated in all series, followed by *Moraxella catarrhalis, Streptococcus pneumoniae* and *Pseudomonas aeruginosa* [7, 17–19]. Viruses may account for 15–25% of all infective exacerbations, particularly influenza/parainfluenza viruses and adenoviruses. In a recent study, 26% of exacerbations of moderate-to-severe COPD patients (mean forced expiratory volume in one second ($FEV1$) 40% of the predicted value) were associated with rhinovirus infection [20].

The role of atypical microorganisms in exacerbations of COPD has recently received increased attention. In a series of 47 patients with exacerbated COPD and a mean $FEV1$ of 41% pred, MOGULKOC *et al.* [21] diagnosed *Chlamydia pneumoniae* infection serologically in 11 (22%), although in three of these cases other pathogenic bacteria were also found. *Mycoplasma pneumoniae* infection was diagnosed in three (6%). Interestingly, no clinical differences were found between patients with or without *Chlamydia* infection. It is important to point out the possibility that *Chlamydia* persists in the body indefinitely after acute infection [22], and this persistence could promote inflammation in the lungs of subjects with COPD and accelerate the progression of disease. However, a recent follow-up study failed to demonstrate any negative effect of chronic *C. pneumoniae* infection on the progression of airflow obstruction [23].

In view of the above, it would be useful to define certain easily obtainable patient characteristics that might indicate the possible aetiology of COPD exacerbations, thereby facilitating specific antibiotic treatment and reducing the high number of failures recorded with empirical treatment. Research in pneumonia has led to the identification of some risk factors associated with an increased probability of different microorganisms causing the episode, such as advanced age, comorbid conditions and alcohol consumption. However, no studies have attempted to identify patients with increased probability of having different causative pathogens in acute exacerbations of COPD. Only recently, two studies suggested that the degree of functional respiratory impairment in COPD patients

Table 1. – Clinical, biochemical and bacteriological characteristics of acute exacerbations of chronic obstructive pulmonary disease

	Purulent exacerbation (probably bacterial)	Mucoid exacerbation (probably nonbacterial)
$FEV1$ % mean±SD	55.9±22	66.8±23
Sputum colour	Yellow/green	White
Positive sputum culture %	90	33
>10^7 cfu·mL^{-1} bacteria in sputum %	83	17
Inflammatory sputum markers		
MPO	++	+
LTB$_4$	++	+
IL-8	++	+
Neutrophil elastase	+++	
Recovery without antibiotics	Unproven	Yes

$FEV1$: forced expiratory volume in one second; cfu: colony-forming unit; MPO: myeloperosidase; LTB$_4$: leukotriene B$_4$; IL-8: interleukin-8. -: no increase; +: slight increase; ++: moderate increase; +++: large increase. Data from [9–12].

indicates the presence of different PPMs in their sputum samples during the course of an exacerbation [18, 24]. Individuals with severe pulmonary function impairment, manifested in an $FEV1$ of <50% pred, are at a six-fold higher risk of suffering acute exacerbations caused by *H. influenzae* or *P. aeruginosa* than patients presenting with an $FEV1$ of >50% pred. In patients with milder COPD, with an $FEV1$ of >50% pred, sputum culture was less effective, since non-PPMs of scant diagnostic value were isolated in most cases. Conversely, in more seriously affected patients, sputum culture often made it possible to identify PPMs in significant concentrations [18]. This result concurs with the findings of GOMPERTZ *et al.* [10], who observed that patients with purulent (infectious) exacerbations had more severely impaired $FEV1$ than those with mucoid exacerbations (table 1). It also points to a greater influence of bacterial infection on exacerbations in this subgroup of patients with severe ventilatory impairment.

The importance of *Pseudomonas* in acute exacerbations in severe COPD has been confirmed by another study in a group of patients with severe exacerbations of COPD requiring mechanical ventilation. This study revealed an unexpectedly high rate of Gram-negative organism and *Pseudomonas/Stenotrophomonas* spp. isolation in respiratory samples from these patients; these pathogens accounted for 44% of all PPMs identified, whereas *H. influenzae* was found in 33% and *S. pneumoniae* constituted only 11% of PPMs isolated [19].

