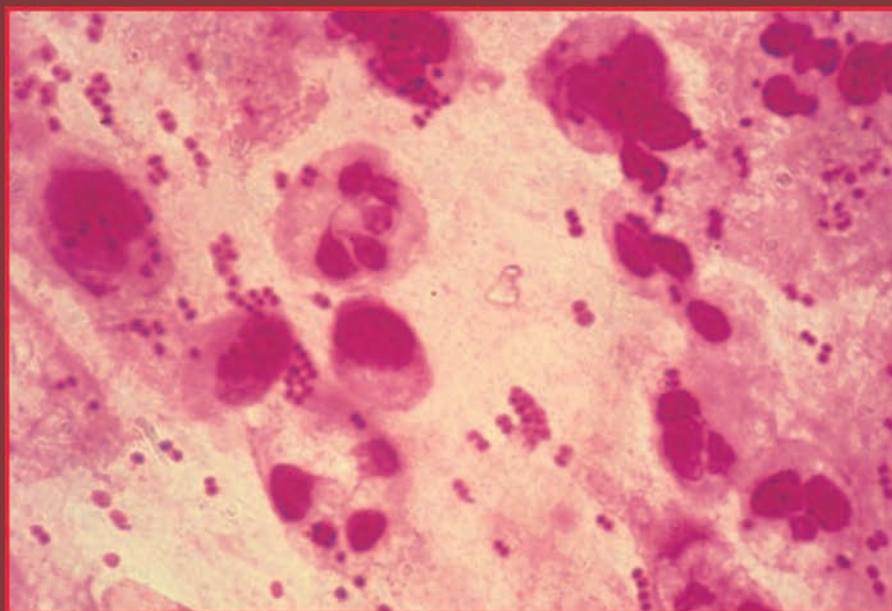


Therapeutic Strategies in **ACUTE EXACERBATIONS IN COPD**

M. Cazzola · S. Sethi · F. Blasi · A. Anzueto



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Therapeutic Strategies

ACUTE EXACERBATIONS IN COPD

Edited by

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COPD exacerbations: definitions and classifications

G. Caramori, I. M. Adcock, A. Papi

INTRODUCTION

The most recent update of the international NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines defines chronic obstructive pulmonary disease (COPD) with respect to its pulmonary and extrapulmonary (systemic) components, but does not mention exacerbations in the main definition, even though they are the main cause of medical intervention and admission to hospital in these patients [1]. In the same guidelines, an exacerbation of COPD is separately defined as *'an event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD'* [1]. The latest GOLD guidelines also provide a classification of the severity of the exacerbations of COPD based on clinical parameters to drive the necessity and the type of antibiotic therapy [1].

Similarly, the latest update of the Canadian Thoracic Society (CTS) recommendations for the management of COPD defines an exacerbation of COPD as *'a sustained worsening of dyspnoea, cough or sputum production leading to an increase in the use of maintenance medications and/or supplementation with additional medications'* [2]. The term *'sustained'* implies a change from baseline lasting 48 h or more. In addition, COPD exacerbations are defined as either purulent or non-purulent on the assumption that this is helpful in predicting the need for antibiotic therapy [2]. Again, in a strict analogy to the latest GOLD guidelines, the CTS update also provides a classification of the severity of purulent exacerbations of COPD, recognising both simple and complicated purulent COPD exacerbations, based on the presence of clinical risk factors that either increase the likelihood of treatment failure or are more likely to be associated with more virulent or resistant bacterial pathogens [2].

Although both the GOLD and CTS definitions and classifications of the severity of COPD exacerbations may provide a useful practical tool for clinical studies, they have not been formally validated in clinical trials and are rather cumbersome and difficult to use in clinical practice. Other definitions derived from the literature are also used and are discussed below.

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There are currently no known biomarkers equivalent to the troponin test for myocardial infarction or D-dimer test in pulmonary embolism included in the definition of COPD exacerbation [3].

A standardised definition of an exacerbation of COPD remains an unmet need in respiratory medicine. Indeed, the absence of a standardised definition of COPD exacerbation makes it very difficult to compare the results of the different studies on the pharmacological treatment and prevention of COPD exacerbations.

A prerequisite for a COPD exacerbation is that the patient has known COPD [4]. It may be difficult to distinguish a COPD exacerbation from other diseases presenting with similar clinical features during the first documented episode. This is very important because, for example, a severe asthmatic exacerbation in an old asthmatic patient who smokes may be confused with an exacerbation of COPD if the presence of asthma is unknown to the physician in charge of the patient [5]. Bronchiectasis is also often confused in general practice with COPD [6, 7].

Furthermore, patients with a definite COPD diagnosis may also have comorbidities that need to be considered in the differential diagnosis when looking for other possible causes of an acute deterioration of respiratory symptoms outside of a true COPD exacerbation. The most common of these alternative diagnoses are acute heart failure [8], pneumonia [9], pulmonary thromboembolism [10–13], cardiac arrhythmia (mainly atrial fibrillation) [14], pneumothorax [15, 16] and lung cancer, amongst others. It is worth noticing that COPD patients have an increased risk of developing lung cancer compared with age-matched smokers with normal lung function and similar smoking history [17]. These clinical conditions, even when co-existing (e.g. heart failure), should always be considered in the differential diagnosis of a true COPD exacerbation.

The measurement of the serum level of brain natriuretic peptide (BNP, or its precursor aminoterminal [NT]-proBNP) and troponins may be useful in the differential diagnosis of the cause (cardiogenic vs. pulmonary) of acute dyspnoea in a COPD patient [18–20] although the broad overlap in BNP and NT-proBNP concentrations suggests poor specificity in this patient population [21]. For this reason, clinical judgment must always be part of the evaluation of BNP or NT-proBNP assay results [22].

Interestingly, the presence of COPD does not affect the diagnostic performance of clinical probability estimate (CPE), D-dimer testing, spiral computed tomographic angiography (SCTA), or pulmonary angiography in the diagnosis of pulmonary thromboembolism in these patients [23].

This chapter endeavours to provide an historical overview of the definitions and classifications of COPD exacerbations underlining their strengths and limitations.

FROM THE ANTHONISEN CRITERIA ONWARDS

Since Fletcher first described ‘chest episodes’ in 1976, interest and research activity in the field of COPD have increased steadily [24]. The best-studied COPD exacerbation definitions were developed for studies of antibiotics for which bacterial exacerbations were required. From such research emerged the classic definition of Anthonisen *et al.* [25]. This description remains the most commonly referenced of all definitions and has formed the basis of many subsequent criteria [26]. There has been much debate in recent years about exactly how a COPD exacerbation should be defined and two contrasting approaches have been proposed.

SYMPTOM-BASED DEFINITIONS OF COPD EXACERBATION

This group contains the most commonly used definition that identifies a COPD exacerbation as ‘a sustained worsening of respiratory symptoms that requires a patient to seek medical help’ [27,

28]. A very similar, but more loosely-based, definition was proposed as a consensus definition of an experts' panel: *'a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD'* [29].

An exacerbation of COPD may also be defined as *'a sustained worsening of respiratory symptoms that is acute in onset and usually requires a patient to seek medical help or alter treatment'* [26]. The deterioration must be more severe than the usual daily variation experienced [30].

Another symptom-based definition of COPD exacerbation used in large controlled clinical trials of drugs includes the parameter of duration and indicates COPD exacerbations to be characterised by *'increase in dyspnoea, cough or associated with a change in quality and quantity of sputum that led the patient to seek medical attention and lasts for at least 3 days'* [31, 32]. However, there is no good evidence that 3 days of symptoms are required to define a COPD exacerbation.

Unlike asthma, patients with COPD do not experience sudden increases in symptoms that may disappear spontaneously or with medication in hours or a few days [33]. Moreover, a delay in initiating treatment for an exacerbation may result in a longer duration of the episode [34]. Consequently, no time limit should be required to define an exacerbation of COPD.

Another proposed definition of COPD exacerbation has been *'an increase in respiratory symptoms over baseline that usually requires medical intervention'* [35, 36].

There are a number of advantages and disadvantages to the use of a symptom-based definition. Symptoms are of fundamental importance and are the primary concern of the patient; it is generally a change in symptoms that prompts contact with healthcare professionals. Assessment of patient symptoms and subsequent improvement with therapy is therefore a fundamental consideration for both patient and physician. Interestingly, approximately two-thirds of COPD patients are aware when an exacerbation is imminent and, in most cases, symptoms are consistent from one exacerbation to another [37].

However, identification of a standardised symptom-based definition is likely to be complicated by the highly variable nature of COPD and of its exacerbations. As patient symptoms vary greatly and an absolute level of dyspnoea or sputum volume cannot be described as diagnostic, a subjective assessment of *'worsening'* is therefore required. In this case, it is a matter of some debate as to who is best placed to make this judgment – the patient or the doctor? [26]. This is particularly important as a patient's perception of disease can vary with the severity [26].

While some scales for symptom assessment do exist and can be used as a basis for future development, the validity of the scales currently available and their sensitivity have not been established in COPD exacerbations. Thus, validating a new scale would be a significant undertaking. The most common approach to monitoring symptom changes over time requires the use of a paper-based diary card. This approach is increasingly controversial as it is associated with a number of intrinsic disadvantages, the most problematic of which are extremely poor adherence to protocol instructions and data validity issues arising from retrospective record entry [26].

COPD exacerbation rates reported on diary cards for symptom-based studies are higher than for event-based studies because a significant percentage (~50%) of exacerbations will not be reported to the physician or healthcare professional [38–41]. This has been suggested to be due to the fact that patients with COPD may not understand their disease and the importance of seeking treatment. They may also be depressed, or lack mobility. It can also sometimes reflect a patient's self-treatment with pre-prescribed *'emergency'* courses of antibiotics and/or glucocorticoids [42].

It also remains unclear whether the COPD exacerbations that are unreported to a physician are clinically relevant [38, 43]. However, it has been observed that patients who report a smaller proportion of their COPD exacerbations tend to have a poorer health-related qual-

ity of life [34]. This difference may be explained by the fact that these patients do not receive treatment and consequently their COPD exacerbations take longer to recover and have a greater impact on the patient's perception of their disease [44].

EVENT-BASED DEFINITIONS OF COPD EXACERBATION

Event-based definitions of COPD exacerbations have been increasingly used in an attempt to circumvent the problems associated with identifying and defining symptoms or groups of symptoms, and simply capture all patients whose condition has changed enough to require an emergency visit, hospitalisation or a change of treatment (generally a requirement for oral glucocorticoids or antibiotics). Classification of exacerbations based on events offers a straightforward approach and is therefore widely used in clinical trials [26, 36, 45–47].

Event-based criteria do, however, require a sequence of decision-making involving both the patient and the doctor. Although this method captures significantly fewer episodes than symptom-based definitions and is likely to select a distinct patient group with more severe COPD exacerbations (see below), in the absence of definitive signs and symptoms on which to base a diagnosis, event-based definitions currently represent the most unambiguous and practical approach to clearly identifying episodes of COPD exacerbation [26]. However, healthcare utilisation definitions of COPD exacerbation are limited by a reliance on factors other than the underlying pathophysiological process. These include access to healthcare and the social and financial situation of the patient [48].

CLASSIFICATION OF SEVERITY OF COPD EXACERBATIONS

The effect of any given therapeutic intervention may be not only to reduce the frequency of COPD exacerbations, but also, and more commonly, to reduce their severity.

No validated scale of severity exists for COPD exacerbations [49]. Some authors have used a composite scale of symptoms to evaluate the resolution of the episode in clinical trials of antibiotics [50] or in observational follow-up studies [51]. However, these scales have not yet been validated in long-term clinical trials of interventions in stable COPD patients. In contrast, most studies have used the intensity of the medical intervention required as a grade of severity, from self-management at home to admission to an intensive care unit (ICU) [49].

The classic definition of Anthonisen *et al.* [25] divided exacerbated COPD patients into three groups according to their symptoms:

- **Type 1** exacerbations were defined by the presence of increased breathlessness, sputum volume and sputum purulence;
- **Type 2** exacerbations were defined by the presence of two of these symptoms; and
- **Type 3** exacerbations were defined by the presence of one of these symptoms in addition to one of the following criteria:
 - ◆ an upper respiratory tract infection in the past 5 days
 - ◆ fever without other cause
 - ◆ increased wheezing or cough
 - ◆ an increase in heart rate or respiratory rate by 20% compared with baseline readings [25].

This definition has been widely used in clinical trials of antibiotics for exacerbations of COPD, but it is not a severity scale, more a classification that indicates the likelihood of bacterial infection as a cause of an exacerbation (i.e. a type 1 exacerbation in a 'mild' patient may have a better prognosis than a type 3 exacerbation in a 'severe' patient).

Using this definition:

- Health-status score results were closely related to the exacerbation frequency, with worse health status in patients with frequent COPD exacerbations [34]; and
- Dyspnoea was the most common and important symptom of a COPD exacerbation [40]. The significance of the minor criteria has never been formally studied.

Mild exacerbations of COPD may be defined as increased breathlessness, possibly associated with increased cough and sputum production, which force the patient to seek medical attention outside the hospital [33]. COPD exacerbations may be defined as severe when they are associated with acute or chronic respiratory failure using standard criteria (arterial oxygen tension $[PaO_2] < 8$ kPa [60 mmHg] with or without arterial carbon dioxide tension $[PaCO_2] > 6$ kPa [45 mmHg] and hydrogen ion concentration > 44 nM [pH < 7.35]) based on arterial blood-gas measurement while breathing room air [33, 52]. Severe COPD exacerbations frequently require admission to hospital and/or an ICU [33].

There are no established criteria for assessing severity in less severely ill patients not requiring hospital assessment. In published studies, treatment with oral or parenteral glucocorticoids constituted a more severe COPD exacerbation (severity B) and the others were classified as mild/moderate (severity A) [53].

The most recent American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of COPD provide the following operational classification of severity of COPD exacerbations to help with ranking the clinical relevance of an episode and its outcome [54]:

- **Level I** – treated at home
- **Level II** – requires hospitalisation
- **Level III** – leads to respiratory failure

The major limitation of this classification is that many COPD exacerbations requiring hospitalisation (level II) are associated with respiratory failure (level III). The criteria for hospital admission may also vary from country to country and in different hospitals.

The proposed severity classification of the recent ATS/ERS statement on outcomes for COPD pharmacological trials includes three categories:

- **Mild** – increase in respiratory symptoms controlled by the patient with an increase in the usual medication;
- **Moderate** – exacerbations requiring treatment with systemic glucocorticoids and/or antibiotics; and
- **Severe** – exacerbations requiring hospitalisation or a visit to the emergency department [49].

The methodology surrounding the use of the severity of a COPD exacerbation as a variable has not been standardised [49]. Many large, controlled clinical trials have defined a severe COPD exacerbation as requiring the introduction of a cycle of treatment with oral glucocorticoids and/or antibiotics [36, 46]. The clinical relevance of this approach is at the very least controversial due to the questionable magnitude of the effect of antibiotics and the relatively small effect of systemic glucocorticoid treatment on COPD exacerbations [55, 56].

Most cases of severe COPD exacerbations occur in patients with GOLD stage 3 or 4 COPD [57, 58]. In the long term, COPD patients who experience severe COPD exacerbations have an increased risk of experiencing more severe exacerbations in the future [51, 59].

Interestingly, in a recent meta-analysis of the markers of severity of COPD exacerbations, only the arterial carbon dioxide tension and the breathing rate were statistically different between all levels of exacerbation severity and between out- and inpatient settings. Most

other measures showed weak relationships with either level or setting, or there were insufficient data to permit meta-analysis [60].

There is a complete absence of validated biomarkers that are useful in predicting the degree of severity of a COPD exacerbation [61]. In a recent study, systemic plasma biomarkers were not helpful in predicting COPD exacerbation severity and the acute-phase response at COPD exacerbation was most strongly related to indices of monocyte function [62].

CLINICAL HETEROGENEITY OF THE CAUSE OF COPD EXACERBATIONS

Many studies have shown the heterogeneous nature of the cause of COPD exacerbations, which vary greatly from person to person. There are no available definitions of COPD exacerbations incorporating the cause and it is still unclear whether different causes are associated with different severity of COPD exacerbations. Virus-associated COPD exacerbations treated similarly with antibiotics and glucocorticoids have longer recovery periods than non-viral COPD exacerbations [63], suggesting that exacerbations of different aetiology may behave differently with interventions. Much more research is needed in this area, however.

Most COPD exacerbations are thought to arise as a result of infections, although the type of infection is often unclear [1, 2]. Independently, both bacterial and viral infections have been detected at increased frequencies during COPD exacerbations. The most frequently seen respiratory viruses involved in the aetiology of COPD exacerbations are represented by rhinoviruses, influenza viruses, coronaviruses (but not the severe acute respiratory syndrome [SARS] associated coronavirus) and respiratory syncytial virus (RSV). More rarely, parainfluenza viruses and human metapneumoviruses (HMPV) have also been incriminated [64]. *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* are the most common bacteria found in the sputum of patients during a COPD exacerbation [1]. However, atypical bacteria such as *Chlamydophila* (formerly *Chlamydia*) *pneumoniae* and *Mycoplasma pneumoniae* are not isolated from severe COPD exacerbations in the UK and Italy [28].

Until now, only a single study has comprehensively investigated both bacteria and viruses during the same severe COPD exacerbations. Viral and/or bacterial infection was detected in 78% of COPD exacerbations, viruses in 48.4% (6.2% when stable) and bacteria in 54.7% (37.5% when stable). Infectious exacerbations (29.7% bacterial, 23.4% viral, 25% viral/bacterial co-infection) had longer hospitalisations and greater impairment of several measures of lung function than non-infectious exacerbations. Importantly, exacerbations with co-infection had more marked lung function impairment and longer hospitalisations [28]. However, the relationships between viral and bacterial infections, especially when combined together, and whether viral infections can lead to bacteriological exacerbation (possibly of previously colonising bacteria) remain unanswered questions that deserve a properly designed longitudinal study to further investigate them [64].

The purulence and colour of the sputum during COPD exacerbations has been proposed in the past as a marker of bacterial infection and this is still considered a reason for starting antibiotic treatment in the most recent GOLD and CTS guidelines [1, 2]. However, COPD exacerbations associated with purulent sputum production have been associated with a large bacterial load in some, but not all, studies [28, 65, 66].

In a small proportion of cases of severe COPD exacerbation, however, there is no evidence of infection, and environmental triggers, such as air pollutants or changes in airway temperature, are thought to be the initiating factors [67].

Another major characteristic of COPD exacerbations is their seasonal variation. This consideration is of primary importance when analysing the clinical relevance of pharmacological trials investigating the effect of drugs in preventing COPD exacerbation frequency during a period of time shorter than 12 months [39, 68].

To date, no sputum or plasma biomarker has been found with good sensitivity and specificity that can identify the cause of a COPD exacerbation [3, 61]. However, two large controlled clinical trials have shown that many COPD exacerbations of variable severity and different sputum purulence may be managed without antibiotic therapy, simply using the level of serum pro-calcitonin as a marker of the presence of bacterial infection [69, 70]. If this is further validated in ongoing studies, this novel biomarker of bacterial infection may soon help to guide decisions regarding the need for antibiotic therapy during a COPD exacerbation.

THE NEED FOR A STANDARDISED DEFINITION OF COPD EXACERBATION IN CONTROLLED CLINICAL TRIALS

Many symptom- and event-based definitions of COPD exacerbation have been adopted in controlled clinical trials of new and old drugs used for the treatment and prevention of COPD exacerbation (recently reviewed in [26]). These have arisen from the need to establish criteria by which to select patients for inclusion and the absence of a clear and widely accepted definition of COPD exacerbation. Controlled clinical trials of old and new drugs conducted today still use a wide variety of definitions by which treatment success is judged, with increasing focus on event-based definition of COPD exacerbations [36, 46, 55, 56, 71–73]. There is, however, no evidence of improving consistency and many publications still feature inadequate descriptions of the definition of COPD exacerbations. The lack of a consistent definition of COPD exacerbation makes comparison of study findings and treatment effect virtually impossible [26].

The choice of definition of COPD exacerbations can significantly affect study outcomes, with varying criteria likely to result in different levels of demonstrated treatment success [26]. Usually, the looser the definition of a COPD exacerbation, the more likely it is that the drug being tested will show some clinical efficacy. For example, the prevention of COPD-related hospital admissions has been demonstrated only using salmeterol, formoterol and tiotropium but not with inhaled glucocorticoids, whereas a prevention of symptoms of COPD exacerbations has been demonstrated with all of the previous pharmacological classes [46, 74, 75].

The methodology concerning the recording of exacerbation frequency as a variable has not been standardised, but it has been used in several clinical trials of inhaled glucocorticoids and/or bronchodilators in COPD [49].

The statistical methodology used to calculate the annual ratio of COPD exacerbations in a given cohort and to compare the different ratios between treatment arms in clinical trials must be described in detail, because large and significant differences have been reported when using different approaches [76].

In observational studies of COPD patients, a skewed distribution of this variable has been found with a large number of patients having 0–2 exacerbations per year and small number of patients having ≥ 10 exacerbations per year [39, 51, 77]. The mean number of COPD exacerbations is generally related to the severity of the baseline disease and the definition used, and in observational studies ranges between 1 and 2.5 episodes per year, but it is highly variable and as many as 40% of COPD patients may not have any exacerbations at all [2, 39, 51, 77]. However, if unreported COPD exacerbations are included, severe patients (GOLD III) have a mean of 3.43 exacerbations per year and GOLD II have a mean of 2.68 exacerbations per year [49, 51]. In the short term (i.e. weeks or months), this variable does not appear to be reproducible due to the small number of episodes per year; the chance of a repeat episode in weeks or months is small. However, in the long term, COPD patients with frequent exacerbations in the past have a larger probability of suffering frequent COPD exacerbations in the future [49, 51, 78]. This suggests that short-term studies

may show a positive effect of a drug on COPD exacerbation rate that is not seen with longer-term studies.

SUMMARY

A decade on from our previous review of this topic our conclusions are unfortunately very similar [33]. The definition of exacerbation of COPD still relies on clinical empiricism with little scientific support. As often happens when reviewing the literature on a clinical topic, one finds more questions than answers. Exacerbations of COPD are certainly clear events in the minds of practising physicians. However, when one tries to provide simple concepts such as definition and classification of severity, it becomes clear how little we know [33]. Efforts to assess the efficacy of new therapies in the treatment and prevention of COPD exacerbations have been hampered by the lack of a widely agreed and consistently used definition. This conclusion should reinforce the necessity for greater investment in research on COPD exacerbations in order to promote a better understanding of and clinical approach to this sometimes dramatic event in the natural history of the disease.

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2

Infectious aetiologies in acute exacerbations of COPD

S. Sethi

INTRODUCTION

Although a reduction in the frequency of exacerbations is possible with the current treatment of COPD, their complete elimination from the natural course of this disease remains unlikely. Until recently, based on data generated several decades ago, prevailing prevalent opinion was that exacerbations were of little consequence in the course of COPD. Current opinion, however, is entirely contrary, with the reduction of exacerbation frequency being the primary objective of several recent and ongoing pharmaceutical intervention studies in COPD [1]. This dramatic change has come about as a result of new information that exacerbations are major determinants of health status, mortality and the cost of care in COPD [2–4]. Furthermore, they contribute to the progression of airflow obstruction, an unfortunate characteristic of this disease [5].

Concomitant with the realisation of the clinical importance of exacerbations in COPD, the need to better understand the aetiology and pathogenesis of exacerbations has grown. It is becoming clear that exacerbations are heterogeneous, with individual episodes caused by one or more of several distinct aetiologies [6–8]. The time course of most exacerbations, with a sub-acute onset over days to a peak of symptoms, followed by resolution over a period of days to weeks, is very suggestive of an infectious aetiology. However, it was unclear until recently whether infection, especially bacterial infection, actually caused exacerbations [9]. Application of new research methodologies has considerably clarified the role of infection as a cause of exacerbations and is discussed below [10].

PATHOGENESIS OF EXACERBATIONS

A considerable amount of empirical evidence has now been accumulated to bolster the concept that exacerbations are acute inflammatory events superimposed on the chronic inflammation that is characteristic of COPD (Figure 2.1). Several inflammatory cells and molecules have been measured in exhaled breath, induced or expectorated sputum, bronchoalveolar lavage or bronchial biopsy and have been found to be elevated during acute exacerbation (Tables 2.1, 2.2) [8, 11–26]. Furthermore, increased levels of plasma fibrinogen, interleukin (IL)-6, C-reactive protein (CRP) and procalcitonin, consistent with a heightened state of systemic inflammation, have been described during exacerbations [12, 27–29].

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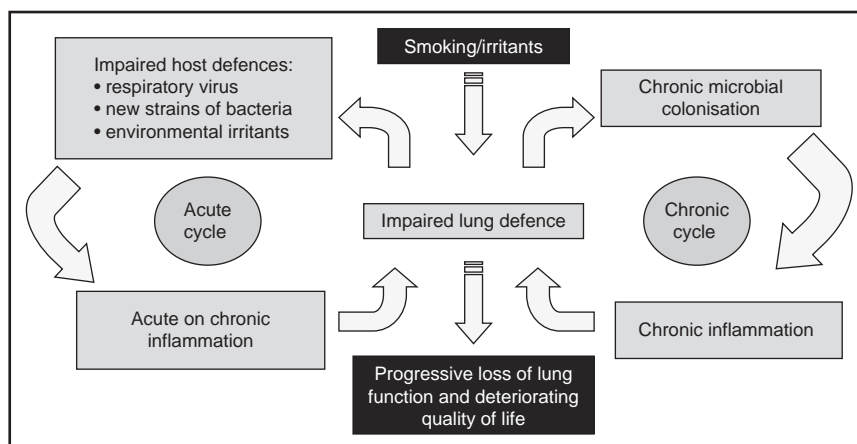


Figure 2.1 Pathogenesis of exacerbations.

Table 2.1 Inflammatory cells involved in exacerbations of COPD, classified by the method used for sampling of respiratory tract

<i>Cells</i>	<i>References</i>
Sputum	
Total leucocytes	Fujimoto <i>et al.</i> [11], Hurst <i>et al.</i> [12]
Neutrophils	Fujimoto <i>et al.</i> [11], Tsoumakidou <i>et al.</i> [13], Papi <i>et al.</i> [8]
Eosinophils	Fujimoto <i>et al.</i> [11], Papi <i>et al.</i> [8]
CD8+ve lymphocytes	Tsoumakidou <i>et al.</i> [13]
Bronchoalveolar lavage	
Neutrophils	Balbi <i>et al.</i> [14]
Eosinophils	Balbi <i>et al.</i> [14]
Bronchial mucosa	
Neutrophils	Qiu <i>et al.</i> [15], Saetta <i>et al.</i> [16]
Eosinophils	Saetta <i>et al.</i> [16], Zhu <i>et al.</i> [17]
CD4+ lymphocytes	Zhu <i>et al.</i> [17]
CD3+ lymphocytes	Saetta <i>et al.</i> [16]

Clinical consequences of the airway and systemic inflammation associated with exacerbations are likely to be protean and an important area of research.

A normal tracheobronchial tree has excellent defence mechanisms to maintain sterility in the face of repeated exposure to microbial pathogens contained either in aerosols or in aspirated upper airway contents. These innate defence mechanisms are compromised in the inflamed airway of COPD, which is less able to deal with these microbial inoculations, allowing proliferation of these pathogens in the lower airway. These proliferating microbial pathogens induce an inflammatory response that is associated with increased secretions in the airway, bronchospasm and mucosal oedema. These pathological changes lead to worsening ventilation – perfusion mismatch and hyperinflation. The clinical consequences of these pathophysiological changes are the novel onset or worsening of dyspnoea, cough, sputum production and sputum purulence [30]. In addition, this inflammatory process in the airways may have systemic effects resulting in the clinical manifestations of fever and fatigue.

Table 2.2 Inflammatory mediators involved in exacerbations of COPD, classified by the method used for sampling of respiratory tract

<i>Mediators</i>	<i>References</i>
Exhaled breath condensate	
Leukotriene B4 (LTB4)	Biernacki <i>et al.</i> [18]
8-isoprostane	Biernacki <i>et al.</i> [18]
Sputum	
Interleukin-8 (IL-8)	Aaron <i>et al.</i> [19], Crooks <i>et al.</i> [20], Fujimoto <i>et al.</i> [11], Sethi <i>et al.</i> [21], White <i>et al.</i> [22]
Tumour necrosis factor α (TNF- α)	Aaron <i>et al.</i> [19], Sethi <i>et al.</i> [21]
LTB4	Gompertz <i>et al.</i> [23], Crooks <i>et al.</i> [20], White <i>et al.</i> [22]
Eosinophil cationic protein (ECP)	Fujimoto <i>et al.</i> [11]
Regulated on activation, normal T-cell expressed and secreted (RANTES)	Fujimoto <i>et al.</i> [11]
Myeloperoxidase (MPO)	Balbi <i>et al.</i> [14]
Neutrophil elastase (NE)	Sethi <i>et al.</i> [21]
Matrix metalloproteinase 9 (MMP-9)	Mercer <i>et al.</i> [24]
Bronchoalveolar lavage	
Granulocyte – macrophage colony stimulatory factor (GM-CSF)	Balbi <i>et al.</i> [14]
Bronchial mucosa	
RANTES	Zhu <i>et al.</i> [17]
Epithelial derived neutrophil attractant -78 (CXCL5)	Qiu <i>et al.</i> [15]
IL-8 (CXCL8)	Qiu <i>et al.</i> [15]

Infectious agents, including bacteria, viruses and atypical pathogens are currently implicated in up to 80% of acute exacerbations [31]. Non-infectious stimuli can induce an acute increase in airway inflammation in COPD and undoubtedly contribute to exacerbations. Environmental pollutants, both particulates and non-particulate gases, are capable of inducing airway inflammation *in vitro* and *in vivo* [32, 33]. Indeed, epidemiological studies have demonstrated increased respiratory symptoms and respiratory mortality among patients with COPD during periods of increased air pollution [34, 35].

COMPROMISED HOST DEFENCE TO MICROBIAL PATHOGENS

Several host defence mechanisms have been shown to be compromised by cigarette smoke exposure and are further compromised with increasing severity of COPD. A major mechanism that maintains the sterility of the normal tracheobronchial tree is the mucociliary escalator, which works by effectively trapping and clearing inhaled particles [36]. Development of chronic bronchitis and airway obstruction in smokers is associated with a deterioration in mucociliary clearance [37, 38]. In one study among light smokers without respiratory disease, average mucociliary clearance was 75% of the predicted value; among moderate smokers with chronic bronchitis the average mucociliary clearance was 52% of predicted and in heavy smokers with COPD, it was 42% of predicted [37].

An increasing number of polypeptides with antimicrobial activity that may play an important role in host defence in the respiratory tract have been identified in the airway surface fluid [39, 40]. Several of these peptides have a variety of other biological activities,

including regulation of the inflammatory response and linking innate and adaptive immunity [40]. These include cationic antimicrobial polypeptides such as lysozyme, lactoferrin, secretory leucocyte protease inhibitor, epithelial defensins and a cathelicidin (LL-37), which exhibit antimicrobial activity only in low ionic strength conditions [39]. Another subgroup of airway antimicrobial peptides is the collectins, which include surfactant protein A (SP-A), surfactant protein D (SP-D), mannose binding lectin, and conglutinin [41].

A limited amount of research has been undertaken to explore the relationship between innate lung defence mechanisms and frequency of exacerbations in COPD. A mannose binding lectin 2 (MBL-2) polymorphism with low serum MBL-2 levels has been associated with more frequent hospitalisations for respiratory infection [42]. Lower sputum secretory leukoprotease inhibitor (SLPI) and salivary lysozyme concentrations have been associated with frequent exacerbation [43, 44]. Further research is required to determine which components of innate lung defence regulate the frequency of exacerbations in COPD and the mechanisms underlying the compromising of innate defence in COPD.

Compromised mucociliary clearance and host defence on the airway surface allows microbial pathogens to persist in the airway and come into contact with the airway epithelium. Subsequent interaction of microbial pathogens and epithelial cells is likely to be a significant determinant of COPD exacerbations. Adherence of bacterial pathogens to airway epithelial cells is the first step in the initiation of a mucosal infection. Increased adherence of bacterial pathogens to oropharyngeal cells has been described in smokers, in individuals prone to respiratory infections and in exacerbation-prone COPD patients [45–49]. Increased adherence has also been associated with more frequent bacterial colonisation of the upper respiratory tract in COPD [47]. Whether the lower respiratory tract airway epithelium exhibits a similar propensity for increased adherence of bacterial pathogens in COPD is not yet known.

The airway epithelium recognises microbial agents through pattern recognition receptors such as Toll-like receptors (TLRs) [50]. This results in the production of inflammatory and chemotactic mediators, as well as antimicrobial substances [51]. An inflammatory response appropriate to the stimulus should result in efficient clearance of the stimulus, but a dysregulated inflammatory response may be disadvantageous to the host. An inappropriately limited inflammatory response could lead to persistence and proliferation of the pathogen, ultimately requiring a strong inflammatory as well as adaptive immune response to clear it. On the other hand, an excessive initial inflammatory response may also be disadvantageous to the host as it induces its own symptoms and can compromise host defences even further [25].

The alveolar macrophage is the resident mononuclear phagocyte of the lung and functions as a key defence against inhaled particulate matter and pathogens [52]. Increasing evidence implicates alveolar macrophages as mediators of the immunological processes that characterise COPD [53]. Recently, it has been observed that the alveolar macrophages of ex-smokers with COPD demonstrate impaired cytokine response to *Haemophilus* antigens when compared to those in ex-smokers without COPD [54]. These antigens included lipooligosaccharide, which signals through the TLR4 receptor, as well as a lipoprotein, outer membrane protein P6, which signals through TLR2 (Figure 2.2). Furthermore, the alveolar macrophages of COPD patients have impaired phagocytic ability for *Haemophilus influenzae* [55]. Thus, immunologically impaired macrophages in COPD may promote increased bacterial persistence and allow COPD exacerbations to occur.

Understanding of the role of compromised innate lung defence mechanisms in the development of infectious exacerbations of COPD is still in its early stages. Although several of these defence mechanisms are likely to be compromised in this disease, it is not yet clear which of them determine the frequency of exacerbations. Determination of these critical mechanisms would enable the development of new therapies in COPD.

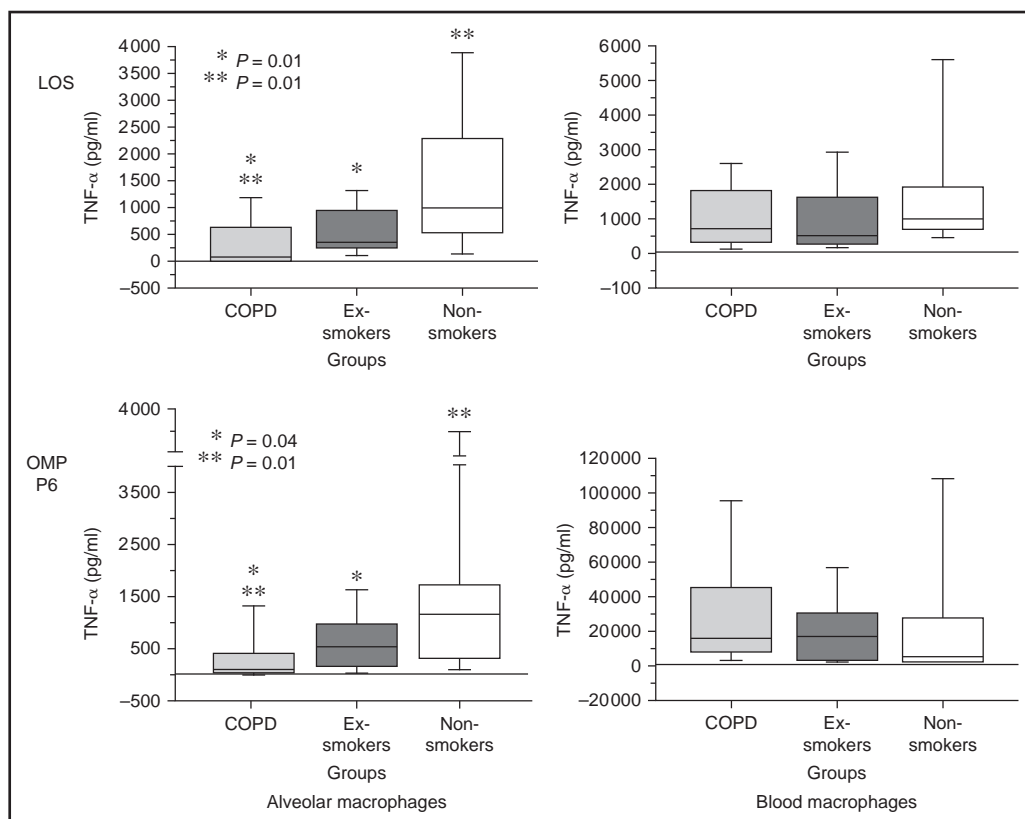


Figure 2.2 Lipooligosaccharide (LOS) and outer membrane protein (OMP) P6 induction of human alveolar and blood macrophage TNF- α . Alveolar (*left column*) and blood macrophages (*right column*) were obtained from former smokers with chronic obstructive pulmonary disease (COPD), former smokers without COPD and non-smokers. Cells were incubated with LOS (*top graphs*) and OMP P6 (*lower graphs*) each at 0.1 $\mu\text{g/ml}$. Supernatant TNF- α concentration was measured at 24 hr (with permission from [54]).

HOST-MICROBIAL INTERACTIONS IN EXACERBATIONS

Exacerbations are regarded as inflammatory events and airway epithelial cells and macrophages as major orchestrators of the inflammatory response to microbial pathogens in the lower airway. Therefore, to better understand the infectious pathogenesis of exacerbations, the interaction of these host cells with pathogens warrants detailed examination. Such study provides an insight into the host mechanisms that are altered in COPD as well as pathogen virulence factors that could contribute to the pathogenesis of exacerbations.

Viral airway epithelial cell interactions have been explored. Intracellular adhesion molecule-1 (ICAM-1) is a major receptor for viral (especially rhinovirus) and bacterial (especially *H. influenzae*) adherence to airway epithelial cells [56, 57]. Smoking induces ICAM-1, allowing more microbial adherence and potentially limiting the clearance of viruses from the lower airway [58]. Interestingly, *H. influenzae* also induces ICAM-1 in airway epithelial cells in culture [57]. This would suggest that bacterial colonisation of the lower airways in COPD could make them more prone to viral infection.

In a smoking mouse model, Drannik *et al.* [59] determined whether the clearance of *Pseudomonas aeruginosa* from the lung was influenced by cigarette smoke exposure. Indeed, smoke-exposed mice cleared *P. aeruginosa* more slowly and had increased levels of lung inflammatory response to *Pseudomonas*. In another interesting study, epithelial cell cultures derived from patients with COPD and controls were compared for IL-8 response to stimulation by tumour necrosis factor-alpha (TNF- α). Cells derived from patients with COPD demonstrated a larger IL-8 response than control cells derived from healthy smokers and non-smokers [60]. A primed epithelial cell from an inflamed airway could form the basis of a vigorous inflammatory response in COPD, which, though helpful in clearing the pathogen, could result in clinical symptoms of exacerbation.

Several host-microbial interactions are therefore important in the pathogenesis of exacerbations. Impaired phagocytosis and cytokine response of macrophages, alongside impaired mucociliary clearance and antimicrobial peptide production, may allow microbial pathogens to persist in the lower respiratory tract [37, 54, 55]. These pathogens, which are able to have a prolonged interaction with the airway epithelial cells, induce an excessive inflammatory response compared to that seen in a healthy airway [60]. This inflammatory response, though beneficial in pathogen clearance, may actually have the potential to further impair host defence and contribute to microbial persistence. Eventually, adaptive immune responses, both mucosal and systemic, are called into play by the persistent microbial stimulus in order to contain or eradicate the infection. In the interim, microbial proliferation and induction of inflammation will cause the symptoms of an exacerbation.

BACTERIAL AETIOLOGY OF EXACERBATIONS OF COPD

Chronic colonisation by bacteria of the lower respiratory tract, which is prevalent in COPD, has previously confounded our ability to understand the role of bacteria in exacerbations. Changes in bacterial concentration (or load) in the airways have been proposed to explain how bacteria cause exacerbations in the face of chronic colonisation [61]. However, there is no clear evidence that such changes in bacterial load are sufficient by themselves to explain the occurrence of exacerbations [6, 7]. Furthermore, the mechanisms underlying these changes in bacterial load are unclear. In fact, a lack of clear evidence of the bacterial aetiology of exacerbations has led many to doubt their role in causing exacerbations, and appropriate antibiotic treatment has sometimes been withheld on that basis [62, 63].

An increased understanding of bacterial pathogenesis has made it clear that previous studies on the bacterial pathogenesis of exacerbations used methods that are considered inadequate by current standards [64, 65]. These include immune response studies that attempted to dissect the immune response to bacterial pathogens in COPD which had yielded confusing and often contradictory results [66].

Recent studies have re-examined the question of the bacterial pathogenesis of exacerbations using newer molecular and immunological techniques, and these form the basis of a new model of bacterial exacerbation pathogenesis (Figure 2.3). From these observations, it is apparent that bacterial exacerbations are related to the acquisition of new strains of *H. influenzae*, *M. catarrhalis* and *S. pneumoniae* from the environment. These three species of bacteria, which are predominant causes of most upper and lower respiratory infections, are exclusively human pathogens whose natural 'niche' is colonisation of the upper respiratory tract. They are readily exchanged between humans by aerosolisation and fomite transfer. However, when acquired by patients with abnormalities in host defence in the respiratory tract, these bacteria cause mucosal and occasionally systemic infections.

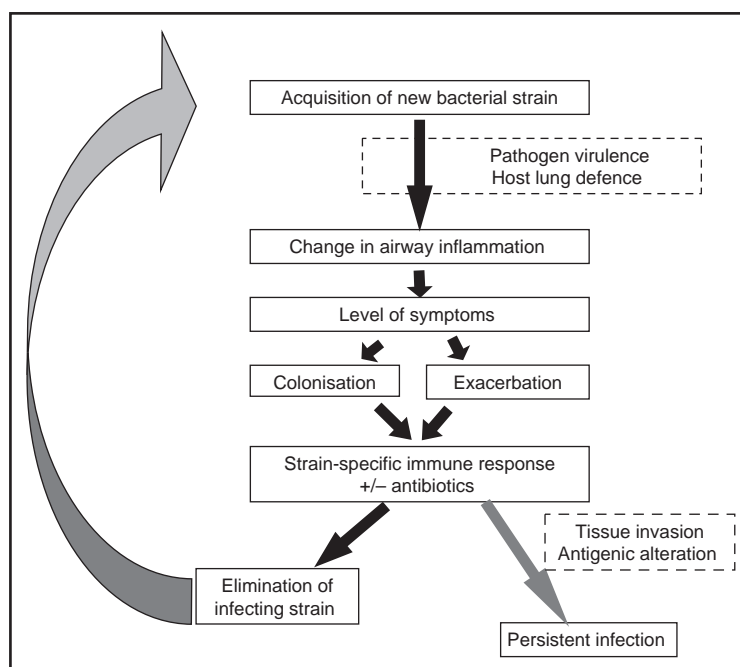


Figure 2.3 Proposed model of bacterial infection in COPD (with permission from [10]).

ACQUISITION OF NEW STRAINS OF BACTERIA AND EXACERBATION

Presence in the lower airway of bacterial pathogens in stable COPD, though clearly abnormal, has been termed colonisation. Use of the term 'colonisation' implies that a specific immune response to these pathogens or their detrimental effects to the host were absent. Although outside the scope of this discussion, recent evidence contradicts these assumptions [67, 68]. Specific immune response and airway inflammation in relation to bacterial presence in the lower airways in COPD have both been demonstrated [67–69].

Several longitudinal cohort investigations with repeated sputum cultures for isolation of bacteria have been conducted to elucidate the role of bacteria in exacerbations of COPD [70, 71]. A higher incidence of bacterial isolation during exacerbations than during stable COPD was the expected result of these studies, thereby explaining the pathogenesis of bacterial exacerbations. This expectation was not met, however, and from these negative results, bacteria were regarded as 'innocent bystanders': their isolation from sputum during exacerbation was thought to be purely coincidental and secondary to chronic colonisation [62, 63, 70, 71]. However, the previous studies comparing bacterial isolation rates in exacerbation with those in stable disease assumed that all isolates of a given species were the same and did not attempt strain differentiation. Variation in the antigenic structure between strains of a bacterial species is now understood to be a major mechanism in the evasion of the human immune response and the causation of bacterial infection [64, 65]. Therefore, simply culturing and enumerating colony counts of pathogens from bodily fluids are inadequate to understand this infectious process.

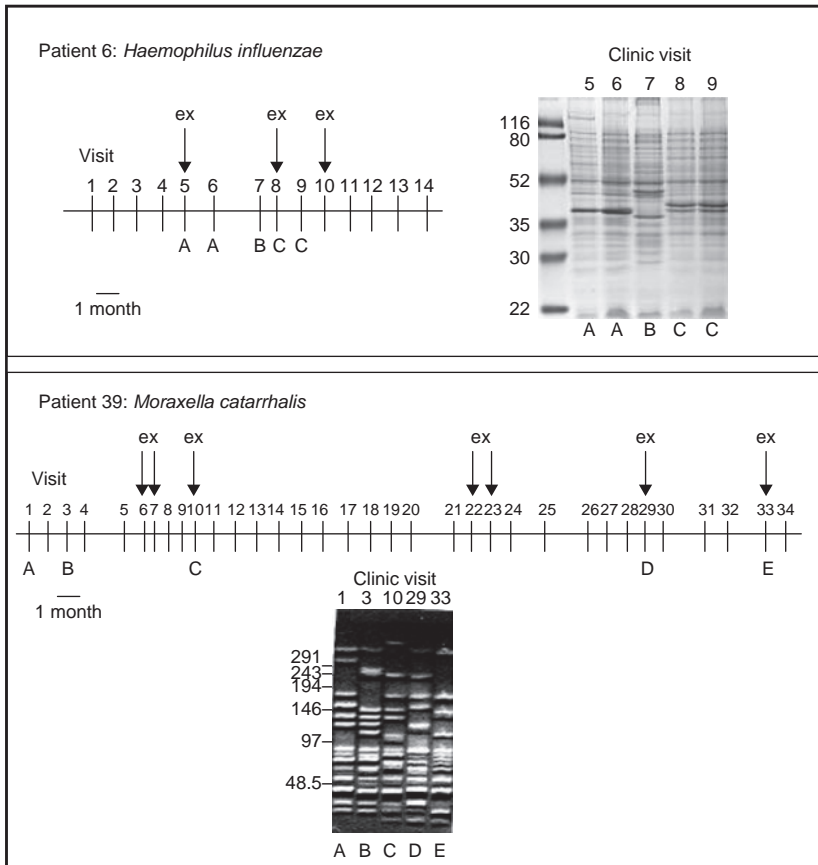


Figure 2.4 Time lines and molecular typing for patients with COPD. The horizontal line is a time line, with each number indicating a clinic visit. The arrows indicate exacerbations. Isolates of *H. influenzae* and *M. catarrhalis* were assigned types based on sodium dodecyl sulfate-polyacrylamide gel and pulsed-field gel electrophoresis respectively. The types are indicated by letters A to E. Molecular mass standards are noted on the left of the gels (with permission from [72]).

A recent longitudinal COPD cohort study has addressed the limitations of previous studies [72]. In this study, strains of potential respiratory pathogens isolated from sputum were characterised by molecular techniques in order to identify when a patient acquired new strains and when those strains were cleared from the respiratory tract. Using this approach, the acquisition of new strains of certain bacterial species has been shown to be clearly associated with a greater than two-fold increased risk of exacerbation of COPD (Figure 2.4, Table 2.3) [72]. The timeframe of increased risk appears to be up to 4–8 weeks after acquisition of a new strain. The increased risk of exacerbations with new strain acquisition was seen for *H. influenzae*, *M. catarrhalis* and *S. pneumoniae*, but not for *P. aeruginosa* (Table 2.3). Subsequent reports with larger numbers of strains demonstrated the relationship between new strain acquisition and exacerbation for *P. aeruginosa* as well (RR, 3.36; 95% CI 1.88–6.03) [73]. Strain characterisation for *Haemophilus parainfluenzae*, *Staphylococcus aureus* and *Enterobacteriaceae* was not performed in this study.

Table 2.3 Isolation of a new strain of a bacterial pathogen and increase in the risk of exacerbation of COPD (with permission from [10], based on data from [72])

<i>New strain</i>	<i>Relative risk of exacerbation</i>	<i>95% confidence interval of relative risk</i>
Any pathogen	2.15*	1.83–2.53
<i>H. influenzae</i>	1.69*	1.37–2.09
<i>M. catarrhalis</i>	2.96*	2.39–3.67
<i>S. pneumoniae</i>	1.77*	1.14–2.75
<i>P. aeruginosa</i>	0.61	0.21–1.82

*Statistically significant increase in risk of exacerbation.

PATHOGEN VIRULENCE AS A DETERMINANT OF EXACERBATION

A complex host–pathogen interaction in the airways is likely to determine the outcome of each new bacterial strain acquisition in COPD. It is unsurprising, therefore, that not every new strain acquisition of bacterial pathogens is associated with exacerbation. The balance between host defence and pathogen virulence determines the level of airway inflammation, which in turn determines the level of symptoms in the patient (Figure 2.3). To add to this complexity, patient perception and physician interpretation of the symptoms are additional determinants of exacerbation.