In conclusion, a variety of causes of acute COPD exacerbations exist. However, infection may account for approximately two-thirds of cases. The role of atypical microorganisms is receiving increasing attention, and, together with viruses, they may be the cause of one-third of infectious exacerbations. The rest are attributed to pathogenic bacteria. Unfortunately, clinical manifestations do not permit identification of the cause of the exacerbation, since viral and atypical exacerbations are associated with the same clinical symptoms and a similar inflammatory response. Only purulence of sputum has been associated with high bacterial load in respiratory secretions during exacerbations. Also, other studies have shown that microorganisms causing acute exacerbations of COPD are distributed unevenly among patients with differing degrees of severity, with those more severely affected showing a greater incidence of *Pseudomonas* and *H. influenzae.* The influence which the application of new empirical treatments according to the degree of functional impairment may have on improving disease progression is a subject which should be developed further in future clinical studies.

Frequency and outcomes of exacerbations: risk factors for relapse

Patients with moderate COPD (mean $FEV1$ of 50–55% pred) have been shown to suffer from a mean of 1.9–2.1 exacerbations·yr^{-1} [25, 26]. In an observational study, patients with a mean $FEV1$ of 47% pred also presented with a mean of 2 exacerbations·yr^{-1}, with the number being dependent on the degree of functional impairment at baseline. Patients with an $FEV1$ <40% pred presented with 2.3 exacerbations·yr^{-1} and those with an $FEV1$ >60% pred only 1.6 exacerbations·yr^{-1} [27]. Interestingly, results of follow-up studies show that patients who suffer a high number of exacerbations during a given period of time continue to suffer frequent exacerbations in the future [28]. Therefore, a high number of exacerbations in the past is one of the best predictors of the risk of frequent exacerbations in the future [29].

Outcomes following ambulatory treatment of acute COPD exacerbations have only recently merited attention. The known failure rates after ambulatory treatment were derived from clinical trials on antibiotics in chronic bronchitis and ranged 7–12% [30, 31]. Nevertheless, these results cannot be extrapolated to everyday practice, since patients included in clinical trials consisted of chronic bronchitis patients (whatever that means) and included subjects with ages ranging 18–90 yrs, a significant proportion of which were never smokers and individuals without ventilatory impairment. Some studies have already shown the low relapse rate and low therapeutic value of antibiotics in such a population [32, 33]. However, during the 1990s, some studies addressed this issue in observational "real-life" studies and showed a failure rate ranging 12–26% [34–39]. Since relapse after initial treatment for acute exacerbation may lead to prolonged disability, a new course of antibiotics, an emergency visit or even hospital admission, it is crucial to identify patients most at risk of relapse. Identification of risk factors for failure of ambulatory treatment may permit the implementation of more aggressive broad-spectrum treatment and closer follow-up. In a further step, risk factors associated with relapse should be incorporated into management guidelines to aid general practitioners (GPs) in identifying at-risk patients. The first management guidelines for acute exacerbations of chronic bronchitis that included stratification of patients according to severity were the Canadian guidelines [40]. The importance of risk factors for relapse was later explicitly recognised in the Latin American [41] and North American guidelines [42] for treatment of COPD exacerbations.

Among the risk factors for relapse, the severity of the underlying disease is one of the most important; patients with more severe dyspnoea at baseline are more at risk of returning to the GP with persistence or increase of symptoms [39]. In a retrospective study of 1,001 COPD patients recruited in primary care, it was observed that increased severity of $FEV1$ impairment was independently associated with increased risk of suffering ⩾2 acute exacerbations·yr^{-1}. Furthermore, $FEV1$ impairment was associated with increased risk of hospital admission during the same period [29]. The consistent and important association of decreasing $FEV1$ with both the risk of frequent exacerbations and admissions is not surprising and needs no further discussion, since low $FEV1$ is a predominant risk factor for mortality from COPD in most epidemiological studies [43–45]. This effect, among others, may be determined by the association of more severely

impaired FEV1 and the isolation of more aggressive bacteria causing the exacerbations [18, 19, 24].

An association between the number of visits to the GP during the previous year for respiratory problems and increased risk of relapse was also observed; the risk of failure increased by 7.6% for each extra visit to the GP [39]. The number of visits and number of previous exacerbations strongly correlated, suggesting that most visits to the GP were due to exacerbation symptoms. Similarly, SEEMUNGAL et al. [4], in a prospective study, found that frequent past exacerbations constituted one of the factors most strongly associated with recurrent exacerbations. In two other studies, the number of previous exacerbations was a risk factor for relapse after ambulatory treatment of an acute exacerbation of chronic bronchitis [34, 36]. These results, together with those of the present author's group, suggest that there exists a subgroup of patients more prone to developing recurrent respiratory infections despite having the same degree of severity of underlying disease.

It has been observed that the presence of coexisting diabetes or significant cardiac disease is associated with increased risk of relapse on univariate analysis. However, after multivariate analysis, only ischaemic heart disease remained significant, with an increased risk of 63% [39]. Similarly, other studies found coexistent cardiopulmonary disease to be a risk factor for referral to hospital after treatment for an acute exacerbation [34, 37], and cardiac comorbidity was found to be among the best predictors of mortality of COPD patients discharged after an acute exacerbation [46, 47]. In a previous retrospective study, it was observed that the presence of ischaemic heart disease or cardiac insufficiency correlated strongly with an increased risk of hospital admission for decompensated COPD with an odds ratio of 1.97 (95% confidence interval 1.24–3.14) [29]. Conversely, ADAMS et al. [37] observed no association between comorbidity and outcome in a hospital-based population of severe COPD patients (29% with an FEV1 of <35% and 27% with oxygen therapy). These results suggest that cardiac comorbidity is a risk factor for poor outcome, particularly in mild-to-moderate COPD patients; however, when the lung disease is severe, impairment of pulmonary function prevails over cardiac disease as a risk factor. Additionally, comorbidity appears to be a risk factor for severe life-threatening exacerbations, which may provoke admission and even be a cause of death, particularly in older patients [48].

Surprisingly, the severity of the exacerbation did not influence the outcome of the study of MIRAVITLLES et al. [39]. However, the severity of the episode was a determinant of outcome in placebo-controlled studies [49]. Since almost all of the present author's patients were receiving broad-spectrum antibiotics, these results suggest that, under broad-spectrum antimicrobial treatment, the severity of exacerbation symptoms is no longer a risk factor for relapse. These results, in a large cohort of patients, confirmed the observations of previous studies [34, 36, 37], which also failed to find any significant effect of exacerbation severity on outcome in smaller populations.

Other risk factors for poor outcome include increasing age [29, 47] and the presence of chronic mucus hypersecretion (CMH), both of which are facilitating factors for exacerbations. In a previous population-based study, CMH was found to be a significant predictor of COPD-related death with implicated pulmonary infection [50]. However, to the present author's knowledge, no previous studies had investigated the relationship between CMH and the probability of admission due to COPD exacerbation. The results of MIRAVITLLES et al. [29] suggest that CMH renders the patient more prone to suffering recurrent exacerbations. Other observations suggest that, in severely exacerbated COPD patients, CMH may also be a risk factor for death [43]. A summary of risk factors for relapse or admission is presented in table 2.

The "fall and rise" or quantitative hypothesis of acute bacterial chronic obstructive pulmonary disease exacerbations

Patients with COPD often exhibit colonisation of their lower airways, with H. influenzae being the bacterium most frequently found in respiratory secretions [53, 54]. Studies using protected specimen brush have demonstrated that patients with exacerbations have increased numbers of cfus of pathogenic bacteria compared with patients in the stable phase [7]. Furthermore, various groups have observed bacterial colonisation to be associated with increased concentrations of inflammatory markers in sputum [53] and bronchoalveolar lavage (BAL) fluid [54], and the severity of the bronchial inflammatory reaction directly correlates with the bacterial load in the airways, in both chronic bronchitis [8] and bronchiectasis [55].