Although *H. influenzae*, *M. catarrhalis* and *S. pneumoniae* are well-recognised respiratory pathogens, it is surprising how little is known regarding their virulence determinants in airway mucosal infection. Putative pathogen virulence factors include adhesion to and invasion of airway epithelial cells, inactivation of host defence mechanisms and the eliciting of inflammatory mediators from airway cells. Chin *et al.* [74], using both *in vitro* and *in vivo* models, compared the virulence of well-characterised *H. influenzae* strains that were isolated from the sputum of patients in the COPD cohort study discussed above. Strains isolated during exacerbations were compared with colonising strains. Exacerbation strains induced greater airway neutrophil recruitment in a mouse pulmonary clearance model than colonising strains. Furthermore, exacerbation strains adhered in significantly higher numbers and elicited more interleukin-8 (IL-8) from primary airway human airway epithelial cells in culture when compared with colonising strains.

Strains of *H. influenzae* associated with symptomatic infection are more likely to produce immunoglobulin A (IgA) protease than strains that colonise the nasopharynx [75]. Utilising a genomics approach, exacerbation and colonising strains of *H. influenzae* from the aforementioned COPD cohort study were compared to determine whether genetic differences underlie the pathogenic potential of these strains. A specific combination of genes was found to be related to exacerbation [76]. One of these genes is a novel IgA protease. Thus, inactivation of host defences is an important determinant of disease expression among bacterial strains. These observations support pathogen virulence as an important determinant of the clinical manifestations of a new bacterial strain acquisition in COPD. Additional observations of pathogen virulence with relevance to COPD are needed.

HOST DEFENCE AS A DETERMINANT OF EXACERBATIONS

Failure of innate defence mechanisms in COPD leads to adaptive immune responses to control and eradicate the infection. When immune responses to new strains of *M. catarrhalis* associated with COPD exacerbation and colonisation were compared, a mucosal IgA response to the infecting strain was more common and vigorous with colonisation, while a

systemic IgG immune response was more common and vigorous with exacerbations [68]. The host immune response could therefore dictate the clinical expression of a bacterial strain acquisition in COPD. A vigorous mucosal immune response could 'exclude' the bacteria from interaction with the epithelial mucosa, resulting in less airway inflammation and therefore favouring colonisation. An alternative explanation is that the clinical scenario determines the consequent immune response, with colonisation resulting in a more mucosal than systemic antigen burden.

Another relationship between host defence and exacerbation occurrence in COPD was found in peripheral blood mononuclear cell proliferation on exposure to a conserved *H. influenzae* antigen, outer membrane protein P6. A history of exacerbation with *H. influenzae* in the preceding 12 months among patients with COPD was associated with a diminished response to P6 [77]. COPD patients who had not experienced such *H. influenzae* exacerbations had proliferative responses to P6 that were comparable to healthy controls. It is possible that a vigorous cellular response to *H. influenzae* antigens suppresses or even eradicates newly acquired strains of *H. influenzae* and therefore prevents exacerbations.

New and unique approaches to preventing and treating exacerbations could emerge from an enhanced understanding of the determinants of host immune response that influence the outcome of bacterial acquisition in a patient with COPD.

AIRWAY INFLAMMATION AS A DETERMINANT OF EXACERBATION

Although exacerbations of COPD appear to be inflammatory events, this inflammatory process is not uniform among exacerbations and is related to the aetiology of the exacerbation. In some studies, exacerbations associated with bacterial pathogens exhibit significantly more neutrophilic inflammation than non-bacterial episodes [21, 43]. Specifically, when compared with non-bacterial exacerbations, exacerbations associated with *H. influenzae* demonstrated significantly higher levels of IL-8, TNF- α and neutrophil elastase (NE) whereas exacerbations associated with *M. catarrhalis* had significantly higher TNF- α and NE [21]. Airway inflammation seen with *H. parainfluenzae* was heterogeneous. Airway bacterial concentrations and the intensity of neutrophilic inflammation are also related, suggesting a stimulus–response relationship [21, 43]. Furthermore, a significant correlation between the clinical severity of an exacerbation and the level of sputum neutrophil elastase has been demonstrated [21].

More recent work has demonstrated that among bacteria associated exacerbations, those with new strain acquisition are associated with an even greater level of neutrophilic inflammation when compared to those episodes in which either bacteria are absent from sputum or represent pre-existing strains [78]. The intensity of exacerbation symptoms is closely linked to the increase in airway inflammation from baseline. Furthermore, resolution of exacerbation symptoms is closely linked to resolution of airway inflammation [78].

Resolution of the symptoms of exacerbations associated with purulent sputum, which are likely to be bacterial in aetiology, is associated with a consistent decrease in neutrophilic airway inflammation as measured in levels of sputum IL-8, leukotriene B4 (LTB4), NE and myeloperoxidase (MPO) [22]. Furthermore, when such clinical resolution is accompanied by bacteriological eradication of the offending pathogen, there is a more marked reduction in airway inflammation when compared with those instances where bacterial pathogens persist in the airway in spite of clinical resolution [22].

Clearly, these observations support the concept of bacteria inducing airway inflammation, which then manifests clinically as exacerbations. The predominant cells in this inflammatory process appear to be neutrophils, while the major mediators include IL-8, TNF- α and LTB4.

STRAIN-SPECIFIC IMMUNE RESPONSE

Development of an adaptive immune response is strong evidence of an infective process. In order to establish the role of bacterial infection in exacerbations, several older studies examined the humoral immune response to bacterial pathogens in COPD following exacerbations [9]. In these studies, serum and sputum samples from COPD patients were compared with samples obtained from healthy controls, with the antigen consisting of a single strain or a panel of a few bacterial strains. The fact that the results of these studies were contradictory and confusing is unsurprising when we consider our current understanding of the antigenic diversity of bacterial strains of the same species. Several considerations are important in the experimental design to reliably study the immune response to bacterial infection. Homologous strains responsible for the infections should be used as the antigen to account for antigenic diversity among strains. Because of the presence of baseline antibodies, samples (serum or mucosal secretions) obtained after infection should be compared with pre-infection samples to clearly distinguish antibodies that develop following infection. Results can be also be confounded by cross-reactive antibodies that often bind to non-surface exposed epitopes of bacteria. Immunoassays used should therefore be specific for antibodies that bind to surface antigens of the bacterial pathogen [9, 79].

Recent studies in which these criteria were met have clearly demonstrated the development of antibodies that bind to the bacterial cell surface following exacerbations associated with *H. influenzae*, *M. catarrhalis* and *S. pneumoniae*, as well as following colonisation with *M. catarrhalis* [66, 68, 80]. Furthermore, for *H. influenzae*, these antibodies have been demonstrated to be bactericidal for the strain and to have a strong degree of strain specificity (Figure 2.5). Strain specificity of the antibodies directed against *M. catarrhalis* and *S. pneumoniae* has not been directly demonstrated until now. However, it is likely to be present based on the observation that once a strain of these pathogens is eliminated from the airway in COPD, re-acquisition of the same strain is a rare event.

Development of adaptive immune responses following exacerbation and colonisation with these respiratory bacterial pathogens supports the pathogenic role of these organisms in the lower airway. The strain specificity of these immune responses accounts for the recurrent exacerbations seen in COPD, as these antibodies are usually not protective against antigenically different strains of the same species.

OTHER POTENTIAL MECHANISMS OF BACTERIAL EXACERBATIONS

Pseudomonas aeruginosa, a significant airway pathogen in bronchiectasis and cystic fibrosis, has been isolated from sputum and bronchoscopic samples in COPD exacerbations, usually with underlying severe airflow obstruction. However, an association between exacerbations and new strain isolation was not identified for *P. aeruginosa* in cystic fibrosis [81]. This suggests that alternative mechanisms underlie the exacerbations due to this pathogen. Biofilms are complex communities enclosed in the matrix of extracellular polymeric substances. *P. aeruginosa* forms biofilms in the airways of patients with cystic fibrosis and a change from this biofilm state to a free floating planktonic state has been associated with exacerbations of cystic fibrosis [82]. A similar mechanism may exist among patients with COPD. Other alternative mechanisms include increased bacterial load or re-infection from an endogenous site.

Other Gram-negative enteric bacteria and *S. aureus* are often isolated from sputum during exacerbations. They have also been found in bronchoscopy samples obtained during exacerbations of severe COPD [83]. Data regarding strain changes and immune and inflammatory responses to these pathogens are unavailable. Therefore, whether these pathogens have an aetiological role in exacerbations, and the mechanism of such exacerbations remains unclear.

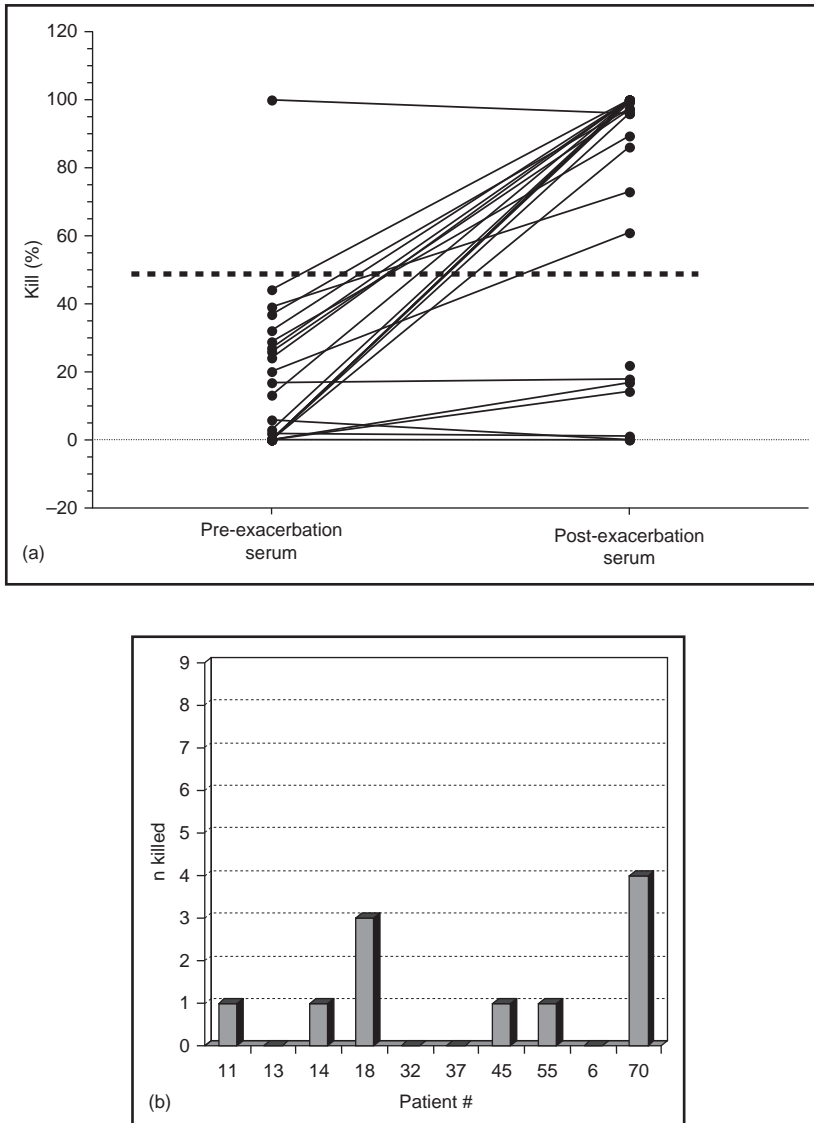


Figure 2.5 Development of serum bactericidal antibodies following exacerbations of COPD. (a) Bactericidal assay results with 26 newly acquired strains of non-typeable *H. influenzae* associated with exacerbations of COPD from a longitudinal cohort study. Lines connect the measured values with pre-exacerbation and post-exacerbation sera with a homologous *H. influenzae* strain. Serum concentration is 20% in all assays. The dashed horizontal line at 50% kill represents the threshold value above which sera were regarded as having bactericidal activity. Seven assay results overlap in the pre-exacerbation (<5%) and post-exacerbation (>95%) values (with permission from [66]). (b) Sera obtained after exacerbation from ten patients that were bactericidal for the infecting strain were tested in bactericidal assays with a panel of nine heterologous strains. The y-axis shows the number of heterologous strains killed with each of the ten sera (with permission from [66]).

Whether increased bacterial load could cause exacerbations independent of new strain acquisition is not known. Such a mechanism may exist, especially with intercurrent viral infection or other insults to the airway, which could alter the equilibrium between a colonising strain and the host defence mechanisms. This may allow the strain to proliferate and contribute to increased airway inflammation and the manifestations of the exacerbation.

VIRUSES AS A CAUSE OF ACUTE EXACERBATIONS

Pro-inflammatory actions of viral pathogens described *in vitro* include airway epithelial damage, muscarinic receptor stimulation and stimulation of the secretion of RANTES, which induces eosinophilic influx. These actions may account for the pathophysiological manifestations characteristic of acute exacerbation when a viral agent infects the lower airway of a patient with COPD. Previous investigations of the viral causation of exacerbations of COPD relied on serological studies and on viral cultures of upper airway samples. In these studies, although viral infection was demonstrated by culture or serology in one-third of exacerbations, it is conceivable that the serological response to the virus may be related to the upper airway infection and the lower airway process was of another aetiology, for example, bacterial infection.

Advances in technology have been applied to determine the role of viruses during exacerbations, with the use of polymerase chain reaction (PCR)-based detection of viral nucleic acids in sputum samples [84, 85]. In one such study, viral nucleic acids were detected in 56% of exacerbations and 19% of controls [86]. In another recent study, Papi *et al.* [8] were able to detect viral nucleic acids in 48% of sputum samples obtained from patients with severe exacerbations requiring hospitalisation, compared with 6% of samples obtained when those patients were stable. In addition, although neutrophil influx to the airway was seen in all exacerbations irrespective of aetiology, increased sputum eosinophils were confined to exacerbations where a viral aetiology was demonstrable [8]. Viruses do, therefore, appear to infect the lower airway in COPD and are associated with a specific inflammatory response comprising eosinophils. With the introduction of the influenza vaccine, rhinovirus has become the predominant virus implicated in exacerbations. The respiratory syncytial virus, long regarded as a major pathogen for children but not for adults, is also capable of causing significant illness in elderly adults with chronic lung and heart disease [87]. Other viruses associated with exacerbations include influenza, parainfluenza, adenovirus and perhaps human metapneumovirus.

ATYPICAL BACTERIA AS A CAUSE OF ACUTE EXACERBATION

The importance and incidence of *Mycoplasma pneumoniae*, *Chlamydophila* (formerly *Chlamydia*) *pneumoniae* and *Legionella* spp. infections in acute exacerbation is controversial. Considerable confusion reigns in the literature and may be related to the definition of exacerbation as well as the diagnostic criteria used for these pathogens in these studies. A minority of investigators included pneumonia as a cause of exacerbations and in their studies, unsurprisingly, the incidence of atypical infections, including *Legionella*, becomes considerable [88]. Most investigators now exclude pneumonia from the definition of an acute exacerbation.

The presence of infection by an atypical pathogen in exacerbations can be determined by cultures of respiratory secretions, PCR detection of microbial DNA and serology. Culture is technically difficult and of extremely low yield. The interpretation of PCR is complicated by a substantial incidence of chronic infection by *C. pneumoniae* in patients with COPD [89]. Serology would be a reliable diagnostic test if a four-fold increase in titre was defined as a positive result and the serological test used was highly specific for the pathogen under investigation. Unfortunately, several studies have chosen to define atypical infection based on a single titre above a certain threshold [90–93]. Such high titres are common in stable

COPD because this patient population is older and has had considerable exposure to cigarette smoke, both factors associated with high titres of antibodies to *C. pneumoniae* in population studies [94]. As an example of the varying results based on the diagnostic criteria chosen, in one such study, 13 of 38 patients with acute exacerbation were reported as having *C. pneumoniae* infection based on a single titre. However, of these 13 patients, only one had a four-fold increase in titre [93].

If one focuses on studies with rigorous methodologies in which pneumonia was excluded and a strict four-fold increase in titre or a positive culture were used to define infection, *M. pneumoniae* or *Legionella* are seen to be rare causes of exacerbation and the incidence of *C. pneumoniae* is 4–5% [95–97].

CO-INFECTION IN EXACERBATIONS OF COPD

Although it is commonly believed that antecedent viral infection is essential for the development of bacterial exacerbations of COPD, few data exist to support this notion. Only a few studies have addressed the issue of co-infection in the pathogenesis of COPD exacerbation. In these studies, exacerbations could be attributed to virus alone, to both viral and bacterial infection and to bacterial infection alone [7, 8, 98]. In the study by Papi *et al.* [8], approximately 25% of exacerbations belonged to each of these three groups. Therefore, although antecedent or simultaneous viral infection does occur, it is likely that several bacterial exacerbations also occur *de novo*.

Co-infection by these two classes of pathogens does seem to increase the severity of exacerbations. In hospitalised patients, there was greater decrement in lung function and longer hospitalisation with co-infection [8]. Among outpatients, co-infection was associated with more symptoms and a larger fall in forced expiratory volume in one second (FEV₁) as well as higher bacterial loads and systemic inflammation [7].

Specific viruses may predispose to infection by specific bacteria. It is likely that the well-known association between the influenza virus and *S. pneumoniae* and *S. aureus* infections in pneumonia may extend to exacerbations of COPD. *M. catarrhalis* exacerbations demonstrate a seasonal pattern reminiscent of rhinovirus infections, suggesting an association between these two pathogens [68]. In one study of severe exacerbations, co-infection with *C. pneumoniae* and bacterial infection was described [83].

Several respiratory viruses have recently been shown to enhance bacterial adherence to respiratory epithelial cells [56]. Furthermore, *H. influenzae* increases the expression of ICAM-1 on respiratory epithelial cells, which would increase viral attachment to these cells [57]. Co-infection in COPD exacerbations is undoubtedly an important phenomenon with clinical relevance and it represents a new frontier for exploration [6].

SUMMARY

Substantial progress has been made in the understanding of the infectious exacerbations in COPD. The availability of animal models of smoking-induced airway disease, which could be infected with the respiratory pathogens that cause exacerbations, will substantially accelerate research in this area. The complexity of the host–pathogen interaction that determines the onset and course of exacerbations has become apparent and needs to be explored further. Examination of cellular and molecular mechanisms in human subjects will add to our knowledge regarding infectious exacerbations. Understanding the virulence determinants of pathogens in the airway and their interaction with airway epithelial cells and macrophages would be invaluable. The interaction of the various stimuli capable of inducing exacerbations, such as viruses, bacteria, atypical bacteria and the environment, needs to be better understood in order to determine whether prevention strategies can be developed based on these interactions. Insight into the mechanisms and

pathophysiology of exacerbations should eventually lead to novel methods of treatment and prevention.

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3

Pathophysiology of COPD exacerbations

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic disease characterised by an airflow limitation that is not fully reversible and a progressive decline in lung function, exercise capacity and health status. This underlying state is punctuated by exacerbations of symptoms that vary in severity and frequency both among different patients and during the course of a single patient's illness [1].

Although exacerbations typically characterise the progression of COPD, controversies remain over their definition and underlying mechanisms. Exacerbations of COPD may be defined by a change in the patient's baseline dyspnoea, cough, and/or sputum that, beyond day-to-day variations, is acute in onset and may require a change in regular medication [2–4]. COPD exacerbations may be considered severe when acute respiratory failure is present [5]. It should be noted, however, that not all exacerbations are characterised by large spirometric changes.

Signs of approaching exacerbations are difficult to detect in clinical practice. Indeed, lung function changes immediately before exacerbation are generally small and not useful in predicting exacerbations. Decreases in peak expiratory flow rate (PEFR) or Forced expiratory volume in one second (FEV₁), even when measured daily, are poorly sensitive in the individual diagnosis of exacerbations, possibly because the individual variability is larger than the mean change occurring during an exacerbation [6, 7]. However, large decreases in PEFR, as well as changes in inspiratory capacity and dynamic hyperinflation, are associated with both the degree of dyspnoea during the exacerbation and the duration of hospitalisation [2, 8, 9].

Although the clinical features characterising COPD patients with frequent exacerbations are difficult to outline, several risk factors have been identified including low body mass index, increased baseline dyspnoea, low FEV₁, hypoxia and reduced levels of physical activity [2, 10]. Moreover, patients who experience frequent exacerbations in one year are likely to have a higher exacerbation frequency in following years [11, 12]. The correlation between

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disease severity and frequency of exacerbations is not particularly close, but several studies have demonstrated that the number of exacerbations is increased in patients with severe COPD [13–15]. Patients with advanced disease are also most likely to develop severe exacerbations characterised by acute respiratory failure [9]. Interestingly, in 2002 the group led by Wisia Wedzicha pointed out that the frequency of exacerbation has a role in the natural history of the disease [16]. Indeed, this group demonstrated for the first time that the frequency of acute exacerbations is one of the factors contributing to the long-term decline in lung function in COPD [16].

Although the aetiology of COPD exacerbations is not clearly established, increased evidence suggests that respiratory infections and air pollution play a crucial role. Recent studies have shown suggests that about 50% of COPD exacerbations are associated with viral infections, the majority of which are due to rhinovirus [17–19]. Even bacterial infections were detected in bronchoscopic sampling of lower respiratory airways in 50% of patients experiencing exacerbation [20–22], but it should be pointed out that viral and bacterial infections often coexist. COPD exacerbations could also be induced by air pollution, which may account for ~6–9 % of hospital admissions, depending on the time of year [23–25].

AIRWAY INFLAMMATION DURING COPD EXACERBATION

For a better understanding of the pathological events occurring during exacerbations, it is important to briefly highlight the pathological milieu of stable COPD. Direct examination of bronchial biopsies and lung tissue demonstrates the presence of a marked inflammatory infiltrate throughout the entire bronchial tree, as well as in lung parenchyma. In central airways, which are the main site of mucus hypersecretion (expressed clinically as chronic bronchitis), the inflammatory infiltrate is characterised by an increase of CD8 T lymphocytes and macrophages [26–28]. Neutrophils, which are scanty in the airway wall, are increased in the airway lumen [28, 29], suggesting a selective passage of neutrophils across the epithelium into the airway lumen. Neutrophils are also increased in the bronchial glands of subjects with COPD [30], and this location may be crucial for the development of mucus hypersecretion, since neutrophil elastase is a remarkably potent secretagogue [31].

In patients with stable COPD, mucus hypersecretion may have important functional consequences even in peripheral airways, which are the main sites of increased resistance and therefore of airflow obstruction. Indeed, an increased number of mucus-secreting goblet cells associated with an increased number of neutrophils have been reported in the peripheral airway epithelium of patients with COPD [32]. The resultant excess of mucus is able to alter the surface tension of the airway lining fluid, rendering the peripheral airways unstable and thereby facilitating their closure. Moreover, the excess of mucus may contribute to lumen occlusion through the formation of mucus plugs and it has recently been shown that airway occlusion by mucus plugs is associated with early mortality in patients with COPD [33].

Goblet cell hyperplasia is only one of the numerous pathological lesions present in the peripheral airways of patients with COPD. These include airway remodelling (fibrosis and smooth muscle hypertrophy) and an increased number of inflammatory cells, particularly of CD8 T lymphocytes [34]. CD8 T lymphocytes, which are increased not only in peripheral but also in central airways and lung parenchyma, seem to play a crucial role in the pathophysiology of COPD [27, 34–36]. Indeed, in all these compartments, CD8 T lymphocytes are not only increased in number but are also correlated to the degree of airflow limitation [27, 34, 36].

The inflammatory process in subjects with COPD is orchestrated by different proinflammatory cytokines including CXCL8 (interleukin-8), a cytokine that promotes neutrophil chemotaxis, tumour necrosis factor alpha (TNF- α) and interleukin-1 β (IL-1 β) which activate adhesion molecules, leukotriene B4 (LTB4) and growth-related oncogene alpha (GRO- α), which are powerful chemoattractants for neutrophils and T lymphocytes [37–40]. Indeed, upregulation of these cytokines in smokers with airway obstruction contributes to the main-

tenance of the inflammatory response. This inflammatory process is amplified during exacerbations with recruitment of neutrophils and eosinophils, which become the major components of the inflammatory response [41, 42].

NEUTROPHILS

There are few pathological studies that have examined COPD patients during an exacerbation. Examination of bronchial biopsies, broncoalveolar lavage and, more recently, spontaneous or induced sputum has consistently shown increased airway inflammation and elevated levels of inflammatory cytokines in these patients [41–46]. In particular, subjects with exacerbations of COPD are characterised by a marked recruitment of neutrophils [47–49], which appears to be mediated by various molecules. Indeed, studies performed on bronchial biopsy and airway secretions in severe and very severe COPD exacerbations showed upregulation of the neutrophil chemoattractants CXCL5 (ENA-78) and CXCL8, and of their receptors CXCR1 and CXCR2 [49, 50]. Furthermore, exacerbations have also been associated with an increase in the expression of LTB₄, myeloperoxidase and TNF- α [44, 51]. LTB₄ is an important mediator of neutrophil recruitment, myeloperoxidase is a marker of neutrophil activation and TNF- α is an inducer of adhesion molecules on endothelial cells, thus facilitating leukocyte influx in the airway tissue.

The enhancement of neutrophilic inflammation seems to be a peculiar feature of COPD exacerbations, independent of the presence and the type of infectious agents. Recently, Papi and co-workers performed sputum analysis in patients with severe COPD exacerbations requiring hospitalisation [22]. They found that 78% of exacerbations were associated with respiratory infections in which either viral, bacterial or a combination of viral and bacterial agents could be detected. Not only were neutrophilia and neutrophil elastase levels increased in bacterial exacerbations, they were equally increased in viral and in non-detected agent exacerbations. Surprisingly, the authors found that sputum purulence was not different in patients with either viral or bacterial infections, supporting the concept that sputum purulence is poorly able to identify the infective agent in COPD exacerbations, contradicting some previous reports [51–52].

Enhanced neutrophilic inflammation may play a crucial role in the pathogenesis of exacerbations. Indeed, neutrophilia is involved in mucous gland hyperplasia and mucus hypersecretion and, therefore, in the worsening of respiratory symptoms that characterises exacerbations. Moreover, in sputum, elevated markers of neutrophilic inflammation were associated with an increased vascular protein leakage that may lead to oedema of the airway wall, therefore contributing to airway narrowing [51]. Finally, it is well known that activated neutrophils in their migration through connective tissue may release proteolytic enzymes able to degrade the extracellular matrix, leading to an imbalance between proteinases and anti-proteinases. During COPD exacerbations, the increased recruitment of neutrophils and the consequent enhanced release of active enzymes may lead to widespread tissue damage that is thought to be crucial to disease progression [51, 53].

Interestingly, in patients with COPD, the percentage of neutrophils in the distal airspace is positively correlated with the severity of airway obstruction, as assessed by the worsening of the FEV₁/FVC (forced vital capacity) ratio with increasing neutrophil inflammation [50]. This observation suggests that neutrophil recruitment during exacerbations may play a significant role in the progression of COPD and that patients experiencing several exacerbations may be more prone to the development of a more rapid decline of lung function [16].

EOSINOPHILS

Studies on bronchial biopsies of patients with mild to moderate COPD exacerbation have shown an increased number of eosinophils in the bronchial mucosa (Figure 3.1) [45, 46].

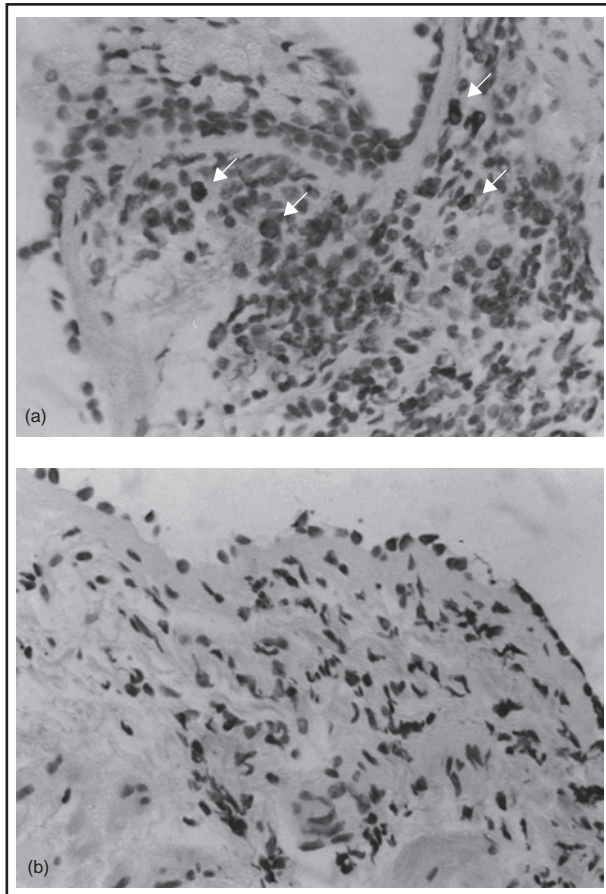


Figure 3.1 Sections from bronchial biopsies showing eosinophil infiltration in a COPD subject examined during an exacerbation (a) as compared with a COPD subject in a stable condition, (b) (immunostaining with anti-EG2).

These pioneering observations were initially debated, but several further studies confirm that eosinophilia is a characteristic feature of the airways in patients with COPD exacerbation [54–56]. In particular, it has been demonstrated that the expression of RANTES (regulated upon activation, normal T cell-expressed and secreted chemokine), which is able to induce eosinophil recruitment, is increased in the airway mucosa at exacerbation [42]. RANTES expression may be mediated by $\text{TNF-}\alpha$ [57], whose increase at exacerbation could potentially drive eosinophil recruitment [58]. Increases of eotaxin-1, a CC chemokine involved in eosinophil recruitment and activation, and its receptor CCR3, have also been reported at exacerbation of COPD [55]. Furthermore, serum and sputum levels of eosinophil cationic protein are higher in patients with exacerbations than in those with stable COPD [22, 56].

The precise role of eosinophilia during exacerbations remains to be determined. Nevertheless it is known that several eosinophil products (eosinophil peroxidase, major basic protein, eosinophil cationic protein, metalloproteinases, platelet activating factor, and cysteinyl leukotrienes) may cause tissue damage to the airways [59] and, together with histamine, may cause bronchospasm.

It is well known that viral infections are able to induce lower airway eosinophilia and production of several proinflammatory mediators promoting eosinophil recruitment [60–62]. An interesting observation in this context is that the number of eosinophils is increased in sputum only in those exacerbations associated with viral infections, suggesting that sputum eosinophils are a good predictor of a viral exacerbation either in the presence or absence of a bacterial co-infection [22].

T LYMPHOCYTES

Although T cell-mediated immunity carries out a crucial task in stable COPD, relatively little is known about its role during exacerbations. A recent study examined changes in sputum T lymphocyte subpopulations in severe COPD exacerbations [63] and showed a decrease of the cell ratio of CD4/CD8 when compared with stable conditions. This evidence suggests that an imbalance in T lymphocyte subpopulations with a further shift towards the CD8-positive cell-mediated immune response might be associated with the development of severe COPD exacerbations.

Moreover, there is evidence that CD8⁺ cells may cooperate with RANTES to enhance apoptosis of virally infected cells [42]. Thus, as hypothesised by Zhu and colleagues [42], when CD8⁺ cells predominate, as in stable COPD, exacerbations and the consequent RANTES overexpression may promote CD8⁺ cell-mediated tissue damage encouraging the development of microscopic emphysema. Increased frequency of viral exacerbations may thus destroy airway and alveolar tissue not only through the recruitment of neutrophils and eosinophils, but also by activation of CD8⁺ cells. Repeated exacerbations may thus enhance emphysema and accelerate decline in lung function. This hypothesis is consistent with the observation, mentioned above, that exacerbation frequency is a determinant of FEV₁ decline in COPD [16].

SOLUBLE MEDIATORS IN COPD EXACERBATIONS

As previously described, several inflammatory markers are increased in the lung during COPD exacerbations. The increase of TNF- α observed in sputum at exacerbation [44, 64] could contribute to upregulation of the expression of endothelial adhesion molecules, thus facilitating cell migration [65]. TNF- α may also increase the expression of RANTES and, through this pathway, modulate eosinophil recruitment and CD8⁺ cell-mediated tissue damage at exacerbation [42].

Sputum IL-6 is increased at exacerbation and, in particular, when exacerbations are associated with symptoms of the common cold [66]. Interestingly, experimental rhinovirus infections have been shown to increase sputum IL-6 [67], suggesting that elevated levels of IL-6 in sputum could be markers of virus-related exacerbation.

Elastases and other proteinases, produced by neutrophils and macrophages, may cause epithelial damage, reduce ciliary beat frequency [68], stimulate mucus secretion by goblet cells [69] and increase the permeability of the bronchial mucosa, resulting in airway oedema and protein exudation into the airways. These changes, especially when involving small airways, may adversely affect airflow and lead to increased breathlessness, as well as to the mucus secretion and purulence that are characteristic of some exacerbations.

With regard to soluble mediators, recent studies reported increased levels of endothelin-1 in induced sputum of COPD subjects examined during exacerbation, suggesting that this factor may play a role in the pathophysiology of the acute episodes [70]. Indeed endothelin-1 has been proposed as a possible mediator for increased airflow obstruction via bronchospasm induction. In addition, endothelin-1 may stimulate mucus secretion, promote airway oedema, increase vascular and airway smooth muscle proliferation and upregulate production of cytokines [7, 70].

During COPD exacerbations, oxidative stress is increased in the lung, probably because of a large burden of activated inflammatory cells [71]. The newly recruited neutrophils participate in oxidative stress through the activation of oxidant-sensitive transcription factors that leads to increased transcription of proinflammatory genes. Critical to the effect of oxidative stress is the protective counterbalance of antioxidant systems. A shift in this oxidant-antioxidant balance could result in an increase in oxidative stress that may cause cellular damage. In this regard, glutathione appears to be an important antioxidant in the lungs, present in high concentrations in the epithelial lining fluid [72]. During severe COPD exacerbations, glutathione is depleted, indicating increased oxidative stress [50]. Several other indirect markers of oxidative stress have been investigated in exhaled breath condensate. Notably, both hydrogen peroxide and 8-isoprostane concentrations are increased at exacerbation [73, 74], suggesting the involvement of oxidative stress in acute episodes.

Plasma biomarkers of inflammation such as C-reactive protein (CRP) and fibrinogen are increased during COPD exacerbations, even though they appear not to be useful in predicting the clinical severity of these acute events [75]. Nevertheless, the level of serum CRP in the presence of worsening symptoms is able to reliably differentiate exacerbation of COPD from day-to-day symptom variation and may therefore be useful in the choice of the appropriate therapeutic intervention [75]. Moreover, patients with frequent exacerbations showed a faster rise in plasma fibrinogen over time [76] and it is known that increased levels of CRP and plasma fibrinogen are associated with an increased risk for cardiovascular morbidity. These data support the recently proposed theory that in COPD patients there is a systemic inflammation that is associated with cardiovascular and systemic effects [77, 78]. The increase of this systemic inflammation during exacerbation may aggravate these extrapulmonary diseases, leading to important chronic and acute clinical manifestations.

SYSTEMIC INVOLVEMENT

COPD is now recognised as a systemic disorder with extrapulmonary manifestations that involve different organs, resulting in skeletal muscle dysfunction, muscle wasting [84], atherosclerosis and its associated complications [7, 79]. A recent meta-analysis of large studies on systemic inflammation in COPD reported increased serum levels of CRP, fibrinogen, leucocytes and TNF- α in patients with stable COPD as compared to healthy controls [76]. Current evidence suggests that this systemic inflammation is involved in the extrapulmonary manifestations of COPD [79]. For example, clinically stable COPD patients may present with significant weight loss that is strictly correlated to increased levels of serum TNF- α [80]. During disease exacerbations, the additional increased level of this cytokine [64, 65] may cause an enhancement of catabolic effects, leading to further weight loss. This is particularly interesting considering that weight loss is a negative prognostic factor in COPD patients [81]. Usually weight loss is associated with skeletal muscle dysfunction, which contributes to limited exercise capacity and reduced quality of life [82]. Of interest, the reduction of peripheral muscle force that occurs during COPD exacerbations requiring hospitalisation only partially recovers when, at discharge, clinical conditions improve [83].

Systemic inflammation, besides being associated with weight loss, is a major risk factor for the genesis, progression and rupture of atheroma in patients affected by atherosclerosis [84]. Therefore, the increased levels of serum soluble markers of systemic inflammation described during COPD exacerbations [85] may increase the risk of cardiovascular mortality.

Among the relevant systemic effects of COPD, alterations of the nervous system, anaemia and osteoporosis appear particularly likely. Several features of the nervous system may be abnormal in patients with COPD and the energy metabolism of the brain is altered in these patients [86]. Depression is highly prevalent [87] and it is possible that it bears some relationship to the systemic inflammation that occurs in COPD [88]. The autonomic nervous

system may also be altered in these patients, particularly in those with low body weight [89]. The presence of mild chronic anaemia has been demonstrated in chronic conditions such as chronic heart failure, a disease often associated with COPD [90]. Finally, the prevalence of osteoporosis is increased in patients with COPD [91, 92]. Since proinflammatory cytokines can significantly alter bone metabolism, excessive osteoporosis in relation to age could also be considered a systemic effect of COPD [93]. During exacerbations, the unavoidable use of systemic steroids could further aggravate the already present state of osteopaenia.

It is conceivable that the enhanced systemic inflammation observed in COPD patients during an exacerbation [79] may aggravate extrapulmonary manifestations of the disease. It is noteworthy that analysis of systemic biomarkers is a simple approach that can be repeated over time. Therefore, identification of plasma biomarkers related to pulmonary or extrapulmonary manifestation of the disease would allow monitoring of COPD patients and optimise therapeutic strategies. Indeed, the systemic involvement of COPD may become the objective of therapeutic interventions that could influence outcomes independent of the capacity to modify lung function.

SUMMARY

COPD is a public health problem around the world, being a major cause of chronic morbidity and mortality. It is characterised by fixed airflow limitation and a progressive decline of lung function, which is punctuated by exacerbations. These can be so severe as to cause admission to hospital or the intensive care unit.

Smokers with stable COPD have an inflammatory response involving the entire tracheobronchial tree, mainly characterised by an increase of CD8 T lymphocytes. This inflammatory pattern changes during exacerbations, with recruitment of neutrophils and eosinophils that become the major components of the inflammatory response. Moreover, COPD exacerbations play a role in the lung function deterioration that characterises disease progression. Finally, the enhanced systemic inflammatory process present in COPD patients during an exacerbation may lead to aggravation of the extrapulmonary manifestations, with several important consequences for patients and healthcare providers.

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4

Acute respiratory failure during exacerbation of COPD

S. Khirani, G. Polese, A. Rossi

INTRODUCTION

Respiratory failure is an important event that occurs frequently in the course of severe exacerbations of chronic obstructive pulmonary disease (COPD). Respiratory failure is due to lung failure resulting in hypoxaemia ($\text{PaO}_2/\text{FiO}_2 >300$ mmHg) and pump failure resulting in alveolar hypoventilation and hypercapnia ($\text{PaCO}_2 >45$ mmHg), with or without respiratory acidosis ($\text{pH} <7.36$). Respiratory failure in the COPD patient who becomes acutely ill may represent deterioration in the patient's premorbid condition, e.g. chronic hypoxaemia or chronic hypercapnia, because of a respiratory tract infection, which may be viral or bacterial [1–4]. Alternatively, these changes may occur for the first time in someone with less severe COPD who encounters a particularly dramatic cause for deterioration, e.g. lobar pneumonia or acute pulmonary oedema. Indeed, patients with severe but stable COPD exist in a very critical balance between increased demands and limited reserves. Any factor that potentially interferes with this balance (either increases demand or decreases reserves) can lead to acute respiratory failure (ARF) [2]. COPD remains one of the most complete and fascinating models of respiratory failure because stringent and continuous interplay of pulmonary and thoracic mechanisms profoundly changes the pathophysiology of the respiratory system as the disease progresses [1]. As suggested by Hopping [5], *'the lungs and the chest wall are joined in an indissoluble marriage for life in health and disease'*.

During COPD exacerbation, acute respiratory failure may also be attributable to comorbidities such as cardiac ischaemia, congestive heart failure, pulmonary embolism, pneumonia or pneumothorax [6, 7]. In any case, the physiological abnormality is invariably the development of a significant degree of hypoxaemia with a variable risk of carbon dioxide retention. When the latter occurs, respiratory acidosis develops and this requires specific management strategies. Inefficient gas exchange is a cardinal feature in patients with exacerbation of COPD.

PATHOPHYSIOLOGY

A successful effort to offer an operational categorisation of respiratory failure, with the purpose of providing practical indications for clinical procedures, was first realised by Roussos

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and Macklem more than 20 years ago [8]. They suggested that respiratory failure was the result of two different pathophysiological pathways:

1. Failure of the lungs as a gas exchange unit; and
2. Failure of the ventilatory pump.

The pump consists of the chest wall, the respiratory muscles that displace the chest wall, the respiratory centres of the central nervous system that control the muscles and the nerves connecting the centres to the muscles [2]. The key function of the lungs is pulmonary gas exchange, requiring adequate levels of alveolar ventilation and perfusion and a normal distribution of their ratio.

This classification suggests that a range of concentrations of oxygen-enriched air administration is indicated in the gas exchange disturbances due to lung diseases, whereas mechanical ventilation (with different modalities and settings) can help to sustain a failing ventilatory pump that cannot maintain adequate CO₂ clearance. Indeed, in most COPD patients, hypoxaemia can be corrected with oxygen-enriched air, even during acute exacerbations, whereas hypercapnia can run out of control. A common pathway to acute respiratory failure is an acute exacerbation in patients who are already chronic CO₂ retainers [9].

HYPOXAEMIA

In general terms, hypoxaemia results from the combination of pulmonary (ventilation–perfusion mismatching, shunt, and reduced alveolar–capillary diffusion capacity) and extrapulmonary (FiO₂, minute ventilation, cardiac output, mixed venous PO₂) determinants of PaO₂ [10]. In exacerbations of COPD, both intrapulmonary and extrapulmonary factors play a distinct role in the mechanisms underlying hypoxaemia.

Stable COPD is characterised by different patterns of abnormal distribution of ventilation–perfusion ratio in the lungs [11]. It is accepted that the abnormal distribution of pulmonary capillary blood flow and alveolar ventilation is the result of parenchymal destruction and small airways disease, respectively [12]. The latter is mainly the effect of inflammatory changes in the bronchiolar wall, mucus in the lumen, distortion and remodelling [13]. The former is also related to inflammation in the periphery of the lungs, leading to loss of elastic recoil and alveolar attachments supporting the small airways [14]. These morphological changes in airways and lungs, in most cases aggravated by airway infection, determine important functional abnormalities [15]:

- Increased dead space, which increases the ventilatory demand;
- Increased airflow resistance and decreased dynamic lung compliance, which increase the work of breathing;
- Expiratory flow limitation and loss of lung elastic recoil, which increase the functional residual capacity (FRC); and
- Regional inequalities and frequency-dependence of compliance and resistance, which cause diffuse inhomogeneity of time constants (i.e. compliance × resistance) within the lungs, leading to uneven distribution of ventilation [16] and VA/Q mismatching [17]. It has been shown that the degree of VA/Q mismatching is poorly related to the magnitude of airflow limitation as reflected by the value of forced expiratory volume in one second (FEV₁).

Collateral ventilation and hypoxic vasoconstriction are compensatory mechanisms that are partially efficient in preventing severe abnormalities in the distribution of VA/Q ratios and hence hypoxaemia, for years. However, with the progression of the disease, the VA/Q mismatching and particularly the distribution of pulmonary blood flow to low VA/Q units becomes more severe and hypoxaemia ensues [17].

In stable COPD there are different patterns of VA/Q mismatching, but when an exacerbation occurs, regardless of the aetiology, VA/Q mismatching worsens, further impairing the gas exchange capability of the lungs (lung failure) [18]. The amount of shunt was consistently found to be negligible and no role was shown for a reduced diffusion capacity of the alveolar–capillary membrane [12]. However, extrapulmonary factors play a role in determining hypoxaemia during COPD exacerbations. The peripheral oxygen consumption increases because of the increased effort of the inspiratory muscles to bear the increased ventilatory mechanical load [19]. The augmented oxygen need of the respiratory muscles increases the peripheral oxygen uptake and may decrease the value of mixed venous PO₂ (PvO₂). Cardiac output may increase because of an increased level of catecholamines and the time of the mixed venous blood passage in the pulmonary capillary circulation decreases. In this way a low PvO₂ passes rapidly through a damaged gas exchanger (VA/Q mismatching) and hypoxaemia ensues (Figure 4.1) [1]. According to the measurement obtained by means of the multiple inert gas elimination technique (MIGET), hypoxaemia during COPD exacerbation is due to the combination of VA/Q mismatching (46%), low PvO₂ (26%) and increased peripheral oxygen uptake (28%) [1]. The true shunt fraction was consistently negligible, such that administration of oxygen-enriched air is generally effective to keep oxyhaemoglobin (HbO₂) saturation (SaO₂) >90%. This is important for clinical practice because a finger or ear pulse oximeter provides an easy way to monitor SaO₂ during therapeutic procedures [20]. However, the discrepancy between pulse oximetry and arterial blood gas measurements is well known and should be taken into account by the caring physicians in the interpretation of the values of peripheral SaO₂ [21–23]. Clearly, pulse oximetry, although much less invasive, and useful for some monitoring, cannot replace periodic sampling of the arterial blood in patients with exacerbation of COPD. Oxygenation is only part of the problem: hypercapnia and respiratory acidosis are also major issues. Indeed, the removal of hypoxic drive by means of oxygen-enriched air is always associated with an increase in PaCO₂ [24]. However, measurements obtained in spontaneously breathing COPD patients with ARF have shown that both oxygen-enriched air and 100% oxygen breathing determined an increase in PaCO₂, which was associated with a decrease in central drive (as evidenced by the drop in pressure generated 100 ms after the onset of an occluded inspiratory effort, P_{0.1}) and a slight reduction in minute ventilation or changes in breathing pattern [25, 26]. Furthermore, during oxygen breathing and hence with suppression of the hypoxic drive, the central drive (P_{0.1}) was still higher than in normal subjects [27]. These data suggested that both CO₂ and O₂ drives were active and that additional mechanisms must explain the increase in PaCO₂ (up to 13 mmHg) during oxygen breathing. The basic mechanisms responsible for this process have been debated since the 1960s [28], with evidence supporting ventilation–perfusion mismatching in very severe cases of ARF [29]. In less severe episodes, hypoventilation secondary to a reduction in hypoxic drive to breathing would lead to CO₂ retention [24].

In this connection, it should be recalled that administration of oxygen-enriched air increases PaCO₂ in spontaneously breathing patients [4, 30] because of:

- A fall in pulmonary ventilation due to the removal of the hypoxic drive;
- A worse VA/Q mismatching due to an increase in the dead space because of the oxygen-induced bronchodilatation; and
- The Haldane effect of CO₂ on the Hb dissociation curve, such that Hb loading O₂ releases CO₂.

The well-documented benefits of long-term oxygen supply at home have made acceptable a slight rise in PaCO₂. However, the potentially harmful consequences of excessive oxygen flow rate must be controlled and excessive rises in PaCO₂ prevented, for example with ventilatory assistance.

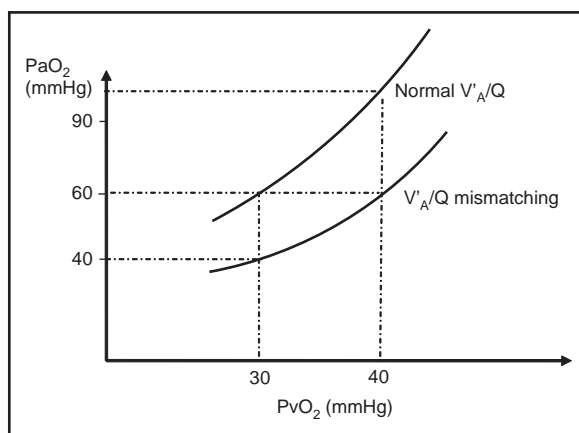


Figure 4.1 Hypoxaemia and distribution of ventilation–perfusion ratio in the lungs. Extrapulmonary factors play a role in determining hypoxaemia during COPD exacerbations. The peripheral oxygen consumption increases because of the increased effort of the inspiratory muscles to bear the increased ventilatory mechanical load. The augmented oxygen need of the respiratory muscles increases the peripheral oxygen uptake and may decrease the value of mixed venous PO_2 . Low PvO_2 passes rapidly through a damaged gas exchanger (VA/Q mismatching) and hypoxaemia ensues. VA/Q = alveolar ventilation/perfusion; PvO_2 = mixed venous PO_2 (extrapolated with permission from [9]).

HYPERCAPNIA

Without supplemental oxygen administration (i.e. while breathing room air), patients with exacerbations of COPD may develop hypercapnia, which is the result of an ineffective ventilatory pattern, characterised by a rapid (high frequency of breathing) and shallow (low tidal volume, V_T) breathing, probably reflecting the failure of the ventilatory pump to sustain adequate alveolar ventilation in the face of severe VA/Q mismatching and abnormal respiratory mechanics [31]. The drop in alveolar ventilation due to the low V_T may not be paralleled by a decrease in total minute ventilation because of the compensatory effect of the increased frequency. Therefore, alveolar hypoventilation is often associated with tachypnoea.

From the point of view of abnormal lung mechanics, the hallmark of COPD is airflow limitation due to inflammatory changes, mucus transport alteration, loss of lung elastic recoil, loss of alveolar attachments sustaining the small airways and remodelling of the periphery of the lungs [15]. The work of breathing (WOB) is greater than normal because of the increase in pulmonary resistance (resistive work) and lung elasticity (elastic work). The former is due to the reduced bronchial calibre and the latter is the consequence of pulmonary hyperinflation [32]. The role of pulmonary hyperinflation in the pathophysiology of respiratory failure in COPD has been extensively reported in many publications, including an official document of the most relevant international scientific societies in the area [19]. Because of the loss of inward lung recoil due to parenchymal destruction, the outward recoil of the chest wall repositions the FRC to a higher lung volume, often corresponding to and even higher than the relaxation volume of the chest wall, i.e. 55–60% of predicted total lung capacity rather than the normal 40–45% in healthy subjects [33]. In advanced COPD, the FRC may be higher than predicted total lung capacity (TLC) [34]. Breathing at a higher lung volume increases the work of breathing because ventilation takes place closer to the upper (flat) portion of the volume–pressure curve.

Exacerbation of COPD is almost invariably associated with increased inflammation and altered mucus transport in the bronchial tree and particularly in the small airways, with

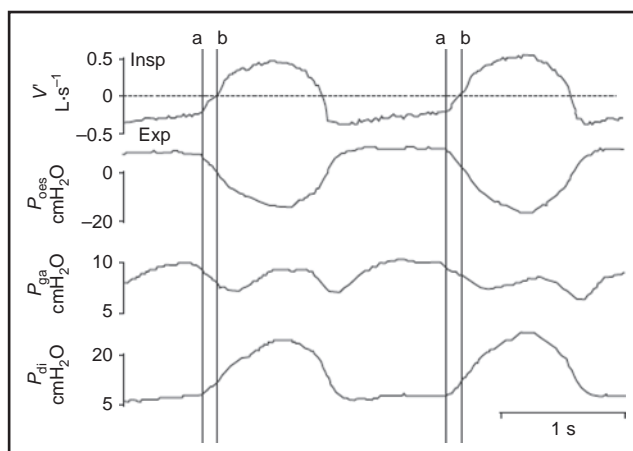


Figure 4.2 Experimental record illustrating the measurement of dynamic intrinsic positive end-expiratory pressure ($PEEPi_{dyn}$) from simultaneous recording of ventilatory flow and oesophageal pressure during spontaneous breathing in a representative patient showing evidence of expiratory muscle activity during an acute exacerbation of chronic obstructive pulmonary disease (COPD). Tracings represent ventilatory flow (V); oesophageal pressure (P_{oes}); gastric pressure (P_{ga}); and transdiaphragmatic pressure (P_{di}). The first vertical line (a) indicates the point corresponding to the onset of the inspiratory effort (P_{di} swing). The second vertical line (b) indicates the point corresponding to the start of inspiratory flow. The dotted horizontal line represents zero flow. Insp = inspiratory flow; Exp = expiratory flow. Tidal volume was 0.33l. Note that P_{ga} increased throughout most of the expiration. By contrast, P_{ga} became less positive from the onset of the inspiratory effort, indicated by the start of positive P_{di} swing to the start of inspiratory flow. In this case $PEEPi_{dyn}$ was measured as the negative P_{oes} deflection between the point corresponding to the onset of P_{di} swing and the point of zero flow subtracted by the amount of P_{ga} negative deflection observed in that interval (with permission from [30]).

consequent increases in airway resistance [35]. The first result of this is the requirement for an augmented amount of inspiratory effort to ventilate the lungs through the narrower airways (increased resistive work) [19]. In addition, increased airflow resistance retards the expiratory flow and hence the rate of lung emptying, such that the time available between the next two inspiratory efforts is not sufficient to decompress the lungs to the relaxation volume [36, 37]. The condition in which the end-expiratory lung volume (EELV) stabilises above the relaxed FRC is termed dynamic pulmonary hyperinflation (DPH) [32, 33]. Under these circumstances, inspiration starts before the end of the preceding expiration and a positive end-expiratory alveolar pressure (conventionally named intrinsic positive end-expiratory pressure or PEEPi) must be counterbalanced by the contracting inspiratory muscles before creating a sub-atmospheric pressure in the central airway and hence inspiratory flow (Figure 4.2) [38].

As a matter of fact, some small levels of PEEPi are present in stable moderate to severe COPD, usually amounting to a few cmH_2O [39–41]. During acute exacerbations, PEEPi increases significantly, thus generating an inspiratory threshold load that adds to the increased WOB [41]. In that condition, the mechanical ventilatory load for the inspiratory muscles increases substantially, challenging progressively their capability to sustain an efficient breathing pattern to clear CO_2 . Studies have found a relationship between the degree of PEEPi and the severity of resting hypercapnia [32]. Furthermore, at high lung volume, the pressure-generating capacity of the inspiratory muscles is remarkably reduced. Although there are compensatory mechanisms [42, 43], they are not sufficient, so the respiratory muscle force is better than might be expected but still lower than normal [44]. The association

of increased mechanical ventilatory load and reduced respiratory muscle force might lead to respiratory muscle fatigue and to the exhaustion of the ventilatory pump which, undoubtedly, is a terminal event. Indeed, with increasing lung volume, the inspiratory muscle fibres shorten such that the inspiratory muscles operate at a shorter length, thus producing less force according to their length–tension characteristics [45–47]. Furthermore, at higher lung volume, the geometry of the chest wall is altered and the diaphragm (the principal inspiratory muscle) flattens such that its inspiratory action becomes less effective because of the marked reduction in the zone of apposition, i.e. the area where the cylindrical portion of the diaphragm is apposed to the inner side of the lower rib cage [48, 49]. It has been shown that the extension of this zone of apposition is an important component for the inspiratory action of the diaphragm and that it is significantly decreased by the change in diaphragmatic shape determined by the increase in lung volume. In this connection it is noteworthy that in COPD, as in many cardiorespiratory diseases, other factors such as malnutrition, deconditioning and impaired cardiac function can also reduce respiratory muscle contractility [48, 50]. Moreover, the adverse effect of acute hypercapnia on diaphragmatic contractility becomes an additional factor in reducing the diaphragmatic pressure-generating capability [51].

When the respiratory muscles are extensively loaded, however, it is likely that feedback mechanisms modify the central drive, which, by exerting ‘central wisdom’, alters the ventilatory pattern and serves to reduce the load and alleviate fatigue, thus protecting the ventilatory pump from exhaustion [2]. Although there are no data from patients to substantiate the existence of ‘central wisdom’ in ventilatory failure, there is some evidence to support this theory. The fact that most hypercapnic patients with COPD can achieve normocapnia by voluntarily increasing their ventilation implies that, although the subjects could increase their ventilation, they choose not to do so. More than 20 years ago, Sorli and colleagues [27] were the first to show that COPD patients with chronic CO_2 retention were not the type of patients who ‘*did not want to breathe*’. Rather they wanted to breathe, as documented by their high neuromuscular drive ($P_{0.1}$), but their ventilatory pattern was inefficient because minute ventilation was maintained with a lower tidal volume and higher frequency when compared with normal subjects, and even with COPD patients without chronic CO_2 retention. Indeed, it is a common observation that patients with respiratory failure develop a shallow and rapid breathing pattern [31]. This has been interpreted as a compensatory mechanism to reduce the mechanical load on the respiratory muscles. In fact, a compensatory increase in the central drive would be even more deleterious because it would require an additional effort by the inspiratory muscles, which are already overloaded by both the increased WOB and the threshold load (PEEPi). In this condition, as already mentioned, a decrease in tidal volume associated with an increase in the breathing frequency seems to remain the only means to defend pulmonary ventilation and prevent respiratory muscle fatigue. Indeed, with small tidal breaths, the respiratory muscles run at a more optimal length that does not substantially affect their geometry.

However, the rapid and shallow breathing pattern is a very poor way to clear CO_2 . Not surprisingly, in these circumstances, an increase in PaCO_2 ensues because of the fall in alveolar ventilation (Figure 4.3). In addition, a high frequency of breathing generates a short expiratory duration which in turn further worsens pulmonary hyperinflation and its deleterious consequences on the mechanics of breathing, in a sort of a ‘vicious circle’ that leads eventually to failure of the ventilatory pump (Figure 4.3) [9]. Assisted ventilation needs to be promptly instituted as a lifesaving procedure [19].

In a study addressing the pathophysiology of ventilator-dependent patients with very extreme COPD [52] and in a recent study addressing the mechanical determinants of early acute ventilatory failure in COPD [31], Purro and co-workers contributed to the elucidation of that general mechanism. They showed that the main characteristics of these patients were:

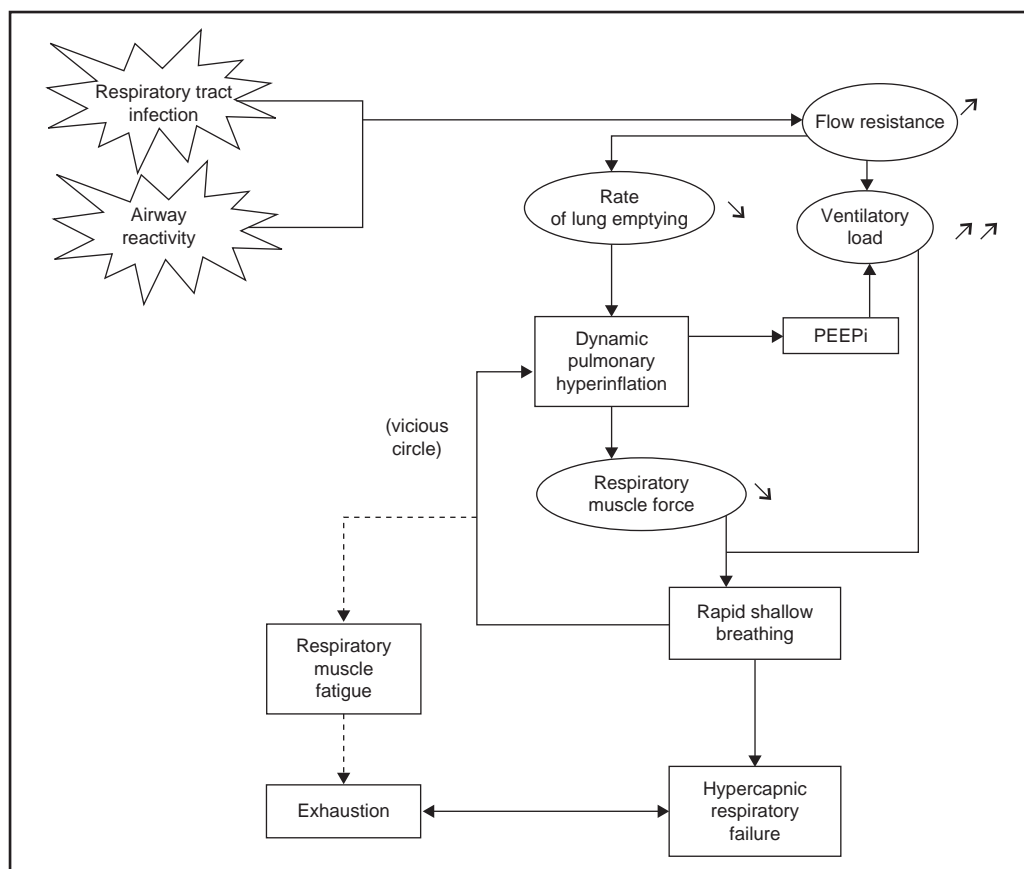


Figure 4.3 Acute respiratory failure in COPD. PEEPi: intrinsic positive end-expiratory pressure (with permission from [6]).

- Shallow breathing pattern, i.e. low tidal volume;
- High $P_{0.1}$ (an index of the total neuromuscular drive) [53], and high effective inspiratory impedance, i.e. the $P_{0.1} / V_T / T_I$ ratio (V_T and T_I are the tidal volume and the inspiratory duration such that their ratio is the mean inspiratory flow) [26]; and
- High P/P_{max} for both transdiaphragmatic (P_{di}) and total pleural (P_{pl}) pressure, indicating that a large amount (>40%) of the total available pressure to be generated by the respiratory muscles was needed for that pattern of breathing [54].

Those findings taken together indicate that even in the extreme condition of very severe COPD, the drive to breathe was not only preserved, but was actually much greater than in patients with a stable condition. However, the mechanical ventilatory load was so large that a big effort was required by the patient's respiratory muscles in order to breathe. As shown by Purro and colleagues [52], a $P_{0.1}/V_T/T_I > 10$ cmH₂O/l/s and a $P_{di}/P_{di_{max}} > 40\%$ were associated with an incapability to sustain spontaneous breathing for more than a few minutes and patients became chronically ventilator-dependent. In other words, those patients wanted to breathe (high $P_{0.1}$), but could not do so because of the large mechanical load (high $P_{di}/P_{di_{max}}$). The ineffective compensatory mechanism with the low tidal volume was

determining chronic CO₂ retention. However, the data from Purro and colleagues [52] were collected in a special long-term weaning unit, such that the patients in the study do not represent the patients seen in a general intensive care unit (ICU). Nevertheless, the results are in line with many other studies showing that COPD patients have a great drive to breathe which has to face a large and sometimes excessive mechanical load, which may hamper their capability to sustain spontaneous breathing for long.

RESPIRATORY ACIDOSIS

When the lungs cannot remove all of the CO₂ produced by the body and alveolar ventilation is decreased, respiratory acidosis occurs, leading to a disturbance of the acid–base balance. Respiratory acidosis is a process in which the PaCO₂ is higher than normal (>45 mmHg) leading to an arterial pH <7.36. In cases of chronic respiratory acidosis (persistently elevated PaCO₂), the kidneys increase their retention of bicarbonate to maintain a quasi-normal acid–base balance in the blood. If a patient with respiratory acidosis breathes ambient air, a life-threatening associated hypoxaemia will develop because of hypoventilation. However, use of supplemental oxygen is not always prescribed appropriately [55] and severe acidosis with a higher PaCO₂ (supercarbia: PaCO₂ >150 mmHg) can take place because of high inspired oxygen concentrations.

Correction of respiratory acidosis should be performed carefully [56]. The goal is to return the pH toward normal limits, not to return the PCO₂ to normal [57–59]. Vigorous attempts to return pH to normal by increasing minute ventilation should be avoided, as this carries the risk of increasing dynamic hyperinflation. When reduction of dynamic hyperinflation is an issue and provided that intracranial hypertension and overt haemodynamic instability do not exist, acceptance of some acidaemia (pH >7.2) may be reasonable [60].

MANAGING RESPIRATORY FAILURE

The management of respiratory failure in COPD is very similar to that used to treat exacerbations of COPD without respiratory failure, but much more attention must be paid to the preservation of appropriate and safe gas exchange (Figure 4.4) [55, 61]. Reduction of airflow resistance is a crucial medical aim in acute respiratory failure because any improvement in airway patency not only reduces the work of breathing, but also diminishes dynamic hyperinflation, reduces PEEPi (i.e. the inspiratory threshold load), and improves the respiratory muscle operational length and geometrical arrangement and hence their force-generating capacity.

The first objective should be to treat the identified precipitating factors, such as respiratory infections or coexisting pulmonary oedema. Then, it is necessary to reverse the impairment in lung mechanics, which is the most common precipitating factor for respiratory failure in COPD. Finally, gas exchange itself must be supported. This is achieved by a treatment with inhaled bronchodilators, low-flow supplemental oxygen, antibiotics and systemic corticosteroids [4, 55, 62, 63]. It is rather easy to adequately oxygenate patients with acute respiratory failure due to COPD, even though one should be aware that there is a major risk of precipitating CO₂ retention and generating significant acidosis. It becomes a significant risk when the inspired oxygen concentration exceeds about 30% [55]. Supplemental oxygen can be safely administered via a venturi-based facemask or through nasal cannulae. The inspired oxygen concentration is less precisely controlled when cannulae are used [64], but they are perhaps more suitable for patients. Three randomised controlled trials indicate that, in both outpatients and inpatients, the severity of the episode of acute exacerbation of COPD is reduced by treatment with oral corticosteroids compared with placebo [65–67]. The improvement of lung function is more rapid and the duration of hospitalisation appears to be shorter.

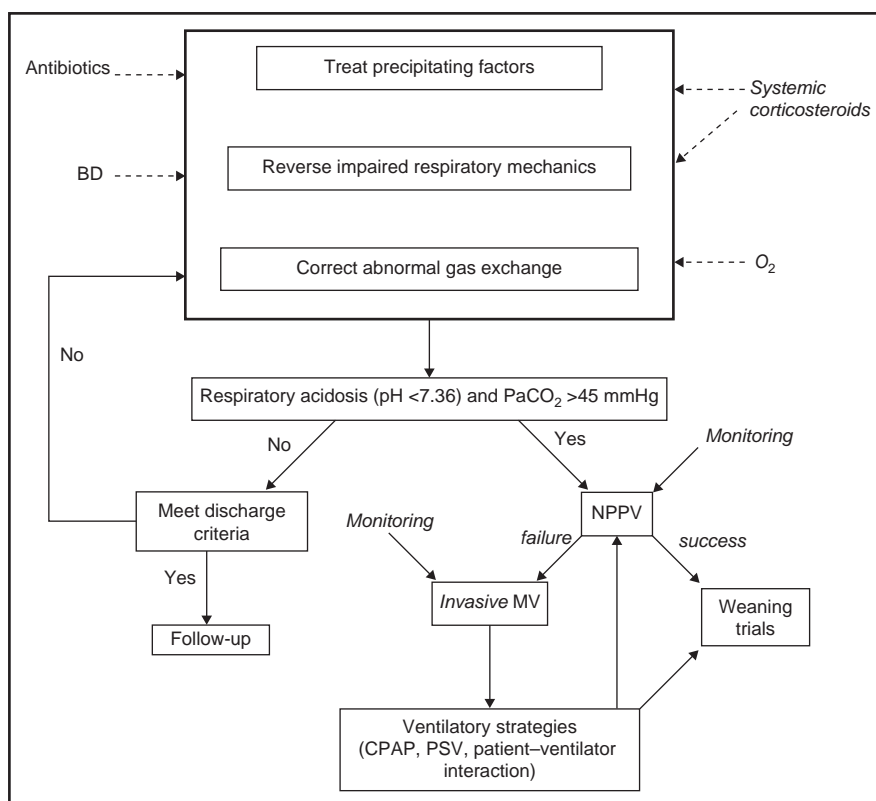


Figure 4.4 Flowchart for management of respiratory failure. BD = bronchodilators; MV = mechanical ventilation; CPAP = continuous positive airway pressure; PSV = pressure support ventilation.

For severe exacerbations characterised by respiratory acidosis and hypercapnia, in cases of intubation and invasive ventilation, effective strategies aim to improve patient-ventilator interaction and reduce the adverse consequences of PEEP_i [56, 62, 63]. If hyperinflation is present, PEEP_i has to be offset first. Low levels of external PEEP could be of some benefit, in order to counterbalance PEEP_i and reduce the amount of a patient's inspiratory effort during assist/control mechanical ventilation [59]. The level of PEEP can vary among patients and individual monitoring of respiratory mechanics is required to prevent excessive increases in lung volume and hence a higher risk of barotrauma. Although intubated patients have the worst prognosis, the vast majority of them can be successfully weaned from mechanical ventilation.

Many studies confirmed the beneficial use of non-invasive positive pressure ventilation (NPPV) [19, 68–72]. The important role of NPPV in managing episodes of respiratory failure is fully discussed elsewhere in this book.

SUMMARY

Unlike asthma exacerbations, which may be rapidly reversible, the median time to recovery from a COPD exacerbation is 7 days [73]. Recovery time is longer with severe exacerbation and severe exacerbation can cause acute respiratory failure [62]. Acute episodes of

respiratory failure due to exacerbation of COPD account for 5–10% of emergency medical admissions to hospital [74]. The failure of the first-line treatment is a regular reason for referral to ICU.

Although there are no adequately validated variables to determine which cases of exacerbation of COPD will require hospitalisation [62], the diagnosis of respiratory failure is clearer, being based on arterial blood gases values. However, the cut-off values are not rigid and they should simply serve as a reference guide in combination with the history and clinical assessment of the individual patient [2]. Indeed, the choice of effective management should be established with regard to the different blood gas levels and in particular the pH (a low pH is an indicator of a severe and acute deterioration) and PaCO₂ (an increase in which is a hallmark of ventilatory failure), but should also be based largely on the assessment of an experienced clinician.

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5

Effects of acute exacerbations on nutritional and metabolic profile in patients with COPD

E. F. M. Wouters

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) comprises a heterogeneous group of conditions, characterised by chronic airflow limitation and destruction of lung parenchyma and with the clinical manifestations of dyspnoea, cough, sputum production and impaired exercise tolerance. The clinical course of COPD is one of gradual progressive impairment, which may eventually lead to respiratory failure. Periods of relative clinical stability are interrupted by recurrent exacerbations. However, the definition of exacerbation remains imprecise and is generally based on varying combinations of symptoms such as an increase in cough or sputum production, worsening of dyspnoea or changes in sputum purulence [1]. Based on the complexity of the sensation of breathlessness, generally considered as a key symptom during exacerbations, it can be hypothesised that acute exacerbation of COPD (AECOPD) is a heterogeneous condition in the clinical course of COPD. The imprecise pathogenesis related to infectious or non-infectious agents, as well as the wide variation in pathophysiological changes, make it very difficult to approach AECOPD as a unique disease condition.

MUSCLE WASTING IN COPD

Several reports have provided evidence that weight loss negatively affects the prevalence and outcome of acute disease exacerbations. The risk of being hospitalised for an acute exacerbation is increased in patients with a low body mass index (BMI) [2]. A low BMI and weight loss have also been reported as unfavourable indexes of outcome during an AECOPD, i.e. predicting the need for mechanical ventilation [3]. Furthermore, the survival time following a disease exacerbation was independently related to the BMI [4]. Early non-elective re-admission of COPD patients with exacerbations has also been found to be associated with weight loss during prior hospitalisation and low body weight on prior admission for an acute exacerbation [5]. Therefore, it is important to systematically review the nutritional and metabolic effects of acute exacerbations. Different metabolic alterations during acute exacerbations can contribute to weight loss and wasting of body cell mass: disturbances in energy metabolism, protein disturbances or possible effects on muscle cell turnover.

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DISTURBANCES IN ENERGY BALANCE

Changes in body weight under chronic conditions such as COPD can be approached by considering alterations in energy metabolism.

Weight loss, in particular loss of fat mass (FM), occurs if energy expenditure (EE) exceeds dietary intake. Total daily energy expenditure is usually divided into three components:

1. Resting energy expenditure (REE), comprising sleeping metabolic rate and the energy cost of arousal;
2. Diet-induced thermogenesis; and
3. Physical activity-induced thermogenesis.

Several studies have reported increases in REE in patients with COPD after adjustment for the metabolically active fat free mass (FFM). REE was found to be elevated in 25% of patients with COPD [6]. Increasing evidence is present in literature to indicate that this increase in REE is related to the level of systemic inflammation [7, 8]. Ngyuen reported a significant relationship between REE and plasma levels of tumour necrosis factor-alpha (TNF- α). This polypeptide also triggers the release of other cytokines that mediate an increase in energy expenditure, as well as mobilisation of amino acids and muscle protein catabolism. Otherwise, changes in total daily energy expenditure seem to be highly related to the energy expended in the activities of patients suffering from COPD [9].

During acute exacerbations, a temporary increase in metabolic rate has been reported (Figure 5.1) [10]. Remarkably, the improvement in energy balance during treatment of the acute exacerbation was accompanied by a significant improvement in symptoms such as dyspnoea and fatigue (Figure 5.2) [10].

In the same study, dietary intake was significantly lower than habitual intake and during the initial phase of the exacerbation, a negative energy balance was present. These temporary disturbances in the energy balance during an acute exacerbation were related to increased leptin concentrations as well as to the systemic inflammatory response (Figure 5.3) [11].

It was found that the elevated leptin concentrations during exacerbations were in turn under control of the systemic inflammatory response and, presumably, the high-dose systemic glucocorticoid treatment. Leptin is a hormone produced by the adipose tissue and its circulating concentrations are proportional to the amount of fat mass. Leptin regulates the energy balance in a feedback mechanism in which the hypothalamus is involved [12]. In animals, administration of leptin results in a reduction in food intake [13] as well as an increase in energy expenditure [14]. The normal leptin feedback mechanism can be disturbed by several factors. In animals, administration of endotoxin, TNF- α or interleukin-1, inflammatory cytokines known for their anorectic effects, resulted (dose-dependently) in an upregulation of leptin messenger ribonucleic acid (mRNA) in fat cells and in an increase in circulating leptin concentrations [15, 16]. Glucocorticosteroids stimulate leptin production directly or via the induction of insulin resistance, since glucose and insulin are also able to induce leptin expression [17–19]. In addition to its function in weight homeostasis, leptin may also play a role in immunoregulation and ventilatory control [20, 21]. Whether these additional functions of leptin play a role during acute exacerbations of the disease deserves further attention.

Recent studies suggest that hyperleptinaemia may play a role in cardiovascular diseases including atherosclerosis. Leptin exerts many potentially atherogenic effects such as induction of endothelial dysfunction, stimulation of inflammatory reaction, oxidative stress, decrease in paraoxonase activity, platelet aggregation and migration, and the hypertrophy and proliferation of vascular smooth muscle cells. Leptin-deficient and leptin receptor-deficient mice are protected from arterial thrombosis and neointimal hyperplasia in response to arterial wall injury. Several clinical studies have demonstrated that a high leptin level

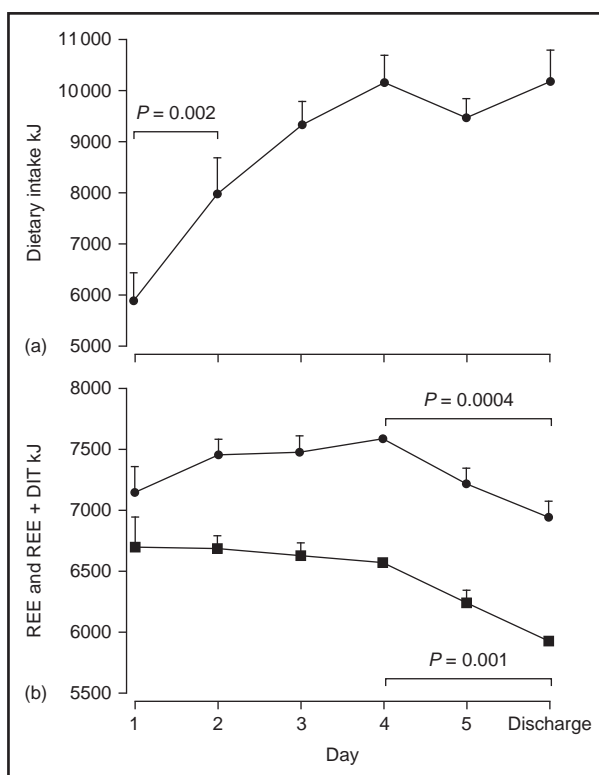


Figure 5.1 (a) Daily course of dietary intake; (b) daily course of measured resting energy expenditure (REE) (■) and REE+diet-induced thermogenesis (DIT) (●) during hospitalisation in 9 patients with COPD. Results are mean \pm SEM.

predicts acute cardiovascular events, restenosis after coronary angioplasty and cerebral stroke independently of traditional risk factors. In addition, plasma leptin correlates with markers of subclinical atherosclerosis such as carotid artery intima thickness and coronary artery calcifications [22]. Further studies are needed to explore the role of leptin and other adipokines in the pathogenesis of cardiovascular events in COPD, particularly when related to episodes of acute exacerbations.

DISTURBANCES IN PROTEIN METABOLISM

The ability to maintain homeostatic regulation of metabolic processes is key to the survival of living organisms. Whilst the regulation of energy balance in relation to weight loss has been extensively explored in COPD, the investigation of intermediary metabolism is in its infancy. Protein turnover refers to a dynamic flux in protein metabolism whereby proteins are degraded and synthesized simultaneously. Protein turnover rates may differ considerably depending on function and specific need. Recently, substantial changes in whole body protein metabolism after overnight fasting were reported in a group of clinically- and weight-stable COPD patients. Significantly, elevated levels of whole body protein synthesis and breakdown were found [23], indicating a disease-related increase in whole body protein turnover. Elevated levels for whole body protein turnover were also found in other chronic

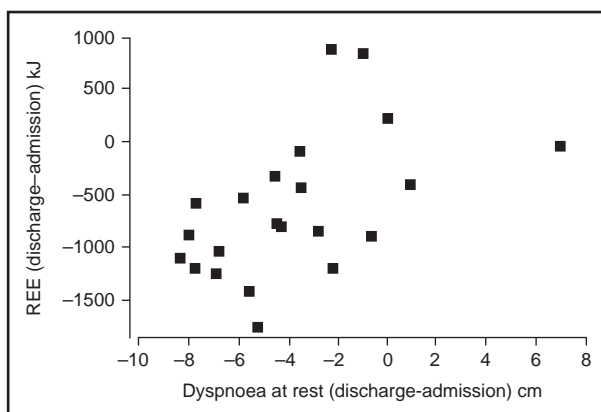


Figure 5.2 A significant relationship between the changes in resting energy expenditure (REE) and dyspnoea sensation during the total hospitalisation period ($r = 0.52$; $P = 0.004$).

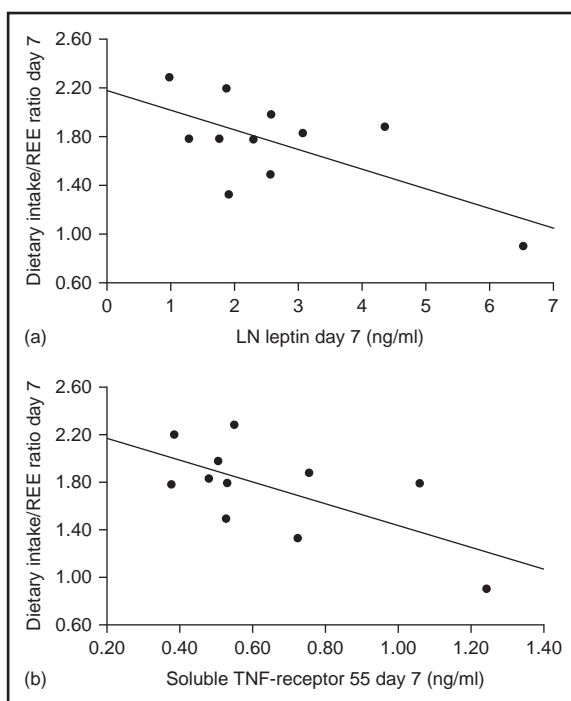


Figure 5.3 Scatterplot of the dietary intake/resting energy expenditure ratio against the natural logarithm of plasma leptin (a) and against plasma-soluble TNF-receptor 55 (b) at day 7 of an acute exacerbation of COPD. Correlation coefficients after adjusting for the influences of sex, age, and fat mass (as a percentage of body weight) are -0.74 ($P = 0.037$) and -0.93 ($P = 0.001$) respectively.

wasting diseases like cancer, human immunodeficiency virus (HIV) infection and advanced chronic renal failure [24–26].

Weight loss and muscle wasting during an exacerbation has to be considered as a complex process, being the consequence of changes in the control of intermediary metabolism.

Protein metabolism in disease states is regulated by various factors that, amongst other things, influence intermediary metabolism. The individual effects of several disease characteristics on intermediary metabolism have been investigated in healthy subjects and in other wasting conditions and are possibly also involved in COPD patients during acute phases of the disease process.

FACTORS ACCELERATING PROTEIN TURNOVER IN COPD

INCREASED INFLAMMATORY RESPONSE

COPD is characterised by the presence of a chronic low-grade systemic inflammatory response [11, 27–29]. Previous studies in other chronic wasting diseases showed that an acute inflammatory condition accelerates protein turnover [24, 30]. Evoked in inflammatory conditions, the acute phase response includes hepatic synthesis of large quantities of proteins with a wide variety of functions. This is an energy-intensive process requiring large quantities of essential amino acids. The need for essential amino acids may drive the loss of skeletal muscle. In line with this, an inverse relationship between the acute phase protein level and the total sum of plasma amino acid levels in stable patients with COPD has been reported [31], suggesting that the elevated protein turnover in COPD may also be mediated by an activation of the cytokine network. It is likely that the increased inflammatory state associated with an exacerbation of COPD further accelerates protein turnover in these patients.

INTRACELLULAR PROTEIN DEGRADATION

The provision of the essential amino acids required for protein synthesis and energy metabolism requires the overall breakdown of cell proteins, especially in the muscles. Mammalian cells contain multiple proteolytic systems that serve distinct functions. However, most cellular proteins are degraded by a multi-enzymatic process, the ubiquitin–proteasome pathway [32]. Degradation of proteins via this multistep pathway requires adenosine triphosphate (ATP) hydrolysis, the protein cofactor ubiquitin, and the 26S proteasome. The proteasome is a very large complex made up of at least 50 subunits, which may comprise as much as 1% of the total cell proteins [33]. Proteins are digested within the central core of the 26S proteasome, the 20S particle, which is a cylindrical complex containing three different proteolytic activities. In most cases, protein substrates are marked for degradation by covalent linkage of a chain of ubiquitin molecules. The ATP-ubiquitin dependent proteolytic system can be activated by different factors: cytokines [32], glucocorticosteroids [34], acidosis [35], inactivity [36] or low insulin levels.

Pro-inflammatory cytokines such as TNF- α and interleukin-6 (IL-6) can activate the ubiquitin–proteasome pathway. In stable COPD patients, muscle wasting was associated with increased serum levels of TNF- α as well as both TNF receptors, IL-6 and soluble IL-6 receptor levels [37].

ACIDOSIS

Respiratory acidosis often accompanies an exacerbation of COPD. Although no studies have been performed examining the effects of respiratory acidosis on intermediary metabolism, the protein metabolic effects of metabolic acidosis have been extensively studied in patients

with chronic renal failure. Acidosis is known to increase degradation of proteins via stimulation of branched-chain amino acid (BCAA) dehydrogenase and to enhance the oxidation of the essential BCAAs [38, 39]. Moreover, acidosis stimulates cortisol secretion, which in itself results in proteolysis. In line with this, correction of acidosis for 4 weeks in haemodialysis patients decreased whole body protein breakdown and synthesis [40].

Glucocorticosteroids are required, together with other signals, for the increase in mRNAs encoding ubiquitin and proteasome subunits and in ubiquitin–protein conjugates in muscles from rats in the fasting state [34, 41]. The chief factor opposing the catabolic effects of glucocorticosteroids is insulin [39]. Activation of muscle proteolysis in the fasting state requires two signals:

1. The presence of glucocorticosteroids; and
2. A decrease in insulin.

In subjects who have an excess of glucocorticosteroids and are not in a fasting state, the high glucocorticoid level overcomes the inhibitory effect of insulin and causes muscle wasting [32]. The catabolic response to acidification also requires glucocorticoids. These negative effects of systemic corticosteroid administration in the management of acute exacerbations are unexplored, yet are based on targeting of the primary organ failure [42].

FACTORS REDUCING PROTEIN TURNOVER IN COPD

HYPOXIA

An acute exacerbation in COPD is often accompanied by arterial hypoxaemia. Hypoxia has been shown to depress the muscle protein synthesis rate in animals and in man: 6 hours of hypoxia (FiO₂ 11%) in rats decreased the muscle protein synthesis rate by 14–17% [43]. In line with this, ischaemia and low flow conditions resulted in reduced protein synthesis in perfused rat hind limb muscle. Protein synthesis (PS) is not the only energy-consuming process (formation of peptide bindings, amino acid transport, RNA turnover): the ubiquitin–proteasome pathway also requires ATP. It is therefore likely that in conditions of decreased ATP availability such as hypoxia, muscle protein turnover is depressed in COPD. However, it remains unclear whether, and to what extent, tissue hypoxia actually occurs during respiratory failure in COPD.

INSULIN RESISTANCE

Insulin has a central role in the regulation of intermediary metabolism. It inhibits glucose production by the liver and kidneys and stimulates peripheral glucose disposal. Previous longitudinal and cross-sectional studies found increased fasting insulin levels and a decreased fasting glucose/insulin ratio in stable COPD patients [44]. Insulin resistance seems to be at the basis of this metabolic disturbance, although available data in COPD are not always consistent [45–47].

Insulin resistance also seems to be present during an exacerbation of COPD, based on the high insulin concentrations found and a temporary increase in glucose concentration [48]. A significant correlation was found between glucose and sTNF-R55 in patients with COPD on day seven of an acute exacerbation [11]. TNF- α is also known for its role in insulin resistance [39]. In addition, the kinetics of glucose and insulin response during the exacerbation may (partly) be related to the ‘tapering off’ of systemic prednisolone treatment. An enhanced chronic and acute inflammatory state and glucocorticosteroid treatment will therefore enhance peripheral insulin resistance in chronic wasting diseases such as COPD. In contrast, hypoxia is known to influence glucose metabolism by increasing glucose production and stimulating peripheral glucose transport, even in insulin-resistant human skeletal muscle. In

healthy subjects, basal glucose production is almost twice as high at chronic high altitude exposure as at sea level. This suggests that the balance between factors positively and negatively influencing insulin sensitivity in COPD will determine its effect on intermediary metabolism.

It is not well understood whether insulin resistance regarding glucose metabolism also extends to the antiproteolytic effect of this hormone. Recently, an association was found between insulin levels and skeletal muscle amino acid status and in particular that of the BCAAs in COPD [44]. Other studies examining the relationship between insulin and leucine metabolism have also indicated that hyperinsulinaemia may negatively influence amino acid and thus protein metabolism. It is therefore possible that insulin resistance, not only at the glucose level, but also at the protein level, may contribute to a loss of muscle mass in COPD.

CORTICOSTEROID THERAPY

Glucocorticosteroids are often used in the treatment of an acute exacerbation of COPD [42]. In Crohn's disease, corticosteroid use for 4 days resulted in decreased values for whole body PS and protein breakdown (PB) [49]. In contrast, in the same disease, corticosteroid use for 7 days resulted in an increase in whole body PS and PB [50]. In the muscle of rheumatoid arthritis patients, negative effects have been shown on PS only. Skeletal muscle protein synthesis was reduced when comparing a group of rheumatoid arthritis patients using 8 mg prednisolone/day for 9 years versus a group who were not using corticosteroids [51].

PHYSICAL INACTIVITY

The protracted decrease in muscle activity that accompanies bed rest is associated with muscle atrophy, weakness and a loss of body nitrogen. Prolonged (14 days) bed rest showed a 50% decrease in skeletal muscle protein synthesis as measured by the arteriovenous flux model based on infusion of tracer as well as by fractional synthetic rate based on tracer incorporation into muscle protein [52]. These results indicate that the loss of body protein with physical inactivity is predominantly due to a decrease in protein synthesis and that this decrease was reflected in whole body measures.

DEPRESSED DIETARY (PROTEIN) INTAKE

An impaired energy balance in patients with COPD was reported during the first days of an acute exacerbation of their disease, predominantly due to severely depressed dietary intake [11]. A depressed dietary (protein) intake is known to negatively influence protein balance. A study by Motil showed that reduced or absent protein intake (short-term starvation) resulted in a sharp reduction in whole body and muscle protein breakdown [53]. Changes in protein synthesis are less reliable.

In conclusion, the pathogenesis of protein wasting during an acute exacerbation of COPD is multifactorially determined (Figure 5.4). Whereas at the molecular level, protein synthesis and degradation appear to be regulated by independent factors and mechanisms, the flux rates of free amino acids to protein synthesis and from protein degradation *in vivo* appear strictly related and changes in the opposite direction are very rare. However, a small difference between the rates of protein synthesis and breakdown determines protein accretion or loss.

The inflammatory condition that evokes an acute phase response is an important stressor increasing protein degradation in muscle during an acute exacerbation of COPD. It can be hypothesised that acute high-grade inflammation may negatively influence the balance

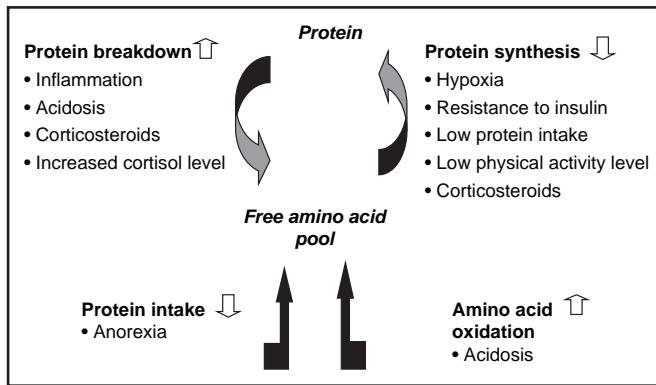


Figure 5.4 Factors contributing to disturbed protein turnover during an acute exacerbation of COPD.

between anabolic and catabolic responses at least partly through insulin resistance. Stressors like acidosis and increased cortisol secretion may further aggravate the acceleration in protein turnover.

A reduced protein-energy intake due to anorexia is likely to be the most common pathophysiological mechanism leading to decreased protein turnover. Other slow protein turnover conditions include low physical activity and insulin resistance. The presence of tissue hypoxia and insulin resistance and its modulating role in intermediary metabolism in conditions such as an acute exacerbation of COPD remains elusive.

Information on the exact contribution of each factor, and insight into the protein metabolic pathways and related mechanisms underlying muscle wasting during an acute exacerbation are warranted in order to improve the efficacy of the current treatment of muscle wasting.

MUSCLE ENERGY METABOLISM AND GAS EXCHANGE DURING AECOPD

Hypoxaemia is a common finding during acute exacerbations of COPD. The consequences of hypoxaemia and particularly impaired tissue oxygenation in the clinical course of acute exacerbations are poorly documented.

Muscle high-energy phosphate content was analysed in quadriceps femoris muscle comparing stable COPD patients to healthy control subjects [54]. Muscle ATP and glycogen levels were lower and muscle creatinine (Cr) and lactate levels were increased in COPD patients. In this study, COPD patients were mildly hypoxaemic (mean PaO_2 7.8kPa). Comparing stable COPD patients with and without chronic respiratory failure [55], lower muscle ATP, PCr and glycogen levels and higher creatine levels were found in patients with chronic respiratory failure. Furthermore, PaO_2 was positively and PaCO_2 negatively related with muscle glycogen and PCr. Another study investigated disturbances in energy metabolism in the resting muscles of patients with stable COPD, and in this study, special attention was paid to the muscle content of inosin monophosphate (IMP), a deamination product of adenosine monophosphate (AMP). IMP formation is thought to reflect an imbalance between resynthesis and utilisation of ATP. The absolute concentrations of high-energy phosphate compounds did not differ between patients and control subjects, but the ATP/ADP (adenosine diphosphate) and the lower phosphocreatinine/creatinine (PCr/Cr) ratio were significantly lower in the patients. IMP was detected in the majority of these stable, slightly hypoxaemic patients. In IMP positive patients particularly, ATP/ADP and PCr/Cr ratios were significantly lower than in IMP negative patients. IMP positive patients were further-

more characterised by a significantly lower diffusing capacity [56]. Muscle energy metabolism during acute exacerbations and the rate of change during recovery have not yet been studied.

The intracellular acidification that accompanies hypercapnia in skeletal muscle cells also affects the energy state of the muscle. It has been proposed that hypercapnia-induced acidosis results in glycolytic enzyme inhibition [57]. Furthermore, it is well known that the creatine kinase reaction is near equilibrium in skeletal muscles [58] and that the equilibrium position of this reaction is pH dependent [59]. Decreases in intracellular pH should therefore result in a significant decrease in PCr levels in intact muscle [60]. Meyer and colleagues [58] clearly demonstrated that the effects of intracellular acidification reflect both the creatine kinase equilibrium as well as the balance between all of the ATPase and ATP synthetase reactions in the cell. They demonstrated that the effect of decreased pH in quiescent slow-twitch muscle is a relative stimulation of ATP synthesis or decrease in ATP hydrolysis rate, resulting in an increase in PCr levels.

Bioenergetics under hypercapnia-induced acidosis seems to be muscle fibre type dependent. Slow oxidative fibres, which have more mitochondria, are stimulated by acidosis [61] and fast fibres, which have fewer mitochondria, are depressed by acidosis [62–65].

The reported findings indicate the need to evaluate the contribution of an imbalance between the utilisation and resynthesis of ATP, particularly in muscles, during periods of acute exacerbation of COPD.

NUTRITIONAL SUPPORT DURING ACUTE EXACERBATIONS

As already discussed, in addition to a disturbed energy balance, COPD patients are at increased risk of negative nitrogen balance during acute exacerbations [66, 67]. The efficacy of nutritional support during a period of negative nitrogen balance in terms of functional improvement depends on whether protein synthesis is decreased or there is accelerated protein breakdown. Protein supplementation will theoretically increase protein synthesis but not affect protein breakdown. During periods of acute protein breakdown, this type of nutritional intervention will therefore not be able to induce a positive protein balance, but could in fact limit the catabolic state. The effectiveness of nutritional intervention during an acute exacerbation of COPD is barely documented. No significant improvement was found in body weight, inspiratory and peripheral muscle strength, but a trend was observed in improvements of well-being scores [66]. Another study investigated the feasibility and effectiveness of oral nutritional supplementation to improve protein and energy intake during hospitalisation for an acute exacerbation, particularly in nutritionally depleted patients with COPD [68]. Interestingly, COPD patients who experienced involuntary weight loss prior to admission for acute exacerbations were characterised by a significantly lower PaO₂. A significant correlation was found between the change in body weight prior to admission and the PaO₂ on admission (Figure 5.5).

Half of the patients reported a decrease in habitual dietary intake prior to admission as well as a decrease in protein intake per kg body weight. The study clearly showed that nutritional supplementation is feasible and is able to increase energy intake, particularly protein intake, in nutritionally depleted COPD patients during hospitalisation for an acute exacerbation. However, no significant differences in body weight gain and functional improvement could be demonstrated between the intervention and the control group. The mean hospital stay of the patients in the study was possibly too short to clearly show the effectiveness of nutritional intervention on functional outcome measures. Therefore, besides optimising nutritional screening and support during hospitalisation, more attention should also be paid to homecare, particular during the first weeks immediately after hospitalisation.

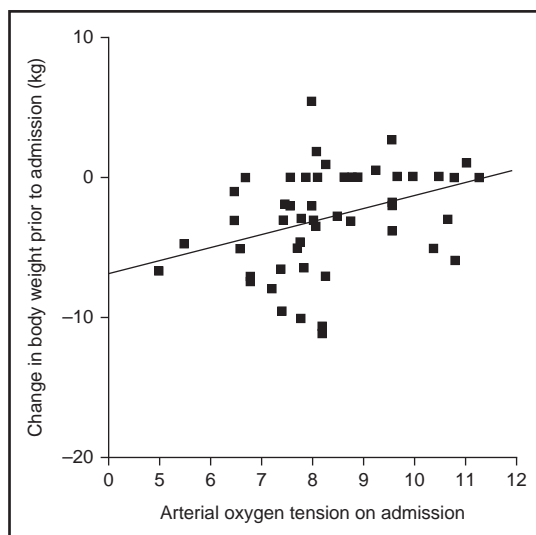


Figure 5.5 The correlation between change in body weight prior to admission and arterial oxygen tension on admission ($r = 0.31$; $P < 0.05$).

SUMMARY

Acute exacerbations of COPD have to be considered as periods of complex inflammatory and metabolic derangement in the normal clinical course of the COPD patient. Gas exchange abnormalities complicating the acute exacerbation can have marked effects on energy and intermediary metabolism, as well as on organ function. A more integrated approach to acute exacerbations may unravel new therapeutic strategies in the management of acute exacerbations of COPD in the future.

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6

Outcomes in exacerbations of COPD

J. A. Murray, D. A. Mahler

INTRODUCTION

The natural history of chronic obstructive pulmonary disease (COPD) is typically one of gradual progression, which is often punctuated by episodic 'flares' or 'attacks'. These exacerbations of COPD (ECOPD) can have a dramatic impact on a variety of outcomes. While the understanding of the nature, causes and consequences of ECOPD has increased greatly in recent years, these advances have largely served to confirm the complex and heterogeneous nature of exacerbations. It has been recognised that patients tend to underestimate the severity and impact of exacerbations of COPD [1, 2]. The outcomes of ECOPD need to be recognised by both patients and the physicians who care for them.

A true understanding of the outcomes of patients who experience an ECOPD is confounded by the fact that there is no universally agreed definition of an exacerbation. Although there are many opinions, consensus as to what defines an exacerbation remains elusive. Typically, patients with COPD report an increase in respiratory symptoms, particularly dyspnoea, sputum purulence and sputum volume [3]. Other symptoms may include cough, wheezing, chest pain and fatigue [4]. Based on a workshop involving experts in COPD, Rodriguez-Roisin [5] proposed the following definition of ECOPD: '*a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD*'. In clinical trials, the definition of a COPD exacerbation usually includes an increase in symptoms for a specific minimal duration that requires treatment with antibiotics, corticosteroids, and/or hospitalisation (i.e. a healthcare utilisation definition). Although various definitions have been used in studies that describe outcomes of ECOPD, a sudden worsening of respiratory symptoms has been a universal requirement.