Table 2. – Risk factors for relapse after ambulatory treatment of acute exacerbation of chronic bronchitis

Risk factors for frequent exacerbations >2 exacerbations·yr⁻¹
Increasing age
Increasing severity of FEV1 impairment
Chronic bronchial mucus hypersecretion
Frequent past exacerbations
Daily cough and wheeze
Bronchitic symptoms
Risk factors for relapse
Coexisting cardiopulmonary disease
Increasing number of previous visits to the GP for
    respiratory problems
Increasing number of previous exacerbations
Increasing baseline dyspnoea
Increasing severity of FEV1 impairment
Use of home oxygen
Risk factors for hospital admission
Significant comorbid conditions
Increasing severity of FEV1 impairment
High admission rates for previous exacerbations
Three or more admissions during previous year
Underprescription of LTOT

FEV1: forced expiratory volume in one second; GP: general practitioner; LTOT: long-term oxygen therapy. Data from [29, 33–39, 43, 46, 48–52].

From these observations, it can be speculated that, for symptoms of acute exacerbation to appear, there must be a minimum bacterial load in the airways, a threshold above which the inflammatory reaction is severe enough to elicit clinical symptoms of exacerbation. This threshold may be difficult to establish and may vary from patient to patient owing to different modifying factors. Factor candidates for modulating the threshold for clinical symptoms may be intrinsic to the patient or extrinsic, and are summarised in table 3.

Intrinsic factors that may lower the threshold, *i.e.* increase the likelihood of an exacerbation, include the following: 1) Impairment of lung function. A decreased FEV1 has been shown to correlate with greater neutrophilic inflammation in BAL fluid [54]. This is related to the common observation that patients with more severe impairment of lung function suffer a greater number of exacerbations [27]. Greater baseline inflammation and smaller respiratory reserve may be responsible for the earlier onset of symptoms, particularly increasing dyspnoea; 2) Active smoking. Smoking is associated with increased probability of colonisation, particularly due to *H. influenzae* [53, 54]. The cumulative amount of smoking positively correlates with the number of neutrophils and intensity of inflammation in BAL fluid [56]. Furthermore, smoking *per se* triggers and enhances bronchial inflammation that may have additive effects with inflammation produced by bacteria in the airways [58]. Consequently, active smokers have been shown to suffer more frequent exacerbations [59]; 3) Bronchial hyperresponsiveness. A complex relationship exists between smoking, bacteria, hyperresponsiveness and eosinophils. For example, colonisation with pathogenic bacteria is associated with increased concentrations of tumour necrosis factor-α (TNF-α) in sputum [11]. Some workers have shown that increased concentrations of TNF-α induce hyperreactivity in respiratory smooth muscle [60], others have demonstrated that exposure to cigarette smoking induces eosinophilic airway inflammation [61], and, finally, patients with COPD may show increased eosinophilic inflammation during not only exacerbations [62] but also the stable phase, with intensity of eosinophilic inflammation correlated directly with concentration of neutrophils and inversely with FEV1 [63]. Thus, bronchial hyperresponsiveness may also have additive effects with

bacterial colonisation, and hyperresponsive patients may react with exaggerated bronchial obstruction and respiratory symptoms to lower levels of bronchial inflammation; 4) Chronic mucus hypersecretion. By favouring colonisation, chronic mucus hypersecretion may facilitate the growth of bacteria and rapid achievement of a cfu concentration above the threshold [64]; 5) Impairment of host defences. Any impairment in host defences, either locally within the bronchial mucosa or systemically, such as impairment of antibody responses [65], may facilitate bacterial adhesion and faster growth; 6) Nonspecific factors. Elderly patients or patients with significant comorbid conditions may feel worse with lower levels of bronchial inflammation and thus the threshold for these patients may be lower.