Describing the outcomes of COPD exacerbations is further confounded by the recognition that nearly 50% of exacerbations may not be reported to physicians [1, 6, 7]. Precious little is known about the outcomes of these unrecognised and untreated episodes. The vast majority of the exacerbations that do come to the attention of a physician are treated in the outpatient clinic or office. A much smaller subset of patients require hospitalisation. Yet, our current understanding about the outcomes of COPD exacerbations relies primarily upon studies of those patients who required hospitalisation for treatment. The reasons for hospital admission in COPD exacerbations are complex, but include severity of underlying disease,

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concurrent comorbidities and failure of outpatient therapy – all features that select for adverse clinical outcomes.

In this review, we describe the major clinical outcomes of an E COPD. These include mortality, lung function, two patient-centred outcomes – health status and symptoms – and a composite index.

MORTALITY

Estimates of the risk of dying from a COPD exacerbation have varied widely. Two of the major difficulties with quantifying mortality from an exacerbation include selection bias and time bias. For example, studies confined to patients that require intensive care unit (ICU) admission and possible invasive mechanical ventilation identify a population with more severe disease and/or a more severe exacerbation. Furthermore, some published studies of mortality with COPD exacerbations date back several decades, to a time when inpatient care, thresholds for hospitalisation, and management of respiratory failure were considerably different [8–11]. Consequently, there is a wide range of published values for in-hospital mortality in patients with COPD who develop an exacerbation.

IN-HOSPITAL MORTALITY

The reported in-hospital mortality rates based on published observational studies are summarised in Table 6.1. Mortality varies considerably as a consequence of the different populations of patients with COPD.

Patil and colleagues [12] performed a cross-sectional study utilising a data set of all hospitalisations from a sample of US hospitals to estimate in-hospital mortality following a COPD exacerbation. An appealing feature of this study is that it is more likely to reflect the mortality risk of the ‘average’ patient admitted to the hospital with a COPD exacerbation in the United States. The study population included over 71 000 patients who were 40 years of age or older and had a diagnosis of an E COPD at discharge. The median length of inpatient stay was five days. Overall, 2.5% of all patients with a COPD exacerbation died in the hospital.

Other studies have reported similar findings for in-hospital mortality due to an E COPD. For example, in an older population (≥ 65 years of age) Cydulka and colleagues [13] reported in-hospital mortality of 5.6% in 131 974 Medicare beneficiaries admitted with a principal diagnosis of COPD. In a cross-sectional study, Iglesia and associates [14] found that 3.9% of 284 patients admitted consecutively with an E COPD died. Connors and colleagues [15] observed an 11% in-hospital mortality rate in a prospective cohort of 1016 patients who were admitted for an exacerbation of COPD. It should be noted, however, that these patients were notably different from an ‘average’ COPD patient, as all had evidence of hypercapnic respiratory failure based on an arterial carbon dioxide tension (PaCO_2) of ≥ 50 mmHg.

Patients who experience respiratory failure and/or require invasive mechanical ventilation have markedly increased mortality rates (Table 6.1). For example, Patil and associates [12] noted that patients who required mechanical ventilation had a much higher mortality rate compared with those who did not require ventilatory support (27.8% vs. 1.7%). This finding is consistent with studies by Seneff and colleagues [16], who reported an in-hospital mortality of 24% among 362 patients who required ICU admission and 31.8% for those who required mechanical ventilation. In a retrospective study, Ai-Ping and co-workers [17] observed a mortality rate of 24.5% for patients admitted to the ICU with an E COPD.

A number of factors have been identified that relate to in-hospital mortality for an E COPD. As reported above, ICU admission and the need for invasive mechanical ventilation have been associated with increased mortality. Various disease parameters that increase in-hospital mortality are hypoxaemia, hypercapnia, longer hospital stay, low peak expiratory flow rates, a history of long-term oxygen use, body mass index and APACHE II scores [14, 18, 19].

Table 6.1 Reported mortality with an exacerbation of COPD (ECOPD)

Reference	Subjects	Inpatient mortality Overall	Mortality after discharge			
			60 day	6 month	1yr	2yr
Ai-Ping [17]	57 pts with ECOPD admitted to ICU	24.5%	–	39%	43%	–
Gunen [18]	205 pts with ECOPD admitted to pulmonary dept	8.3%	–	24%	33%	39%
Iglesia [14]	284 pts with ECOPD admitted to short stay unit	3.9%	–	–	–	–
Patil [12]	71 130 with ECOPD as discharge diagnosis	2.5%	–	–	–	–
Groenewegen [22]	171 pts with ECOPD admitted to pulmonary ward	8%	–	18%	23%	–
Almagro [23]	135 pts with ECOPD admitted to the hospital	–	13%	–	22%	36%
Cydulka [13]	131 974 pts ≥ 65 , COPD as principal diagnosis	5.6%	–	–	–	–
Connors [15]	1016 pts with ECOPD and PaCO ₂ >50mmHg	11%	20%	33%	43%	49%
Seneff [16]	167 pts ≥ 65 , with ECOPD admitted to ICU	–	–	47%	59%	–
Fuso [24]	590 pts with ECOPD, 22% requiring mechanical ventilation	14.4%	–	–	–	–

Patient-related factors that influence in-hospital mortality include advanced age and a higher number of comorbidities. In one study, increased mortality was noted in male patients, those from zip codes with higher reported incomes, patients who had Medicare insurance and patients transferred from another hospital or admitted from emergency departments, long-term care facilities, or law enforcement facilities [12].

In-hospital mortality may also be affected by regional healthcare practices (Table 6.2). There were significant differences in hospital mortality and in the percentage of patients requiring mechanical ventilation based on the geographical region of the hospital (Northeast, Midwest, South and West), the teaching status of the hospital and the hospital location (urban vs. rural) [12]. The concept that in-hospital mortality rates may vary according to regional factors is not unique to the United States. In 1997, the British Thoracic Society/Royal College of Physicians audit of acute hospital care of patients with COPD observed wide variability in mortality between hospitals [20]. A subsequent pilot study suggested that smaller sized hospitals had a higher mortality compared with teaching hospitals and with larger sized hospitals when corrected for various factors [21]. The study also suggested that higher mortality was associated with fewer physicians working at the respective hospitals and with fewer patients under the care of a respiratory specialist.

In summary, it appears that in-hospital mortality is determined by the interaction of multiple factors, some of which are understood, while others remain undefined. The need for ICU admission and/or mechanical ventilation is likely to represent the impact of an exacerbation in those with more advanced COPD and poor ventilatory reserve, comorbidities such

Table 6.2 Mortality outcomes for patients admitted with an exacerbation of COPD stratified by hospital region and hospital teaching status

Outcomes	Hospital region				Teaching status	
	West	South	Midwest	Northeast	Teaching	Non-teaching
In-hospital mortality, %	2.8*	2.2	2.2	3.1	2.9*	2.4
Mortality in those requiring mechanical ventilation, %	22.7*	31.7	22.7	30.0	38.3*	32

**P* <0.001 by χ^2 test for differences in outcome across hospital region and teaching status. Redrawn with permission from [13].

as cardiac disease, as well as host responses. Regional differences and resource availability are also potential factors that contribute to in-hospital mortality.

MORTALITY FOLLOWING HOSPITALISATION

Despite the varied in-patient mortality, the majority of patients with COPD who experience an exacerbation are successfully discharged from the hospital – even those who required ICU admission and/or invasive mechanical ventilation. Several studies have described mortality after different time intervals following discharge from the hospital for an ECOPD. Unfortunately, these reports are clearly susceptible to selection bias. In a prospective study of 171 patients admitted to a single centre with COPD exacerbations over the course of a year, 158 were discharged [22]. After one year of follow-up, approximately 55% had one or more re-admissions during the course of the year and 15% of patients had died.

Connors and colleagues [15] evaluated survival after hospital discharge in over 1000 patients with COPD who required hospitalisation for an acute exacerbation with hypercapnia ($\text{PaCO}_2 > 50$ mmHg) and were followed for a period of up to two years. The mortality rates were 20% at 60 days, 33% at 180 days, 43% at one year and 49% at two years. Moreover, approximately one-half of this population required one or more re-admissions within six months of discharge. The major characteristics of the patients that were associated with death over the six months after discharge were severity of acute illness as determined by acute physiology score, the arterial oxygen tension (PaO_2) : fraction of inspired oxygen (FiO_2) ratio, chronic health status (as determined by age, functional status and comorbid illnesses), nutritional status (as determined by body mass index and albumin level) and the presence of cardiac disease [15].

In a prospective study of 205 consecutive patients hospitalised with exacerbations of COPD (22% of whom required ICU admission) mortality rates were: 24% at six months; 33% at one year; 39% at two years; and 49% at three years [18]. Long-term mortality was associated with lower albumin, lower PaO_2 and lower body mass index. In a more severe population of 167 patients who were ≥ 65 years of age, who were discharged after an admission to the ICU for an ECOPD, mortality was 41% at 90 days, 47% at 180 days, and 59% at one year [16].

Based on these observational studies, it appears that long-term mortality is substantial and is markedly higher for patients who develop respiratory failure and require ICU services. However, it is unclear whether the long-term mortality of those that suffer an exacerbation is different compared with a similar population of patients with COPD who did not experience an exacerbation. These collective studies suggest that age, comorbidities, nutritional status and severity of illness are associated with an increase in mortality after discharge from a hospitalisation for an ECOPD. Not surprisingly, these parameters are similar

to the factors that impact in-hospital mortality and also predict survival in patients with stable COPD [15, 18, 19, 25–27].

The emergency department (ED) is a frequent venue for patients with COPD to seek medical care for an acute exacerbation. The mortality following ED visits for ECOPD has been described, but includes patients who are subsequently admitted to the hospital, as well as those discharged from the ED. It has been shown that approximately 60% of patients with ECOPD presenting to the ED are admitted to the hospital [28]. In a retrospective cohort study, Kim and colleagues [27] described 482 visits to the emergency room by a population ≥ 55 years old with exacerbations of COPD, 62% of whom were subsequently admitted. The sequential mortality was 5% at 30 days, 9% at 60 days, 11% at 90 days, 23% at one year, and 32% at two years. Median follow-up was 3.1 years, at which time 46% of patients had died. On multivariate analysis, independent predictors of mortality included increasing age, the presence of congestive heart failure and hospitalisation for an ECOPD exacerbation during the previous year. The mortality after ED visits reflects, in part, the subsequent mortality in the hospital and/or following discharge.

LUNG FUNCTION

Limited information is available on the changes in lung function associated with an exacerbation of COPD. Although most definitions of an ECOPD refer to worsening of symptoms, in clinical practice the diagnosis and therapy of an ECOPD rarely involve measuring spirometry. However, decrements in lung function are a predictable occurrence during an exacerbation of COPD.

In patients seen in outpatient clinics, emergency departments, or those who require hospitalisation, modest to severe reductions in forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and peak expiratory flow rate (PEFR) have been reported [7, 30–39]. Seemungal and colleagues [1] prospectively followed a cohort of 101 patients with moderate to severe COPD who recorded morning PEFR and changes in respiratory symptoms on diary cards over a period of 2.5 years. Interestingly, the symptoms of the exacerbation developed prior to any decline in lung function. In fact, the changes in lung function were often small, albeit persistent (Figure 6.1). Although 75% of those who experienced an exacerbation recovered lung function at five weeks, 7% of patients did not return to baseline by three months. Patients who had a delayed recovery in PEFR were more likely to have had large declines in lung function and more symptoms at the onset of the exacerbation.

Parker and colleagues [34] evaluated the impact of an ECOPD on lung function in patients referred for an exacerbation from the offices of family physicians and from the emergency department of a tertiary care hospital. In the 12 of 20 subjects considered as ‘symptomatically recovered’, the major improvements in spirometry and lung volume measurements occurred by 14 days and were sustained until the end of the study at day 63 (Figure 6.2, panels (b) and (c)). However, these changes in lung function were not uniform. For example, five of the eight patients who were ‘symptomatically non-recovered’ were too ill to complete the planned physiological testing at the final visit of the study.

Studies by Stevenson and colleagues [35] and Pinto-Plata and associates [36] found modest increments in FEV_1 and in FVC within the first 48 h of treatment of an ECOPD, but a greater improvement in inspiratory capacity (IC) over the initial 2–3 days. By 6–8 weeks after the onset of the exacerbation, additional increases were observed in lung function, although the magnitude of change (absolute and % predicted) was greater for IC than for FVC or FEV_1 [35, 36].

The reasons for incomplete recovery of lung function are not clear, but are a feature of exacerbations that are reported as well as those that go unreported to physicians [1]. Incomplete or delayed recovery may be related to the magnitude of acute deterioration of lung function

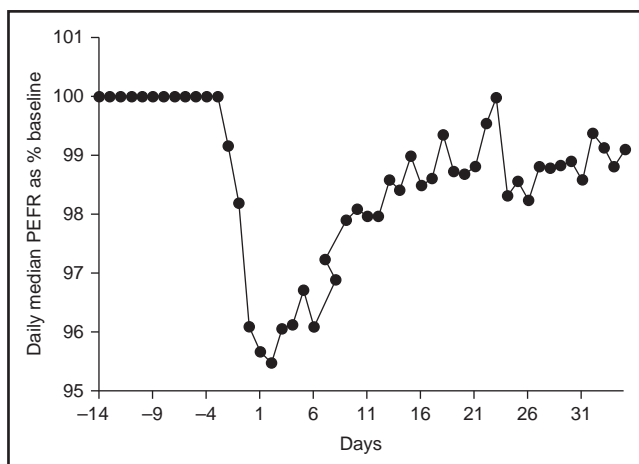


Figure 6.1 Median peak expiratory flow rates (PEFR) expressed as a percentage of baseline peak flow from 14 days prior to and 35 days after onset of an acute exacerbation ($n = 504$ episodes) in 91 patients. The declines in PEFr starting at day 0 were significant ($P < 0.001$) (with permission from [1]).

as well as to the persistence of airway inflammation [1, 36]. Inadequate or delayed treatment may also contribute to the failure of complete recovery of lung function [37].

HEALTH STATUS

Health status is a term used to refer to assessments that quantify the impact of the disease on the health or well-being of a group of patients. This patient-centred outcome is typically quantified by using a respiratory-specific questionnaire that is likely to be more sensitive to small changes than a generic health assessment instrument. Of the various disease-specific instruments that have been validated in patients with COPD, the St George's Respiratory Questionnaire (SGRQ) has been the most widely used in clinical studies evaluating ECOPD. This questionnaire is composed of three components:

1. Symptoms (distress as a result of cough, wheeze, or dyspnoea);
2. Activities (disturbances of activity or mobility); and
3. Impacts (the psychosocial effects of the disease).

HEALTH STATUS AND THE DEVELOPMENT OF AN ECOPD

In general, patients with COPD who have low or poor health status appear to experience more ECOPD. For example, patients with COPD who were in the lowest quartile on the physical function component of the Seattle Obstructive Lung Disease Questionnaire had an odds ratio of hospitalisation for a COPD exacerbation that was five times higher than patients with scores in the highest quartile (Figure 6.3) [40]. In another study in which 70 patients experienced 190 exacerbations over a one-year period, health status, as measured by the SGRQ, was strongly related to the number of exacerbations over the study period, as well as to the number of previous exacerbations [41]. Based on data from the ISOLDE trial, Spencer and co-workers [42] showed that frequent exacerbations were independently associated with a worse baseline SGRQ score ($P < 0.001$) and a more rapid rate of decline in health status ($P < 0.0003$).

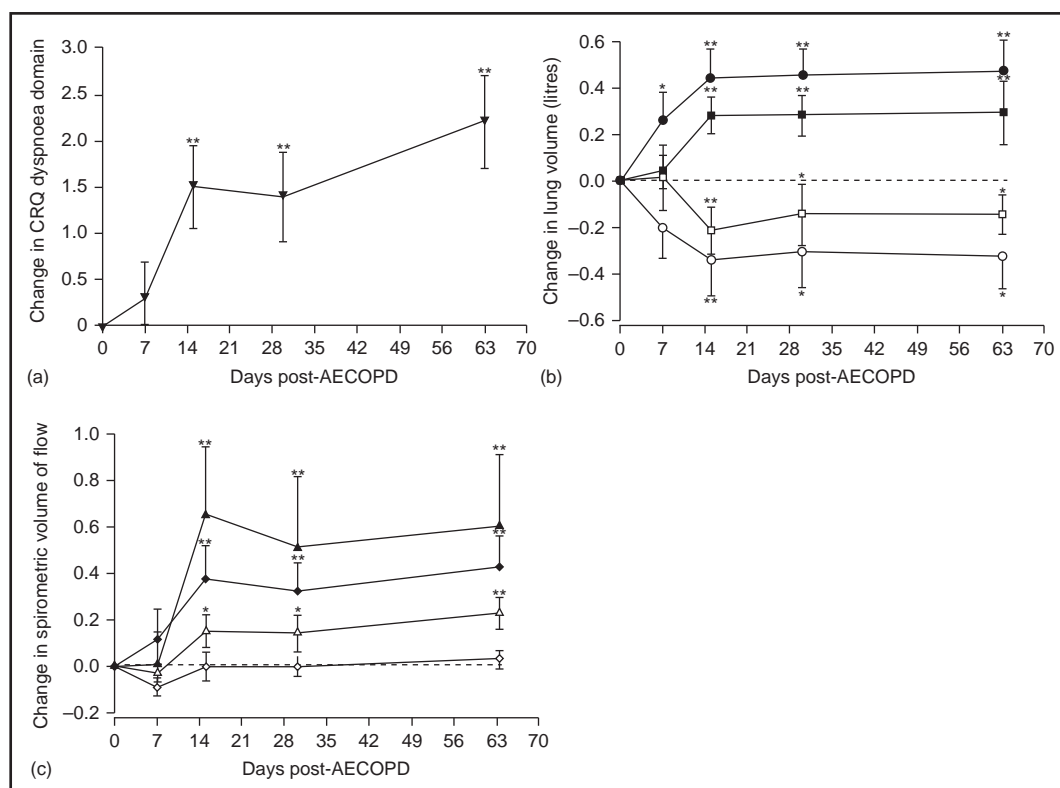


Figure 6.2 Changes in Chronic Respiratory Questionnaire (CRQ) dyspnoea and lung function during recovery from an ECOPD (with permission from [35]). ● = slow vital capacity; ■ = inspiratory capacity; □ = functional residual capacity; ○ = residual volume; ▲ = peak expiratory flow rate; ◆ = forced vital capacity; △ = forced expiratory (data in the subgroup that reached symptom recovery during the study period; $n = 12$, except day 7 data only available in $n = 7$) volume in one second; ◇ = forced mid-expiratory flow. * = $P < 0.05$ significant difference from day 0; ** = $P < 0.01$.

IMPACT OF AN ECOPD ON HEALTH STATUS

The impact of an ECOPD on health status is generally negative. In an observational study, Seemungal and colleagues [41] reported that the total score of the SGRQ was significantly worse in the group of patients who had frequent ($n = 3-8$) compared with those who had infrequent ($n = 0-2$) exacerbations (mean difference = 14.8; $P < 0.001$).

Two studies have reported the recovery of health status with treatment of an exacerbation. Aaron and colleagues [30] studied 66 patients with an ECOPD who presented to the emergency department and were discharged home with 10 days of medical therapy. The 17 patients who had a relapse (defined as an urgent hospital revisit within 10 days because of worsening respiratory symptoms) did not improve health status as measured on the Chronic Respiratory Questionnaire (CRQ). In the 49 patients who did not relapse, there were moderate to large improvements in all four domains of the CRQ. Thus, the majority of outpatients treated for an ECOPD experience significant short-term improvements in health status.

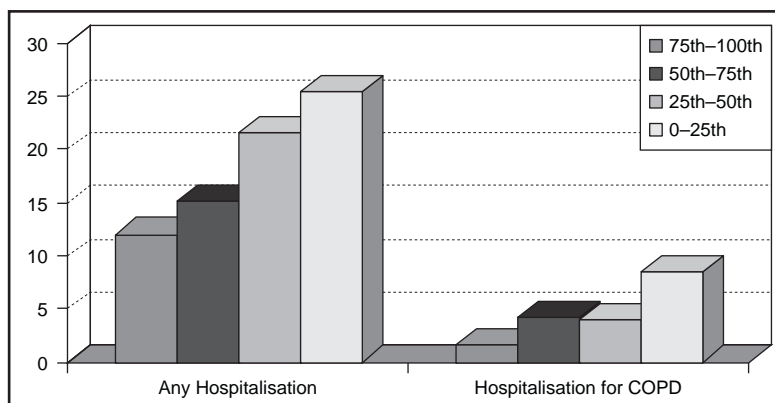


Figure 6.3 Unadjusted hospitalisation rates according to baseline physical function score on the Seattle Obstructive Lung Disease Questionnaire (SOLDQ) (with permission from [40]).

Spencer and Jones [43] described the time course of recovery of health status following an exacerbation of chronic bronchitis in 438 patients with COPD. In general, the greatest improvement in the SGRQ occurred within four weeks of initial presentation followed by a slower phase of recovery over some months (Figure 6.4). The magnitude of recovery in health status was substantial, but only if the patient did not experience another exacerbation. Spencer and Jones [43] also reported that if a subsequent exacerbation occurred within six months, the improvement in health status was usually small. The difference in SGRQ scores between those that suffered a re-exacerbation and those that did not was statistically and clinically significant at four weeks. By six months, the difference in SGRQ total score was over twice that considered to be clinically important.

These studies collectively suggest that an increased frequency of ECOPD appears to be associated with an accelerated decline in health status [30, 41, 43].

SYMPTOMS

As previously described, most definitions of an ECOPD include worsening of symptoms (dyspnoea, sputum purulence and sputum volume). In a telephone survey of 1100 patients identified as having COPD, Miravittles *et al.* [44] found that the major symptoms of an exacerbation that 'had a strong impact on well-being' were: increased cough (42%), increased shortness of breath (37%), fatigue (37%), and increased production of sputum (35%). Perera and associates [38] described an increase in the total symptom score of 5 units using a daily diary at the onset of the exacerbation. Cote and colleagues [39] reported that the modified Medical Research Council (MRC) scale increased by 0.47 units (i.e. patients were more breathless) within 48 h of the onset of symptoms.

A few studies have examined the time course for resolution of symptoms during treatment/recovery from an exacerbation. Seemungal and co-workers [1] found that the median time to recovery of symptoms was six days; however, full recovery of symptoms in patients who presented with increased dyspnoea had not occurred by five weeks.

At least four groups of investigators have examined improvements in dyspnoea with treatment of an ECOPD. Aaron and associates [30] reported that there were substantial improvements in the Transition Dyspnoea Index (TDI) score ($+2.9 \pm 0.7$; $P = 0.0001$) and in the dyspnoea domain of the CRQ ($+1.3 \pm 0.2$; $P < 0.001$) after 10 days of treatment. Not surprisingly, dyspnoea improved in those patients who did not relapse ($n = 49$) compared with

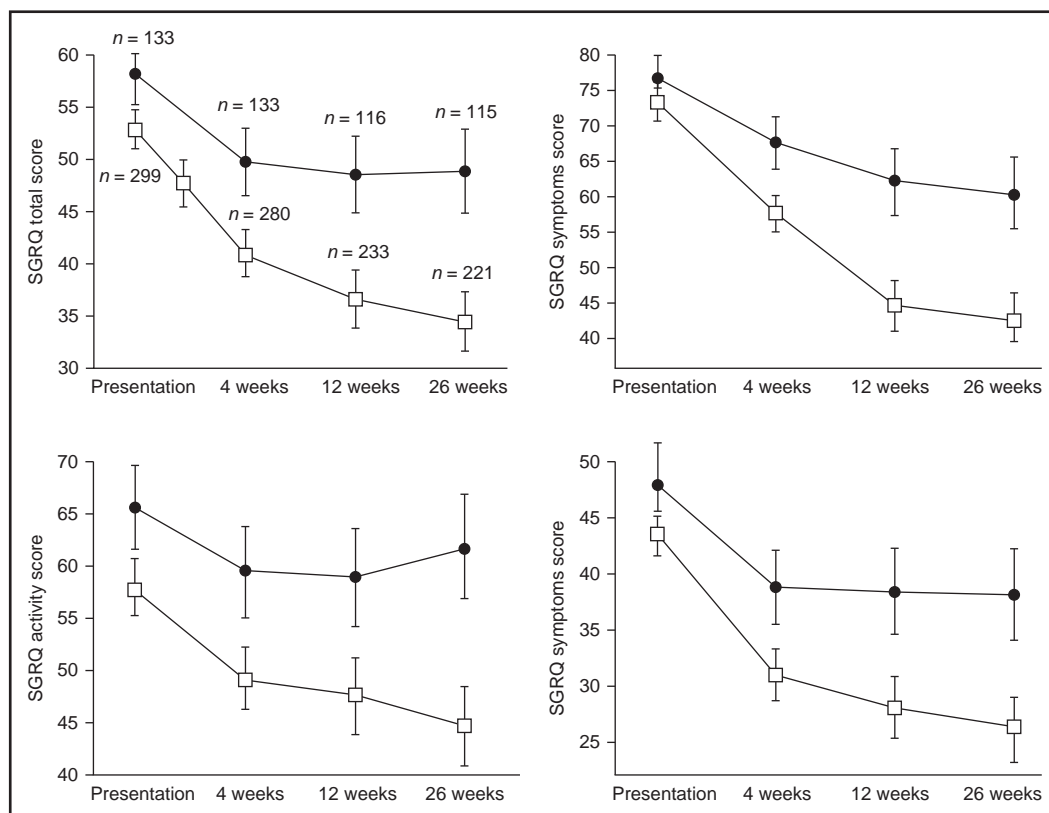


Figure 6.4 Scores on the St George's Respiratory Questionnaire (SGRQ) at different time periods of an exacerbation of COPD. Symbols are mean values and bars indicate 95% confidence intervals in patients with no exacerbation (■) and patients with a further exacerbation during the follow-up period (●). The numbers in the top left figure represent patients remaining in the study at that time point (with permission from [43]).

a worsening of breathlessness in those patients who experienced a relapse ($n = 17$) within the 10 days of the study period.

Parker and colleagues [34] examined both physiological and dyspnoea responses in 20 patients who had an ECOPD and were treated as outpatients. The major improvement in dyspnoea occurred within the first 14 days following the start of treatment and then continued to slowly improve until the last visit (Figure 6.2, panel (a)). For all 20 patients, the TDI improved by $+2.8 \pm 0.8$ ($P < 0.01$), while the dyspnoea domain of the CRQ improved by $+1.6 \pm 0.4$ ($P < 0.01$) at 60 days. However, eight of the 20 patients failed to recover to their pre-exacerbation or baseline levels of dyspnoea during the study. This observation reflects the heterogeneity of the dyspnoea response to therapy when patients with COPD experience an exacerbation. In general, the improvements in dyspnoea were associated with changes in both expiratory flow rates and lung volumes.

Stevenson and colleagues [35] studied patients admitted to the hospital and found that the resting post-bronchodilator breathlessness score on the 0–10 scale by Borg was 3.7 ± 0.3 (range 0.5–7). Although breathlessness at rest decreased by 1.7 ± 0.4 units at discharge for the group, 6 of 22 patients (27%) reported no reduction in resting breathlessness by discharge from the hospital. In patients who improved their breathlessness during hospitalisa-

tion there were significant increases in lung function compared with initial testing, whereas neither FEV₁ nor IC increased significantly in those who did not experience any improvement in dyspnoea. The investigators found that the magnitude of change in breathlessness from admission to discharge or follow-up was unrelated to the change in any parameter of lung function.

In the study by Pinto-Plata and colleagues [36] the 20 patients reported a resting value for breathlessness of 6.8 ± 1.8 on the 0–10 visual analogue scale (VAS) upon admission to the hospital. With treatment, breathlessness improved (i.e. lower scores) to 4.8 ± 2.8 units by 48 h and 2.1 ± 2.3 units at 8 weeks ($P < 0.001$ at both time periods). Interestingly, the changes in breathlessness (Δ VAS) between hospital admission and recovery at eight weeks were significantly correlated with the corresponding changes in FEV₁ ($r = -0.42$), interleukin-6 ($r = 0.61$), and interleukin-8 ($r = 0.56$). The authors proposed that the burst of increased systemic inflammation during the acute event was associated with the physiological changes and contributed to the worsened breathlessness.

COMPOSITE INDEX

The BODE index represents a composite score that includes body mass index, FEV₁ – which reflects the severity of airflow obstruction, dyspnoea as measured by the modified MRC scale, and exercise capacity as reflected by the 6-minute walking distance [27]. In a comparison of patients with COPD who had exacerbations ($n = 130$) and those who did not have an exacerbation ($n = 75$), Cote and colleagues [39] found a worsening of 1.38 units in the BODE index score during the episode. The BODE index score remained above baseline at 1 and 2 years following the onset of the exacerbation.

SUMMARY

All of the clinical consequences of an exacerbation of COPD are undesirable. Patients experience a decline in lung function with an ECOPD that can lead to respiratory distress/failure. There is a significant in-hospital and post-discharge mortality associated with an ECOPD, which is markedly increased among patients who are admitted to the ICU for therapy. More importantly from the perspective of the patient, deterioration occurs in health status and in symptoms, particularly breathlessness, with an exacerbation. Furthermore, the recovery of lung function, health status and dyspnoea following an ECOPD can be significantly prolonged in some patients for reasons that remain unclear at present. The various studies demonstrate considerable heterogeneity in the development and resolution of the outcomes associated with exacerbations.

Haughney and colleagues [45] interviewed patients with moderate to severe COPD in an effort to understand their concerns/experiences during an exacerbation. With the technique of discrete choice modelling, the patient is instructed to select the least preferable situation from paired scenarios that are presented. These data showed that the paramount concerns of patients related to the impact of the exacerbations on their everyday life (20%), the need for medical care (16%), the number of future attacks (12%) and episodes of breathlessness (11%). However, patients most feared being hospitalised, housebound or bedridden; in fact, these issues were more important than symptom improvement.

This review summarizes information about major clinical outcomes associated with ECOPD. Certainly, it is quite challenging for investigators as well as for patients to collect data at the time when patients experience an acute worsening of their respiratory symptoms. It may be difficult for subjects to perform pulmonary function testing and to complete questionnaires at a time when they experience 'a struggle to breathe'. However, it is essential to quantify these outcomes in order to enhance our understanding of an ECOPD and to assess the effectiveness of different treatments.

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7

Antibiotics in the treatment of acute exacerbations of COPD

A. Anzueto

INTRODUCTION

The use of antibiotics in the treatment of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) remains controversial. In this chapter, we will review the aetiology of AECOPD [1]. Many patients with AECOPD may have a combination of viral and bacterial infections and in some circumstances may not be infectious in nature. Bacterial organisms are isolated more commonly after viral infections in patients with chronic obstructive pulmonary disease (COPD). The role that bacterial infections play in AECOPD remains an important area for research [2]. Issues related to antibiotic selection include efficacy, potential benefit [3], clinical parameters to stratify patients' disease severity, different groups of antibiotics that can be used [3] and prevention with vaccination [4]. Other chapters of this book describe the infectious aetiology of AECOPD; airway inflammation; pathophysiology; and the relationship between pharmacokinetics and pharmacodynamics in choosing appropriate antibiotics regimens.

AETIOLOGY

Although respiratory infections are assumed to be the main risk factors for exacerbation of COPD, other factors are also involved [1–3]. Pharmacotherapy, smoking cessation, and pulmonary rehabilitation are all considered helpful in preventing exacerbations [3–5].

During bacterial infection in AECOPD, a variety of microorganisms have been shown to be associated with these exacerbations including *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* [1, 6–8]. It has been described that a minority of these patients have atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, but because of limitations with the diagnosis, the true prevalence of these organisms is not known (Figure 7.1) [9, 10].

Recent studies have demonstrated that patients with the most severe obstructive lung disease have a significantly higher prevalence of Gram-negative organisms such as *Enterobacteriaceae* spp. and *Pseudomonas* spp. [11–13]. One of the first groups of investigators to report these findings was Eller and colleagues [11] who evaluated sputum cultures from 112 inpatients with AECOPD. Sixty-four per cent of patients with a predicted forced expiratory volume in one second (FEV_1) $\leq 35\%$ versus only 30% of those with $FEV_1 \geq 50\%$ ($P = 0.016$) had evidence of the presence of Gram-negative organisms. The most commonly isolated organisms (from patients

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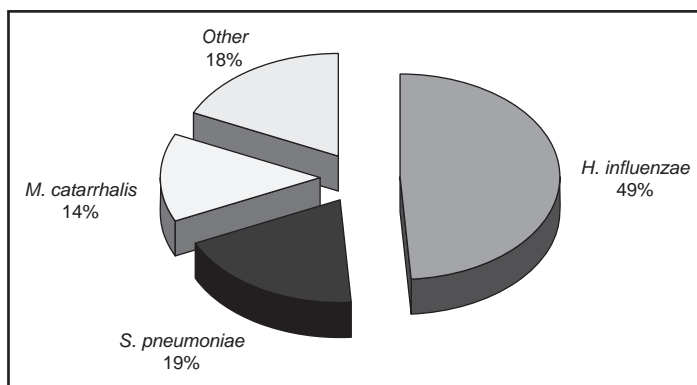


Figure 7.1 Frequent micro-organisms isolated in acute exacerbation of COPD. When sputum is cultured from a patient with chronic bronchitis, bacteria are frequently present, with *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*, being the most commonly recovered pathogens. It is likely that 80% of acute exacerbations of chronic bronchitis (AECB) are infectious in origin, with 40–50% caused by bacteria. Concomitant infections by more than one infectious pathogen appear to occur in 10–20% of patients.

with severe obstructive lung disease) included *Enterobacteriaceae* and *Pseudomonas* spp., *Proteus vulgaris*, *Serratia marcescens*, *Stenotrophomonas maltophilia* and *Escherichia coli*. Miravittles *et al.* [12] recently published a study with similar results that supported these findings. These investigators evaluated the relationship between FEV₁ and the isolation of diverse pathogens in the sputum of 91 patients with COPD who presented with Type 1 (severe) or Type 2 (moderate) symptoms of AECOPD. Patients were separated into groups by FEV₁ ($\geq 50\%$ vs. $< 50\%$ predicted). There were significantly larger numbers of *H. influenzae* and *Pseudomonas aeruginosa* in the group with FEV₁ $< 50\%$ predicted ($P < 0.05$). In contrast, there were significantly larger numbers of potentially non-pathogenic microorganisms in the group with FEV₁ $\geq 50\%$ ($P < 0.05$). These authors also performed a multivariate analysis with logistic regression and found that *H. influenzae* was cultured significantly more commonly in patients who were actively smoking (odds ratio [OR] 8.2; confidence interval [CI] 1.9–43) and whose FEV₁ was $< 50\%$ predicted (OR 6.85; CI 1.6–52). *P. aeruginosa* was also cultured significantly more frequently in those with poor lung function; FEV₁ $< 50\%$ (OR 6.6; CI 1.2–124) (Figure 7.2).

ISSUES RELATED TO ANTIBIOTICS SELECTION

EFFICACY

The specific aetiology of AECOPD is difficult to determine in an outpatient office setting on the basis of symptoms and signs. Sputum studies, although potentially useful, have significant limitations related to the delay in obtaining results, high cost and a lack of sensitivity and specificity. Recent treatment guidelines for AECOPD reflect the lack of evidence-based data to provide specific recommendations for the use of antibiotics [14, 15]. More recently GOLD [3], and ATS/ERS [2] guidelines recommend antibiotic choices on the basis of local sensitivity patterns of the most common pathogens associated with this condition.

There have been a number of clinical trials examining the use of antibiotics in the treatment of AECOPD. Many of the earlier studies showed either no benefit or minimal benefit when antibiotics were prescribed. In 1995, Saint *et al.* [16] published the results of a meta-analysis examining the role of antibiotics in the treatment of AECOPD (Figure 7.3). These investigators analysed nine randomised, placebo-controlled trials published between 1957

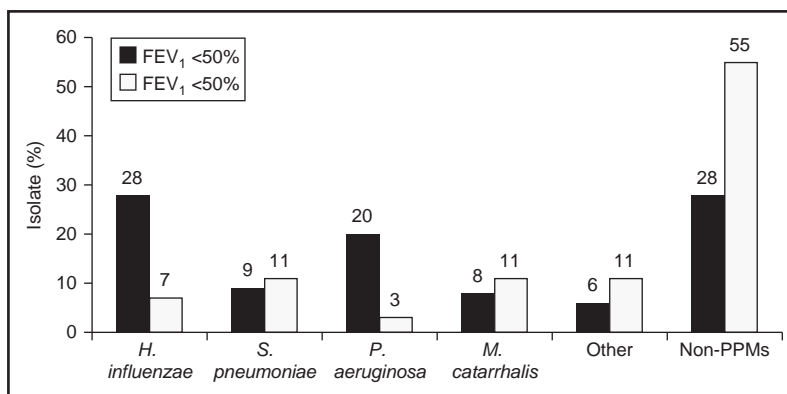


Figure 7.2 The relationship between the pathogens isolated in patients with COPD and the severity of lung function (FEV₁) (with permission from [22]).

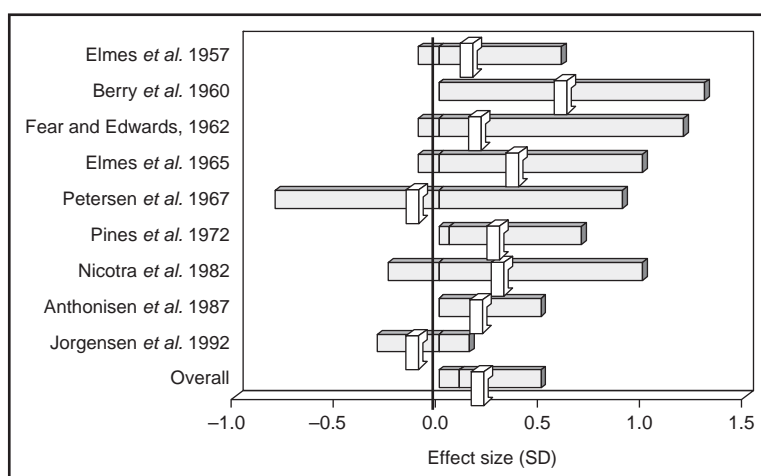


Figure 7.3 Effect sizes (mean differences in outcome / the pooled standard deviation) in nine studies of the use of antibiotics for exacerbations of COPD. Horizontal bars denote 95% confidence intervals. The data indicate a significant improvement due to antibiotic therapy (with permission from [34]).

and 1992. Unfortunately, there was not a single common outcome reported in each of the studies included in this analysis. However, some outcomes that were available for analysis and comparison in many of the studies included:

- The mean number of days of illness;
- The overall symptom score; and
- The changes in peak expiratory flow rate.

Using this form of analysis, there was an overall statistically significant benefit for the antibiotic-treated patients. Analysis of the studies that provided data on expiratory flow rates noted an improvement of 10.75 l/min in the antibiotic-treated groups. The authors concluded that this antibiotic-associated improvement was likely to be clinically significant; particularly in patients with low baseline peak flow rates and limited respiratory reserve.

In 1987, Anthonisen *et al.* [17] reported the results of a large-scale placebo-controlled trial designed to determine the effectiveness of antibiotics in the treatment of AECOPD. In this study, 173 patients with chronic bronchitis were followed for 3.5 years, during which time they had 362 exacerbations. This study finally brought some conformity to the definition of AECOPD and gave the first widely accepted classification for the severity of presenting symptoms. Patients who are classified in the severe range of 'AECOPD' include those with all three clinical symptoms (of increased shortness of breath, increased sputum production and a change in sputum purulence) at initial presentation. The patients were randomised to either antibiotics or placebo in a double-blind, crossover fashion. Three oral antibiotics were used (chosen by the primary physician) for 10 days: amoxicillin, trimethoprim/sulfamethoxazole (co-trimoxazole), and doxycycline. Approximately 40% of all exacerbations were Type 1 (severe), 40% were Type 2 (moderate), and only 20% were Type 3 (mild). Patients with the most severe exacerbations (Type 1) received a significant benefit from antibiotics, whereas there was no significant difference between antibiotic and placebo in patients who had only one of the defined symptoms (Type 3). Overall, the antibiotic-treated patients showed a more rapid improvement in peak flow, a greater percentage of clinical successes and a smaller percentage of clinical failures than those who received placebo. In addition, the length of illness was two days shorter for the antibiotic-treated group. The major criticisms of this study were that no microbiology was performed and that all antibiotics were assumed to be equivalent.

Allegra *et al.* [18] found significant benefit with the use of amoxicillin/clavulanate acid (Augmentin®) therapy compared with placebo in patients with severe disease. Patients who received this antibiotic exhibited a higher success rate (86.4% vs. 50.3% in the placebo group, $P < 0.01$) and a lower frequency of recurrent exacerbations.

POTENTIAL BENEFITS

There are additional potential benefits of antibiotic therapy for patients with AECOPD. Antibiotics can reduce the burden of bacteria in the airway [19]. Bronchoscopic studies, using a sterile protected specimen brush, have demonstrated that approximately 25% of stable COPD patients are colonised (usually $\leq 10^3$ organisms) with potentially pathogenic bacteria [20, 21]. However, a much larger percentage (50–75%) of patients with acute exacerbations have potentially pathogenic microorganisms in addition to significantly higher concentrations (frequently $\geq 10^4$ organisms) of bacteria in the large airways [13, 21–23]. Since treatment with appropriate antibiotics significantly decreases the bacterial burden (and frequently eradicates the organisms that are sensitive) at the 72-hour follow-up bronchoscopy, it is speculated that the proper choice of antibiotic reduces the risk of progression to more severe infections, such as pneumonia. The eradication of bacteria by antibiotics is thought to break the vicious cycle of infection, i.e. lung destruction leading to progression of the lung disease. To demonstrate this issue, Noiura *et al.* [24] published a prospective, randomised, double-blind, placebo-controlled trial evaluating the use of ofloxacin in 90 consecutive patients with AECOPD who required mechanical ventilation. This study demonstrated that significant numbers of patients were infected with Gram-negative organisms (including *E. coli*, *Proteus mirabilis*, and *P. aeruginosa*) in this population with severe AECOPD. In addition to supporting the findings of the previously reported studies, this trial demonstrated that treating these pathogens was important for improving outcomes. The antibiotic-treated group had a significantly lower in-hospital mortality rate (4% vs. 22%; $P = 0.01$) and significantly reduced length of stay in the hospital (14.9 vs. 24.5; $P = 0.01$) compared with the placebo group. In addition, the patients receiving antibiotics were less likely to develop pneumonia than those on placebo, especially during the first week of mechanical ventilation (7.2 ± 2.2 days [range 4–11] vs. 10.6 ± 2.9 days [range 9–14]; $P = 0.04$ by log-rank test) (Figure 7.4).

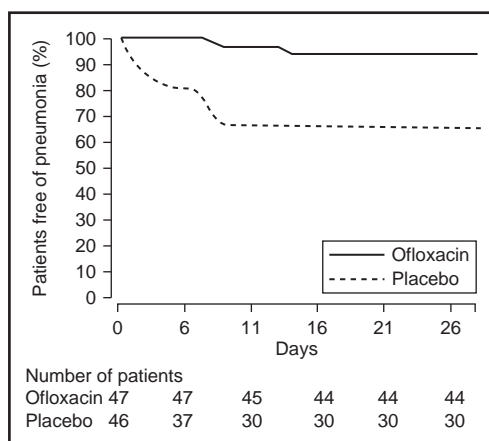


Figure 7.4 Kaplan-Meier survival analysis of pneumonia-free interval comparing patients hospitalised with acute exacerbation of chronic bronchitis and treated with antibiotics or placebo. The risk of developing pneumonia is significantly higher during the first six days after admission in the placebo-treated patients (with permission from [25]).

If the use of antibiotics to treat AECOPD has all of the potential benefits discussed, does it matter which agent is chosen? In Anthonisen's study [17], the assumption was made that all of the antibiotics were equivalent, thus the specific agent prescribed was not considered important. Moreover, most of the recently published antibiotic trials were designed to compare a new antibiotic with an established compound for the purpose of new product registration and licensing. Equivalence is the desired outcome of such trials and therefore the agent chosen for comparison is not considered important. In addition, these trials frequently include patients with poorly defined disease severity (often without any obstructive lung disease) and acute illness of minor severity.

Another problem with interpreting the literature on AECOPD is the large variation in time frame (48 h–28 days) that is used to assess patients for relapse (or the resolution of symptoms). 'Relapse' can most clearly be defined as treatment failure resulting in a return visit due to persistent or worsening symptoms [25]. However, many of these patients do not seek medical care, despite persistent symptoms. The published relapse rates for patients with AECOPD are 17–32% [25–27]. Despite the problems with many of the published antibiotic trials, there are some retrospective trials that emphasise the importance of choosing the correct antibiotic for treatment of patients with AECOPD in order to prevent treatment failures. A recent retrospective study of outpatients with documented COPD, conducted at our institution, evaluated the risk factors for therapy failure at 14 days after an acute exacerbation [27]. The participating patients had a total of 362 exacerbations over an 18-month period. One group received antibiotics (270 visits) and the other group (92 visits) did not. Both groups had similar demographics and severity of underlying COPD. The patients' mean age was 67 ± 10 years (\pm SD), 100% of patients had a >50 pack-per-year smoking history, and 45% were active smokers. Based on the American Thoracic Society's COPD classification, 39% had mild disease, 47% moderate, and 14% severe. The majority (95%) with severe symptoms at presentation (Type 1) received antibiotics versus only 40% with mild symptoms. The overall relapse rate (defined as a return visit with persistent or worsening symptoms within 14 days) was 22%. After an extensive multivariate analysis, the major risk factor for relapse was a lack of antibiotic therapy (32% vs. 19%; $P < 0.001$ compared to the antibiotic-treated group). The type of antibiotic used was also an important variable associated with the 14-day treatment failure. Patients treated with amoxicillin had a 54% relapse

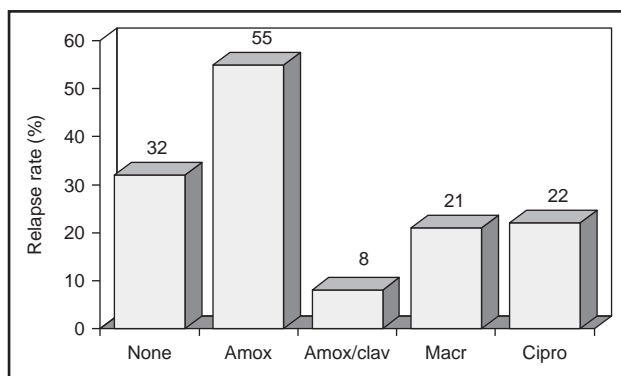


Figure 7.5 Acute exacerbations of chronic obstructive pulmonary disease: 14-day relapse rates after treatment with or without antibiotics and the different types of antibiotics (with permission from [28]).

rate compared with only 13% for the other antibiotics ($P < 0.01$). Furthermore, treatment with amoxicillin resulted in a higher incidence of failure, even when compared with those who did not receive antibiotics ($P = 0.006$) (Figure 7.5). Other variables, such as COPD severity, types of exacerbation, prior or concomitant use of corticosteroids and current use of chronic oxygen therapy were not significantly associated with the 14-day relapse. This study showed that the use of antibiotics was associated with a significantly lower rate of therapy failure. In contrast to Anthonisen's data [17], our data show that antibiotics were beneficial regardless of the severity of AECOPD (i.e. those with mild AECOPD still gained benefit from treatment with antibiotics). Furthermore, the patients who received antibiotics and failed within 14 days had a significantly higher rate of hospital admissions than those who did not receive antibiotics. Although there may be many explanations for these treatment failures, the most likely is that the pathogens were resistant to amoxicillin.

Destache *et al.* [28] reported the impact of antibiotic selection, antimicrobial efficacy and related cost in AECOPD. This study was a retrospective review of 60 outpatients from the pulmonary clinic of a teaching institution who had diagnoses of COPD and chronic bronchitis. The participating patients had a total of 224 episodes of AECOPD requiring antibiotic treatment. The antibiotics were arbitrarily divided into three groups: 'first-line' (amoxicillin, co-trimoxazole, erythromycin and tetracycline), 'second-line' (cephradine, cefuroxime, cefaclor, cefprozil), and 'third-line' (amoxicillin/clavulanate, azithromycin and ciprofloxacin) agents. The failure rates at 14 days were significantly higher for the first-line compared with the third-line agents (19% vs. 7%; $P < 0.05$). When compared with those who received the first-line agents, the patients treated with the third-line agents had significantly longer times between exacerbations (34 weeks vs. 17 weeks; $P < 0.02$), overall fewer hospitalisations (3/26 [12%] vs. 18/26 [69%] patients; $P < 0.02$) and a considerably lower total cost of treatment (\$542 vs. \$942; $P < 0.0001$) (Table 7.1).

Based on the results of these studies in addition to widespread reports of increasing antimicrobial resistance to the common pathogens isolated in patients with AECOPD, appropriate antibiotic selection is extremely important. Therefore, it is not only essential to treat these patients with antibiotics; it is actually critical to choose the appropriate one.

It is important to point out that antibiotics should be used in combination with other therapies including bronchodilators, corticosteroids, supplemental oxygen etc. A recent report by Lindenauer *et al.* [29] evaluated the quality of care provided to patients hospitalised for AECOPD and found in a large cohort of patients that antibiotics were given to 85%, corticosteroids to 85% and bronchodilators to 97%. When the investigators analysed the combination of diagnostic procedures and treatment modalities, a large number of patients

Table 7.1 Differences in characteristics based on antibiotic selection

	<i>First-line</i>	<i>Second-line</i>	<i>Third-line</i>
Days of therapy	8.9 ± 3.3	8.3 ± 2.3	7.5 ± 2.5*
Weeks between AECOPD	17.1 ± 22	22.7 ± 30	34.3 ± 35.5*
14-day failure rate (<i>n</i> = 36)	19%	16%	7%*
Hospitalisations (% of total failures)	53%	14%	8%*
Cost per episode (US\$)	942 ± 2173	563 ± 2296	542 ± 1946
Data are presented in percentages (as indicated) and otherwise in mean ± standard deviation.			
* <i>P</i> ≤ 0.05 third-line versus first-line.			
Adapted with permission from [29].			

(up to 45%) received at least one of the non-recommended therapies, thus only 33% received ideal care.

ENDPOINT FOR THE TREATMENT OF AECOPD

Conventional endpoints for efficacy of antibiotics treatment in AECOPD include the symptoms and bacteriological resolution measured 2–3 weeks after the treatment was started. Most of these endpoints rely solely on the subjective report of symptom improvement. These endpoints have been used for drug registration purposes but lack clinical relevance [30]. It has been suggested by several reports that the infection-free interval (i.e. the time to next episode of AECOPD) may be a more suitable endpoint in this patient population [31–33]. Recently, Wilson *et al.* [34, 35], showed a significant increase in the infection-free interval in patients with AECOPD treated with gemifloxacin, when compared with patients treated using clarithromycin. This endpoint may reflect the ability of the antibiotic to achieve adequate bacteriological eradication of the airway. The study showed that this endpoint was associated with decreased hospitalisation rates, which can be translated into cost savings, improved quality of life and potentially slower progression of the underlying airway obstruction.

CLINICAL PARAMETERS TO STRATIFY PATIENTS INTO RISK GROUPS

Since the morbidity and mortality of AECOPD are high, many investigators have attempted to describe characteristics that could be used to stratify the risk of patients with AECOPD. The clinical parameters that identify high-risk patients with AECOPD include:

1. Older age (>65 years);
2. Severe underlying COPD (FEV₁ <35% predicted);
3. Frequent exacerbations (≥4/year)
4. More severe symptoms at presentation (Type 1 [severe] and Type 2 [moderate]) [17];
5. Comorbidities (especially cardiopulmonary disease, but also congestive heart failure, diabetes mellitus, chronic renal failure and chronic liver disease); and
6. Prolonged history of COPD (>10 years) [2, 3, 7, 8].

Some authors state that many infections in AECOPD are non-invasive or viral and will eventually resolve spontaneously [14, 15]. However, because the costs of treatment failure remain so high, better strategies are needed for the treatment of these exacerbations. Niederman *et al.* [36] reported that age (patients >65 years) and inpatient treatment are the major determinants of the overall cost of AECOPD. The total cost was estimated at \$1.2 billion

Table 7.2 Cost of treatment of acute exacerbation of chronic bronchitis

<i>Age group</i>	<i>Hospital costs (\$US millions)</i>	<i>Outpatient costs (\$US millions)</i>
≥65 years	1141	34
<65 years	408	14
All ages	1549	48

Adapted with permission from [35].

Table 7.3 Patient profiles

<p>Acute bronchitis (Group 1) Healthy people without previous respiratory problems</p> <p>'Simple' chronic bronchitis (Group 2) Age ≤65 years old <i>and</i> <4 exacerbations per year <i>and</i> Minimal or no impairment in pulmonary function <i>and</i> No comorbid conditions</p> <p>'Complicated' chronic bronchitis (Group 3) Age >65 years old <i>or</i> FEV₁ <50% predicted <i>or</i> ≥4 exacerbations per year</p> <p>'Complicated' chronic bronchitis with comorbid illness (Group 4) Above criteria for Group 3, plus: Congestive heart failure <i>or</i> Diabetes <i>or</i> Chronic renal failure <i>or</i> Chronic liver disease <i>or</i> Other chronic disease</p>
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Adapted with permission from [2, 3, 7, 8].

Table 7.4 Our recommendations for antibiotic therapy

<i>Category</i>	<i>Probable pathogen</i>	<i>Oral therapy</i>
Acute bronchitis (Group 1) 'Simple' AECOPD (Group 2)	Viral <i>Haemophilus</i> spp. (<i>H. influenzae</i>) <i>M. catarrhalis</i> , <i>S. pneumoniae</i> , atypical organisms (possibly)	Symptomatic Doxycycline <i>or</i> newer macrolide (azithromycin/clarithromycin) <i>or</i> newer cephalosporins
'Complicated' AECOPD (Groups 3 & 4)	As above, with the possible addition of <i>Pseudomonas</i> spp, <i>Enterobacteriaceae</i> and other Gram-negative organisms	Fluoroquinolones* Amoxicillin-clavulanate

*If at risk for *Pseudomonas* infection, use ciprofloxacin or high-dose levofloxacin.
Adapted with permission from [2, 3, 7, 8].

for the 207 540 inpatients ≥ 65 years old versus only \$452 million for 5.8 million outpatients in the same age group. The mean length of stay was longer and the in-hospital mortality rate was significantly higher for those >65 years of age (Table 7.2). Miravittles *et al.* [36] in Spain estimated that the mean total cost of an acute COPD exacerbation was €140 in a recent study on primary care, the major part being due to hospitalisations, which represented 58% of the total cost followed by the total drug acquisition cost of 32.2%. These costs may not be applicable to other countries because of the differences in reference prices, management practices and healthcare systems; however, if we consider the high prevalence of COPD and the frequency of exacerbations, it is very easy to understand the magnitude of the healthcare burden derived from this disease.

Based on the concept of risk stratification of patients by clinical parameters, a target approach for the treatment of AECOPD has been proposed by different scientific societies [2, 3, 7, 8]. When evaluating patients presenting with symptoms of AECOPD, the clinician should take into consideration the following parameters:

1. Number and severity of acute symptoms;
2. Patient's age;
3. Severity of airflow obstruction (measured by FEV_1);
4. Frequency of exacerbations; and
5. History of comorbid conditions.

Using these characteristics, patients could be stratified into different categories of exacerbations. Acute bronchitis (Group 1) includes healthy people without previous respiratory problems or COPD. 'Simple' AECOPD (Group 2) includes those patients whose age is <65 years, those who have had ≤ 4 exacerbations per year, those with minimal or no impairment in lung function (by pulmonary function tests) **and** those without any comorbid conditions. 'Complicated' AECOPD (Group 3) includes patients older than 65 years, those with $FEV_1 < 50\%$ predicted **or** those with ≥ 4 exacerbations per year. Finally, 'complicated' AECOPD with associated comorbid illnesses (Group 4) includes patients with congestive heart failure, liver disease, diabetes or chronic renal failure (Table 7.3).

CHARACTERISTICS OF THE 'IDEAL' ANTIBIOTIC FOR THE TREATMENT OF AECOPD

Characteristics of the 'ideal' antibiotics that are important to consider when choosing these agents for patients with AECOPD include:

1. Significant activity against the most common pathogens isolated in patients with AECOPD and whether there are substantial gaps in the coverage of these organisms.
2. Adequate coverage of the most likely pathogens in patients with AECOPD based on patient profiles that define the most likely spectrum of aetiological pathogens. As previously described, this is especially important in patients with severe underlying obstructive lung disease, who are more commonly infected with Gram-negative organisms than those with mild COPD. In addition, patients with risk factors for a more complicated course (those in Group 3 ['complicated'] and Group 4 ['complicated' with comorbid conditions]) should be prescribed antibiotics with adequate coverage for the usual pathogens in AECOPD, as well as for Gram-negative organisms. Current recommendations from patient stratification and treatment are summarised in Table 7.4.
3. Susceptibility of the antimicrobial agent to the likely pathogens in AECOPD. There is an increasing prevalence of *H. influenzae* and *M. catarrhalis* that produce bacterial enzymes which inactivate traditional β -lactam antibiotics [37, 38]. In addition, a growing number of these organisms are resistant to many of the antibiotics that are currently available [39]. It is important to know which of the mechanisms of resistance of these agents

are clinically important for the treatment of AECOPD. It is also critical to know the local resistance rates of these microorganisms prior to prescribing a specific antibiotic for therapy.

4. Good penetration into sputum, bronchial mucosa and epithelial lining. The goal of antimicrobial therapy is to deliver the appropriate drug to the specific site of infection. In AECOPD, the bacteria are predominantly found in the airway lumens, along the mucosal cell surfaces and within the mucosal tissue. Various antibiotic classes exhibit markedly different degrees of penetration into the tissues and secretions of the respiratory tract [40, 41]. Although there are no studies that demonstrate that the concentration of antibiotics at one particular intrapulmonary site is better than any other site, the concentrations of antibiotics in sputum, bronchial mucosa, epithelial lining fluid and macrophages are thought to be predictive of clinical efficacy.
5. Easy to take with minimal side effects. In a recent survey, patient compliance was demonstrated to be significantly improved when medications were given once or twice a day, rather than three or more times [42]. In addition, shorter courses of therapy (3–5 days) were associated with better compliance. Of the patients interviewed, >80% stated a preference for once or twice daily dosing and >54% admitted to non-compliance with the prescribed regimen (taking the antibiotic sporadically or not completing the full course).
6. Cost-effective, considering more than just the acquisition cost of the antibiotics. It is clear that multiple factors should be considered when selecting an antibiotic for the treatment of AECOPD, in addition to just the acquisition cost. These other economic endpoints are important when defining the cost-effectiveness of any particular antibiotic, such as (i) the cost of treatment failures (including the need for further antibiotics and the days of lost work); (ii) the amount saved by preventing hospitalisation; (iii) the duration of disease-free intervals; and (iv) the development of antimicrobial resistance. Although there are limited cost-effectiveness data, the importance of these factors is supported by studies previously discussed [28, 35, 36].

INDIVIDUAL ANTIBIOTIC AGENTS

The characteristics described above for selecting the ‘ideal’ antibiotic, are outlined below for each of the major classes of antibiotics prescribed for the treatment of AECOPD.

PENICILLINS

This group of antibiotics was one of the first classes used for treatment of patients with AECOPD. The medications in this class include: amoxicillin and amoxicillin/clavulanate (Augmentin®). Amoxicillin was previously one of the most commonly prescribed antibiotics for AECOPD, but the development of β -lactamase by *H. influenzae* and *M. catarrhalis* currently limits their usefulness. Amoxicillin has been shown to be an effective therapy (in early studies) for those with mild AECOPD; however, it is not currently recommended unless the local resistance rates are monitored closely and are very low [37–39]. Dosing of this agent is 3 or 4 times a day, which also decreases its usefulness due to compliance issues. In contrast, Augmentin® is taken once or twice a day, has a much wider spectrum of activity (including Gram-negative organisms), and is effective against resistant pathogens such as β -lactamase-producing organisms and in high doses in penicillin-resistant *S. pneumoniae*. Augmentin® is recommended for patients with AECOPD in Groups 3 and 4 [3, 7, 8]. The pharmacokinetically enhanced formulation of amoxicillin/clavulanate (2000/125 mg) was designed to achieve high levels of amoxicillin over the dosing duration to eradicate isolates of *S. pneumoniae* with amoxicillin minimum inhibitory concentrations (MICs) $\leq 4 \mu\text{g/ml}$. A recent study showed that

this combination was at least as effective clinically and bacteriologically and was as well tolerated as levofloxacin in the treatment of AECOPD [43]. The uses of higher doses of amoxicillin up to 2 g/day have been shown to be effective against *S. pneumoniae*. The side-effects of these two agents are similar, and primarily involve gastrointestinal symptoms (especially diarrhoea). The acquisition cost of amoxicillin is very low; however, the overall cost is probably much higher in some institutions due to the significant numbers of treatment failures [27].

The currently available preparations are: amoxicillin 500–750 mg tid or qid and Augmentin® 125/500 mg tid or 500/875 mg bid for 10 days; or 1g/500 mg, two tablets twice a day; Augmentin® XL 2000/125 mg once a day.

CEPHALOSPORINS

First generation cephalosporins had relatively poor antibacterial activity against most common pathogens and sub-optimal respiratory pharmacokinetics, although these limitations have been overcome with more recent formulations. Cefuroxime and cefdinir are being used in the management of acute exacerbations of chronic bronchitis (AECB). Newer cephalosporins, mainly cefdinir, have been shown to have improved efficacy and safety.

Available medications in this group include: cefprozil (Cefzil®) 250/500 mg bid for 10 days; cefuroxime axetil (Ceftin®) 250/500 mg bid for 10 days; and cefdinir (Omnicef®) 300 mg for 7 days.

TRIMETHOPRIM/SULFAMETHOXAZOLE

This antibiotic became very popular in the late 1970s, most likely due to enhanced compliance with the twice a day regimen. Many of the early comparison studies against cephalosporins and amoxicillin did not demonstrate any significant differences; however, these trials were performed prior to the marked increases in antimicrobial resistance [5]. Currently, the penicillin-resistant strains of *S. pneumoniae* and β -lactamase-producing *H. influenzae* and *M. catarrhalis* are highly resistant to these drugs [38, 39]. There have also been concerns about the toxicities of trimethoprim/sulfamethoxazole, including acute renal insufficiency and the risk of severe skin reactions, particularly in elderly patients. Because many of the new agents available today have fewer side-effects as well as potentially enhanced activity, there has been a dramatic decline in the usefulness of this compound.

TETRACYCLINE

This group of antibiotics includes a naturally occurring molecule (tetracycline) and semi-synthetic molecules (doxycycline and minocycline). Several of the early studies with tetracycline (performed in the 1960s and 1970s) concluded that these antibiotics were effective in the treatment of AECOPD. However, the more recent studies have shown that tetracycline has poor activity against *H. influenzae* as well as many of the other organisms commonly isolated in these patients [38, 39]. In contrast, doxycycline (Vibramycin® and Doryx®) has been found to be especially active against *M. catarrhalis*, while minocycline is more active against *H. influenzae* and *S. pneumoniae*. Other advantages of these semi-synthetic antibiotics include better oral absorption and a prolonged half-life, which allows for twice-daily dosing [44]. The sputum concentrations are lower for doxycycline than for minocycline. Despite these differences in the pharmacokinetic properties, Maesen *et al.* [45] in a randomised, double-blind prospective study demonstrated that there were no significant differences in the response rates between doxycycline and minocycline in the treatment of AECOPD. The most important limitation to the widespread use of this class of drugs is the increasing emergence of microbial resistance. This class of antibiotics is useful in patients who have allergies to other medications and for treatment of patients in Group 2 ('simple' AECOPD). This class

of antibiotics is not recommended for the treatment of AECB due to a marked increase of bacteria resistant to these antibiotics.

MACROLIDES

Erythromycin, a macrolide derived from *Streptomyces*, inhibits RNA-dependent protein synthesis by reversibly binding to the 50S ribosomal subunit of susceptible microorganisms. Azithromycin and clarithromycin are semi-synthetic derivatives of erythromycin. These 'advanced' macrolides have significantly better tissue penetration and pharmacokinetics as a result of structural modifications [46]. Of the macrolides, erythromycin has the lowest *in vitro* activity against *H. influenzae*, while azithromycin has the highest. Due to the predominance of this organism in AECOPD, erythromycin should not be used to treat this condition. Recently, the Food and Drug Administration (FDA) has approved the use of higher doses of azithromycin and an extended release form of clarithromycin for the treatment of AECOPD. Azithromycin 500 mg for 3 days was shown to be as effective as 500 mg on day one and then 250 mg once a day for 4 days [47]. Extended released clarithromycin (two tablets of 500 mg once a day for 7 days) was as effective as amoxicillin/clavulanate (875/125 mg) twice a day for 10 days [48].

As previously discussed, the rates of antimicrobial resistance, mainly of *S. pneumoniae*, have increased significantly. The patterns of *S. pneumoniae* macrolide resistance are complex and involve at least two mechanisms [49]. One involves an alteration in ribosomal targets (ribosomal methylase [*ermAM*]) of the bacteria, which is known to result in true clinical resistance. The second mechanism is more prevalent (>75%) and involves the organism actively pumping the macrolide out of the cell (macrolide efflux [*mefE*] mutant strains). It is not known if these strains actually result in clinical resistance, since treatment failures are uncommon in patients treated with these macrolides. Gottfried *et al.* [50] found no significant differences in the clinical outcomes of patients at their institution who were infected with macrolide-resistant *S. pneumoniae* compared with macrolide-sensitive strains. In another publication, Gottfried [51] examined several studies involving the eradication rate of *S. pneumoniae* in patients treated for AECOPD. Although approximately 15% of the pneumococcal isolates were resistant to clarithromycin *in vitro*, the bacteriological eradication rate was between 91–93% for the clarithromycin-treated patients. Therefore, the reported increases in the prevalence of *in vitro* resistance of *S. pneumoniae* to these macrolides do not appear to be associated with a proportional rise in the rate of clinical failures.

The dosing of the macrolides varies between the different antibiotics. Erythromycin must be given every 6–8 h (usually for a 10-day course). Azithromycin is given only once a day and is effective with dosing regimens of 3–5 days. Direct comparison of azithromycin (3-day course) and clarithromycin (10-day course) showed no difference in response rate or adverse reactions [52]. A recent study with the new extended release preparation of clarithromycin has been shown to be effective when given once a day for 5–7 days [48].

In general, macrolides are well-tolerated antibiotics. Treatment with erythromycin often results in significant gastrointestinal symptoms including nausea, vomiting, abdominal cramps and diarrhoea. This drug also has significant interaction with drugs that are metabolised in the liver via the P-450 enzyme system [46]. The newer-generation macrolides are better tolerated, have minimal gastrointestinal symptoms and fewer drug interactions. However, clarithromycin has a distinctive taste that is less common with the extended release preparation. Macrolides have also been associated with a prolonged QTc interval, thus the FDA recommends that these antibiotics should not be given to patients receiving class IA or class III anti-arrhythmic agents or in patients with known prolongation of the QTc interval.

Available macrolides to treat AECOPD include: erythromycin 250/500 mg every 6–8 h for 10 days; clarithromycin (Biaxin® and Biaxin XL®) 250/500 mg bid for 10 days, or extended released formulation (XL) 500 mg once a day for 7 days; Azithromycin (Zitromax®) 500 mg on day 1, then 250 mg qd on days 2–5 or 500 mg once a day for 3 days.

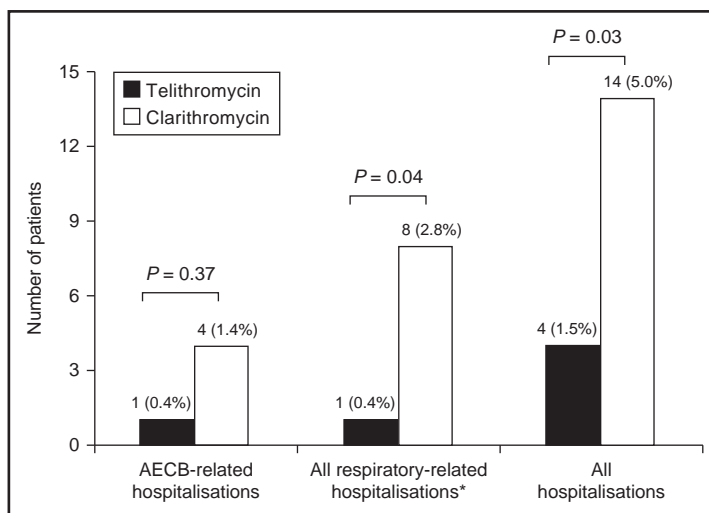


Figure 7.6 Hospital admissions in patients treated with telithromycin 500 mg once a day for 5 days, or clarithromycin 500 mg twice a day for 10 days. *Indicates exacerbation-related hospitalisation and all other respiratory-related hospitalisations (with permission from [60]).

FLUOROQUINOLONES

The fluoroquinolones offer broad-spectrum coverage against the most common organisms related to AECOPD. The more recently developed quinolones have enhanced activities against many Gram-positive species (i.e. *S. pneumoniae*), atypical pathogens (i.e. *C. pneumoniae*, *M. pneumoniae*, and *Legionella pneumophila*) and anaerobes [53]. The quinolones have a unique mechanism of action in that they interfere with bacterial replication by inhibiting enzymes (called topoisomerases) that are responsible for maintaining bacterial DNA supercoiling [54]. Although four types of topoisomerases exist, only two of these are targeted by the quinolones:

1. Topoisomerase IV; and
2. DNA gyrase.

The bactericidal activity against Gram-positive bacteria is primarily a result of the quinolones targeting topoisomerase IV, whereas the activity against Gram-negative organisms involves DNA gyrase [55]. The overall resistance rates of the quinolones have remained low among community-acquired respiratory pathogens, but have increased among nosocomial pathogens. The three known mechanisms involved in the development of quinolone resistance include:

1. Mutational changes in microbial DNA topoisomerases;
2. Selected alterations in bacterial outer membrane proteins; and
3. The development of a highly active efflux system that pumps the antibiotic out of the cell [56].

The fluoroquinolones exhibit concentration-dependent bactericidal activity and clinical outcomes correlate to peak concentrations. The quinolones have important characteristics such as high tissue concentration, including sputum, epithelium lining fluid and bronchial mucosa [57].

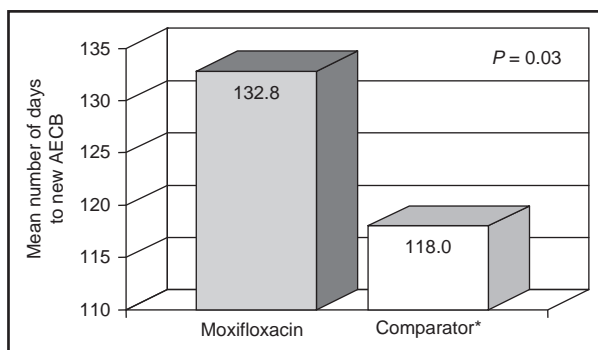


Figure 7.7 MOSAIC study: long-term follow-up assessment. Mean (SD) times to the next AECB were 132.8 (67.5) days and 118.0 (67.9) days for moxifloxacin and comparator, respectively, and the difference was statistically significant ($P = 0.03$) (with permission from [36, 66]).

The efficacy of the quinolones in the treatment of AECB has been demonstrated in multiple clinical trials. Ball *et al.* [56] summarised the early clinical trials comparing individual quinolones with other antibiotics that are frequently used for these lower respiratory tract infections. Several pivotal studies using fluoroquinolones have recently been published. The Gemifloxacin Long-term Outcomes in Bronchitis Exacerbations (GLOBE) trial studied the efficacy and safety of a 5-day course of gemifloxacin (320 mg once daily) compared with a standard 7-day regimen of clarithromycin (500 mg twice daily) in a prospective, randomised, controlled, double-blind study of patients with AECOPD [34]. Clinical success rates were similar for both treatment arms, but bacteriological success rates were higher for gemifloxacin. *H. influenzae* was eradicated from 7/7 gemifloxacin-treated patients versus 3/9 for clarithromycin after one day of therapy. By day six, *H. influenzae* could not be recovered from any gemifloxacin-treated patients but was still present in 1/3 clarithromycin-treated patients. At the 25–38 day follow-up the bacteriological efficacy of gemifloxacin was statistically superior to clarithromycin. During the long-term phase of the study, significantly more patients receiving gemifloxacin (120/169; 71.0%) than clarithromycin (100/171; 58.5%) remained free of AECB recurrences ($P = 0.016$) at the 26-week follow-up. Additionally, the cumulative number of patients hospitalised for respiratory tract infection-related conditions over the 26-week period was lower in the gemifloxacin group (5 patients; 2.3%) compared to the clarithromycin group (14 patients; 6.3%). Wilson *et al.* [35, 57] also reported the short- and long-term outcomes of moxifloxacin compared with standard antibiotic treatment in AECOPD (MOSAIC study). Patients were prospectively randomised (stratified based on corticosteroid use) between moxifloxacin (400 mg/day for 5 days) and standard antibiotic therapy (amoxicillin [500 mg 3 times daily for 7 days], clarithromycin [500 mg twice daily for 7 days] or cefuroxime/axetil [250 mg twice daily for 7 days]). Outpatients with >45 years of stable chronic bronchitis, smoking >20 packs/year, two or more AECOPD in the previous year and $FEV_1 > 85\%$ of predicted value were studied. Patients were enrolled when stable and those exacerbating within 12 months of enrolment were randomised: 354 patients received moxifloxacin and 376 patients standard antibiotic therapy. Clinical success was seen in 83.0–87.6% of patients across treatment arms and populations, with statistical equivalence in all populations except for a significant difference in favour of moxifloxacin in patients not receiving steroids. Cure rates were superior with moxifloxacin. A significantly smaller proportion of patients required additional antimicrobials in the moxifloxacin arm. Time to next exacerbation was longer with moxifloxacin: median and mean times to new AECB in patients who did not require any further antibiotic were 131.0 and 132.8 days for moxifloxacin and 103.5 and 118.0 days for the comparator ($P = 0.03$) (Figure 7.7). Treatment failure, new exac-

erabation or use of any further antibiotic were less frequent in the moxifloxacin group for up to 5 months ($P = 0.03$). Bacteriological eradication was superior with moxifloxacin. These studies demonstrated that fluoroquinolones are superior to standard antibiotic therapy for clinically relevant measures including cure rate, need for additional antimicrobial treatment, greater rates of bacteriologic eradication and longer time to next exacerbation.

The safety and efficacy of short course (3 days) 750 mg levofloxacin for AECB have recently been reported [58]. In this randomised, multicentre, phase 3b study, AECB patients were categorised as uncomplicated (U-AECB) or complicated (C-AECB), based on FEV₁, the presence of medical comorbidities and the frequency of exacerbations per year. U-AECB patients received levofloxacin 750 mg once a day for 3 days or azithromycin 500 mg (day 1) followed by 250 mg once a day for days 2–5. C-AECB patients received levofloxacin 750 mg once a day for 5 days or amoxicillin/clavulanate 875/125 mg bid for 10 days. A total of 763 patients were enrolled (394 U-AECB and 369 C-AECB). Clinical success rates for clinically evaluable patients at post-therapy were similar for both groups. The patients in the C-AECB group treated with levofloxacin showed a significant improvement in their symptoms at the on-therapy visit (3–5 days). Microbiological eradication rates for microbiologically evaluable patients at post-therapy for the levofloxacin group were superior to those of the azithromycin treatment group (94% vs. 83%, respectively; 95% CI –21 and –0.8 respectively) in U-AECB patients and were similar for levofloxacin and amoxicillin/clavulanate (81% vs. 80%; 95% CI –13.9 and 10.7 respectively) in C-AECB patients. The safety profiles for levofloxacin and comparator treatment groups were comparable. These results indicate that levofloxacin 750 mg once a day for 3–5 days is at least as effective and well tolerated as standard regimens of azithromycin and amoxicillin/clavulanate in the treatment of AECB.

In general, the quinolones are well tolerated and have an adverse event rate of approximately 4–5% [59]. These adverse effects, which are generally mild and transient, include rash, dizziness, headache, gastrointestinal disturbances (usually nausea, vomiting, dyspepsia, diarrhoea, abdominal pain, etc.) and minor haematological abnormalities. The gastrointestinal side-effects of the quinolones are usually as severe and as frequent as those associated with macrolides or with amoxicillin/clavulanate. Some drugs that are not available were associated with severe phototoxic reactions, a disturbing metallic taste and liver toxicity. Quinolones have also been associated with a prolonged QTc interval. The FDA recommends that all quinolones be avoided in patients receiving class IA or class III anti-arrhythmic agents, in patients with known prolongation of the QTc interval and in those with uncorrected hypokalaemia [60]. Recent clinical trials have demonstrated the cardiac safety of fluoroquinolones [61].

Drug interactions of quinolones include a reduction in gastrointestinal absorption by medications that contain multivalent cations (e.g. antacids containing magnesium or aluminium, sucralfate, iron, zinc and calcium). These agents should therefore be dosed at least 2–4 h before or after the administration of the antibiotics [62]. Some of the quinolone preparations can interact with medications that are metabolised by the hepatic cytochrome P-450 system.

Available drugs from this group include: ciprofloxacin (Cipro®) 500/750 mg twice a day for 10 days, levofloxacin (Levaquin®) 500 mg (once a day or twice a day in some countries) for 10 days; 750 mg once a day for 3 days for patients with uncomplicated exacerbation and 750 mg once a day for 5 days for patients with complicated exacerbations; gemifloxacin (Factive®) 320 mg once a day for 5 days; moxifloxacin (Avelox®) 400 mg once a day for 5 days.

SPECIFIC ANTIBIOTIC RECOMMENDATIONS

The recommendations for antibiotic therapy are summarised in Table 7.4. Acute tracheo-bronchitis in patients without underlying lung disease should be managed with symptom-

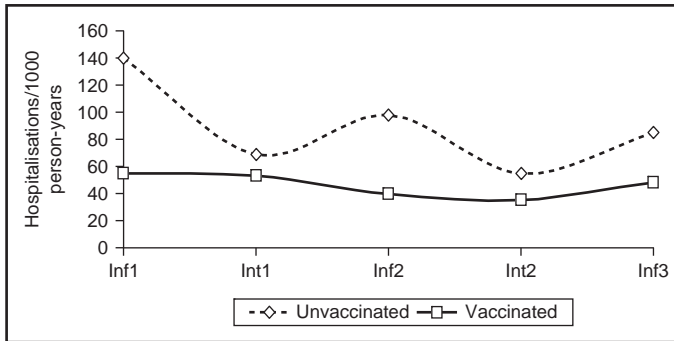


Figure 7.8 Observed annualised rates of hospitalisation for pneumonia and influenza among vaccinated and unvaccinated persons for each study period (with permission from [64]).

atic therapy (decongestants, antihistamines and pain relievers). If the symptoms persist, acute sinus infection or *Mycoplasma* infection may be present.

In patients with 'uncomplicated' COPD, the infection is produced by the core organisms. The use of so-called first-line antibiotics including aminopenicillins (amoxicillin/ampicillin) can no longer be recommended due to the increasing prevalence of bacterial resistance to these antibiotics. Pneumococcal resistance and side-effects are of concern with the use of trimethoprim/sulphamethoxazole. Antibiotics such as new generation macrolides (azithromycin, alarithromycin), newer cephalosporins (cefzil [Omnicef®], cefuroxime axetil [Ceftin®], loracarbef [Lorabid®]) or fluoroquinolones are preferred.

In patients with 'complicated' COPD, clinical data support the use of fluoroquinolones. High-dose amoxicillin/clavulanate acid and telithromycin are recommended in patients who cannot tolerate fluoroquinolones. Patients at risk for *P. aeruginosa* infection should be treated with high-dose levofloxacin or ciprofloxacin or parenteral therapy with a β -lactamase inhibitor or anti-pseudomonas penicillin.

PREVENTION

The two most important prevention measures are smoking cessation and active immunisations, including influenza and pneumococcal vaccinations. Active smoking cessation should be included in the therapy of these patients. Influenza is an important cause of lower respiratory tract infections. Influenza A and B often reach epidemic proportions during the winter months. The impact of influenza is critical to the development of other lower respiratory infections including AECOPD and pneumonia. Epidemiological studies have shown that the frequency of lower respiratory infections, their morbidity and mortality are markedly reduced with influenza vaccination [63]. In order to define the effects of influenza and the benefits of influenza vaccination in elderly persons with chronic lung disease, Nichol *et al.* [64] conducted a retrospective, multi-season cohort study in a large managed care organisation. The outcomes in vaccinated and unvaccinated individuals were compared after adjustment for baseline demographics and health characteristics. This study showed that vaccination rates were greater than 70%. In patients not vaccinated, the hospitalisation rates for pneumonia and influenza were twice as high in the influenza season when compared with the non-influenza periods (Figure 7.8). Vaccinated patients had fewer outpatient visits, fewer hospitalisations and fewer deaths. Consequently, the influenza vaccine should be given to patients with COPD.

The polyvalent vaccine based on pneumococcal capsule serotypes has been shown to be effective in preventing pneumococcal bacteraemia and pneumonia [65]. The available 23 serotype vaccine has been shown to have an aggregate efficacy of more than 60%. The efficacy tends to decline with age and the patient's immune state [66]. The vaccine is also recommended in patients with COPD. There are no contraindications for the use of either pneumococcal or influenza vaccine immediately after an episode of pneumonia or an AECOPD. Vaccines can be given simultaneously without affecting their potency. There are no other vaccines available in adults to prevent lower respiratory tract infections. Vaccines intended to prevent infections due to non-typeable *Haemophilus* spp. or *Pseudomonas* spp. are being developed but are not yet available.

SUMMARY

The cost, morbidity and mortality related to AECOPD remain unacceptably high, especially in patients with significant underlying obstructive lung disease. Since those with AECOPD are a heterogeneous group, it is important to risk-stratify them based on clinical parameters and patient demographics. It is also important to administer the appropriate antimicrobial agent at the outset of therapy, so that the risks of treatment failure and the morbidity of AECOPD may be minimised. It is important to point out that antibiotics should be used in combination with other therapies including bronchodilators, corticosteroids and supplemental oxygen.

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8

Antibiotics in COPD: pharmacokinetic/ pharmacodynamic dosing concepts

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INTRODUCTION

As with any treatment, the goal of therapy is to treat the problem and/or its symptoms without causing excessive unwanted side-effects. However, whereas with a disease such as hypertension or hypercholesterolaemia a patient would be prescribed a relatively standard starting dose of an appropriate medication and have the dose titrated to achieve the desired effect over time, this luxury and type of approach is ill-advised and unavailable in the treatment of infectious diseases. Rather, taking a titration approach as is done with other types of medications would produce a much greater likelihood of bacterial resistance development and selection, as well as the potential for clinical failures. That being said, with the increasing global presence of various types of resistance affecting multiple pathogens and antibiotics used for the treatment of any infection, let alone community-acquired respiratory infections, finding a way to dose antibiotics so that there is the best potential for providing adequate exposure and ensuring optimal kill and cure is of supreme importance. Whereas many antibiotics were prescribed at set doses for years, there is a need with all antibiotics to find an appropriate way to effectively utilise them in this time of resistance.

Although glimmers of the use of an antibiotic's pharmacokinetic properties to optimise its pharmacodynamics date back to the 1950s, a true focus on the concept did not evolve until the 1990s [1–3]. Since then, investigators around the world have attempted to develop broad-based pharmacokinetic/pharmacodynamic (PK/PD) dosing concepts that not only optimise outcomes and minimise the emergence of resistance but are also applicable at the bedside [2]. Those concepts that have emerged as the most recognised and/or referenced are all based on free serum concentrations of the antibiotics as compared (in ratio format) with the pathogen's minimum inhibitory concentration (MIC), and more recently the mutant prevention concentration (MPC), to the drug in question [2–4]. These concepts, the issues surrounding them and suggestions for the best ways to utilise them in choosing an antibiotic regimen for the treatment of acute bacterial exacerbations of chronic bronchitis (AECB) will be discussed in this chapter.

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PHARMACOKINETIC/PHARMACODYNAMIC DOSING CONCEPTS

Regardless of whether an antibiotic or class of antibiotics has bacteriostatic or bactericidal activity, their optimal use generally falls under one of two categories; time-dependent or concentration-dependent killers [3]. For time-dependent antibiotics, the goal of dosing is to produce serum concentrations that are above the MIC or MPC ($T > \text{MIC}$) for a percentage of the dosing interval that has been identified as necessary to achieve bacteriostatic and/or bactericidal activity. Although the temptation is always to give higher doses of a drug to achieve maximal effect, this is not necessarily more effective with time-dependent agents as high drug concentrations do not result in higher/faster killing than concentrations that are just above the MIC/MPC. In terms of the treatment of AECB, the antibiotics that demonstrate this type of activity would include all the β -lactams (regardless of whether they are combined with a β -lactamase inhibitor or not), vancomycin (for hospitalised patients), and possibly clindamycin, the macrolides (with the exception of azithromycin) and doxycycline [2, 3]. Using the β -lactams as an example, when concentrations are above the MIC for 30–40% of the dosing interval, bacteriostatic activity is noted *in vivo*. In contrast, maximal killing is noted when concentrations remain above the MIC of Gram-negative bacilli or streptococci for 60–70% of the dosing interval. Clinical evidence of the attainment (or not) of these thresholds with time-dependent agents has been described in terms of mortality in animal models. Whereas mortality was almost universal when concentrations were above the MIC for <20% of the dosing interval, survival was between 90% and 100% when concentrations exceeded the MIC for >40–50% of the interval [2, 5].

Although significantly increasing the doses may not be as effective as giving slightly higher doses more frequently with time-dependent killers, it is usually a very effective method of optimising concentration-dependent antibiotics. For these types of antibiotics there is an inherent need to have the peak serum concentrations (C_{max}) well above the MIC of the infecting pathogen and the amount of and/or rapidity of kill is enhanced when the concentrations are raised further. Depending on the severity of the AECB, the antibiotics that are considered concentration-dependent killers would include the aminoglycosides (for hospitalised patients) and potentially the fluoroquinolones [2, 3]. In the case of aminoglycosides, a trial by Keating and colleagues examined the outcomes of febrile neutropaenic cancer patients who were administered infusions of one of three aminoglycosides in combination with carbenicillin [3, 6]. When concentration:MIC ratios were analysed, a correlation was noted with response rate such that those achieving C_{max} :MIC ratios of 1–4, 4–10 and >10 demonstrated response rates of 57%, 67% and 85%, respectively [6]. In a more recent study by Kashuba and associates, aminoglycoside C_{max} :MIC ratios were examined in 78 inpatients with Gram-negative pneumonia in terms of cure/fail and the surrogate markers of fever and white blood cell count (WBC) resolution [3, 7]. Although outcome could not be correlated due to so few failures (92% cure rate), there was a strong relationship (90% probability) between achieving a C_{max} :MIC ratio of >10 and the patient becoming afebrile by day 7. Even though the data do not take into account the potential for any increase in adverse events from achieving this threshold ratio, they strongly demonstrate a relationship between achieving this ratio and the earlier and greater chance of surrogate marker normalisation [7]. Unlike the trial by Keating and co-workers, one of the main strengths of the latter study is that the authors statistically analysed concurrent antimicrobial therapy, which turned out not to be a significant variable in marker normalisation or outcome [3, 6, 8]. In the case of fluoroquinolones, Preston and colleagues analysed 134 patients with microbiologically documented Gram-positive or -negative respiratory, skin or urinary tract infections for any association between clinical and microbiological outcomes and PK/PD parameters [8]. Based on their analyses it was demonstrated that if a plasma C_{max} :MIC ratio of >12.2 was achieved, clinical success and microbiological eradication rates were 99% and 100%, respectively, as opposed to 83.3% and 80.8%, respectively if ratios of <12.2 were achieved [8].

Although these data appear compelling, certain issues need to be taken into account when considering them. Firstly, the authors used plasma concentrations rather than the active free drug serum concentrations, so it could be questioned whether the ratio is accurate when one considers levofloxacin's 24–38% albumin-based plasma protein binding. Secondly, since levofloxacin is ~100% renally cleared, the plasma concentrations used in their model are not reflective of the concentrations achieved in the urine which can be log-folds higher. Because of these much higher urinary concentrations, the outcomes are neither reflective nor dependent on the concurrent plasma/serum concentrations and, as such, should have been excluded from the analyses.

Despite antibiotics typically being separated based on their pharmacodynamic time- or concentration-dependence, a third variable based on a patient's 24-h serum exposure (AUC, area under the serum concentration–time curve) to a drug, regardless of the number of doses administered, has also demonstrated relevance with several antibiotics such as azithromycin and the fluoroquinolones. Although this variable (AUC₂₄:MIC) can be interpreted as incorporating properties of both time- and concentration-dependence, it is most closely linked to concentration-dependent pharmacodynamic concepts, as studies demonstrating the correlation of C_{max}:MIC many times also show good correlation with AUC₂₄:MIC [3, 9]. Other than which pharmacokinetic parameter is used in the ratio calculation, the main difference between this and the other previously described PK/PD dosing concepts is that the goal ratio breakpoint varies based on whether you are attempting to treat a Gram-positive or Gram-negative pathogen. Whereas it has been demonstrated that the breakpoint ratio needs to be approximately 30–40 SIT⁻¹.h (inverse serum inhibitory titre over time) for effective treatment of Gram-positive pathogens, the ratio for Gram-negative coverage is sharply higher at between 125–250 SIT⁻¹.h [2, 3, 9–12]. As an example with Gram-positive pathogens, a retrospective analysis by Ambrose and associates examined the microbiological response rates of patients with pneumococcal community-acquired pneumonia treated with fluoroquinolones [11]. When free drug AUC₂₄:MIC ratios were >33.7, SIT⁻¹.h microbiologic response rates were 100%. In contrast, when they were <33.7, SIT/hr response was demonstrated in only 64% of patients. When compared with clinical cure rates, patients with a fluoroquinolone ratio of >40 SIT⁻¹.h had a 92% cure rate versus 70% if the ratio fell below this threshold [11]. In terms of Gram-negative coverage, Forrest and co-workers examined the clinical and microbiological response rates of 74 acutely ill patients (the vast majority had nosocomial pneumonia) that were all treated with intravenous ciprofloxacin [12]. For those that achieved an AUC₂₄:MIC ratio of less than 125 SIT⁻¹.h, clinical and microbiological cure rates were 42% and 26%, respectively. When the values exceeded 125 SIT⁻¹.h, the rates increased to 80% and 82%, respectively. When the ratios were further analysed in terms of median time to eradication, those that achieved ratios of <125, 125–250 and >250 SIT⁻¹.h achieved eradication in >32, 6.6 and 1.9 days, respectively [12].

PK/PD DOSING CONCEPTS ARE HELPFUL, BUT...

At first glance, it is comforting to think that there are tried and tested scientific solutions to optimising the effects of an antibiotic as well as maximising its longevity in terms of utility. However, when interpreting these data, it is important to look at the science that relates to their use with the various commonly used AECB classes of antibiotics to ensure that this science translates into clinical medicine and outcomes. This is especially true when there are indicators that, although the theories may be appropriate, the way they are applied and the related data interpreted may be mistaken in some cases.

One of the key issues with using and interpreting these dosing concepts is that all ratios as noted above have been developed using serum concentration data. As the primary infection focus for any infection, including AECB, is not the bloodstream but rather the infected

tissue's extracellular interstitial fluid for most pathogens (the exception being certain intracellular atypicals), the PK/PD concepts by default assume that serum concentrations are in equilibrium with these tissue spaces. Since this is not always true and is many times dependent on the tissue concentration measurement technique used, it is important to define when it truly may be appropriate to make these *de facto* assumptions. Firstly, it is important to understand whether a study truly measured interstitial fluid concentrations at the desired tissue or not. This becomes an issue as many tissue penetration studies do not look specifically at the interstitial concentrations but rather a total concentration that reflects the concentration/amount of drug present in both the extracellular interstitial space/fluid as well as the intracellular compartment. This is done as it is much easier to dose an animal or human, harvest a piece of tissue and then homogenise it for assay rather than to utilise a more 'correct' technique such as microdialysis [8, 13]. As such, when this homogenate method is used, it makes antimicrobials that fail to penetrate host cells, such as β -lactams, appear (falsely) to have tissue concentrations that are a small fraction of their serum concentrations and therefore to be potentially ineffective. In reality, as explained by a recent review of antimicrobial lung penetration, free interstitial β -lactam concentrations in healthy volunteers are in equilibrium with their serum concentrations and this penetration can become variable in extreme physiological states such as sepsis [13]. Based on this and the fact that β -lactams are only used for extracellular pathogens, it is reasonable to state that using serum concentration data in PK/PD optimisation calculations for β -lactams should be relatively accurate and predictive. Clinical evidence that this is a safe assumption comes from the continued use of various β -lactams for the treatment of pneumococcal infections, especially in regions with high levels of resistance such as Southern Europe. In a seminal study by Pallares and colleagues, regardless of pneumococcal susceptibility to penicillin, ampicillin, ceftriaxone and cefotaxime, all inpatients with pneumococcal pneumonia received one of these as primary treatment [14]. At the conclusion of the study it was seen that, regardless of whether the baseline pneumococcal sensitivity was susceptible or resistant, patients had equal outcome/mortality rates [14]. Although one would expect there to be a mortality difference, the explanation for the lack of difference was in the investigators' methods, in which they used twice the doses of each of the β -lactams than they had in the past. By doing so, they not only raised the serum concentrations and concurrent infection site interstitial concentrations of the drugs but also inherently optimised their pharmacodynamics by re-establishing an adequate $T > MIC$ for even the most resistant isolates. This concept continues to be utilised worldwide not only for the treatment of pneumococcal pneumonia but also otitis media and, in an extreme manner, for pneumococcal meningitis [14, 15].

In contrast to β -lactams, other commonly used classes of antibiotics for AECB, such as the macrolides and fluoroquinolones, do not demonstrate this equilibrium between serum and interstitium. Rather, their infected tissue concentrations are significantly higher than concurrent serum concentrations not only due to penetration into various tissue cells such as fibroblasts and passive, equilibrium-based diffusion, but also in the acute reactive cells of the immune system that are responding to the infection via chemotaxis. This latter polymorphonuclear leukocyte (PMN), monocyte, lymphocyte and alveolar macrophage (AM) cellular penetration is the main method of delivery of these antibiotics to the infection site [16]. Because of this inflammation-related delivery, it is important to ensure that lung or tissue penetration studies are not only non-neutropaenic models but also use infected patients as opposed to healthy volunteers, who are often used inappropriately [17, 18]. Since infection site interstitial concentrations of these drugs tend to be multiples of their concurrent serum concentrations and the phagocytic cells actually clearing the bacteria from the infection site/body have anything from between five and ten times to over 2-log-fold their concurrent serum concentrations, common sense should dictate that serum concentrations are not predictive of their effect [9, 13, 19]. A classic example of this paradox is

with azithromycin. If one were to evaluate the potential effectiveness of azithromycin against a Gram-positive pathogen like pneumococcus, despite its having an excellent and prolonged clinical and microbiological efficacy track record, one would expect it to fail in 100% of cases by using its serum concentration data in PK/PD calculations. This is because a single 500 mg oral dose of azithromycin has a 24-h serum AUC of only 2.1 mg·hr/l [20]. Since the $AUC_{24}:\text{MIC}$ goal is 30 $\text{SIT}^{-1}\cdot\text{h}$ for a Gram-positive pathogen, this means that to be effective, the pneumococcus could not have an MIC higher than 0.06 mg/l, which it already did prior to azithromycin's launch in the early 1990s (0.125 mg/l) [20–22]. However, if we compare this to the PMN and AM exposures that are observed in 24 hours from the same oral dose (~1500 mg·h/l and ~12 000 mg·h/l), the MICs (50 and 400 mg/l, respectively) resulting from the $AUC_{24}:\text{MIC}$ calculations demonstrate why azithromycin not only has activity against susceptible isolates, but also potentially why there are not more failures clinically, even when faced with highly resistant isolates [20–22]. Since bacteria are cleared by these cells regardless of whether the bacteria are intra- or extracellular pathogens, are at the infection site or are one of the fraction that escapes into the bloodstream in the form of bacteraemia, it is logical to assume that these are the true 24-h exposures that a bacteria is exposed to when it is being cleared from the body, as opposed to 24-h serum exposures. This is a reasonable assumption because of the continued utility of these drugs even in regions with significant pneumococcal resistance such as Southern Europe and Southeast Asia [23, 24].

An example of this paradox with the fluoroquinolones would be from applying serum concentration data to the $C_{\text{max}}:\text{MIC}$ ratio of >12.2 that was identified as being necessary to achieve optimal clinical outcomes [8]. As the average MIC of levofloxacin for pneumococci is 1–2 mg/l globally, this means that the peak needed to achieve optimal clinical and microbiological effect would range from 12.2–24.4 mg/l. Since time is of the essence in achieving effective antimicrobial coverage for lower respiratory tract infections, these peak concentrations and the resulting ratios would have to be achieved with the very first dose of the approved 500 mg daily regimen of levofloxacin for AECB. However, regardless of whether oral or intravenous levofloxacin is administered, average first dose peak values are 5.1 and 6.2 mg/l, respectively [25, 26]. If one were to utilise the more recently introduced 750 mg dose and daily regimen for lower respiratory tract infections, the respective peak concentrations would be up to 9.3 and 11.5 mg/l [25]. As is evident, regardless of whether an AECB patient with a pneumococcal related-exacerbation was started on either the oral or intravenous formulations, or the currently recommended 500 mg or the potentially higher 750 mg regimens, the necessary minimal ratios of 12.2–24.4 would not be achieved, and by the PK/PD theory would most likely result in clinical and microbiological failure in the patient. However, that being said, one might argue that using the $AUC_{24}:\text{MIC}$ theory instead results in the necessary ratio of 30 $\text{SIT}^{-1}\cdot\text{h}$ if the MIC is 1 mg/l since the AUC for 500 mg oral and intravenous doses is approximately 48 mg·h/l. Although this may be true, one would expect both theories to show that a dose of a fluoroquinolone would be active, as both theories have demonstrated significant correlation to quinolone outcome with one (or the other) being slightly more significant. Since the theories do not agree and levofloxacin still has significant global activity in lower respiratory tract infections, it is likely that their application with serum concentration data is in error. Rather, like the macrolides, it may be the peak intracellular concentrations a pathogen is exposed to upon phagocytosis by acute reactant cells, which are 8–10 times their concurrent serum concentrations, that better explain the continued activity of the drug despite it failing proposed efficacy PK/PD optimisation calculations. Further support for the extrapolation of these PK/PD concepts to intracellular concentrations for the macrolides and fluoroquinolones comes from research that demonstrated activity against intracellular pneumococci despite this being an extracellular pathogen [27].