Extrinsic factors that may decrease the threshold include the following: 1) Type of bacteria colonising the airway. Some studies have shown that bacteria differ in their ability to elicit an inflammatory response [8, 11]. Therefore, the magnitude of the response varies among different species. This factor may complement the effect of impairment of pulmonary function, since patients with more severe airflow limitation suffer more frequently from exacerbations caused by more aggressive bacteria such as *H. influenzae* or *P. aeruginosa* [18, 24], both of these bacteria being among those that provoke a greater inflammatory reaction in the host [8, 11]. Consequently, impairment of pulmonary function may decrease the threshold owing to both a lower respiratory reserve and the association with more pro-inflammatory bacteria; 2) Lower temperature. Some studies have shown lower temperature to be associated with decreased lung function in patients with COPD [14]. Thus, a lower inflammatory burden may be required to trigger exacerbations during winter months; 3) Air pollution. Air pollution has been associated with increased number of acute exacerbations [15]. Pollutants may induce bronchial inflammation similar to that induced by cigarette smoking, which adds to the inflammation originating from bacteria; 4) Treatment of COPD. From the description of these factors, it is easy to assume that any drug that improves pulmonary function (increases FEV1) may exhibit a protective effect against exacerbations by raising the threshold. Such exacerbation-preventing effects have been observed with various bronchodilators (ipratropium bromide [66], salmeterol xinafoate [67], and tiotropium [68]). It is reasonable to suppose that the greater and more persistent the bronchodilator effect the better the prevention of exacerbations will be. If the hypothesis that eosinophils play a major role in exacerbations of COPD is true, it may explain the observed effect of inhaled steroids on prevention [25] and/or decreasing the severity of exacerbations [26] by modulating inflammation produced by colonisation and again raising the threshold. Patients treated with long-term inhaled steroids may need very high bacterial loads to overcome the anti-inflammatory effect of such drugs.

Based on this hypothesis, acute exacerbation of COPD is an inflammatory process driven by bacteria in the airways. The presence of one or more modifying

Table 3. – Factors that may potentially modify the threshold for acute bacterial exacerbations of chronic obstructive pulmonary disease (COPD)

Intrinsic factors
Impairment of lung function
Active smoking
Bronchial hyperresponsiveness
Chronic mucus hypersecretion
Impairment of defence mechanisms
Nonspecific factors: increasing age, comorbid conditions
Extrinsic factors
Type of bacteria
Lower environmental temperature
Air pollution
Treatment of stable and exacerbated COPD

factor implies that different cfu concentrations are required in different patients to initiate an exacerbation. When many modifying factors are present, the number of bacteria needed for an exacerbation to occur will be very low or even zero (mucoid or non-infectious exacerbations), whereas, when few or no modifying factors are present, high bacterial loads are required for clinical symptoms to appear. In this latter case, the signs of bacterial infection will be evident with purulence and high bacterial loads in sputum (purulent or infectious exacerbations; see table 1).

The inflammatory nature of the exacerbation explains the beneficial effect of oral steroids in this indication, whereas the effect of antibiotics is controversial. Antibiotics may not have a significant effect on exacerbations with many modifying factors (low threshold/low bacterial load), but are beneficial in exacerbations with few modifying factors (high threshold/high bacterial load), which can be identified by the characteristics of the sputum [9].

Basic research is still required to support or reject this hypothesis; however, some observations support it. In clinical trials with antibiotics in acute exacerbations of chronic bronchitis, a prolonged time to the next exacerbation has been observed in patients in whom the bronchial pathogen is eradicated after an acute exacerbation [69]. This favours the "fall and rise" hypothesis, since patients from whom bacteria are effectively eradicated would require longer for the threshold of bacterial numbers to be reached compared with patients who were cured of the exacerbation but in whom bacteria still persisted after antibiotic treatment. This hypothesis would also explain why patients with acute exacerbations may be clinically cured even without eradication of the bacterial pathogen [70]. It is not proof that this particular bacterium is not the cause of the exacerbation, but a demonstration that the antibiotic needs only to reduce bacterial counts to below the threshold to eliminate symptoms. Nevertheless, if eradication also occurs, the time required for the number of cfu to rise above the threshold will be longer (fig. 1).