OTHER MITIGATING FACTORS

Although the issues with the PK/PD dosing/optimisation concepts being serum concentration-based could potentially be taken into account and their use varied, based on the antibiotic class being prescribed for the AECB event, there are other issues that probably cannot be corrected for. Despite the inability to correct for these factors, it is important to at least be aware of them as one considers utilising PK/PD dosing concepts.

Despite the first sections of this chapter concentrating mostly on the pharmacokinetics part of the optimisation concepts, the denominator of all of them has issues as well. Historically, microbiologists and clinicians have always assumed that the MIC is a true *in vivo* reflection of the susceptibility of a pathogen to a given antibiotic. As a result, very few people ever question whether the number (concentration) that is reported is a true reflection of what the antibiotic has to overcome *in vivo* or not. However, it is important to look at the MIC determination process and reflect on how much this is really representative of the human body. In most clinical laboratories, the MIC is determined by one of three methods. The first, disk diffusion, provides the least information as the diameter of the bacteria-free zone around the antibiotic disk merely correlates with general cut-offs that are thought to reflect whether a pathogen is Susceptible, Intermediate, or Resistant to the tested antibiotic. The other common method is broth microdilution, which generally exposes a pathogen to increasing 2-fold dilutions of an antibiotic to determine the actual concentration that provides inhibition of the pathogen and that is reported as the MIC. A newer method, the E-test, is a hybrid of these two historical methods and utilises a strip of paper impregnated with a gradient of an antibiotic, thereby allowing the easy testing of disk diffusion but also getting an actual MIC much more easily than using the labour intensive broth microdilution process. What all of these methods have in common is that they are conducted in plastic or glass tubes/dishes/trays with whatever growth medium has been identified by experts as most appropriate for the pathogen being tested. What they also have in common is that none of them has an immune system, acute reactant phagocytes or the inherent activity of other bodily fluids such as human serum. As such, they all inherently assume that the antibiotic is solely responsible for the reversal of infection and the clearance of bacteria from the body – simply put, the assumption is that the world is neutropaenic. While this explanation may seem simplistic, outlandish and heretical in the same breath, there are multiple everyday examples of how wrong we are to assume that our bodies are ‘passive observers’ during an infection and that the antibiotic is the ‘cure-all’. Whilst the MIC process provides a guide as to how to use (or not use) a specific antibiotic, to treat it as ‘gospel’ would mean that any time anyone flossed or even brushed their teeth, they would need antibiotic prophylaxis, or that anyone who snores would need to use nightly antimicrobial prophylaxis to prevent them from dying from the pneumonia created by the microaspirations associated with snoring and obstructive sleep apnoea. These same assumptions are commonly extrapolated in animal models of infectious diseases testing the pharmacodynamics of an antibiotic as well. These assumptions are further complicated by the neutropaenia, not only because of a discounting of the role of the immune system in clearing an infection, but also in terms of underestimating drug delivery by drugs such as macrolides and fluoroquinolones that are picked up by phagocytes responding to an infection. Without this absorption and delivery to the infection site by acute reactant phagocytes, the concentrations being tested and measured at these animal model infection sites are only reflective of passive diffusion and release by tissue cells such as fibroblasts, which may absorb the drug to some extent. As a result, they are falsely low and not a true clinical reflection.

The scientific evidence as to why these issues should be discussed is most prevalent with antibiotics and/or the pathogens common to community-acquired respiratory tract infections such as AECB. The simplest of the evidence involves an innocent modification of one of the susceptibility testing methods. As macrolides are commonly used for suspected pneu-

mococcal infections or infections such as AECB, where it is one of the primary empiric pathogens, susceptibility testing commonly involves at least one macrolide in the panel. Although it is usually recommended to grow cultures in an ambient environment for pneumococcus, there are many examples in the literature of investigators adding 5% CO₂ to the environment to better ensure optimal growth and testing. However, when broth microdilution for azithromycin and clarithromycin versus *S. pneumoniae* in an ambient environment was compared using the E-test method with 5% CO₂, the same isolates had MICs that varied by at least two dilutions. This anomaly is now recognised with the E-test method and is thought to be largely due to the carbonic acid that the CO₂ adds to the media during incubation, which falsely elevates the pneumococcal macrolide MICs due to the macrolides' basic chemical structure [22, 28].

As stated above, since *in vitro* testing takes place in a false environment of media and glass/plastic, there is no recognition of the body's part in combating an infection or what it may do to an antibiotic or pathogen. As an example, it has been demonstrated that the addition of 50% human serum to *in vitro* media results in pneumococcal MICs for clarithromycin decreasing by 1–2 dilutions and 2–6 dilutions for azithromycin due to its buffering effects [22, 29]. The addition of 40% human serum can lower azithromycin MICs for *Staphylococcus aureus* by as much as 15-fold [30]. As humans are comprised of 100% human serum, it begs the question as to what the MIC of the pathogen really is *in vivo* as opposed to the *in vitro* result from the laboratory. It also begs the question as to whether the incidences of resistance of a pathogen to specific antibiotics are real or merely occur *in vitro*. In terms of cell-mediated immunity, research has demonstrated repeatedly that there may be an additive or even synergistic interaction between antimicrobials and the immune system that the *in vitro* susceptibility testing methods, as well as neutropaenic *in vivo* models, wholly fail to identify. In a study by Meyer and co-workers, the MICs of *S. aureus* were shown to decrease for azithromycin when the MIC was tested after the staphylococci were phagocytosed by macrophages as compared to when they were measured in an extracellular environment [31]. Multiple examples studying several commonly used antibiotics including fluoroquinolones, penicillin, doxycycline and clindamycin have also demonstrated that mice with intact immune systems have enhanced killing and clearance of bacteria when compared with neutropaenic mice with the same pneumococcal thigh infections [32–34]. This enhancement is evidenced by greater clearance at T > MICs that are less than optimal, significantly enhanced post-antibiotic effects and more rapid clearance of bacterial loads [32–34].

Based on all of these less tangible issues, the question arises as to how reliable and/or direct our historical methods for estimating an antibiotic's effects against a clinically isolated pathogen really are. They may also help to explain why many commonly used antibiotics are still highly and widely effective, even in regions with high incidences of high-level resistance, or in bacteria that may still be identified as susceptible but whose MICs as compared to pharmacokinetics can no longer fully explain their continued utility [9, 19, 22].

SUMMARY

PK/PD DOSING/OPTIMISATION OR NOT?

Although, based on the above text, a reader may be confused about the utility of PK/PD dose optimisation when treating AECB or any infection in general, it is possible to draw some conclusions.

It is unlikely that individualised PK/PD dosing will ever be available to the general practitioner as it is financially prohibitive to have assays for all commonly used antibiotics readily available in order to provide an immediate turnaround of serum samples for concentration quantitation and bedside optimisation. As such, any use of PK/PD dosing concepts will have to be undertaken in a more general, population-based manner. Although it is always

desirable to provide the best care for any given patient, population-based treatment methods will provide guidance for general practitioners as to how best to dose a given antibiotic or antibiotic class to provide optimal care and even potentially overcome a growing regional/national resistance issue. On this latter note, it would also allow the physician to decide when a drug is no longer of use due to resistance in an informed manner as opposed to using historical methods of comparing surveillance MICs to serum concentrations. In terms of our ability to effectively use the information discussed above and the key issues to keep in mind, the most direct use of PK/PD for AECB and other infections will be with the β -lactams and other antibiotics whose serum concentrations are in relative equilibrium with their interstitial infection site concentrations. Since both the pharmacokinetic and pharmacodynamic parts of the equation can be quantitated the most easily and directly in terms of the infection site, clinicians will have the most confidence in making these changes when they become necessary due to resistance.

In contrast to drugs like the β -lactams, the explanations presented above bring into question how PK/PD concepts are currently applied for drugs whose serum concentrations do not match those the pathogen is exposed to as it is being cleared from the body. They also demonstrate how a more invasive but accurate application of the same PK/PD parameters for these drugs helps to explain their continued utility despite rising MICs and significant resistance incidence. Whilst these explanations inherently appear to make sense, they will always be debated, as the proposed alterations of their application are difficult to quantitate. While such debate and conjecture is understandable, it is hoped that further insights into these applications/alterations may allow drugs whose serum-based PK/PD concepts suggest a lack of efficacy to continue to provide good clinical effect and be used rather than abandoned without thought.

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9

Acute exacerbations of COPD: application of evidence-based guidelines

F. Blasi, P. Tarsia, R. Cosentini, S. Aliberti

INTRODUCTION

Evidence-based guidelines are statements expressed by a consensus of experts or professional societies that condense current knowledge regarding specific pathologic conditions. Guidelines should be tools that allow better disease management by clinicians working at the patient's bedside. One of the main limits to the widespread application of clinical guidelines is that the indications expressed may be too complex to translate simply to use in busy daily practice. Conversely, oversimplification of important issues, although allowing easier 'diffusion' of information, may limit the scientific utility of the statements expressed. Successful guidelines should therefore strike a balance by issuing easily applicable, state-of-the-art recommendations.

Evidence-based guidelines are particularly welcome in the management of acute exacerbations of chronic obstructive pulmonary disease (COPD). These events encompass widely differing clinical conditions from very mild cases, best managed with simple bronchodilator adjustments, to life-threatening situations requiring intensive care admission and mechanical ventilation. Specific aspects derived from guidelines that may be of clinical use include the better definition of exacerbations, severity assessments to determine hospitalisation needs and proper pharmacological management, particularly with regard to the need for antibiotics.

A number of published guidelines deal with COPD. Compared with the first guidelines published in the mid 1990s [1, 2], more recent guidelines have placed greater emphasis on the management of exacerbations. The guidelines expressed by the Global Initiative for Chronic Lung Diseases (GOLD) [3], the joint European Respiratory Society (ERS), the American Thoracic Society (ATS) [4], and the British Thoracic Society (BTS) [5] encompass all aspects of the condition, whereas others [6–8] focus primarily on antibiotic selection.

As in other evidence-based guidelines, the ERS/ESCMID (European Society of Clinical Microbiology and Infectious Diseases) [8] guidelines were based on systematic review of the literature relating to lower respiratory tract infections published between 1966 and December

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2002. The retrieved articles were critically appraised and each furnished with a rating for pertinent clinical evidence. These ratings were summarised using 'levels of evidence' and the best available clinical evidence was translated into graded clinical recommendations to be used in the management of patients with lower respiratory tract infections, including COPD exacerbations.

ANTIBIOTIC SELECTION PROCESS IN COPD EXACERBATIONS

PATIENT STRATIFICATION

The need for antibiotic treatment in COPD exacerbations has been hotly debated in recent decades. It is now clear that not all COPD patients presenting with an exacerbation need to be treated with antibiotics. Recent evidence-based guidelines have condensed data from the literature in order to help clinicians decide which patients do not need to receive antibiotics and, conversely, those in whom antibiotics will be potentially useful. Physicians should therefore be aware of patient baseline characteristics and exacerbation manifestations most likely to benefit from antimicrobial therapy.

The landmark study by Anthonisen and colleagues [9] in the 1980s identified three cardinal symptoms:

1. Increase in dyspnoea;
2. Increase in sputum volume; and
3. Increase in sputum purulence.

The presence of all three symptoms (Type 1 exacerbation) was associated with beneficial effects following antimicrobial treatment. Among the symptoms of an exacerbation, a clear relationship has emerged between the presence of sputum purulence and airway bacterial load [10]. Specifically, the presence of green, purulent sputum was 94.4% sensitive and 77.0% specific for the yield of a high bacterial load. This information may be linked with data from the Anthonisen study, in that patients who present with two of the three of the cardinal symptoms (Type 2 exacerbation), including the presence of purulence, should also benefit from antibiotic treatment.

Patients' baseline severity must also be considered as antibiotics have not been proven to be beneficial in ambulatory patients with mild symptoms (simple chronic bronchitis) [11], whereas they do have an effect on patient survival and hospital stay in severe cases requiring mechanical ventilation [12].

Putting together all the above information, the ERS/ESCMID guidelines propose a system of patient stratification in order to direct antibiotic treatment of exacerbations of COPD (Table 9.1). There are three different groups:

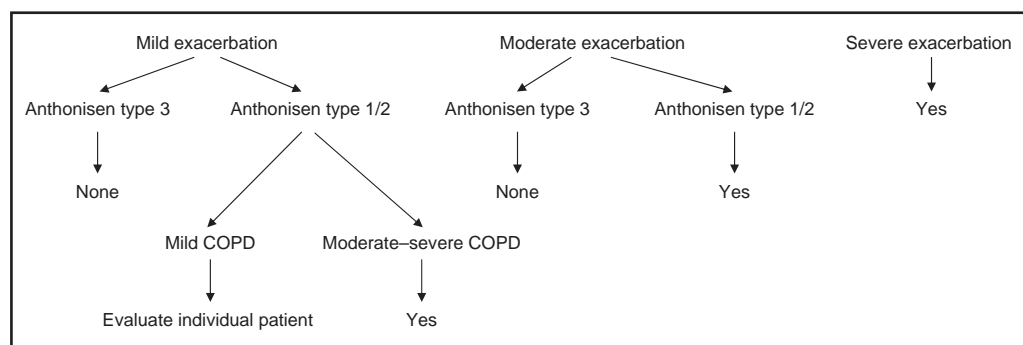
- **Group A** includes patients not requiring hospitalisation (mild COPD);
- **Group B** includes patients who are admitted to hospital (moderate–severe COPD) without risk factors for *Pseudomonas aeruginosa* infection; and
- **Group C** comprises patients admitted to hospital (moderate–severe COPD) with risk factors for *P. aeruginosa*.

In Group A outpatients, an antibiotic should be given during exacerbations of COPD in the presence of a Type 1 exacerbation presenting all three of the cardinal symptoms: increased dyspnoea, increased sputum volume and increased sputum purulence. In addition, antibiotics should be considered for exacerbations in patients with severe underlying COPD, irrespective of exacerbation intensity.

In patients with Group B or C exacerbations requiring hospitalisation, antibiotics should be given to the following:

Table 9.1 Patient stratification to direct treatment during COPD exacerbations according to the ERS/ESCMID 2005 guidelines (with permission from [8])

Group A	Patients may not require hospitalisation (mild COPD)
Group B	Patients admitted to hospital (moderate–severe COPD) without risk factors for <i>Pseudomonas aeruginosa</i> infection
Group C	Admitted to hospital (moderate–severe COPD) with risk factors for <i>Pseudomonas aeruginosa</i>

**Figure 9.1** An algorithm for indications for antimicrobial treatment of acute COPD exacerbations based on severity of exacerbation.

- Patients with a Type 1 Anthonisen exacerbation;
- Patients with a Type 2 Anthonisen exacerbation when increased purulence of sputum is one of the two cardinal symptoms; and
- Patients with a severe exacerbation that requires invasive or non-invasive mechanical ventilation.

Antibiotics are generally not recommended in Anthonisen Type 2 exacerbations without purulence and Type 3 patients (Figure 9.1).

ANTIBIOTIC SELECTION

One argument against the use of antibiotics during COPD exacerbations is that many patients show long-term airway bacterial colonisation during stable phases of the disease and studies on sputum culture have failed to demonstrate significant differences in bacterial retrieval between exacerbations and steady-state disease [13, 14]. However, potential contamination must be kept in mind before accepting sputum culture results as truly representative of the lower airway's microbiology, as commensal pharyngeal flora may interfere with investigations. In fact, bronchoscopic sampling of the distal airway using protected brush specimens to minimise upper airway contamination confirms, on the one hand, that some COPD patients are chronically colonised by bacteria during stable periods. On the other hand, however, it has been shown that at least 50% of patients may have bacteria in high concentrations in their lower airways during exacerbations and that high-load bacterial retrieval is more common in the acute phase than in stable disease [15].

Studies analysing bronchial secretions may underestimate the presence of bacteria, as these may proliferate within the epithelial cell layer and submucosa with little shedding into

Table 9.2 Stratifying antibiotic treatment by comorbidities and pathogens (with permission from [8])

Group A Group B Group C		
Mild COPD: no comorbidity	Moderate–severe COPD: no risk factors for <i>Pseudomonas aeruginosa</i>	Moderate–severe COPD: with risk factors for <i>Pseudomonas aeruginosa</i>
<i>H. influenzae</i> <i>S. pneumoniae</i> <i>M. catarrhalis</i> <i>(M. pneumoniae)</i> <i>(C. pneumoniae)</i> Viruses	Like Group A plus <i>Enterobacteriaceae</i> sp.	As in group B plus <i>Pseudomonas aeruginosa</i>

the lumen [16]. Bandi and associates [17] cultured *Haemophilus influenzae* in only 7% of exacerbated COPD patients but demonstrated intracellular *H. influenzae* in bronchial biopsies from 87% of patients with exacerbations.

Sethi and co-workers [18] used molecular typing to identify new strains within a bacterial species in sputum isolates collected during an exacerbation and in a stable phase. Exacerbations were associated with 33% of visits in which new strains were identified, compared with only 15% of visits in which no new strains were found ($P < 0.001$). A subsequent study by the same group [19] demonstrated a strain-specific immune response in exacerbated patients with evidence of new *H. influenzae* strain acquisition. Thus, at least as far as *H. influenzae* is concerned, COPD exacerbations may either result from relapses by endogenous organisms, genomically identical to those of a previous exacerbation episode, or from exogenous reinfections with genomically different strains. Taken together, these findings support an important role for bacteria as a cause of exacerbations.

Potential pathogens involved in an exacerbation

It is now accepted that airway microbiology changes during the different stages of severity of the disease and these findings must be kept in mind when choosing appropriate empiric antimicrobial therapy in exacerbated COPD patients. Studies in patients with mild exacerbations [20], which do not require hospital admission, have shown that the predominant microorganisms are *H. influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*. In contrast, in patients requiring mechanical ventilation (mean forced expiratory volume in one second (FEV₁) <30% of predicted) [21], the role of the above agents is less important and other pathogens, such as enteric Gram-negative bacilli and *P. aeruginosa* may be more frequent. Other observations support the concept that COPD severity (as expressed by FEV₁ impairment) is an important determinant of the type of pathogen associated with an exacerbation [22, 23] (Table 9.2).

Overall, the reported percentage of *Pseudomonas* infection is approximately 10–15% in patients with COPD exacerbations requiring hospitalisation and who have severe disease (FEV₁ <50% of predicted). This percentage is increased in patients admitted to the intensive care unit (ICU) needing mechanical ventilation. These subjects present a 6-fold higher risk

Table 9.3 Risk factors for the presence of *Pseudomonas aeruginosa* infection in COPD exacerbations (with permission from [8])

(At least two out of the four below)

1. Recent hospitalisation
2. Frequent (>4 courses per year) or recent administration of antibiotics (last 3 months)
3. Severe disease (FEV₁ <30%)
4. Previous isolation of *P. aeruginosa* during an exacerbation or patient colonised by *P. aeruginosa*

of being colonised by virulent Gram-negative bacteria such as *P. aeruginosa* and *Enterobacteriaceae* species than do patients with an FEV₁ >50% of predicted.

The clinician must therefore be aware of the risk factors for presence of *P. aeruginosa* during an exacerbation. Empirical antimicrobial treatment is radically different from that used in patients without risk factors for this pathogen and it appears that failure to administer anti-pseudomonal antibiotics promptly may be associated with worse outcomes [21]. Identified risk factors for *P. aeruginosa* infection include:

- Recent hospitalisation;
- Frequent administration of antibiotics (four courses in the last year);
- Very severe COPD (FEV₁ <30%); and
- Isolation of *P. aeruginosa* during a previous exacerbation or colonisation during a stable period [22, 23] (Table 9.3).

During the 1990s, a number of studies addressed the possible involvement of atypical pathogens (*Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*) in COPD exacerbations. Based on current evidence, *Legionella* infection does not appear to be a significant issue in this setting. Conversely, most studies show that *C. pneumoniae* is found in approximately 4–20% of exacerbations [24, 25], with *M. pneumoniae* being less frequent.

Viruses also appear to be common causes of COPD exacerbations. A better awareness of the role of viruses in exacerbations derives from the availability of more sophisticated diagnostic techniques. Seemungal and colleagues [26] found evidence of viral infection in 39% of exacerbations, rhinovirus and respiratory syncytial virus (RSV) being the most frequent. Viruses and atypical organisms may be involved in exacerbations by causing a primary infection that increases lower airway inflammation, enhancing bacterial proliferation and leading to secondary bacterial involvement in these episodes.

Antibiotic resistance issues

Over the last few decades, penicillin-resistant *S. pneumoniae* strains have been isolated in most countries worldwide, showing marked regional variations. Penicillin-resistant strain rates above 40% have been described in the USA, France, Spain, Hungary and Japan [27, 28]. In parallel, resistance to erythromycin is observed in 1–42% of *S. pneumoniae* isolates when the national data of individual European countries are considered.

Reduced susceptibility of *S. pneumoniae* to β -lactams is the result of the remodelling of the penicillin binding proteins (PBPs) so that there is decreased antibiotic binding affinity to the bacterium. Antibiotic susceptibility is an *in vitro* determination based on minimal inhibitory concentration (MIC) values observed for the isolated strain. Current *S. pneumoniae* break-points for penicillin are established to predict efficacy in infections such as meningitis, where the antibiotic must reach the cerebrospinal fluid. In lung infections, peak serum and tissue concentrations of intravenously administered β -lactam antimicrobials may be considerably higher than the MIC values of intermediate or resistant pneumococci. Pharmacokinetic/pharmacodynamic data suggest that respiratory pneumococcal infections should give rise

Table 9.4 Proposed antibiotic choices in patients with COPD exacerbations based on patient stratification (with permission from [8])

		<i>Oral treatment</i>	<i>Alternative</i>	<i>Parenteral treatment</i>
Group A	Mild COPD Antibiotic therapy may not be required	Amoxicillin Tetracycline	Macrolide [^] Amoxicillin- Clavulanate Levofloxacin Moxifloxacin	–
Group B	Moderate–severe COPD without risk factors for <i>P. aeruginosa</i>	Amoxicillin- Clavulanate	Levofloxacin ⁺ Moxifloxacin ⁺	Amoxicillin Amoxicillin- Clavulanate 2nd or 3rd generation Cephalosporin* Levofloxacin Moxifloxacin
Group C	Moderate or severe COPD with risk factors for <i>P. aeruginosa</i>	Ciprofloxacin		Ciprofloxacin or β -lactam [§] with <i>P. aeruginosa</i> activity + aminoglycosides [°]
<p>In countries with high incidence of penicillin-resistant <i>Streptococcus pneumoniae</i>, high doses of amoxicillin or amoxicillin-clavulanate are suggested.</p> <p>⁺ Levofloxacin and moxifloxacin show better coverage towards <i>S. pneumoniae</i> than ciprofloxacin.</p> <p>* Ceftriaxone or cefotaxime. [§] Cefepime, piperacillin-tazobactam, or a carbapenem. [°] There are no data on the benefit of combination therapy for <i>Pseudomonas aeruginosa</i> treatment in COPD exacerbations.</p> <p>[^] Erythromycin, clarithromycin, roxithromycin or azithromycin. Telithromycin may be an alternative for consideration in the community or in hospitals for COPD exacerbation or community-acquired pneumonia (CAP). However, clinical experience with this antibiotic is currently too limited to make specific recommendations. Oral cephalosporins are generally not recommended due to poor pharmacokinetics.</p>				

to clinical failures following β -lactam treatment in only the ~2% of *S. pneumoniae* isolates showing MIC values ≥ 4 $\mu\text{g/ml}$ [29]. Factors associated with increased risk of infections with drug-resistant pneumococci include previous antibiotic treatment with a β -lactam, age over 65 years, presence of comorbidity and use of systemic steroids.

Resistance to macrolides is mediated by two principal mechanisms. Methylation of the ribosome target through modification in the erythromycin ribosomal methylase (*erm*) genes causes conformational changes reducing antimicrobial affinity [30]. This mechanism is associated with cross-resistance to clindamycin and high MIC values (>64 $\mu\text{g/ml}$ for erythromycin) and is more common in Europe. Conversely, modifications in the *mefE* gene alter bacterial efflux pump mechanisms facilitating drug efflux from the cells. This form of resistance is more common in the United States, is associated with lower MIC values (1–32 $\mu\text{g/ml}$ for erythromycin) and does not confer cross-resistance to clindamycin [30].

The number of macrolide-resistant *S. pneumoniae* strains is also on the rise. Results from the Alexander Project indicate that in 1996 and 1997, the global rate of pneumococcal macrolide resistance was 16.5–21.9% [28]; by 1998–2000, the resistance rate had increased to 24.6% [31]. The true clinical significance of increasing macrolide-resistant bacterial strains is as yet uncertain. On the one hand, the specific pharmacokinetic/dynamic properties of macrolides

allow high and prolonged tissue and inflammatory cell concentrations, overcoming MIC concerns, but on the other, clinical failures have been reported in the treatment of macrolide-resistant bacteraemic pneumococci [32].

Although penicillin resistance among pneumococcal strains has taken several decades to develop, the prevalence of *S. pneumoniae* resistance to the newer fluoroquinolones has rapidly become substantial in some countries [33]. Outside these limited areas, the worldwide prevalence is still <2%.

β -lactamases are bacterial enzymes that destroy penicillins and cephalosporins by hydrolysis and account for most of the resistance to β -lactams in *H. influenzae* and *M. catarrhalis* [34]. Specifically, TEM-1 and TEM-2 enzymes are the β -lactamases most commonly encountered for *H. influenzae* [35], whereas ROB-1 and ROB-2 enzymes are produced by *M. catarrhalis* [36]. The proportion of β -lactamase positive *H. influenzae* varies from 2–22% in Europe, [37] and 30–40% in North America. Since the late 1990s, over 90% of *M. catarrhalis* strains produce β -lactamases in most countries of the world [38]. There are no clinical clues that can predict the presence of β -lactamase-producing bacteria during exacerbations, except that patients with these organisms tend to have had more previous courses of antibiotics.

In summary, the exact clinical role of antimicrobial resistance in clinical practice is still being debated, but antibiotic prescription habits must consider potential resistance issues. Data indicate that appropriate doses of β -lactams should achieve adequate drug concentrations to treat pneumococcal strains thought to be non-susceptible. Similarly, the extremely high tissue concentrations reached by newer macrolides might effectively inhibit resistant *S. pneumoniae* strains. However, increased risk of death or treatment failures have been reported for infections with high-level penicillin-resistant and macrolide-resistant bacteraemic pneumococci. Wide geographic variations are observed in resistance rates, making knowledge of local microbiological conditions imperative in guiding treatment. Finally, the ERS/ESCMID guidelines [8] identify a number of risk factors associated with the presence of resistant organisms: prior antibiotic or oral steroid treatment, prolonged course of the disease, more than four exacerbations per year and FEV₁ <30% of predicted.

Is microbiological workup useful in COPD exacerbations?

Fewer data are available regarding the utility of microbiological testing in COPD exacerbations compared with pneumonia patients. Based on the data reported above, it seems reasonable to sample respiratory secretions in patients with purulent sputum as there is a high probability of bacterial yield. Furthermore, in the presence of factors associated with antimicrobial resistance, microbiological data may be useful to correct initial empirical antibiotic therapy. Lastly, severe COPD exacerbations (Group C patients) may harbour difficult-to-treat pathogens (*P. aeruginosa*, *S. aureus*) and should therefore undergo sputum cultures or endotracheal aspirates (in mechanically ventilated patients).

Empirical initial antimicrobial treatment for patients with COPD exacerbation

As reported above, Group A patients present with mild COPD, generally do not require hospitalisation, and antibiotics should be considered in the presence of all three of the Anthonisen criteria (Type 1 exacerbation). The more frequently isolated pathogens in this group are *H. influenzae* followed by *S. pneumoniae* and *M. catarrhalis*. The ERS/ESCMID guidelines [8] suggest the use of amoxicillin (1 g every 8 h), ampicillin (1.5 g every 8 h) or a tetracycline (doxycyclin 100 mg every 12 h) (Table 9.4), although this may be a concern in countries with high levels of antibiotic resistances of *S. pneumoniae* and β -lactamase-producing *H. influenzae*, where these drugs may be associated with a high relapse rate. Alternatively, high-dose amoxicillin/clavulanate (1 g every 8 h) is active against both *S. pneumoniae* and *H. influenzae*. Although macrolide-resistant *S. pneumoniae* can be high and most *H. influenzae* strains are resistant to clarithromycin, clinical trials have shown a good

activity of newer macrolides (clarithromycin 500 mg twice daily, azithromycin 500 mg once daily) compared with other antibiotics [39]. Telithromycin (800 mg once daily) is a ketolide derived from macrolides that is effective against *S. pneumoniae* strains resistant to penicillins and macrolides and is effective against *H. influenzae*. Clinical experience with this drug is still limited and it is therefore only mentioned, but not recommended, by current guidelines. In Group A patients requiring antimicrobial therapy, oral treatment is generally sufficient.

In acute phase COPD requiring hospitalisation but presenting no risk factors for *P. aeruginosa* (Group B), antibiotic treatment is indicated in Type 1 exacerbations, Type 2 exacerbations (provided sputum purulence is present) and in severe disease. In addition to the pathogens present in Group A patients, other Gram-negative microorganisms such as *Enterobacteriaceae* must be kept in mind, in addition to drug-resistant bacteria. Amoxicillin/clavulanate is a suitable first choice drug, although the new quinolones should be considered (Table 9.4). Levofloxacin and moxifloxacin are more active than ciprofloxacin against most *S. pneumoniae* strains and achieve high concentrations in bronchial secretions. In addition, they are active against Gram-negative bacilli other than *P. aeruginosa*. Treatment with medications directed at resistant organisms, such as a fluoroquinolone or amoxicillin/clavulanate, should perform better than amoxicillin or other traditional first-line agents. In addition, there is increasing evidence suggesting that the enhanced bacterial eradication associated with fluoroquinolones leads to faster symptom resolution and results in more prolonged disease-free intervals compared with cephalosporins and extended spectrum macrolides. The oral route is preferred, but in some situations the parenteral route has to be used. In this case, the same antibiotics recommended above can be given parenterally. Non-anti-pseudomonal third-generation cephalosporins, such as ceftriaxone (1–2 g daily) and cefotaxime (1–2 g every 8–12 h) also show good activity against the majority of microorganisms. The advantage of ceftriaxone over cefotaxime is that it can be given intramuscularly and can be useful in some non-hospitalised cases.

In hospitalised exacerbated moderate–severe COPD patients with risk factors for *P. aeruginosa* (Group C), the selection of one or other antibiotic will depend on:

- The severity of the exacerbation;
- Local patterns of resistance;
- Tolerability;
- Cost; and
- Potential compliance.

The most active orally administered anti-pseudomonal antibiotic is ciprofloxacin. This antibiotic is active against *H. influenzae*, *M. catarrhalis*, other Gram-negative bacilli and atypical pathogens. A major limitation with ciprofloxacin is its poor activity against *S. pneumoniae*, although this pathogen may be more uncommon in Group C compared with less compromised patients. Another concern is the increasing rates of resistance to *P. aeruginosa* observed in some European countries. High dosages of ciprofloxacin are recommended (oral 750 mg twice daily; i.v. 400 mg every 8–12 h) to achieve higher serum and bronchial concentrations [40]. The activity of levofloxacin against *P. aeruginosa* has recently been approved by the US Food and Drug Administration (750 mg once daily), although clinical experience with this drug remains limited.

In moderate–severe patients, oral antibiotic administration may be considered if the patient is able to eat. If this is not the case, the i.v. route has to be used. Switching to oral treatment may be considered when there is clinical stabilisation 3–5 days after admission. In the most severely ill patients (particularly when admitted to an ICU), i.v. administration of antibiotics is mandatory. In this category of patients, particularly when *P. aeruginosa* is suspected, combinations of antibiotics are advisable (Table 9.4). Anti-pseudomonal β -lactams include ceftazidime (2 g every 8 h i.v.), cefepime (2 g every 8 h), piperacillin/tazobactam

(4.5 g every 8 h), or a carbapenem (imipenem/cilastatin 500 mg–1 g every 8 h i.v.; meropenem 1 g every 8 h). A fluoroquinolone or one of the above anti-pseudomonal β -lactams may be associated with an aminoglycoside (amikacin 15 mg/kg/day).

Although there are no definitive data on the subject, antibiotic treatment in exacerbated COPD patients should be maintained for an average of 7–10 days. Shorter courses (5 days) of newer fluoroquinolones have been shown to be as effective as 10 days of treatment with β -lactams in some trials [41–43].

Non-responders to empirical antibiotic treatment

Up to 10–20% of patients with moderate–severe exacerbations do not respond to initial antibiotic treatment and may require a change in therapy [44]. Some failures may be related to pathogens not covered by the empirical regimen. *P. aeruginosa*, *Staphylococcus aureus* (including methicillin-resistant strains), acinetobacter and other non-fermenters are the most frequent causes of failure. *Aspergillus* spp. has been more commonly described in the recent years, particularly in patients with prolonged systemic steroid treatment. Alternatively, high-level antibiotic resistance to common pathogens (such as *S. pneumoniae*) must also be considered. In some cases, the hospitalised COPD patients may acquire a nosocomial respiratory infection, particularly among ventilated ICU patients [21]. Guidelines recommend a close evaluation for non-infectious causes of failure (i.e. inadequate medical treatment, embolisms, cardiac failure or other causes), followed by a careful microbiological reassessment. In cases of failure, new antibiotic treatment must include good coverage against *P. aeruginosa*, drug-resistant *S. pneumoniae* and non-fermenters. Therapy may later be tailored according to microbiological results.

SUMMARY

LIMITS IN CURRENT GUIDELINE RECOMMENDATIONS

In the intentions of experts drafting guidelines, recommendations regarding antibiotics should be based on both evidence of benefit and harm for single agents. However, strong evidence to support individual recommendations is generally absent. Antibiotic efficacy studies on which guidelines base their recommendations are fraught with a number of limitations. In older studies, a precise definition of COPD was often absent, with rather over-generous inclusion criteria allowing enrolment of never-smokers, subjects under 40 years of age or patients with simple chronic bronchitis without airflow obstruction, in whom exacerbations are frequently a self-limited disease, thus hampering the demonstration of any potential benefit of antibiotic therapy. In addition, many studies offered unsatisfactory definitions of exacerbation, often including Anthonisen Type 3 events. Furthermore, the population heterogeneity in the trials was very high, including patients with several degrees of baseline pulmonary disease severity. Results on clinical and bacteriological efficacy were often not stratified according to FEV₁. The superiority of antibiotics may have been due to better results in the more severe population or may have extended to the whole spectrum of severity of COPD. Results in different severity subgroups of patients would therefore be useful.

The persistence of bacteria after treatment of the exacerbation (residual bacterial colonisation) has been shown to influence the frequency and severity of subsequent exacerbations. It is therefore reasonable to assume that an antibiotic that induces faster and more complete eradication *in vitro* will result in better clinical outcomes. Suggested novel endpoints in clinical trials include the need for repeated courses of antibiotics for the exacerbation as a surrogate marker of relapse and the time free from exacerbation at long-term follow-up. These factors may be of extreme importance in COPD patients, since the frequency of exacer-

bations has been associated with a faster decline in pulmonary function, increased costs and impairment in the quality of life.

Another key variable not tested for in most studies is the administration of steroids (both before randomisation and during the exacerbation). Steroids modulate local and systemic inflammatory response and may be a confounding factor when evaluating the efficacy of antibiotics in exacerbations.

The majority of placebo-controlled studies showing beneficial results from the use of antibiotics were performed more than 10 years ago, using older antibiotics such as ampicillin, tetracycline or trimethoprim/sulphamethoxazole. Current concerns regarding emerging antimicrobial resistance, the role of more virulent Gram-negative organisms in patients with severe disease and the development of more potent antimicrobials have forced a re-examination of treatment choices. It has been argued that the recently introduced brands of antibiotics are expensive and usually not appropriate, but a reduction in failure and relapse rates associated with newer agents would considerably reduce the overall costs of COPD exacerbations.

The aim of many trials of antibiotics in exacerbations was to demonstrate that any new antibiotic is 'at least as good as' the 'standard therapy'. These studies may be appropriate for pharmaceutical companies to launch their new antibiotics, but offer only very modest information to the clinician. In testing new antibiotics in COPD exacerbations, some studies have pooled two or more comparators in the analysis, which exhibit very different antimicrobial spectrum and activity. Positive results in this kind of study indicate that the tested antibiotic is superior to the group of comparators considered together, but not to any of them considered individually. Stratification of the results for each of the comparators would be of use for valid conclusions to be drawn. Two recent retrospective cohort studies from The Netherlands showed that adding antibiotics to oral corticosteroids was associated with reduced risk of subsequent exacerbation, particularly in patients with recurrent exacerbations and reduced risk of all-cause mortality [45, 46]. If confirmed by future prospective studies, these observations may have a major impact on exacerbation management in chronic obstructive pulmonary disease patients.

Future studies should also be based on a specific approach to COPD that takes into account its unique characteristics. This would give rise to highly informative data that could be translated into solid antibiotic treatment recommendations in future guidelines on the antibiotic management of COPD exacerbations.

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Economic evaluation of antibiotic treatment of exacerbations of COPD

M. Miravittles

INTRODUCTION

Obstructive lung diseases, particularly chronic obstructive pulmonary disease (COPD) are one of the main causes of morbidity and mortality in developed countries. It is estimated that more than 15 million individuals in the United States suffer from COPD and more than 12 million from chronic bronchitis [1]. Furthermore, the number of individuals affected has grown in recent decades. The age-adjusted mortality rate from COPD doubled from 1970 to 2002 in the United States, whereas rates from stroke and heart disease decreased by 63% and 52%, respectively [2].

The prevalence of COPD in Spain is 9% in adults between 40 and 70 years of age, although only 22% are diagnosed [3]. This situation will not improve in the future. A recent international survey showed that up to 11.8% of subjects aged between 20 and 44 years had Global Initiative for Obstructive Lung Disease (GOLD) 0 COPD, characterised by chronic respiratory symptoms and 3.6% had GOLD stages I–III COPD with impairment in lung function [4], which is remarkable considering the young age of the participants.

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. Exacerbations have been shown to have a negative impact on the quality of life of patients with COPD [5, 6]. Furthermore, acute exacerbations are the most frequent cause of medical visits, hospital admissions and death among patients with chronic lung disease [7].

Considering its high prevalence and the chronic and progressive course of COPD, it is easy to understand that this disease represents a high societal and economic burden. Studies performed in America and various European countries have tried to estimate the healthcare costs associated with the management of COPD patients. The results obtained may differ in absolute numbers but they represent a significant proportion of the healthcare costs in each country in *all* cases. Another similarity is the importance of exacerbations, since these episodes, particularly the most severe ones that require hospital admission, are the main cause of the high use of resources by these patients [8, 9]. Strategies aimed at reducing the rate of hospitalisations will, therefore, be the most cost-effective interventions.

A significant proportion of hospitalisations derive from failure of ambulatory treatment of exacerbations. Different studies consistently show a failure rate of ambulatory treatment of exacerbations that ranges from 15–26% [10–12]. Since relapse after initial treatment for the

acute exacerbation may lead to prolonged disability, impairment in health-related quality of life (HRQL) and increased costs, it is crucial to identify those patients most at risk of relapse.

COSTS OF COPD

It is necessary to understand the high burden associated with the management of COPD before analysing the impact of exacerbations and the possible strategies to improve economic outcomes.

Studies of the costs of COPD have been performed in different countries and differ in both their approach and methodology. In order to compare results between studies it is important to verify how the study was designed. Basically, the differences derive from the inclusion (or exclusion) of indirect costs, which refer to the morbidity and mortality caused by the disease. They measure the impact that the disease studied may have on national production. The most commonly used method of calculation is based on human capital in which days off work, whether because of disease or death, are transformed into monetary units by the application of the mean returns. This method has been extensively criticised, one reason for this being that it does not include the impact on the 'collectives' which are not integrated into the labour market such as children, the elderly, housewives, etc. In contrast, the direct costs are those related to the detection, treatment, prevention and rehabilitation of the disease studied. Most studies of this type concentrate on the analysis of the costs incurred by the hospital, and ambulatory and pharmacological care related to the disease in question. Other direct costs apart from healthcare, such as social services, are usually not included due to a lack of available information [13].

Another source of variation is the type of analysis. One option would be to calculate the cost of the disease starting with total figures at a national level for all diseases together and, thereafter, reaching the level at which the disease studied lies through a disaggregation process, called 'top-down' analysis. The second option would be to start by taking a group of subjects with the disease analysed as a base for the calculation and study the consumption of resources during the time period considered. The national total may be determined by extrapolation of the costs of this subset of the population, so-called 'bottom-up' analysis [13].

An example of the variation that can be observed in the calculation of costs is provided by the analysis of different studies in the same country. Top-down estimates have been carried out on the costs generated by COPD in Spain using statistical and epidemiological data. These studies have reported figures of around €800 million annually in 1994 [14], including both direct and indirect costs. In a microeconomic study performed in 1510 patients with ambulatory COPD followed over one year (bottom-up), the average annual cost per patient was \$1876 [15]. With this study, the approximate direct annual cost generated by COPD in Spain may be calculated from the prevalence. If we take into account data obtained in the IBERPOC population-based epidemiological study [3], the prevalence of COPD was estimated to be 9% in the 40–69 years age group, of which only 22% were diagnosed and received treatment of some kind [3]. Therefore, a total of 270 000 subjects would be diagnosed and treated for COPD which, when multiplied by the annual average (\$1876), produces a total of \$506.52 million annually in direct healthcare costs generated by COPD. This figure is greater than that obtained in the former study, which may be due to methodological differences and also, in part, to differences in the management of the disease that took place during the period from 1994 to 1999, when information for the latter study was collected. It is interesting to compare the distribution of the costs estimated in both models. In the top-down calculation, the hospital costs constituted 36.3%, the expenses attributed to drugs 42.2%, and the clinical consultations and diagnostic tests 22.5% [14]. In the study using the bottom-up focus, the hospital costs represented 43% of the total, drugs 40%, and consultations and complementary tests 17% [15]. Despite the differences observed in the

absolute values between the two types of studies, the distribution of the costs was very similar. If the total direct cost of COPD is divided between the total of the country's population, healthcare for COPD patients costs each citizen \$13.32 annually. To put this figure into perspective, a study carried out in the Netherlands reported a cost of \$23 per capita in the association of asthma and COPD [16]. The differences may be due to the inclusion of asthma in this latter study and a lower index of underdiagnosis in the Netherlands, among others.

Another Spanish study observed a mean direct cost of COPD of only \$909.50. Differences may be attributed to the different selection criteria of the patients. This study was a population-based study, with some patients identified being very mild and some who had not been previously diagnosed with COPD [17]. To highlight these differences, a more recent study observed even higher costs, ranging from \$1657 for patients in stage I of the American Thoracic Society (ATS) guidelines, to \$3303 for patients in stage III [18]. Again, these differences were derived from the selection of patients. In the latter study, 82% of the patients were followed by respiratory physicians, compared with the previous study in which all patients were recruited in primary care, probably representing a population with milder disease and consequently lower healthcare costs [15].

The economic impact of COPD in 1993 was estimated to be more than \$15.5 billion in the USA, with \$6.1 billion for hospitalisation [19]. In a recent study undertaken in the United States following the bottom-up focus in a cohort of 413 patients with COPD, direct costs were found to range from \$1681 for patients in stage I to \$5037 for patients in stage II and \$10 812 for those in stage III [19]. These costs are much higher than those observed in Spain, which may be due to a variety of factors, among which the most important was that the patients in the North American study were selected from a population with COPD registered in the hospital. Other studies carried out regarding the cost of COPD in different countries are shown in Table 10.1.

All estimates indicate that the situation will not improve in the near future. The impact of ageing and changes in smoking habits are responsible for an estimated increase of more than 60% of total life-years lost and an increased loss of 75% of disability-adjusted life-years (DALYs) from 1990 to 2020 in the Netherlands [20]. New projections as far as 2025 provide similar results, with an increase in prevalence and costs of COPD despite the many campaigns against tobacco smoking [21].

ECONOMIC IMPACT OF EXACERBATIONS

Exacerbations are a frequent event in the natural history of COPD. Patients included in clinical trials have a mean of 1.5–2.5 exacerbations per year [22]. In an observational study performed in the community, patients also presented a mean of 2 episodes per year, this number being dependent on the degree of functional impairment at baseline. Patients with forced expiratory volume in one second (FEV_1) <40% of predicted presented 2.3 exacerbations/year and those with FEV_1 >60% of predicted only 1.6 [23]. It is important to underline that many exacerbations remain unreported to the physician and are underestimated by the patient or self-treated at home [5]. As a consequence, the frequency of exacerbations depends on the definition used. Studies using a symptom-based definition provide higher estimates than those studies following a healthcare use approach [24].

The mortality of patients admitted to hospital with a COPD exacerbation is about 10–14% and the mortality of those admitted to an intensive care unit (ICU) for exacerbations may be as high as 24% [25]. Hospitalisation has an important impact on COPD patients. Severe exacerbations, particularly if they require hospitalisation, have an independent negative impact on patient prognosis [26]. After the first admission to hospital, the mean survival time has been estimated to be 5.7 years, with COPD together with lung cancer being the main causes of death [27]. Severe patients with a mean FEV_1 of only 0.8 l

Table 10.1 Comparison of the costs published on COPD in different countries

<i>Study [ref.]</i>	<i>Country</i>	<i>Focus</i>	<i>Costs</i>	<i>Cost/patient/year</i>	<i>Global cost /year</i>
Morera, 1992 [14]	Spain	Top-down	Direct and indirect	€959	Direct €319m Indirect €541m
Sullivan, 2000 [58]	USA	Top-down	Direct	\$2300	\$1700m
Hilleman, 2000 [19]	USA	Bottom-up	Direct	Stage I = \$1681 Stage II = \$5037 Stage III = \$10 812	
Jacobson, 2000 [29]	Sweden	Top-down	Direct and indirect		Direct €109m Indirect €541m
Wilson, 2000 [30]	USA	Top-down	Direct	Emphysema \$1341 Chronic bronchitis \$816	\$14 500m
Rutten van Mólken, 2000 [16]	Netherlands	Top-down	Direct	\$876	
Dal Negro, 2002 [59]	Italy	Bottom-up	Direct	Stage I = €151 Stage II = €3001 Stage III = €3912	
Jansson, 2002 [61]	Sweden	Bottom-up	Direct and indirect	\$1284	\$871m
Miravittles, 2003 [15]	Spain	Bottom-up	Direct	Stage I = €1185 Stage II = €1640 Stage III = €2333	€427m
Masa, 2004 [17]	Spain	Bottom-up Cross-sectional	Direct	€909.5	€238.8m
Izquierdo-Alonso 2004 [18]	Spain	Bottom-up	Direct	Stage I = €1657 Stage II = €2425 Stage III = €3303	
Borg, 2004 [60]	Sweden	Top-down	Direct and indirect	Direct costs GOLD I = €92 GOLD IIA = €631 GOLD IIB = €2144 GOLD III = €8678	

\$ = costs in US dollars; € = costs in Euros; m = million.
Modified with permission from [13].

admitted for an exacerbation and hypercarbia presented a poor prognosis with a mortality of 11% during admission and almost 50% during the first two years after hospitalisation [28].

A study performed in the United States based on national statistics estimated that the total burden of exacerbations was \$1592 million (for 1995) [8]. The mean cost of an exacerbation managed in an outpatient clinic was \$159 and, interestingly, drug costs represented only 11.2% of the costs in inpatients and 15% in outpatients [8]. The average cost of hospitalisation for COPD in a cohort of severe patients in the US was estimated to be \$7100 [28]. Some studies have determined that hospitalisation costs represent between 40% and 57% of

total direct costs generated by patients with COPD [15, 17, 29, 30] and this percentage may be as high as 63% in severe patients [29]. Since acute exacerbations are the main cause of hospitalisation among COPD patients [7, 28], it can be concluded that the economic burden of acute exacerbations is considerable. However, only a small proportion of exacerbations require hospitalisation. A recent observational study performed in a cohort of COPD patients followed by primary care physicians observed that 22% were admitted during one year [23]. In another prospective study performed in primary care, 16.5% of all exacerbations required hospital admission [12]. The costs of exacerbations that require hospitalisation increase dramatically compared with those that can be treated in an ambulatory setting. Another analysis derived from a clinical trial in patients with COPD demonstrated that 15% of exacerbations – those requiring admission – generated 90% of the costs associated with exacerbations [31]. In fact, a small group of COPD patients may generate most of the hospital visits and admissions. This highly demanding population usually has an older age, more severe indices of bronchial obstruction and more hypoxaemia at rest [32]. In addition, a previous admission is a risk factor for higher use of healthcare resources and costs in the future [33]. Previous hospitalisation and frequent exacerbations are also significant and independent risk factors for failure in future exacerbations of COPD [34].

A Swedish study observed that exacerbations accounted for 35–45% of the total per capita healthcare costs for COPD [35]. Another report observed that exacerbations generated a mean yearly cost of €415 in severe patients, €382 in moderate patients, and €228 in mild patients [18].

The mean total cost of an acute exacerbation of COPD was estimated to be \$159 in a recent study on primary care in Spain, the main part being due to hospitalisations, which represented 58% of the total cost, followed by the total drug acquisition cost of 32.2% [9]. Interestingly, this was exactly the same estimate obtained by Niederman *et al.* [8] for the US in 1995, using a different methodology. Using the unit costs in different Latin American countries and applying the same method of cost calculation, estimates of the cost of exacerbations may be obtained for these countries. A large variation exists, based mainly on the large differences in costs for healthcare resources. The highest cost was observed in Argentina with an equivalent of \$329 (in the year 2000) and the lowest, of \$98, was seen in Colombia [36].