If this hypothesis of "fall and rise" in bacterial load were true, it would have implications for treatment, since a combination of antibiotics and corticosteroids should then almost always be given. The combination of both should provide better results in terms of speed of recovery, lower relapse rates and, particularly, longer symptom-free intervals than either of them separately. Furthermore, the use of more active bactericidal antibiotics would be associated with longer symptom-free intervals [69], and, therefore, energetic antibiotic treatment of the exacerbation will translate not only into more rapid relief of symptoms [71], but also act prophylactically against the next exacerbation.

Impact of colonisation and infection on chronic obstructive pulmonary disease patients

The bronchial epithelium has a limited number of possible responses to insults. When bronchial epithelial cells are exposed to cigarette smoke, an
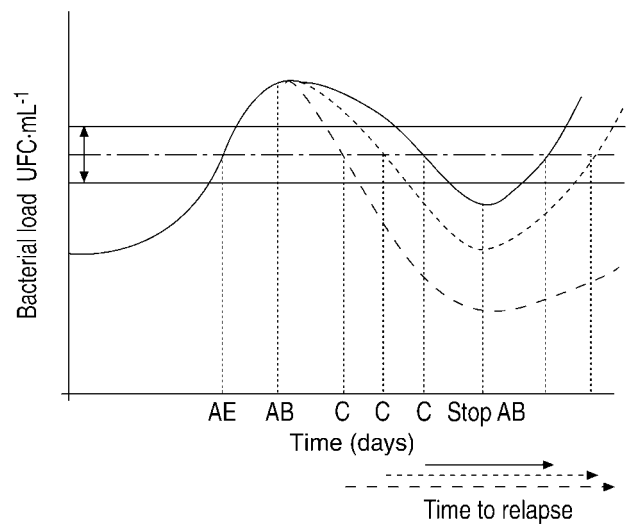

Fig. 1. – The "fall and rise" hypothesis of bacterial exacerbations of chronic obstructive pulmonary disease (COPD). Some patients with COPD show bacterial colonisation of the lower airways. This colonisation is usually due to potentially pathogenic microorganisms (PPMs) in low concentrations. Under specific circumstances, these PPMs may proliferate and produce an increased inflammatory reaction in the host. When this proliferation exceeds a certain clinical threshold (– - –), symptoms of acute exacerbation (AE) appear. Under antibiotic (AB) therapy (——: AB1; - - - -: AB2; – – –: AB3), the concentration of PPMs decreases, and, when the threshold is crossed again, the clinical symptoms disappear (cure (C)). When the intensity and speed of the bactericidal activity of the AB is increased, recovery occurs more rapidly and the time to the next exacerbation (double-headed horizontal arrow) is prolonged. AB activity produces a "fall" in bacterial concentrations, which, if not completely eradicated after the pressure of the antimicrobial agent is removed, "rise" again. Some modifying factors may change the threshold of clinical symptoms (double-headed vertical arrow). A list of possible modifying factors is presented in table 3.

inflammatory reaction, with dose-related release of different cytokines, among which interleukin (IL)-8 plays a major role, is generated [58]. IL-8 is a specific inflammatory mediator in COPD, since it is not found in increased concentrations in other bronchial diseases such as asthma or in healthy smokers [72]. This cytokine has a potent chemotactic effect on neutrophils, and therefore a linear correlation has been observed between bronchial and alveolar IL-8 concentrations and neutrophil counts at both sites [58]. Interestingly, this bronchial inflammatory reaction with release of IL-8 is not specific to tobacco smoke. BRESSER et al. [73] observed that, when epithelial cells were exposed to strains of H. influenzae, an inflammatory reaction with release of IL-8 was triggered. One of the main actions of IL-8 is as a chemoattractant for neutrophils; thus, under both circumstances, smoking and infection, neutrophils are attracted to the respiratory tract. This has been confirmed by studies demonstrating that bacterial colonisation of the lower airways is associated with increased numbers of neutrophils and myeloperoxidase concentration and with more severe airflow obstruction [56].