Failure implies a cost that is three times higher than that of exacerbation management, particularly due to the high cost of hospitalisation (Figure 10.1). If percentages of relapse could be reduced, especially in severe cases, or if switching a patient from parenteral to oral therapy could reduce the length of hospital stay, valuable resources could be saved. The cost of failure depends on disease severity in the study population. In a study on respiratory infections in one general practice, Davey *et al.* [37] observed that repeated consultation due to failure incurred a maximum cost of £28.54, including indirect costs. It is of note that their population included patients of all ages with a great variety of respiratory infections, some of which were benign. This population of previously well patients with lower respiratory tract disease demonstrated a very low rate of relapse and outcomes were independent of the use (or not) of an antibiotic [38, 39]. Patients with exacerbated COPD treated in the community present a failure rate ranging from 15% to 26% [10–12] and costs of failure represent from 40% to 65% of the total costs associated with the treatment of ambulatory patients [8, 9, 36, 40]. As an example, from the total mean cost obtained of \$159 in a large study in the community, \$100.30 is derived from the cost of relapse. Ideally, if relapse in the global population were completely avoided, the mean cost of exacerbation would be reduced to only \$58.70, or if the relapse rate could be reduced by half, costs would be reduced to \$107 [9]. Based on these results, it can be speculated that a new treatment that is able to reduce failure rate, particularly in severe patients with high risk of hospitalisation, may easily be a highly cost-effective strategy.

Another example of the high burden of exacerbations of COPD derives from the calculation of the excess cost generated by this patient population when compared with a control

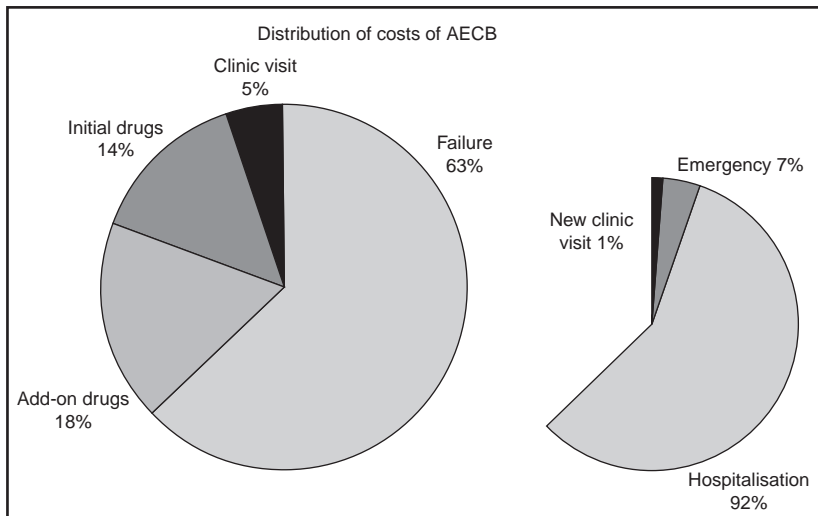


Figure 10.1 Distribution of costs of exacerbations of COPD (with permission from [9]).

population without the disease. This exercise was performed for England and Wales from 1994 to 1995 and the total excess cost of primary care associated with exacerbations was calculated at £35.7 million [41]. The largest component of primary care costs was the excess cost of all prescription medicines, which totalled £27.8 million and the excess cost arising from inpatient hospital episodes was £8.3 million [41]. A summary of studies reporting costs of exacerbations of COPD is presented in Table 10.2.

EVALUATION OF COST-EFFECTIVENESS OF ANTIBIOTIC TREATMENT OF EXACERBATIONS

There are multiple interventions that can be potentially cost-saving in COPD. This overview will focus on antibiotic treatment of exacerbations. The reader can find a description of costs and savings associated with multiple interventions in a comprehensive review [42].

Acquisition cost alone is inadequate for completing a comprehensive cost-effectiveness analysis. The cost per day of treatment and cost per episode of care are clear concepts and indicators needed to understand the magnitude of the resources required for the attention to a given patient population. However, the total cost per outcome of care is the most important and comprehensive [43]. True cost-effectiveness must compare the total stream of costs of an intervention with the total stream of outcomes and demands a follow-up of an appropriate and sufficiently long duration to fully evaluate the relevant outcomes. In the case of exacerbations of COPD, the first studies modelled after pneumonia followed patients for 2–3 weeks after completion of antibiotic therapy, but recent studies have suggested that full evaluation of the effects of antibiotics requires at least six months of follow-up to investigate the impact of antibiotic treatment on relapse [44, 45].

Many different types of health economic analysis can be conducted. The types of costs and benefits included depend on the point of view of the analysis. Cost-effectiveness analysis is driven both by the regulatory agencies and the marketplace. In either case, choosing the right outcome parameter is particularly difficult [43]. In the case of exacerbations of COPD, parameters used for chronic diseases, such as mortality, may not be appropriate. The use of quality-adjusted life-years (QALYs) requires a long follow-up in order to quantify changes in health status. The number of successful treatments or number of exacerbations

Table 10.2 Comparison of the costs of exacerbations of COPD in different countries

<i>Study [ref.]</i>	<i>Country</i>	<i>Design</i>	<i>Setting</i>	<i>Cost/episode</i>
Connors, 1996 [28]	USA	Observational study in five hospitals	Admitted patients with pCO ₂ >50 mmHg	Median cost \$7100 (IQ range \$4100 to \$16 000)
Niederman, 1999 [8]	USA	Estimation from national statistics	Inpatients and outpatients with chronic bronchitis	Hospital cost (>65 yrs) \$5497 Ambulatory \$159
McGuire, 2001 [41]	USA	Prevalence-based, excess-cost-of-illness analysis based on national statistics	Primary care	Excess cost associated with AECB was £35.7m per year
Andersson, 2002 [35]	Sweden	Mail survey to 202 patients with COPD	Outpatients and inpatients	Mean cost SEK 3163 Ranging from mild exacerbations SEK 120 to severe SEK 21 852
Grassi, 2002 [56]	Italy	Randomised, open-label clinical trial	Inpatients and outpatients	Moxifloxacin treated €1993 and ceftriaxone treated €2219
Miravittles, 2002 [9]	Spain	Observational study on 2414 patients	Outpatients in primary care	Exacerbation cost \$159 Cost per failure \$477.50
Miravittles, 2003 [36]	Latin America	Estimation from local statistics	Outpatients in primary care	Costs ranged from \$98 in Colombia to \$329 in Argentina Failure accounted for 52% of costs
Borg, 2004 [60]	International	Computer simulation model	Outpatients and inpatients	Mild SEK 191, moderate SEK 2111, severe SEK 21 852
Izquierdo-Alonso 2004 [18]	Spain	Observational study on 570 patients	Outpatients	Mild COPD €228/year; moderate COPD €382/year and severe COPD €415/year
Llor, 2004 [40]	Spain	Observational study on 1456 patients	Outpatients in primary care	Mean cost €118.6 (95% CI 92.2–144.9)

avoided seems to be more adequate and easy to perform. In addition, phase IV trials are needed to determine costs and outcomes relating to actual clinical use, as opposed to the idealised circumstances of phase III clinical trials [43]. Most cost analyses are based on randomised clinical trial data, which invariably use highly selective inclusion and exclusion criteria and thus may not accurately reflect COPD patients treated in the general population [46].

There are four possible results of cost-effectiveness analysis (Figure 10.2). If a new antibiotic reduces costs and increases the efficacy, then it is readily accepted as the dominant therapy. Similarly, if the new antibiotic increases costs but decreases efficacy, it is easily rejected. Decisions are more difficult in the remaining two situations. For example, most new interventions raise both costs and improve quality, meaning that cost-effectiveness does not necessarily require cost savings [43, 47]. This rise in cost observed in cost-effectiveness analysis as a consequence of the use of a more expensive therapy with a better outcome is called the incremental cost.

Incremental cost is a method for helping the healthcare purchaser to decide between two or more therapeutic options [48]. It is based on the cost-effectiveness ratio according to the following formula:

$$\text{Incremental cost} = \frac{\text{Difference in cost}}{\text{Difference in efficacy}}$$

The application of this formula can be illustrated with one simulated example. The standard treatment for exacerbations of COPD in one practice is amoxicillin with a cost of €12 per course of treatment and a clinical efficacy of 86%. We want to analyse the effectiveness of a change to a new antibiotic, either antibiotic A or antibiotic B. Costs of a course of treatment are €32 and €38, with a clinical efficacy of 88% and 93%, respectively. The incremental cost of A would be $32 - 12 / 88 - 86 = 10$, and that of B would be $38 - 12 / 93 - 86 = 3.7$. In this case, the comparison would be in favour of B despite its higher acquisition cost. Results show that the decision-maker needs to pay €10 for each unit of increase in efficacy with A and only €3.7 to gain an additional unit of efficacy with B.

This approach can also be used in the design of clinical trials, by starting from an estimate of a maximum cost of treatment failure and working back to calculate the difference in efficacy that must be demonstrated [49]. As an example, a new antibiotic is expected to reduce failures of exacerbated COPD patients treated initially in the community. In a previous study, a failure of ambulatory treatment has been quantified as a mean of \$477.50 [9] and, supposedly, the new antibiotic has an increase in cost of \$20 compared with the 'old' treatment. To calculate the increase in efficacy required for this alternative to be acceptable by decision-makers, the same formula is used:

$$\text{Incremental cost or saving (\$477.50)} = \frac{\text{Difference in cost (\$20)}}{\text{Difference in efficacy (??)}}$$

The difference (increase) in efficacy should be at least $20 / 477.50 = 0.042$ or 4.2%. It is easy to understand that the higher the cost of the new treatment, the higher the increase in efficacy that must be demonstrated to be acceptable to the healthcare purchaser.

There are two main problems with this analysis:

1. The difference in efficacy between different treatment options should be clinically relevant, but must also be statistically significant to be included in the equation. The required sample size to demonstrate a significant superiority of the clinical efficacy of a new antibiotic is very large. Most clinical trials of antibiotics have been designed to

		Cost	
		↑	↓
Effectiveness	↑	Incremental cost	Dominant
	↓	Reject	Evaluate

Figure 10.2 The four possible outcomes of cost-effectiveness analysis.

fulfil the regulatory agencies' requirements, with the aim of demonstrating that a new antibiotic is 'at least as good as' the existing 'standard' therapy. The sample size needed for these studies is markedly lower. Although these trials may be required for the pharmaceutical companies to launch their new antibiotics, they offer limited, if any, useful information to the clinician and do not allow a cost-effectiveness analysis [47, 50].

- There is very little information about the costs of clinical failure. These costs may vary greatly depending on the setting of the study (primary care, specialised care, hospital), the severity of the patient population studied and according to the local costs of health-care resources in any given country.

Cost-effectiveness analysis is increasingly important in the evaluation of new treatments for chronic diseases. Although there is no threshold for what is considered to be an acceptable incremental cost for decision-makers, there is some guidance based on the results of the evaluation of interventions by regulatory agencies. If a new intervention demonstrates an incremental cost of less than \$20 000 per QALY gained, there is a strong likelihood of it being accepted, whereas an incremental cost of more than \$100 000 is very unlikely to be acceptable [51]. Interventions with incremental costs within this range may have different considerations depending on a variety of factors: economic, medical, societal and others [52]. When the outcome used in the evaluation is measured in QALYs, the analysis is called a cost-utility analysis. Unfortunately, there are no guidelines for acceptable incremental cost in exacerbations of COPD in terms of the willingness to pay for any increase in clinical efficacy or exacerbation avoided.

ECONOMIC EVALUATION OF ANTIBIOTIC TREATMENT OF EXACERBATIONS OF COPD

Economic evaluation of antimicrobial therapy has been increasingly considered in clinical trials and observational studies (Table 10.3). A Canadian multicentre, randomised, open-label study compared ciprofloxacin with the usual therapy for exacerbations of chronic bronchitis [53]. Patients were followed for one year after the presenting episode to evaluate costs and changes in health status. The use of ciprofloxacin was associated with an annual mean increase in cost of \$578 Canadian per patient. The cost-effectiveness analysis showed that the incremental cost associated with ciprofloxacin treatment required to avoid each additional symptom day was \$209 (\$578/2.8 symptom days averted). Additionally, the cost-utility analysis showed an incremental cost per QALY gained for ciprofloxacin of \$18 588 (\$578/0.031 QALYs gained). When considering this analysis, it is important to note that the gain in QALYs with ciprofloxacin was not significant (95% confidence interval [CI] -0.012–0.077). Interestingly, in the group of patients with more risk factors, the incremental treatment difference in favour of ciprofloxacin for QALYs and symptom days increased and was a dominating alternative (less expensive and more effective) [53].

In a retrospective review, Destache *et al.* [54] compared the costs and outcomes of antibiotics classified as first-line (amoxicillin, tetracyclines and erythromycin), second-line

Table 10.3 Some studies addressing the economic evaluation of antibiotic treatment of chronic bronchitis or COPD

<i>Study [ref.]</i>	<i>Design</i>	<i>Comparators</i>	<i>Type of analysis</i>	<i>Results</i>
Grossman, 1998 [53]	Randomised, open-label	Ciprofloxacin vs. usual care	Cost-effectiveness, cost-utility	Can \$209 for symptom day averted and Can \$18 588 for QALY
Destache, 1999 [54]	Retrospective review	First vs. second vs. third line (see text)	Cost and consequences	Third line produced savings of US \$21 vs. second line and US \$400 vs. first line
Backhouse, 1995 [62]	Decision-analytic model-based cost-effectiveness analysis	Amoxicillin, amoxicillin/clavulanic acid, ciprofloxacin and cefaclor	Cost-effectiveness	Amoxicillin/clavulanic acid dominates over amoxicillin. Ciprofloxacin had an incremental cost of £3.87 per successfully treated case relative to amoxicillin
Van Barlingen, 1998 [55]	Simple decision analytic model	Macrolides, ciprofloxacin, penicillins, cephalosporins	Cost and cost-effectiveness (no incremental costs calculated)	Ciprofloxacin was the most cost-effective first-line option. None of the antibacterials considered was consistently found to be the most cost-effective across the full range of scenarios investigated.
Grassi, 2002 [56]	Randomised, open-label	Moxifloxacin vs. ceftriaxone	Cost analysis	Savings with moxifloxacin of €448.23 per episode from a societal perspective
Llor, 2004 [40]	Observational	Moxifloxacin, amoxicillin/clavulanic acid and clarithromycin	Cost analysis	Exacerbation costs were €111.46 (95% CI 73.4–149.5) for moxifloxacin; €109.45 (95% CI 68.2–150.7) for amoxicillin/clavulanic acid, and €138.95 (95% CI 89.4–188.5) for clarithromycin

(cefradine, cefuroxime, cefaclor and cefpodoxil), and third-line (amoxicillin/clavulanic acid, azithromycin and ciprofloxacin) in a group of 60 outpatients who presented a total of 224 episodes. The results showed that, despite a higher acquisition cost for third-line drugs, their superior effectiveness resulted in net cost savings, particularly due to the significant reduction in frequency of hospitalisations.

Two other studies presented results based on analytic models comparing different antibiotic therapies for exacerbations. Interestingly, in the study by van Barlingen *et al.* [55], the sensitivity analysis showed that none of the antibacterials considered was consistently found to be the most cost-effective across the full range of scenarios investigated. These results concurred with the Canadian study [53] and highlighted the need for stratification of patients to choose the most cost-effective alternative based on their characteristics and risk factors for relapse.

In an Italian randomised, open-label, clinical trial comparing moxifloxacin with ceftriaxone, the authors found a net saving per episode with the use of moxifloxacin of €448.23 from the societal perspective and of €226.57 from the Italian National Health Service perspective. Differences were basically due to higher hospital costs associated with the use of ceftriaxone [56]. Finally, an observational study performed in 1456 ambulatory patients in primary care in Spain quantified the costs of treatment of exacerbations, including costs associated with clinical failure, for patients treated with moxifloxacin, amoxicillin/clavulanic acid and clarithromycin [40]. The results showed that clarithromycin-treated patients had the highest costs €138.95 (95% CI 89.4–188.5) per episode compared with moxifloxacin €111.46 (95% CI 73.4–149.5) and amoxicillin/clavulanic acid €109.45 (95% CI 68.2–150.7).

There are a variety of factors influencing the results of cost-effectiveness analysis. These factors have been extensively reviewed elsewhere [57]. Briefly, the likelihood of bacterial aetiology of exacerbation, the choice of outcome measure, the drug acquisition costs, the risk factors for treatment failure, the risk factors for hospitalisation and non-compliance with treatment are amongst the most important [57].

SUMMARY

The costs of management of acute exacerbations of chronic bronchitis are high, largely as a result of the high costs associated with relapse. Strategies to improve the outcome of ambulatory treatment of exacerbations may easily be cost-effective, especially in more severe patients who are at increased risk of hospital admission as a consequence of therapeutic failure. New antibiotics with extended spectrum and fast bacterial killing should provide better clinical results, particularly in severe patients who are more at risk for relapse. Unfortunately, existing clinical trials are designed to demonstrate equivalence and usually include mild patients with low incidence of treatment failure. Consequently, it is not possible to perform reliable cost-effectiveness analysis from data obtained in the great majority of the existing trials.

There is an urgent need for superiority trials for antibiotics in exacerbations of COPD, especially in high-risk populations. In addition, phase IV studies should provide evidence of how these new antibiotics perform in the community, far from the ideal circumstances of a clinical trial.

Economic evaluation of new treatments is increasingly recognised as an important part of the evaluation of a new drug, not only by healthcare purchasers, but also by clinicians. Researchers must provide the data necessary for this analysis to be adequately performed.

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11

Managing acute exacerbations in COPD with bronchodilators and corticosteroids

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INTRODUCTION

The pharmacological approach to exacerbations of chronic obstructive pulmonary disease (COPD) can be called the 'ABC approach', an acronym that reflects the three classes of drugs (Antibiotics, Bronchodilators and Corticosteroids) commonly used for exacerbations of COPD [1]. However, if we consider only the highest levels of evidence [2], this is only valid for bronchodilators and systemic steroids.

SHORT-ACTING β_2 -AGONISTS IN THE TREATMENT OF ACUTE EXACERBATIONS OF COPD

Acute exacerbations of COPD may result in deterioration of the underlying bronchospasm. This worsened airflow obstruction may be reversed in some patients by the use of bronchodilators [3]. Although the amount of reversibility achieved may be relatively small, any improvement in airflow could be extremely important in the management of these patients [4].

For this reason, despite a complete absence of placebo-controlled trials, few people would question the efficacy of bronchodilators in an acute exacerbation of COPD. In fact, the Global Initiative for Obstructive Lung Disease (GOLD) guidelines [2] affirm that the management of COPD exacerbations involves increasing the dose and/or frequency of existing bronchodilator therapy. In particular, short-acting inhaled β_2 -agonists such as salbutamol and terbutaline are usually the preferred bronchodilators for treatment of exacerbations of COPD. Some studies suggest that these agents, as a class, are of benefit, showing improvements in lung function and dyspnoea scores [5].

Patients with an acute exacerbation of COPD have often said that their inhalers had stopped having a useful effect and that their symptoms were only relieved by nebulised therapy on arriving at the hospital. Surprisingly, this is not reflected by clinical trial evidence. A meta-analysis [6] of the effectiveness of nebuliser versus metered dose inhaler (MDI) as a mode of delivery for bronchodilators in exacerbations found no significant difference in their effect on forced expiratory volume in one second (FEV₁). Unfortunately, however, the duration of the bronchodilator effect of short-acting β_2 -agonists is decreased in COPD exacerbation [7]. This finding might justify the feeling of reduced effectiveness that is reported by patients.

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In order to overcome the reduced functional half-life of β_2 -agonists, some authors have suggested not only using larger-than-usual doses that are sometimes necessary to relieve airway obstruction, but also shortening the posologic interval [5, 8]. However, there is no apparent advantage to giving salbutamol more frequently than once every 60 minutes [5]. Thus, when 3–4 puffs every 4 h have not been effective, 3–4 puffs of short-acting, inhaled β_2 -agonists should be administered every 1–2 h, if tolerated, under close supervision (including electrocardiogram [ECG] monitoring) until clinical improvement occurs. In particular, the American Thoracic Society (ATS) recommendation for severe COPD exacerbation is 6–8 puffs every 2 h [9]. In any case, the maximal effective dose of short-acting β_2 -agonists in COPD exacerbations is not known. Obviously, these bronchodilators should be titrated to maximal effect when possible, whilst monitoring the patient closely for adverse effects of the larger-than-usual doses that are sometimes necessary to relieve airway obstruction.

LONG-ACTING β_2 -AGONISTS AS AN ALTERNATIVE OPTION

Rodriguez-Roisin [10] defined an acute exacerbation of COPD as '*a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations, which is acute in onset and necessitates a change in regular medication in a patient with underlying COPD*'. The sustained worsening of the patient's condition is the best reason to use a higher than customary dose of a long-acting β_2 -agonist in the treatment of an acute exacerbation of COPD [11]. However, these drugs are currently not approved for use in this disorder because they are intended for maintenance treatment and not immediate symptom relief.

This opinion, however, contrasts with the evidence that at least formoterol produces dose-proportional bronchodilation in COPD patients with a reversible component [12]. The onset of action of formoterol is as rapid as both salbutamol and terbutaline [13, 14] and a significant effect occurs with formoterol within minutes of inhalation of a therapeutic dose [15]. In particular, it has been demonstrated that inhaled formoterol 12 μg and 24 μg and inhaled salbutamol 400 μg and 800 μg are equi-effective doses in inducing a rapid onset of action in patients with stable COPD [16]. Evidence that formoterol has a fast onset of action similar to salbutamol indicates that formoterol may be considered as an alternative to salbutamol in patients suffering from acute exacerbation of COPD.

A preliminary study that examined the effects of formoterol used 'as needed' in 20 patients with acute exacerbations of COPD, documented that this long-acting β_2 -agonist elicits a rapid and significant bronchodilation and can be used for 'as needed' medication in many patients suffering from this pathological condition [17]. A dose of 24 μg formoterol administered via Turbuhaler[®] seemed to induce a clinically relevant effect in these patients. However, since several patients benefited from a higher dose, it was concluded that it is advisable to administer at least a cumulative 36 μg delivered dose of formoterol as rescue medication to bring about rapid relief of bronchospasm in patients with acute exacerbation of COPD.

In a subsequent study [18] that enrolled a small, selected group of patients with mild acute exacerbations of COPD, formoterol via Turbuhaler[®] induced a fast bronchodilation that was dose-dependent and not significantly different from that caused by salbutamol (Figure 11.1). Furthermore, formoterol appeared to be as well tolerated as salbutamol. Evidence that formoterol had a rapid onset of action that is not significantly different from that produced by salbutamol in patients with acute exacerbations of COPD suggested that this long-acting β_2 -agonist could be considered an alternative therapy to salbutamol in this pathological condition.

Nonetheless, some clinicians avoid the use of formoterol as relief medication in patients already taking it as regular treatment. Although not seen clinically [19], it has been suggested that there could be a greater tendency for bronchodilator subsensitivity to develop with longer-acting than with shorter-acting β_2 -agonists because of the longer duration of

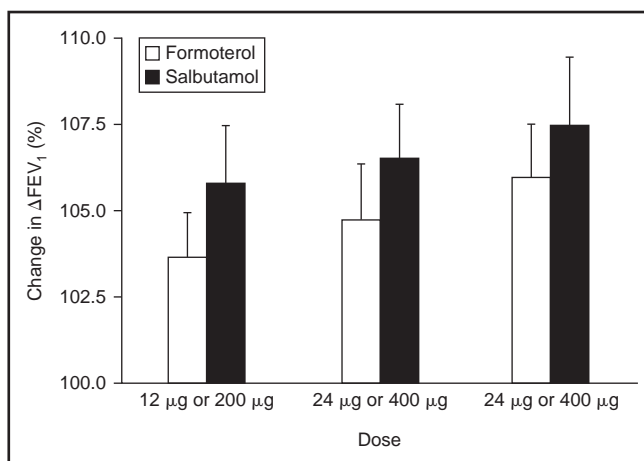


Figure 11.1 Changes in forced expiratory volume in 1 second (FEV_1) as percent of predicted (ΔFEV_1) for formoterol and salbutamol in patients attending outpatient clinics because of mild acute exacerbations of COPD (with permission from [18]).

β_2 -adrenoceptor occupancy and consequent down-regulation. However, the development of bronchodilator subsensitivity is only partial [20]. A study that explored whether there was a potential *in vivo* interaction between formoterol used as maintenance therapy and formoterol used as relief medication in patients with partially reversible COPD showed that regular treatment with formoterol did not compromise the bronchodilator response to further cumulative inhalations of formoterol [21]. Therefore, it is possible to administer a higher than customary dose of formoterol to patients with COPD who are under regular treatment with formoterol when they need additional help because of severe dyspnoea.

As a result of a great deal of controversy regarding the timing and optimal dosing of inhaled β_2 -agonists in acute exacerbations of COPD, the bronchodilating effect and the safety of inhaled formoterol administered using either a cumulative dose regimen or the equivalent single dose in patients with this pathological condition have been compared [22]. Data from this study indicate that delivery of a single high dose of 36 μ g formoterol is as effective as the same dose administered in a cumulative manner in patients with acute exacerbation of COPD (Figure 11.2). This is an important finding, because it has been hypothesized that the non-cumulative technique causes a greater response than the dose–response curves in patients with COPD because in COPD the airflow is limited mainly by structural alterations within and around peripheral airways [23]. These anatomical changes prevent access of β -agonists to the periphery of the lung where the highest concentration of β -adrenoceptors is found [24]. Consequently, better penetration of aerosol into the airways that are partially dilated by preceding treatment is unimportant in this case. On the contrary, the non-cumulative technique permits the inhalation of a high amount of drug that reaches β_2 -adrenoceptors, which are present also in the larger airways, and activates a larger number of these receptors.

Although the potential role of formoterol in acute exacerbation of COPD is an intriguing finding, it must be highlighted that it has been observed that the relationship between initial FEV_1 % of predicted and the change in FEV_1 (ΔFEV_1) % of predicted at the top of the formoterol dose–response curve did not show the substantial increase at low initial FEV_1 % of predicted that is the case in the most severe patients (Figure 11.3) [18].

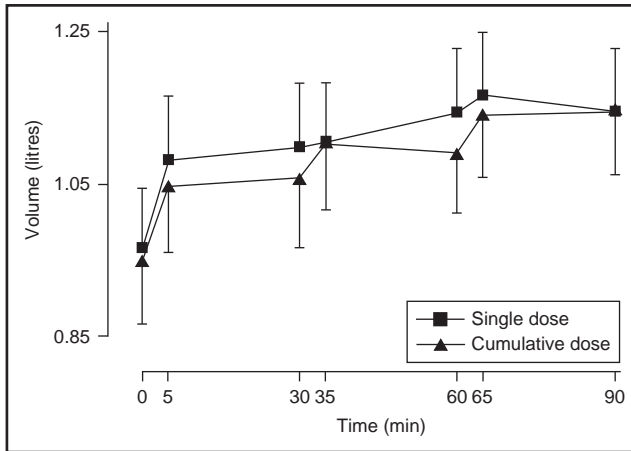


Figure 11.2 Changes in FEV₁ induced by the inhalation of a single 36 µg dose of formoterol Turbuhaler® or the same dose administered in a cumulative manner (three 12 µg doses were administered at 30-min intervals, with measurements being made 5 and 30 min after each dose) in patients with acute exacerbation of COPD (with permission from [22]).

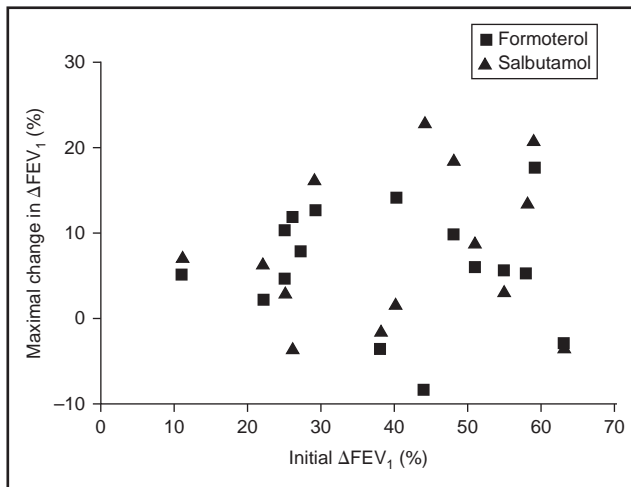


Figure 11.3 Relation of maximal change in forced expiratory volume in 1 second (Δ FEV₁) expressed as a percentage of the predicted FEV₁ (Δ FEV₁ % predicted) to initial FEV₁ % predicted after inhalation of formoterol ($r = -0.090$) and salbutamol ($r = 0.141$) in patients attending outpatient clinics because of mild acute exacerbations of COPD (with permission from [18]).

Since acute exacerbations must be treated by increasing the dose and/or frequency of bronchodilators [2], adverse effects are a real risk. The adverse effects of formoterol, as for all inhaled β_2 -agonists, include tremors, headache, nausea, vomiting and palpitations. Adverse cardiovascular effects such as changes in heart rate and the ECG are also possible but rare, and prevalent in patients with coexisting cardiac disease [25]. Several studies, which have involved patients suffering from acute exacerbation of COPD and often older

than 65 years, have been unable to document a significant impact of a higher than customary dose of formoterol on heart rate. Only minor changes in heart rate have been observed after the inhalation of 48 µg formoterol [17, 18, 22, 26]. Moreover, formoterol did not induce significant modifications in SpO₂ in patients suffering from acute exacerbation of COPD, although some patients presented a decrease in SpO₂ to <90% [17, 18, 22, 26]. This is an important finding because it is known that the administration of β-adrenergic agents to patients with airways obstruction often results in a transient decrease in the partial pressure of oxygen in arterial blood (PaO₂) despite concomitant bronchodilation. This is the so-called paradoxical hypoxaemia [27]. The transient hypoxaemia after β₂-agonist administration has been attributed to the potent pulmonary vasodilator action of these agents, mediated via β₂-adrenoceptors relieving hypoxic pulmonary vasoconstriction. By increasing blood flow to poorly ventilated lung regions, ventilation–perfusion inequality increases [28, 29].

Khoukaz and Gross [30] documented small but statistically significant declines in PaO₂ after administration of both salmeterol and salbutamol in patients with stable COPD. The decline in PaO₂ after salmeterol was of lesser magnitude but was more prolonged than that after salbutamol, the greatest mean change being 2.74 ± 0.89 mmHg at 30 min after salmeterol and 3.45 ± 0.92 mmHg at 20 min after salbutamol. A recent study has documented that a treatment with formoterol or salmeterol resulted in significant improvement in lung function and significant but small decreases in PaO₂ and increases in P(A–a)O₂ [31]. However, the average decreases in PaO₂ and increases in P(A–a)O₂ were quite small and of questionable clinical significance. In fact, the average 5 mmHg decrease in PaO₂ from 75 to 70 mmHg that was observed did not affect oxygen saturation and hence it was not clinically relevant.

The effect of β₂-agonists on PaO₂ is potentially dangerous for patients suffering from acute exacerbation of COPD and hypoxaemia. Small but statistically significant declines in PaO₂ were found after administration of both formoterol 9 and 18 µg, without major changes in PaCO₂ in patients hospitalised with a severe acute exacerbation of COPD and arterial hypoxaemia (Figure 11.4) [32]. The magnitude of decline in PaO₂ did not significantly increase with the highest dose, the greatest mean change being –4.0 mmHg at 30 min after formoterol 9 µg, and –5.5 mmHg at 60 min after formoterol 18 µg. Moreover, at 120 min, the magnitude of decline was –2.2 mmHg after formoterol 9 µg and –4.0 mmHg after formoterol 18 µg.

An important issue is to establish the importance of the impact of long-acting β₂-agonists on ventilation–perfusion inequality. β₂-agonists have been suggested to induce a fall in pulmonary vascular resistance because of an increase in cardiac output [33, 34] and right ventricular ejection fraction [34, 35]. A direct vasodilatation due to the activation of β-adrenoceptors that are present in pulmonary vessels [36] is a more likely mechanism of action of formoterol and salmeterol in inducing the decrease in systolic pulmonary artery pressure (sPAP). It is well known that increased β-adrenergic activity is associated with marked reductions in the pulmonary vasoconstrictor responses to hypoxia [37]. In fact, pulmonary arterial smooth muscle cells carry β₂-adrenoceptors [38] that mediate the vasodilating effects of endogenous catecholamines. These β-adrenoceptors cause vasodilatation by activating adenylyl cyclase that is followed by an increase in the intracellular adenosine 3',5'-cyclic monophosphate (cAMP) content [39]. In effect, a recent trial has demonstrated that both formoterol and salmeterol have a significant short-term effect on sPAP in COPD patients [40]. Salmeterol and formoterol have been equally able in reducing sPAP in these patients (maximum decrease –4.0 mmHg and –3.6 mmHg, respectively). This finding clearly indicates that long-acting β₂-agonists impact on ventilation–perfusion inequality, but this effect seems to be short and without real clinical importance.

All of these results indicate that long-acting β₂-agonists, when taken in recommended dosages, result in significant declines in PaO₂ in patients suffering from acute exacerbation of COPD that could be attributed to their pulmonary vasodilator effects mediated via β₂-adrenoceptors on vascular smooth muscle. Therefore, the use of high doses of these agents must always be prudent.

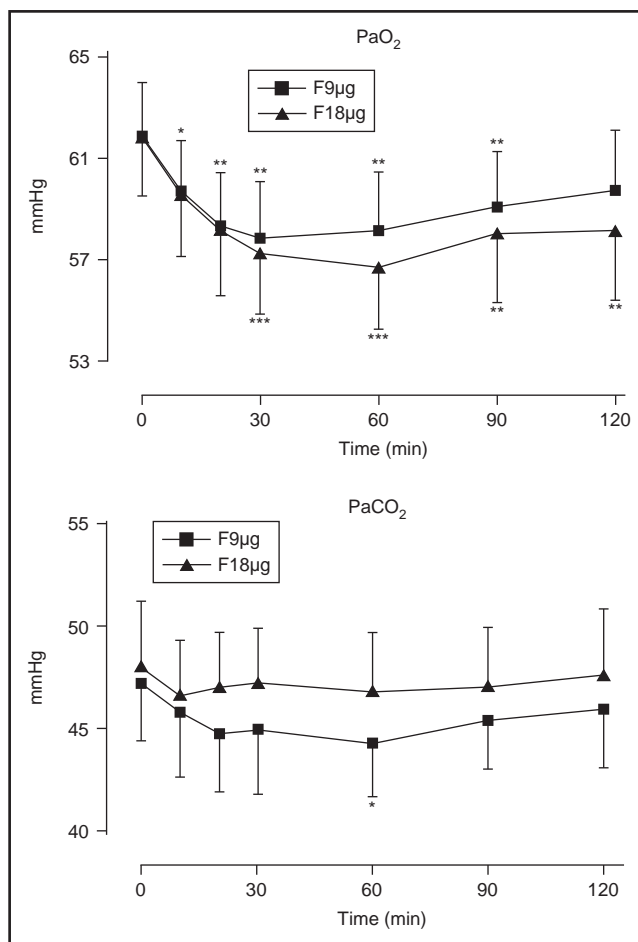


Figure 11.4 Mean changes (\pm SE) in PaO₂ and PaCO₂ with time after administration of two different doses of formoterol (9 and 18 mg) via Turbuhaler® in patients with acute exacerbation of COPD (with permission from [32]). * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$ vs. baseline.

ANTICHOLINERGIC AGENTS FOR ACUTE EXACERBATIONS OF COPD

Few studies have examined the use of short-acting anticholinergic agents in acute exacerbations of COPD [41, 42]. One study that compared the effectiveness of ipratropium bromide with a short-acting β_2 -agonist showed that each drug produced a small but significant improvement in pulmonary function [41]. Inhaled ipratropium bromide also produced a small but significant increase in PaO₂ within 30 minutes of its delivery.

In any case, the addition of a short-acting anticholinergic agent if the clinical response is not immediately favourable is also recommended, despite the uncertainties about combinations of short-acting bronchodilators in this setting [2]. However, a Cochrane review has documented that not only was there no evidence that the degree of bronchodilation achieved with ipratropium bromide was greater than that using a short-acting β_2 -agonist, but also that the combination of a β_2 -agonist and ipratropium did not appear to increase the effect on FEV₁ more than either agent used alone [43].

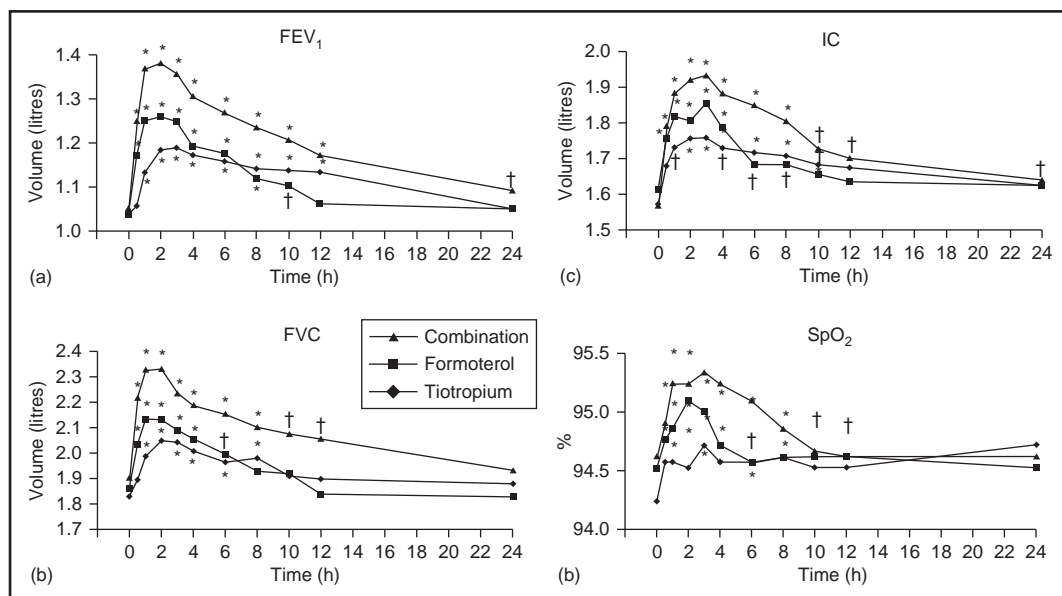


Figure 11.5 Effect of formoterol, tiotropium and their combination in patients with acute exacerbation of COPD (with permission from [44]).

A recent study has investigated the pharmacodynamic effects of one-day treatments with formoterol, tiotropium and their combination in patients with acute exacerbations of COPD [44]. The results showed that the combination of formoterol and tiotropium induced a greater overall bronchodilation, as expressed by FEV₁ area under the curve (AUC) both after 12 and 24 h, than the individual drugs administered singly. As expected, formoterol elicited a fast onset of action that, intriguingly, was enhanced by the concomitant inhalation of tiotropium. This finding is important because one of the goals of management of acute exacerbations of COPD is the prompt resolution of symptoms [2] that can be achieved by a rapid bronchodilation. Interestingly, the maximum bronchodilation obtained by the combination was higher than that recorded after the administration of the single drugs. On the other hand, the bronchodilator effect of formoterol disappeared after 12 h and that of tiotropium after 24 h (Figure 11.5). This trend was in accordance with the previously mentioned documentation that the duration of the bronchodilator effect of short-acting, inhaled β_2 -agonists is decreased in COPD exacerbation [7]. The speculative explanation of this shorter bronchodilation may be as a result of the increased bronchial inflammation that is present during exacerbation [45, 46]. It is possible that this inflammation modifies the pharmacokinetic and pharmacodynamic properties of inhalatory drugs, although we must emphasise that the amount of bronchodilation, expressed as maximum response, did not differ significantly from that found in patients with stable COPD [47]. In any case, the combination of formoterol and tiotropium allowed a sustained improvement in FEV₁ up to 24 h. It must be highlighted that the effect of treatment on SpO₂, although statistically significant, was not clinically relevant.

METHYLXANTHINES (THEOPHYLLINE)

Theophylline has been relegated to second-line intravenous treatment for the management of exacerbations in patients with an inadequate or insufficient response to short-acting bronchodilators [48]. Compared with placebo, most studies using intravenous theophylline have

shown marginal effects on symptoms, hospital admission rate, acid–base balance and lung function (FEV₁ and arterial blood gases) in non-acidotic patients [49, 50]. When used in the clinical setting, physicians should be aware of its many unwanted side-effects and interactions with other metabolic factors [48].

SYSTEMIC CORTICOSTEROIDS

Systemic corticosteroids are increasingly used in acute exacerbations of COPD and are recommended in the GOLD report [2]. A large Veterans Affairs Cooperative Study found that corticosteroids reduced the rate of treatment failures (defined as death from any cause or the need for mechanical ventilation) by about 10% for up to 90 days (Figure 11.6) and also the length of hospitalisations in patients hospitalised with exacerbations of COPD [51]. A subgroup analysis suggested that the benefits of corticosteroid treatment were associated with a more favourable outcome in patients with previous exacerbations who needed admission to hospital. A group in the UK looked at 56 hospitalised patients with acute exacerbations of COPD and found that oral prednisolone 30 mg once daily for two weeks improved spirometry and reduced hospital length of stay [52]. Thompson and colleagues [53] established that using oral corticosteroids in the outpatient treatment of acute exacerbations of COPD improved gas exchange, spirometry and symptoms. It must be highlighted that few studies have reported changes in FEV₁ measurements >72 h after initial treatment. A Cochrane systematic review [54] documented that by this time, the benefit of corticosteroid treatment had disappeared and there was no significant difference between treatments, weighted mean difference 30 ml (95% confidence interval [CI] –40 to 100).

The length of treatment necessary has been debated in the literature. The Veterans Affairs Cooperative Study found that an 8-week regimen of corticosteroids was not superior to a 2-week regimen [51]. A more recent study in Turkey compared a 3-day regimen of methylprednisolone with a ten-day regimen and found the longer regimen to be superior [55]. The GOLD report [2] recommends the use of a ten-day regimen and argues against long-term treatment with systemic corticosteroids. It would appear that a short course of systemic corticosteroids is warranted in patients with moderate to severe acute exacerbations of COPD. The optimal dosage for systemic corticosteroids in the treatment of COPD has not been clearly established in the literature: various randomised trials have used dosages ranging from 20 mg/day of methylprednisolone (equivalent) to 500 mg/day [56].

Despite proofs of efficacy, some concerns remain about using systemic glucocorticosteroids to treat all patients with exacerbations of COPD. Firstly, it was calculated that nine patients required treatment with systemic corticosteroids to avoid one treatment failure [54]. This was mainly because the short-term advantages of these agents were outweighed by the occurrence of adverse effects such as hyperglycaemia, myopathy [57] and osteoporosis [58]. Moreover, suppression of the adrenal response is common after short-term, high-dose corticosteroid treatment [59].

INHALED CORTICOSTEROIDS AS AN ALTERNATIVE TO SYSTEMIC CORTICOSTEROIDS

In this context, the possibility of treating patients with acute exacerbations of COPD with inhaled corticosteroids that have fewer systemic adverse effects is of particular interest.

One large study indicated that 2 mg of nebulised budesonide every 6 h may be an alternative to 30 mg of oral prednisolone every 12 h in the treatment of non-acidotic COPD exacerbations [60], but whether the additional expense was justified in all cases was unclear [61]. In any case, compared with prednisolone, nebulised budesonide was associated with fewer occurrences of hyperglycaemia, a potential advantage for patients with COPD who have such comorbid conditions.

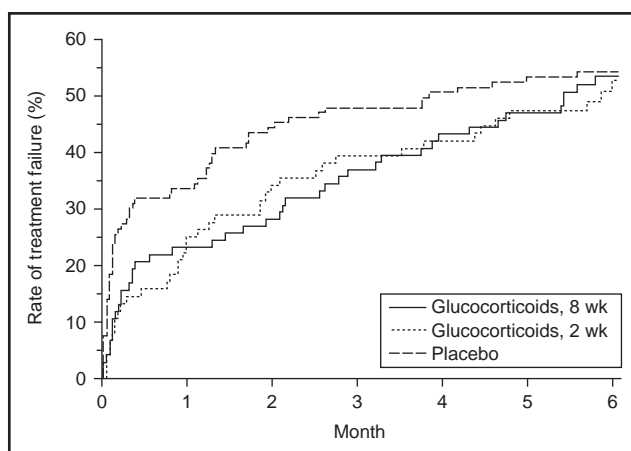


Figure 11.6 Systemic corticosteroids reduced the rate of treatment failures by about 10% for up to 90 days when used for patients hospitalised with exacerbations of COPD. Significant treatment benefits were no longer evident at 6 months. The 8-week regimen of therapy was not superior to the 2-week regimen (with permission from [51]).

A smaller trial has shown that 2 mg of nebulised budesonide every 6 h may be an alternative to parenteral (intravenous) prednisolone 40 mg daily in the treatment of acute exacerbations of COPD [62]. In both groups of treatment, differences were significant ($P < 0.001$) for PEFR, SaO_2 and PaO_2 , but not for PaCO_2 and pH, in comparison with their baseline values. Interestingly, there were no significant differences between groups for all parameters (PEFR, PaO_2 , PaCO_2 , pH and SaO_2) at all time periods. No adverse events were recorded in either group.

Recently, nebulised budesonide has been compared with standard bronchodilator treatment (nebulised salbutamol, 2.5 mg qid, and nebulised ipratropium bromide, 0.5 mg qid) and systemic corticosteroids (40 mg prednisolone) in combination with standard bronchodilator treatment [63]. In the acute phase of the treatment, the recovery rates with regard to spirometric and arterial blood gas parameters did not differ between the groups utilising systemic and nebulised forms of corticosteroids, although the recovery rates were significantly better in the corticosteroid groups than in the group receiving only bronchodilator treatment. In particular, high-dose nebulised budesonide was found to be as effective as systemic corticosteroids in short- and long-term treatment of patients hospitalised with exacerbations of COPD, except in very severe cases. In addition to this, nebulised budesonide exerted less systemic activity than systemic corticosteroid administration, as indicated by serial blood glucose measurements (Table 11.1).

CORTICOSTEROID AND LONG-ACTING β -AGONIST COMBINATION THERAPY

These studies, together with the above-described findings on the effects of long-acting β_2 -agonists, raise two important questions:

1. Might inhaled budesonide and inhaled formoterol be an alternative to oral prednisolone and short-acting β_2 -agonists, respectively, in the treatment of acute exacerbations of COPD?
2. If this is the case, might we use a combination therapy with single inhaler budesonide-formoterol in this pathologic condition?

Table 11.1 Patients hospitalised with exacerbations of COPD ($n = 159$) were randomised into three groups. Group 1 received only standard bronchodilator treatment, group 2 received a systemic corticosteroid (40 mg prednisolone) plus standard bronchodilator treatment and group 3 received nebulised budesonide (1500 μg qid) plus standard bronchodilator treatment. The study demonstrates that nebulised budesonide may be an effective and safe alternative to systemic corticosteroids in the treatment of exacerbations of COPD (with permission from [63])

Characteristics	Group	Baseline	At 24 h	At 72 h	At 7 days	At 10 days
FVC % pred	1	64.5 \pm 21.5	64.7 \pm 20.8	66.1 \pm 22.9	66.6 \pm 20	70.1 \pm 22.3
	2	57.5 \pm 17.7	61.4 \pm 16.9	64.5 \pm 19.3	70.2 \pm 22.1	73.8 \pm 22.6
	3	64.3 \pm 20.4	68.7 \pm 21.6	70.0 \pm 19.7	75.5 \pm 23.9	78.8 \pm 21.8
FEV ₁ % pred	1	36.7 \pm 11.9	36.5 \pm 11.2	37.1 \pm 13.4	38.6 \pm 14.9	40.7 \pm 15.0
	2	35.3 \pm 11.7	36.4 \pm 12.8	38.4 \pm 15.3	42.9 \pm 13.9	44.2 \pm 14.6
	3	39.6 \pm 12.9	43.9 \pm 11.8	45.1 \pm 15.6	48.0 \pm 14.2	50.8 \pm 15.8
FEV ₁ /FVC	1	46.8 \pm 15.9	46.3 \pm 15.6	46.1 \pm 14.6	45.9 \pm 14.8	45.6 \pm 13.4
	2	48.4 \pm 13.4	47.5 \pm 12.1	48.4 \pm 13.7	48.1 \pm 11.9	47.5 \pm 11.7
	3	48.4 \pm 13.2	48.2 \pm 14.1	49.1 \pm 12.6	50.3 \pm 13.0	51.1 \pm 14.0
FEF _{25-75%} % pred	1	16.4 \pm 7.8	15.8 \pm 8.7	16.6 \pm 7.4	17.0 \pm 8.9	17.7 \pm 9.1
	2	15.7 \pm 8.4	15.9 \pm 9.3	16.4 \pm 10.4	16.6 \pm 9.9	17.4 \pm 10.0
	3	20.6 \pm 16.1	21.1 \pm 15.8	20.7 \pm 16.1	21.6 \pm 12.0	22.9 \pm 11.7
PaO ₂ mmHg	1	53.4 \pm 11.1	54.4 \pm 10.9	55.7 \pm 12.3	56.1 \pm 12.7	57.5 \pm 11.4
	2	49.1 \pm 12.6	54.7 \pm 10.3	59.5 \pm 11.8	60.6 \pm 13.3	62.5 \pm 12.3
	3	50.1 \pm 14.8	55.4 \pm 14.1	57.2 \pm 13.9	61.4 \pm 14.5	62.2 \pm 13.8
PaCO ₂ mmHg	1	47.4 \pm 16.7	47.1 \pm 15.4	46.2 \pm 11.9	43.5 \pm 10.7	43.9 \pm 9.8
	2	51.4 \pm 10.3	50.9 \pm 11.3	48.1 \pm 9.7	45.9 \pm 10.0	45.2 \pm 9.8
	3	46.8 \pm 12.7	47.8 \pm 9.8	46.2 \pm 10.2	45.1 \pm 10.7	44.5 \pm 10.5
SaO ₂ %	1	83.6 \pm 10.0	84.7 \pm 9.1	86.1 \pm 8.2	88.2 \pm 7.2	88.7 \pm 6.4
	2	80.1 \pm 12.4	82.2 \pm 10.1	85.4 \pm 9.7	88.9 \pm 7.1	90.5 \pm 6.8
	3	79.9 \pm 13.7	81.9 \pm 11.7	85.8 \pm 8.8	89.7 \pm 6.3	90.9 \pm 5.3
Glucose mg. dl ⁻¹	1	114.0 \pm 31.7	110.0 \pm 33.5	106.6 \pm 25.5	104.5 \pm 18.9	102.8 \pm 16.4
	2	126.4 \pm 37.8	114.9 \pm 35.1	112.3 \pm 29.8	127.1 \pm 27.7	129.1 \pm 23.4
	3	114.3 \pm 24.9	113.7 \pm 27.9	110.4 \pm 31.1	107.1 \pm 25.5	104.6 \pm 22.7

Data are presented as mean \pm SD. FVC = forced vital capacity; % pred = % predicted; FEV₁ = forced expiratory volume in one second; FEF_{25-75%} = mean forced expiratory flow between 25 and 75% of FVC; PaO₂ = arterial oxygen tension; PaCO₂ = arterial carbon dioxide tension; SaO₂ = arterial oxygen saturation. 1 mmHg=0.133 kPa.