Inflammation related to bacterial colonisation is not limited to that caused by IL-8. Recent work has shown increased TNF-α concentrations in the sputum of patients colonised by H. influenzae [55, 73]. The

same authors have demonstrated that inflammation intensity is not related to the degree of airway obstruction but to colonisation by *H. influenzae* of respiratory secretions [56]; consequently, *H. influenzae* is a stronger inflammatory stimulus than COPD severity. However, a relationship exists between the degree of airway limitation and prevalence of colonisation; ZALACAIN *et al.* [53] observed that 40% of their 88 patients with stable COPD (mean FEV_1 of 55% pred) were colonised, mainly by *H. influenzae*. They found that severe airflow obstruction was associated with a relative risk of colonisation of 5.1 compared to mild obstruction. Similarly, MONSÓ *et al.* [54] found bacterial colonisation in 22% of their patients, with this low frequency probably being due to the milder disease of this group of patients (mean FEV_1 of 74% pred). In any event, these results, obtained with very sensitive and specific techniques, such as the protected specimen bush, highlight the high frequency of bacterial colonisation in COPD, even in mild COPD patients. However, this high frequency does not mean that colonisation is a "normal" or innocent finding.

The inflammation associated with bronchial colonisation is not an "all or nothing" phenomenon. Different species elicit different degrees of inflammatory reaction. The most intense inflammation is generated by *P. aeruginosa*, followed by *H. influenzae*, whereas *M. catarrhalis* and *H. parainfluenzae* provoke a significantly milder reaction [8, 11]. Another important aspect of bronchial inflammation is the association between increased bacterial load in respiratory secretions and the increased amount of cytokine release [8, 57]. This observation supports the quantitative hypothesis (fall and rise) of bacterial exacerbations, since the intensity of inflammation parallels the increase in bacterial load. In agreement with this hypothesis, exacerbated patients show increased concentrations of bacteria in their respiratory secretions [7] and increased concentrations of granulocyte inflammatory markers (myeloperoxidase, IL-8 and TNF-α) together with IL-6 [74] and leukotriene B$_4$ [10, 12], all of which return to normal levels after antibiotic treatment [10, 12]. However, some inflammatory activity persists even after 1 month, as evidenced by some cytokine concentrations [75] or by increased exhaled nitric oxide levels [76]. This inflammation parallels the appearance of clinical symptoms and impairment of pulmonary function, which, in as much as 25% of cases, do not return to pre-exacerbation values, even after 35 days [75].

The impact of repeated exacerbations on pulmonary function is a matter of intense debate [78, 79]. It would seem logical that repeated episodes may potentially damage lung tissues and lead to an accelerated rate of decline in pulmonary function. This is supported by a number of experimental observations. 1) Exacerbations are associated with transient decreases in pulmonary function, which, in some cases, take weeks to return to baseline levels [77]. 2) Patients suffering from recurrent exacerbations have been shown to exhibit increased concentrations of inflammatory markers in their sputum even in the stable phase, suggesting persistent inflammation and potential lung damage [12]. 3) Neutrophils are attracted into the airway lumen during exacerbations [80]. Neutrophils release proteinases, which are incompletely neutralised, during phagocytosis [10, 12]. Increased levels of neutrophils in sputum correlated with a rapid decline in FEV_1 in a 15-yr follow-up study [81]. 4) In cross-sectional studies, a greater bacterial load in respiratory secretions has been associated with increased inflammation and decreased lung function [56]. 5) The urinary excretion of desmosine and isodesmosine, products of the degradation of lung elastin, are significantly increased during exacerbations of COPD compared with the stable phase [82], coinciding with an increase in free elastase levels during exacerbations [10, 12]. Furthermore, higher urinary concentrations of desmosine have been associated with a faster decline in FEV_1 in COPD [83]. 6) A correlation has been found between the number of previous exacerbations and the extent of emphysema by computed tomography (CT) [84].

The negative impact of exacerbations on lung function has been demonstrated in a longitudinal study in patients with emphysema due to α$_1$-antitrypsin deficiency. In this 2-yr follow-up study, DOWSON *et al.* [85] observed a significant correlation between exacerbation frequency and rate of decline in FEV_1. Interestingly, lung density, as assessed by quantitative high-resolution CT (HRCT) and transfer factor of the lung for carbon monoxide (TL,CO), was more sensitive to changes than FEV_1.

Very recently, results from the Lung Health Study, involving 5,887 smokers followed up for 5 yrs, demonstrated that the number of respiratory infections influenced the rate of decline in FEV_1 in those who continued smoking [59]. Smokers suffered an extra 7-mL decline in FEV_1 for every additional exacerbation.

Why is it so difficult to demonstrate the influence of respiratory infections on the rate of decline in FEV_1 despite all the existing evidence? Several reasons account for this difficulty. Firstly, longitudinal studies are difficult and expensive to perform. Furthermore, owing to the slow progression of COPD, large populations must be followed up for prolonged periods of time, with appropriate control groups, for small effects to become evident. Secondly, exacerbations are limited in number; an average patient may suffer 1 or 2 exacerbations·yr^{-1}, which represents 7–20 days with symptoms or 10–50 days·yr^{-1} with increased inflammation. Even if an effect exists, many years would be required to accumulate enough days with increased inflammation for this effect to become clinically evident. Thirdly, no clear definition of exacerbation exists and many exacerbations are not reported to the attending physician [4, 77], making it difficult to investigate the influence of such episodes on the progression of the disease. Finally, FEV_1 may not be sufficiently sensitive to detect small effects on the progression of COPD. Other outcome measures such as HRCT or TL,CO may be more sensitive in detecting the deleterious effects of infections on disease progression [85].

The influence of infections on the progression of COPD has become evident in patients with added risk factors for rapid progression of the disease, such as

active smokers [59] or patients with α_1-antitrypsin deficiency [85]. These observations suggest that respiratory infections have a real effect on the progression of the disease, but that the magnitude is so small that in individuals with no other risk factors, large groups of patients with extended follow-up periods are required to detect such a small effect.

A further consequence of acute exacerbations of COPD is the great economic burden associated with attention to exacerbated COPD patients. The mean total cost of an acute COPD exacerbation was estimated to be 140 Euros in a recent study on primary care in Spain, the major part being due to hospitalisations, which represented 58% of the total cost, followed by the drug acquisition cost at 32.2% [86]. These costs may not be applicable to other countries because of the differences in reference prices, management practices and healthcare systems; however, if the high prevalence of COPD and the frequency of exacerbations are considered, it is very easy to understand the magnitude of the healthcare burden derived from this disease.

Unanswered questions

Although many research teams have joined the investigation into COPD in general and exacerbations in particular during the 1990s, a number of unanswered questions remain regarding infection and COPD.

The significance and prevalence of viral infection in COPD exacerbations have been increasingly recognised [20, 87]. Viral infections have been associated with increased inflammation [20, 87] and viruses may persist in the airways [87]. Furthermore, latent adenoviral infection has been implicated in increased inflammation in patients with COPD [88]. However, the prevalence of viral infection as a cause of exacerbations, the role of viruses in the progression of ventilatory impairment and the possible interaction between viruses and bacteria in the lower airways have yet to be defined.

Another aspect that requires further investigation is the impact of bronchial bacterial colonisation and infection on the progression of the disease, as commented on previously. *Haemophilus influenzae* has been detected intracellularly in patients with chronic obstructive pulmonary disease exacerbations [16] and the same pathogen has been detected diffusely in the bronchial epithelium, submucosa of bronchi, bronchioles, interstitium and alveolar epithelium of patients with end-stage chronic obstructive pulmonary disease, suggesting a relationship with the pathogenesis of the disease [51]. New evidence is required regarding the complex relationship between microorganisms and host, particularly considering that important therapeutic implications may derive from these findings. Controversy still exists as to the need for antibiotic therapy in exacerbations, but, in the near future, other issues such as bacterial eradication, speed of recovery, prevention of exacerbations or even treatment of colonisation may figure in the debate.

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