It has been documented that the addition of budesonide influences the fast onset of action of formoterol in patients with COPD who are not using inhaled or oral corticosteroids, at least when the two drugs are administered via a single inhaler (Figure 11.7) [64]. Apparently, the addition of budesonide to formoterol does not induce an increase in heart rate in patients with COPD who are not using inhaled or oral corticosteroids when the two drugs are administered via a single inhaler.

It is difficult to explain why budesonide influences the onset of action of formoterol. The classical genomic actions of corticosteroids require nuclear localisation of the steroid recep-

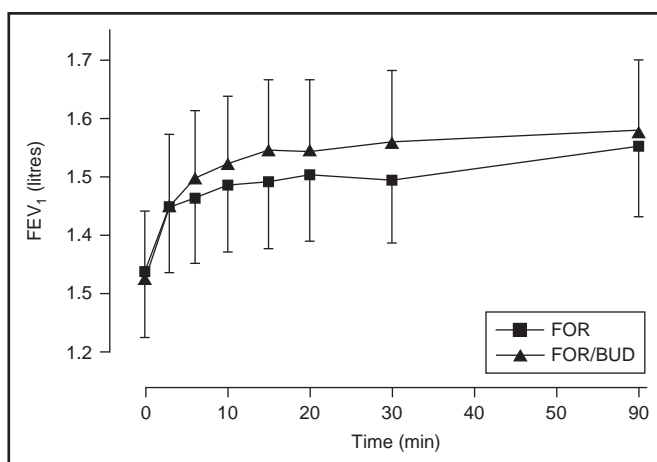


Figure 11.7 The addition of budesonide influences the fast onset of action of formoterol in patients with COPD who are not using inhaled or oral corticosteroids, at least when the two drugs are administered via a single inhaler (with permission from [64]).

tor and take ~30–60 min. In contrast, corticosteroid actions that occur within seconds to a few minutes have been referred to as ‘non-genomic’ or rapid action of steroids and are non-classical actions [65]. Therefore, the capacity of budesonide to influence the onset of action of formoterol might be explained by actions that can broadly be termed non-genomic. Increasing evidence for rapid non-genomic steroid effects has been generated, effects that are likely to be transmitted via specific membrane receptors for steroids [66]. Unfortunately, reports of rapid corticosteroid actions have been infrequent, but on the basis of the literature [67, 68], it is possible to speculate that budesonide enhances responsiveness to formoterol by increasing the activity of the G α protein as documented in human isolated bronchi with beclomethasone [68]. In particular, the finding that corticosteroid effects on Gs protein expression may vary between cell types [67] might explain the discrepancy that has been observed between the responses of the airways and the heart.

Since the airway circulation has an important role in the clearance of inhaled drugs (e.g. bronchodilators) from the respiratory tract, the inflammatory increase in airway blood flow is likely to have clinically undesirable effects in the acute exacerbation of COPD [69]. Corticosteroids are able to decrease airway blood flow. This effect might be explained by the capacity of corticosteroids to interfere with noradrenaline uptake by smooth muscle cells of the human bronchial arteries (extraneural uptake: uptake₂). This could consequently increase noradrenaline concentration at α -adrenergic receptor sites on the bronchial vascular smooth muscle [70]. The pulmonary vasculature expresses α -adrenoceptors and the stimulation of these receptors induces vasoconstriction [71]. The corticosteroid-induced vasoconstriction peaks rapidly (within 30 min after drug inhalation) [72]. With respect to airway disposal of inhaled drugs, this effect is likely to enhance the action of inhaled bronchodilators by diminishing their clearance from the airway. Thus, the rapid airway vasoconstriction induced by inhaled budesonide might be responsible for enhancing the bronchodilator action of inhaled formoterol.

The fact that budesonide influences the onset of action of formoterol suggests that use of the formoterol–budesonide combination is preferable to that of formoterol alone when a rescue action is needed, as in the case of acute exacerbations of COPD. It is likely, in fact, that the faster onset of action might influence the control of symptoms in such a pathological condition. Rapid onset of bronchodilation is an absolute requirement for any inhaled bron-

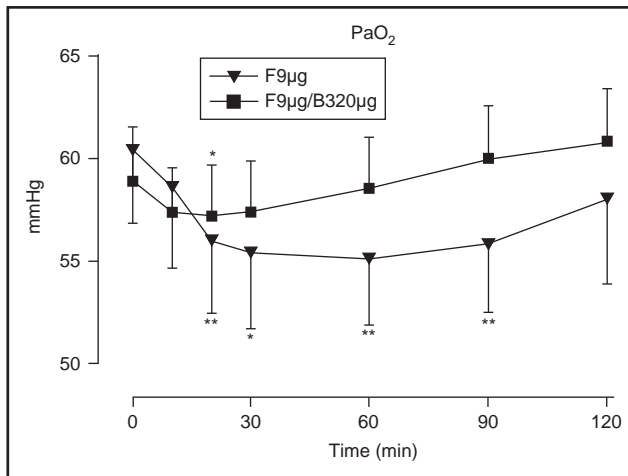


Figure 11.8 The simultaneous administration of budesonide 320 µg significantly reduced the acute effect of formoterol on PaO₂ in patients suffering from acute exacerbation of COPD and hypoxaemia (with permission from [32]). * = $P < 0.05$; ** = $P < 0.01$ vs. baseline.

chodilator administered on demand. The use of the formoterol–budesonide combination is preferable to that of formoterol alone because it has also been documented that the simultaneous administration of budesonide 320 µg significantly reduced the acute effect of formoterol on PaO₂ in patients suffering from acute exacerbation of COPD and hypoxaemia (Figure 11.8) [32]. The corticosteroid-induced vasoconstriction might divert blood flow away from poorly ventilated alveoli to the regions that are better ventilated, thereby optimising ventilation–perfusion ratio matching, and maintaining an adequate systemic PaO₂ [71].

EFFICACY OF A COMBINATION THERAPY WITH SINGLE INHALER BUDESONIDE–FORMOTEROL IN THE TREATMENT OF ACUTE EXACERBATIONS OF COPD

Because of the safety profile of budesonide–formoterol combination therapy and its effectiveness, the incremental benefit over 24 h of adding the budesonide–formoterol combination in a single inhaler to a standardised regimen of medications commonly used in the acute management of COPD has been assessed in 46 subjects who had been hospitalised for a severe acute exacerbation of COPD, but did not have acute respiratory failure requiring mechanical ventilation [73]. They received a standard protocol consisting of the i.v. administration of methylprednisolone (in a standardised dosage of 0.5 mg/kg), aminophylline and antibiotics every 12 h. All patients were randomly allocated to receive either budesonide–formoterol combination (360/9 µg delivered dose) via Turbuhaler® or salbutamol (200 µg metered dose) via MDI q6/h. The budesonide–formoterol combination group elicited a greater improvement in FEV₁ from baseline to 24 h, but the difference between the two treatments was not significant (Figure 11.9). In addition, the differences in heart rate and in PaO₂ between the two treatments were not significant, although both the budesonide–formoterol combination and salbutamol induced a slight decrease in PaO₂ 30 min after the first administration of these treatments that was smaller with the budesonide–formoterol combination. The frequency of side-effects in the two groups was similar.

A second trial has compared the efficacy of a combination therapy with single inhaler budesonide–formoterol and a parenteral combination of aminophylline and prednisolone

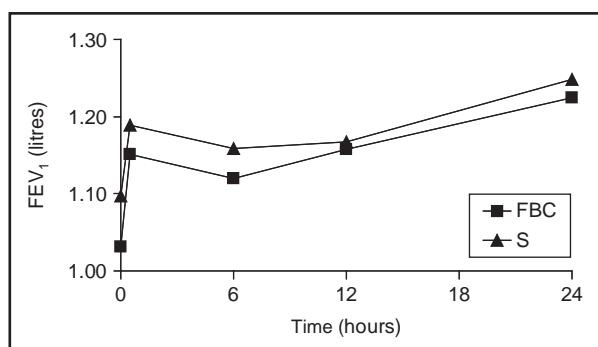


Figure 11.9 Formoterol–budesonide (FBC) in 46 patients with acute exacerbation of COPD who received i.v. methylprednisolone, i.v. aminophylline and antibiotics every 12 h and were allocated to receive either FBC 9/320 µg via Turbuhaler® or salbutamol (S) 200 µg via MDI every 6 h.

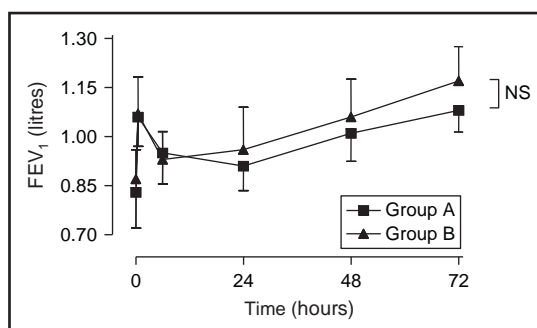


Figure 11.10 Broncholytic efficacy of a combination therapy with single inhaler budesonide–formoterol in the treatment of acute exacerbations of COPD. Group A: budesonide–formoterol 160/4.5 µg × 4 inhalations every 6 h; Group B: i.v. aminophylline 240 mg + i.v. prednisolone 20 mg every 12 h + inhaled salbutamol 400 µg every 6 h.

plus inhaled salbutamol in another 46 patients hospitalised because of a severe acute exacerbation of COPD, but without acute respiratory failure requiring mechanical ventilation [74]. Patients were randomised to receive either budesonide–formoterol combination 160/4.5 µg × 4 inhalations every 6 h or aminophylline 240 mg + prednisolone 20 mg intravenous every 12 h + inhaled salbutamol 400 µg every 6 h. All patients received oral antibiotics and supplemental oxygen. At the end of treatment, increases in FEV₁ and PaO₂ values were statistically significant in each group, whereas changes in PaCO₂ and pH were not significant. The differences between groups in FEV₁ (Figure 11.10) and PaO₂ were not significant. No adverse effects were experienced in either group.

Recently, a double-blind, randomised, non-inferiority, parallel-group, multicentre study has compared two treatment strategies (two weeks' treatment with inhaled budesonide/formoterol [320/9 µg, qid] was compared with prednisolone [30 mg once daily] plus inhaled formoterol [9 µg, bid]) in 109 patients with acute exacerbations of COPD attending a primary healthcare centre [75]. Non-inferiority of budesonide/formoterol was proven because the lower limit of FEV₁ change (97.5% CI) was above 90% of the efficacy of the alternative treatment. Symptoms, quality of life, treatment failures and the need for reliever medication (and exacerbations during follow-up) did not differ between the groups. No safety concerns were identified.

The results of these studies support the use of the budesonide–formoterol when a rescue action is needed, as in the case of acute exacerbations of COPD. It is likely, in fact, that the faster onset of action might influence the control of symptoms in such a pathological condition. Rapid onset of bronchodilatation is an absolute requirement for any inhaled bronchodilator administered on demand. Moreover, such a combination allows the supply of a corticosteroid that is effective and exerts less systemic activity than systemic corticosteroid administration.

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Non-invasive positive pressure ventilation for the treatment of respiratory failure due to exacerbations of COPD

S. Nava, P. Navalesi

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) exacerbation may need hospital admission when the symptoms of increased dyspnoea, cough or sputum production are accompanied by a lack of response to treatment of the exacerbation, an inability to feed or sleep caused by dyspnoea, an inability to comply with treatment at home, progressive or prolonged symptoms, altered mental status, worsening of hypoxaemia, new or progressive hypercapnia, the presence of new signs or worsening of previous signs of *cor pulmonare*, as well as any intercurrent process that adversely affect pulmonary function.

Patients affected by acute respiratory failure (ARF) secondary to COPD exacerbation have traditionally been treated by endotracheal intubation and mechanical ventilation to correct the acute respiratory acidosis, while reducing dyspnoea and inspiratory effort [1]. Even though invasive mechanical ventilation is a life-saving procedure, endotracheal intubation is the most important risk factor for nosocomial pneumonia [2] and may damage the tracheal mucosa [3]. Furthermore, it increases patients' discomfort and need for sedatives.

Non-invasive ventilation (NIV) is now widely recognised as a valid means to avoid intubation and its associated side-effects and complications in patients with ARF [4–6]. NIV preserves airway defence mechanisms, speech and swallowing. Furthermore, NIV affords greater flexibility in applying and removing ventilatory assistance [2].

NIV may be used in COPD patients with an acute exacerbation at different times:

1. To prevent the occurrence of impending (but not established) acute or post-extubation failure;
2. At an early stage, when respiratory failure is already established, to avert the need for endotracheal intubation; and
3. As an alternative to invasive ventilation at a more advanced stage of acute respiratory failure or to facilitate the process of weaning from mechanical ventilation.

NIV duration and intensity strongly depend on the time at which it is instituted.

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NIV TO PREVENT ACUTE RESPIRATORY FAILURE

Very few studies have so far assessed the efficacy of NIV at preventing the occurrence of acute respiratory failure and all of those that did so included patients with a relatively mild exacerbation of COPD. Bardi and colleagues [7] randomised 30 patients, the large majority of whom had a pH >7.35, to early NIV or medical therapy alone. No significant improvement in mortality, need for endotracheal intubation or time spent in hospital was found. In a similar population, Keenan and associates [8] reported no difference in any clinical outcome, but a significant reduction in dyspnoea with NIV, although mask ventilation was found to be very poorly tolerated.

In summary, according to these studies, anticipating the use of NIV in patients with an exacerbation of COPD to prevent, rather than to treat, respiratory distress and ventilatory failure is futile and would therefore represent an unnecessary loss of resources.

NIV TO PREVENT ENDOTRACHEAL INTUBATION

Patients with acute respiratory acidosis and rapid clinical deterioration secondary to an exacerbation of COPD benefit most from NIV [4]. When acute hypercapnic respiratory failure occurs, standard medical treatment, whose primary aims are (i) to supply adequate tissue oxygenation by judicious administration of low-flow oxygen; (ii) to attempt to treat the cause of exacerbation by administering antibiotics; and (iii) to reduce bronchial obstruction and inflammation by giving aerosolised bronchodilators and systemic glucocorticoids is prone to a high failure rate of 27–74% [9, 10].

Arterial pH is by far the most important determinant in deciding whether to institute NIV, but other clinical indicators such as the severity of the dyspnoea, tachypnoea and the use of accessory muscles are also considered [4]. There is therefore the potential to prevent further clinical deterioration by increasing alveolar ventilation [11] and reducing inspiratory effort [12].

In the last decade, several randomised controlled trials [9, 10, 13–18] have shown that the addition of NIV to medical treatment relieves dyspnoea [9, 13], improves vital signs and gas exchange [9, 10, 13], prevents endotracheal intubation [9, 10, 14], reduces complications [10, 18], lowers mortality [9, 10] and shortens the time spent in hospital [9, 15–17]. Brochard and co-workers [10], however, found that the benefits of NIV over standard treatment vanished when only those patients in whom treatment failed and who required intubation were considered: in particular, after adjustment for intubation, there was no difference in mortality.

With few exceptions [9, 10], the above-cited clinical trials included relatively small numbers of patients and were accordingly underpowered. Systematic review and meta-analysis of several studies has therefore been carried out in recent years [19–23]. By analysing pooled results from different trials, these studies confirmed that the addition of NIV to standard therapy decreases the need for endotracheal intubation [19, 21–23], reduces complications [6, 23], lowers mortality rate [6, 19, 21–23], shortens the time spent in hospital [6, 22, 23] and reduces costs [20] in patients with acute hypercapnic respiratory failure secondary to an exacerbation of COPD.

Notwithstanding a general consensus resulting from this large body of evidence on the value of NIV to avert the need for endotracheal intubation and invasive ventilation [4, 24], some aspects still deserve consideration. It is difficult to objectively define a threshold value of pH that indicates when a patient should or should not be treated with NIV. For example, one randomised trial found that adding NIV to standard treatment in hypercapnic COPD patients admitted to a respiratory ward with very mild ARF did not produce further advantages; the success rate, however, was 100% for both NIV and standard treatment [25]. Moreover, a recent systematic review [22] concluded that, unlike patients with severe exacerbation and established acidosis, patients with extremely mild or no respiratory acidosis did not benefit from NIV. On the other hand, in a large multicentre trial including mildly to

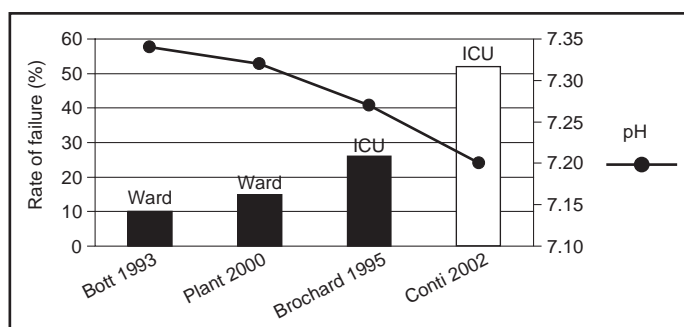


Figure 12.1 Rates of NIV failure and corresponding average pH values of four randomised controlled trials [9, 10, 13, 35]. The three studies indicated by the black bars are those where NIV was used in patients with mild to moderate acute respiratory failure in order to prevent endotracheal intubation [9, 10, 13], while the white bar indicates the study in which NIV was used as an alternative to invasive mechanical ventilation in more severe patients deemed to require ventilatory assistance [35]. The labels on top of the bars depict the setting where NIV was utilised (see text for further explanation) (with permission from Nava S, Navalesi P, Conti G. Time of non-invasive ventilation. *Intensive Care Medicine* 2006; 32:361–370).

moderately acidotic COPD patients (initial pH ≤ 7.35 and ≥ 7.25) admitted to a medical ward, Plant and colleagues [9] found that the rate of failure was lower with NIV than with standard therapy alone; subgroup analysis showed that NIV improved the outcome of patients whose pH at enrolment was ≥ 7.30 , whilst the rate of failure and mortality did not differ between the two treatment groups among patients whose enrolment pH was < 7.30 . These findings suggest that more severely ill patients need a higher dependency setting with a more favourable nurse-to-patient ratio and a higher level of monitoring [26]. Since the need for intubation, although markedly reduced, is not entirely abolished by NIV, it is advisable, whenever possible, to immediately manage patients with more advanced ARF in a location where endotracheal intubation can be rapidly performed when needed and to move from the ward to the intensive care unit (ICU) those patients who deteriorate or do not improve despite application of NIV [27–30].

The higher the ARF severity, as indicated by a lower pH, the more likely is NIV failure (Figure 12.1). Unfortunately, however, clear-cut predictors of NIV success are lacking, although a few studies suggest that, in general, patients with higher severity scores and lower levels of consciousness on admission, and those who do not show a positive initial response to NIV, are the most likely candidates for failure of NIV [27–30].

In contrast to invasive mechanical ventilation, discontinuing and resuming ventilator support is not a cumbersome procedure and can be easily carried out a number of times in a day. When used to prevent intubation, NIV is commonly applied intermittently for a variable number of hours (generally 6–18), depending on ARF severity and patient tolerance. The median daily NIV use was 7.6 h (range 1–23) in the study by Bott and colleagues [13] and 8, 7 and 5 h on days 1, 2, and 3 respectively in the study by Plant and co-workers [9], while Brochard and associates [10] and Kramer and colleagues [14] applied NIV for a minimum of 6 and 8 h per day, respectively. Although, to our knowledge, not specifically investigated by any study, it was commonly felt that the higher the hours of NIV application during the day, the more likely were the occurrence of NIV-related side-effects and complications such as eye irritation, erythema and skin abrasions. These are all sources of pain, discomfort, intolerance and agitation, often leading to treatment failure [31].

Despite the robust evidence of its effectiveness in COPD patients, NIV seems to be somewhat underused in routine clinical practice. An observational study evaluating the outcomes

of 166 COPD patients who had undergone invasive mechanical ventilation in the ICU reported that a trial of NIV was performed before intubation in only two of these patients [32]. In a large cohort study based on data collected from 349 ICUs in North America, South America and Europe, NIV was utilised in ~44% of all COPD patients receiving mechanical ventilation [33]. A survey including 42 medical ICUs in France found that NIV was used in almost 50% of all patients with acute or chronic respiratory failure, however, the rate of application ranged between 0% (in eight centres) and 67% (in a single ICU) [30]. Although logistic differences between centres may exist, NIV utilisation nevertheless seems to follow an 'all-or-nothing' pattern of behaviour that might be related to the reluctance of the staff to use this technique. Although a relatively straightforward practice, NIV is characterised by unique aspects requiring specific knowledge, and the familiarity and expertise of the team with the technique are major determinants of success [5, 34], which further promotes motivation.

Considering the strong evidence of efficacy, the relatively few hours of daily use and, compared with other treatment modalities, its fairly low rate of failure, the use of NIV to avoid intubation in COPD patients with mild to moderate ARF (i.e. pH <7.35 and >7.25) is strongly advisable and probably represents the best approach for the units that are willing to implement this technique.

NIV AS AN ALTERNATIVE TO INVASIVE VENTILATION

Early use of NIV in COPD patients with an exacerbation determining respiratory acidosis and impending respiratory muscle failure is effective in preventing further clinical deterioration and avoiding endotracheal intubation. Because of the abrupt onset of ARF, its rapid progression and/or delays in receiving medical evaluation and appropriate treatment, some patients may worsen so much that mechanical ventilation becomes mandatory. However, if endotracheal intubation in such patients is not strictly required because of gasping for air, unconsciousness or the need to protect the airway, NIV might still be advantageous compared with invasive ventilation, as it eliminates the risks associated with intubation.

There is only one randomised controlled trial that compares NIV with invasive ventilation in COPD patients with severe ARF in whom ventilatory support was deemed necessary [35]. Twenty-three and 26 patients were randomised to receive NIV and conventional invasive ventilation respectively. The average pH on study entry was 7.20 for both groups, indicating that these patients had more severe ARF than those enrolled in the clinical trials in which NIV was used at an earlier stage (Figure 12.1). In the NIV group, treatment failed in 12 patients (52%), who were thus intubated to receive invasive mechanical ventilation. The authors found no significant differences between the two groups in ICU and hospital mortality, overall complications, duration of mechanical ventilation and ICU stay. The patients in the NIV group had a lower rate of sepsis and septic shock and showed a trend toward a lower incidence of nosocomial pneumonia during their time in the ICU. In addition, at a 12-month follow-up, the rate of hospital re-admissions and the number of patients on long-term oxygen therapy were lower in the NIV group. Unfortunately, because of the relatively small number of patients included, this study was exposed to the risk of a type II error and, in addition, it was not possible to perform a *post hoc* analysis to assess whether or not the patients in whom NIV failed were harmed by delayed intubation and invasive ventilation.

These results were confirmed by a subsequent case-controlled clinical trial including 64 consecutive COPD patients with severe ARF caused by exacerbation or community-acquired pneumonia [36]. Data from these patients were prospectively collected and compared with those from a tightly matched historical control group taken from a large database of COPD patients treated in the same ICU with conventional invasive ventilation during the previous two years. The average pH of the patients and controls on entry into the study was

7.18. NIV failed in 40 patients (62%), who were then intubated. The mortality rate, duration of mechanical ventilation, time spent in the ICU and duration of post-ICU hospitalisation were similar in the two groups, but patients in the NIV group had fewer complications and showed a trend toward a lower probability of remaining on mechanical ventilation after 30 days. Apart from confirming the results obtained by Conti and co-workers [35], the large sample of patients and high rate of NIV failures allowed a subgroup analysis that showed that the outcomes of the 40 patients in whom NIV failed and of the 64 controls were no different, while the 24 patients in whom NIV was successful had better outcomes.

In both the aforementioned studies, NIV was used in an ICU and the study protocols had predefined criteria for NIV failure, which led in all cases to a prompt intubation when required. Unlike the clinical trials in which NIV was used to avoid intubation and was then intermittently applied for relatively few hours [9, 10, 13, 14], in these two studies patients received almost continuous ventilatory support, at least for the first 24–48 h. This might account for the ~40% of patients in whom NIV failed because of mask intolerance and discomfort, as reported by Squadrone and colleagues [36].

In conclusion, in patients with COPD deemed severe enough to require ventilatory support, the use of NIV at a more advanced stage of ARF is more likely to fail. A trial of NIV before proceeding to intubation and invasive ventilation does not, however, harm the patient and may be cautiously attempted whilst closely monitoring the patient in an ICU and avoiding any delay of intubation if required.

NIV TO WEAN PATIENTS OFF THE VENTILATOR

In the majority of cases, withdrawal of mechanical ventilation and extubation are possible immediately after resolution of the underlying problems responsible for ARF. However there is a group of ventilated patients who require more gradual and longer withdrawal of mechanical ventilation.

NIV is theoretically able to counteract several physiological mechanisms associated with weaning failure or difficulties. In ventilator-dependent COPD patients NIV has been shown to be as effective as invasive ventilation in reducing inspiratory effort and improving arterial blood gases [37]. In fact, following some uncontrolled clinical studies in which NIV was used as a bridge to weaning [38–42], the first randomised controlled study of this strategy was performed in severely ill COPD patients ventilated through an endotracheal tube [43]. Patients who failed the T-piece trial were randomised to either extubation with immediate application of NIV, or to continued weaning with the endotracheal tube in place. Overall, this study showed that the likelihood of weaning success was increased, while the duration of mechanical ventilation and ICU stay was decreased, when NIV was used as a weaning technique.

A second randomised controlled study in a single ICU was conducted on patients with chronic respiratory disorders, intubated for an episode of acute respiratory failure [44]. Thirty-three patients were randomised to receive 'traditional' weaning or NIV. This study also found a shorter duration of invasive mechanical ventilation in the groups weaned non-invasively, although no differences were found in ICU or hospital stay or three-month survival between the two groups.

In a third recent randomised controlled trial, Ferrer and colleagues [45] studied patients who failed spontaneous breathing trials on three consecutive days and were randomised to be extubated and receive NIV, or to remain intubated and continue a conventional weaning protocol. Most of the patients (~80%) were affected by hypercapnic respiratory failure. The duration of conventional mechanical ventilation, time spent in the ICU and the duration of hospitalisation were significantly reduced in the NIV group. Patients treated with NIV also had lower rates of nosocomial pneumonia and septic shock and better ICU and 90-day survival.

Further studies are clearly needed to assess the benefits of NIV in weaning in other forms of respiratory failure, such as acute respiratory distress syndrome, post-surgical complications or cardiac impairment.

In conclusion, NIV may be safely and successfully used in the ICU to shorten the process of liberation from mechanical ventilation in stable patients recovering from an episode of hypercapnic ARF who had previously failed a weaning trial.

SUMMARY

NIV should primarily be used for the early treatment of established episodes of ARF in COPD patients in order to avoid further deterioration and intubation and eventually to shorten the duration of invasive mechanical ventilation. A skilled team may also advantageously use NIV in the ICU as an alternative to invasive ventilation in patients with more advanced ARF episodes. Instituting this strategy at a more advanced stage does, however, imply the use of many consecutive hours of NIV, increasing the risk of side-effects leading to patient discomfort.

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13

'Home hospitals' for acute exacerbations of COPD

J. Roca, A. Alonso, C. Hernandez

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality that generates a significant burden on healthcare systems worldwide [1–2]. Despite recent important progress in the understanding of the disease mechanisms and in treatment standardisation [2], episodes of severe exacerbations continue to be the major cause of unplanned hospitalisations in COPD patients, particularly in those with advanced-stage disease [3]. This phenomenon, however, is also partly explained by the impact of commonly associated comorbidities and poor social circumstances on COPD outcomes [4].

A recent analysis of the burden of all chronic conditions on tertiary care hospitalisations [5] showed that COPD was the fourth most common cause of admission as a primary diagnosis. Its impact, however, was markedly higher in the subset of patients presenting multiple admissions over one year. This study showed that patients with cardiopulmonary disorders and COPD were mostly (up to 80%) admitted via the emergency room as unplanned hospitalisations. It is well known that the two disease conditions show high degrees of clustering [6–8]. Moreover, the literature [9] reports an unacceptably high rate of re-admissions in patients with respiratory disorders. In combination, these data indicate the need to revisit aspects of the management of exacerbated COPD patients with the aim of enhancing not only the efficacy of care during the exacerbations, but also preventing severe episodes of COPD exacerbations.

In view of the high social and economic burden generated by COPD hospitalisations, new modalities of care aiming to decrease admissions by empowering patients to self-detect exacerbations and to implement alternatives to conventional hospitalisation have been developed in recent years [10–15]. Short-stay units, respiratory day hospitals and home-based programmes are good examples of innovative services aimed at COPD patients.

The term 'home hospitalisation' refers to home treatment of selected COPD patients with severe exacerbations who are discharged either directly from the emergency room or after a short period of conventional hospitalisation. This modality of care was initially promoted to keep the patient in his/her own environment, to reduce the risk of hospital-acquired infections and to decrease the number of hospital beds being occupied by chronically ill patients. Further studies have demonstrated that home hospitalisation structured

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as an integrated care intervention shows a high potential for enhancing clinical outcomes in COPD patients [9].

Home hospitalisation of COPD patients is a short-term high-intensity intervention carried out by specialised personnel. Different studies [9, 16–20] and one systematic review analysis [12] assessing home hospitalisation and early discharge have essentially shown that the approach is safe and has a comparable efficacy compared with conventional hospitalisation. Moreover, Hernandez and colleagues [9] clearly demonstrated beneficial effects of home hospitalisation compared with conventional care, indicating in addition that improvement of clinical outcomes went hand-in-hand with a significant reduction of direct costs.

Home hospitalisation is only suitable, however, in a subset of exacerbations (<40% of cases) that must be selected at the hospital after proper assessment by a specialised team. The best results of home hospitalisation are obtained when the intervention is conceived as part of an integrated approach to chronic care [9]. In this scenario, home hospitalisation should be taken as an alternative to conventional hospitalisation showing valid results in a subset of selected COPD patients. Despite the promising results of this new approach in the management of COPD exacerbations, several important challenges still need to be faced.

The different small-scale pilot studies on home hospitalisation [9, 12–20] carried out to date prompt the need for the extensive deployment of this innovative approach as part of the regular healthcare provision for exacerbated COPD patients under the framework of a properly designed cost-effectiveness analysis.

HOME HOSPITALISATION REVISITED

Home hospitalisation carried out following a structured integrated care intervention [9], as described in Table 13.1 and Figure 13.1, generates better outcomes than conventional care of COPD exacerbations, namely:

1. Lower hospitalisation rates;
2. Lower rate of short-term relapses requiring emergency room admissions;
3. Clinically relevant improvement in health-related quality of life, as assessed by the St George's Respiratory Questionnaire (SGRQ) [21];
4. Higher degree of patient satisfaction; and
5. An important positive impact on knowledge of the disease and on patient self-management of the chronic condition (Figure 13.2).

The positive outcomes obtained in the study probably reflect the combined effects of the comprehensive homecare intervention displayed in Table 13.1. It is of note, however, that while the reduction in emergency room admissions in the home hospitalisation group was clear, the impact on short-term hospital re-admissions was rather modest, as seen in other reports [17]. The results were obtained with a rather modest use of the resources [9]. Only a small proportion of the five potential nurse visits was used (on average 1.7 nurse visits at home) during the two-month follow-up period. Although free-phone access to advice and information was provided to all patients, the average number of patients' phone calls to the nurse was only 0.76. Somewhat unexpectedly, the study showed that home hospitalisation was less costly than conventional care. A key issue in this approach, as stressed by several different studies [9, 12–20], is that home hospitalisation is suitable only in a subset of exacerbated COPD patients, who must be selected at the hospital after proper assessment by a specialised team.

It is remarkable that similar positive results were obtained in the different home hospitalisation studies [9, 12–20] despite noticeable country-specific differences in terms of interactions between primary care and tertiary hospitals. Whilst in Barcelona ~70% of the

Table 13.1 Description of the intervention in the home hospitalisation group [9]

<p><i>1. Assessment on emergency room (ER) admission by the specialised team</i></p> <p>1.1. Characteristics of the exacerbation, comorbidities, and response to treatment at the ER</p> <p>1.2. Baseline conditions of the patient (duration 1.5 h)</p> <p>(a) Health-related quality of life</p> <p>(b) Healthcare resources in the previous year</p> <p>(c) Fragility risk factors</p> <p>(d) Knowledge of the disease and compliance with therapy</p> <p>1.3. Decision on discharge from the ER or after a short period of inpatient hospitalisation based on 1.1 and 1.2.</p>
<p><i>2. Treatment at discharge</i></p> <p>2.1. Pharmacological therapy of COPD and comorbidities</p> <p>2.2. Non-pharmacological treatment (duration 2 h)</p> <p>(a) Education on knowledge of the disease; adherence to treatment; and recognition/prevention of triggers of exacerbation</p> <p>(b) Selection of appropriate equipment at home; training on administration of pharmacological treatment</p> <p>(c) Smoking cessation</p> <p>(d) Patient empowerment on daily life activities: hygiene, dressing, household tasks; leisure activities; breathing exercises; and skeletal muscle activity</p> <p>(e) Nutrition recommendations</p> <p>(f) Socialisation and changes in lifestyle</p>
<p><i>3. Home hospitalisation and 8-week follow-up</i></p> <p>3.1. First nurse visit at home at 24 h (duration 1 h)</p> <p>(a) Assessment of the response to pharmacological treatment</p> <p>(b) Introduction of changes under remote physician's supervision</p> <p>(c) On-site assessment of fragility factors</p> <p>(d) Action plan revisited and education reinforced</p> <p>3.2. 8-week follow-up</p> <p>(a) Number of home visits and duration of home hospitalisation were decided by the nurse</p> <p>(b) Patient free-phone access to the nurse was ensured</p> <p>(c) Nurse phone calls to patient to reinforce the action plan</p> <p>3.3. Failure of the programme</p> <p>(a) >5 nurse home visits during the 8-week follow-up</p> <p>(b) New problem requiring ER admission</p>
<p><i>4. Assessment after 2 months follow-up</i></p>

emergency room admissions in tertiary hospitals for COPD exacerbations corresponded to self-referrals [9, 22], this figure fell to ~30% on average in the United Kingdom and as low as 1% in the report by Skwarska and associates [17]. These results seem to support the notion that the efficacy of home hospitalisation is not dependent on the specificities of the health-care system, provided the logistics of the homecare services are fully managed by specialised teams linked to the hospital.

All of the studies on home hospitalisation and early discharge [9, 12–20] show a strong internal validity but a questionable external validity because of an elevated rate of exclusions among eligible patients fulfilling inclusion criteria (Figure 13.1) [9]. This is, however, a common problem in all disease-specific studies. It must be taken into account that among those patients eligible for specific integrated care programmes, ~60% of exclusions are generally due to severe comorbid conditions that can potentially be managed through

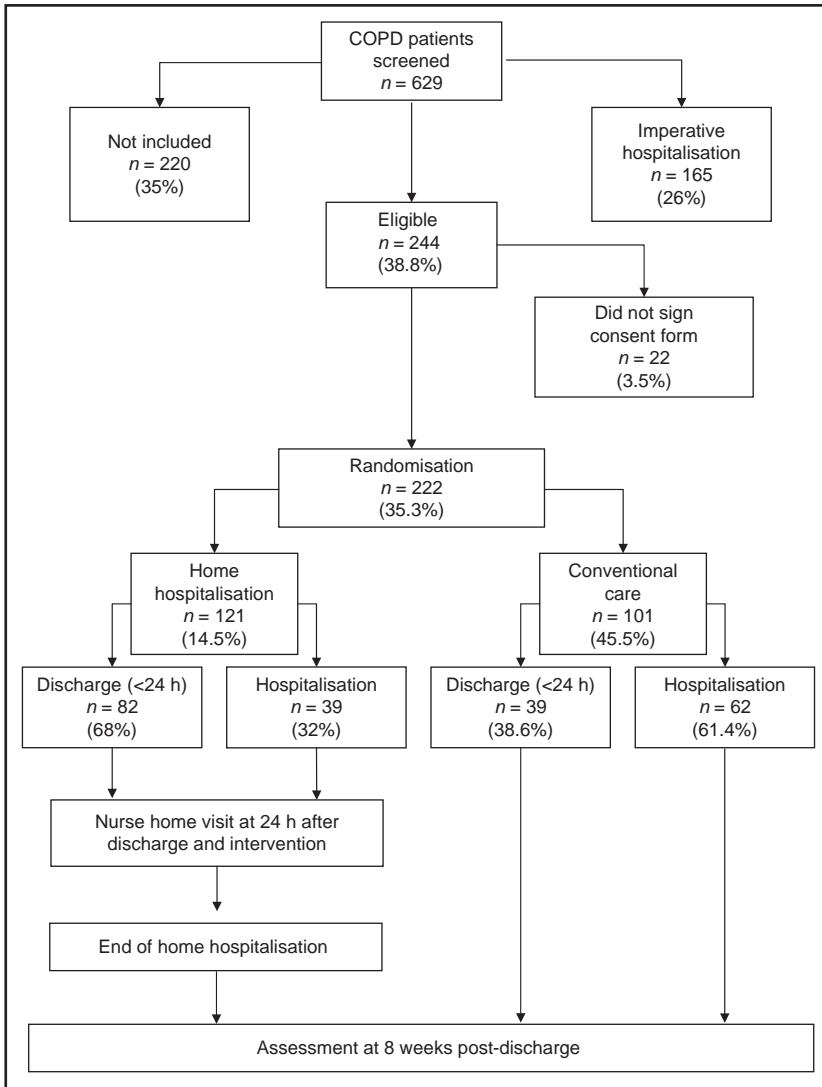


Figure 13.1 Study profile. From the 629 patients screened, 26% ($n = 165$) required imperative hospitalisation [10] while up to 35% ($n = 220$) were not eligible (see text). The remaining 244 patients (38.8%) were candidates for the study, but 22 patients (3.5%) did not sign the consent form. 222 patients were included (home hospitalisation: 121 and conventional care: 101) (with permission from [9]).

transversal programmes addressed to frail patients with multiple severe chronic disorders. The second most important exclusion factor, often present in frail patients, is a lack of appropriate social support, which reinforces the need for bridging healthcare and community services (as supported by the Innovative Care for Chronic Conditions [ICCC] framework proposed by the World Health Organization [WHO] [23–26]) following a distributed model of care based on a close collaboration between healthcare levels, community services and patients/carers (Figure 13.3).

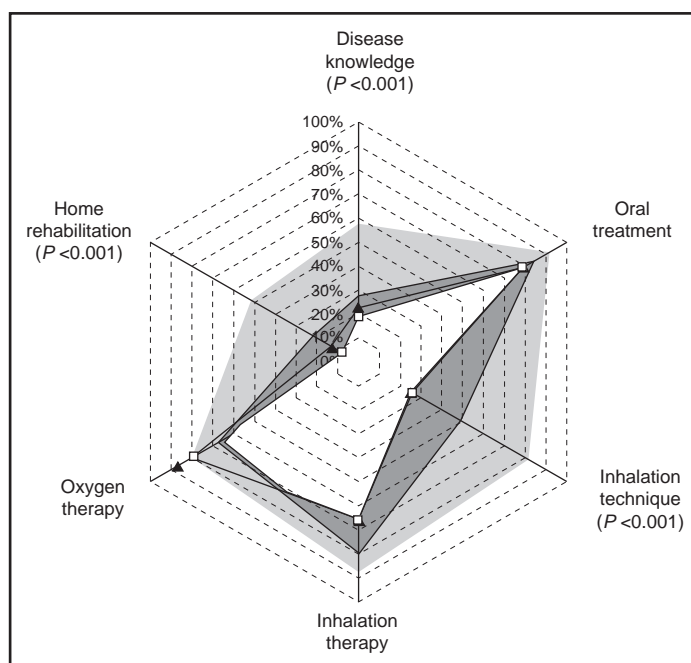


Figure 13.2 Knowledge of the disease and self-management of the chronic condition. Results are expressed as percent of patients. On admission (inner limits: HH, triangles; and, controls, squares), no differences were seen in any of the six dimensions of the graph. No changes in the control group (dark grey area) were seen during the 8-week follow-up period, but marked beneficial effects were detected in the HH group (light grey area) (with permission from [9]). HH = home hospitalisation.

COST ASSESSMENT

The overall economic burden of COPD (direct and indirect costs) has been estimated as being equivalent to 0.32% of USA gross domestic product in 2001 and direct medical costs attributed to COPD accounted for 1.5% of US healthcare expenditure [27]. Empirical evidence in many countries showed that expenditure for COPD patients is more than 2.4 times that of the healthy, insured population [28]. Moreover, expenditure for hospitalisations represents approximately 70% of all COPD-related medical care costs [29].

There has been controversy regarding the effects of home hospitalisation schemes on costs. Two randomised controlled trials [30, 31] reported that home hospitalisation significantly increased healthcare costs for COPD patients. The two trials, however, analysed a very small sample of patients whose severity of illness was not delineated. In contrast, four controlled trials conducted in the United Kingdom [16–19] and in Spain [9, 32] have shown both good safety and cost reduction when these type of services, either home hospitalisation directly from the emergency rooms or early discharge from the hospital, are applied to appropriately selected COPD patients with a well-defined home intervention.

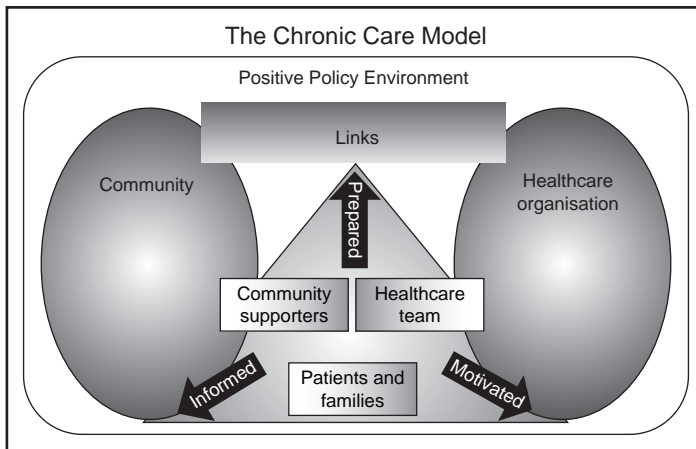


Figure 13.3 Diagram of the integrated care model proposed by the Innovative Care for Chronic Conditions (ICCC) initiative launched by the World Health Organization (with permission from [20–23]).

A COST MINIMISATION ANALYSIS

In the study by Puig-Junoy and co-workers [32], using the information generated in [9], the authors demonstrated that home hospitalisation decreased direct patient health costs by 36% compared with conventional care. The results obtained from the multivariate cost function displayed in Table 13.2 and Figure 13.4 clearly provided a useful insight into the efficiency gains than can be expected from integrated home care programmes in the management of COPD exacerbations. The multivariate cost function proved to be useful for disease cost forecasting and for evaluation and budgeting purposes.

In the analysis, the authors assumed no differences in clinical outcomes between home hospitalisation and conventional care, although better outcomes with home hospitalisation were proven in [9]. Under such an assumption, it might be considered that the two alternative programmes may be viewed as equivalent in outcome, such that a simple cost minimisation analysis could be adopted [33]. Using this approach, the authors [32] tested the primary economic hypothesis of weak dominance. That is, home hospitalisation showed similar safety and effectiveness to conventional care, but the former was less costly. The results of the analysis were consistent with the hypothesis. The average marginal impact of home hospitalisation in comparison with conventional care represented a mean cost saving of €647 per patient.

This economic evaluation [9, 32] may be affected by several limitations. Firstly, the perspective of the evaluation was that of the public healthcare insurer, excluding non-healthcare (indirect) costs. However, the short time horizon of the study (8-week follow-up) and the high cost of COPD exacerbations could indicate that a small proportion of the total cost of resources was not included in the analysis. A second limitation is that average costs were used to value hospital care. In fact, the existence of fixed hospital costs could amplify the value of any potential savings resulting from a reduction in bed-days. However, average cost may appropriately represent the value of freed resources, assuming that patients can be admitted to empty beds. A third limitation of the economic evaluation [32] comes from the fact that the clinical outcomes refer to a short period of time, given that the time horizon is restricted to the eight-week follow-up. In fact, there was no evidence of persistence of these results in a longer period of time.

Table 13.2 Multivariate estimate of patient costs

<i>Dependent variable log (cost)</i>			
<i>Covariates</i>	<i>Estimated coefficient</i>	<i>Standard error</i>	
Constant	6.979586	0.294397**	
FEV ₁	-0.009642	0.004817*	
Total SGRQ score	0.006030	0.002978*	
Exacerbations requiring in-hospital admission in the previous year	0.169333	0.072935*	
Intervention group (HH = 1)	-0.406642	0.160144*	
Smearing factor	1.5811		
<i>R-squared</i>	<i>0.138</i>	<i>Adjusted R-squared</i>	<i>0.118</i>

P* <0.01; *P* <0.05.
 FEV₁ = forced expiratory volume during the first second at 8 weeks of follow-up; HH = home hospitalisation; SGRQ = St George's Respiratory Questionnaire.

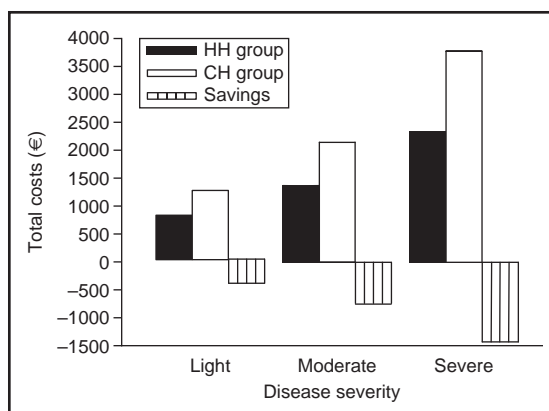


Figure 13.4 Total costs predictions as expressed by different levels of disease severity; home hospitalisation intervention (HH) was cheaper for any level of disease severity and severely ill patients obtained largest savings. CH = conventional hospitalisation.

The cost analysis [9, 32] demonstrates that a well-defined home-based integrated care programme for the management of COPD exacerbations is of interest, even if we adopt the weak dominant alternative, as assumed in the cost minimisation analysis carried out in the present analysis. An additional implication of our study for budgeting management policies in health services comes from the observed differences in the cost by categories (cost mix) between the two alternative programmes. Conventional budgeting practices in many health-care systems, fuelled by cost containment policies, impose budget ceilings separately for different types of inputs. This is especially true for pharmaceuticals. The data illustrate how an efficient alternative to the management of exacerbated COPD patients resulted in a higher consumption of pharmaceuticals per patient. It was, however, accompanied by an increase in patient compliance [9], as displayed in Figure 13.2.

A potentially relevant policy-related implication of the results reported by Hernandez and colleagues [9] could arise from the fact that the magnitude of resource savings under home hospitalisation was higher when the intervention was applied to more severe exacerbated COPD patients. Such a statement might be controversial, and it probably deserves more attention and future research. In this regard, there is a need to point out three considerations. Firstly, it has been well established in the clinical literature that COPD costs are positively correlated with disease severity. Absolute savings could then be higher for the provision of efficient management of more severe COPD patients. Secondly, the largest savings for more severe patients could be arbitrarily imposed by the empirical specification of the cost function, given that, since the dependent variable is log-transformed, the retransformation yields an exponential increase. Last but not least, the result only holds true for more severe exacerbated COPD patients (among those eligible for the home hospitalisation programme), thus excluding some of the more severely ill COPD patients.

Home hospitalisation should be analysed in the context of chronic disease care, in the so-called chronic care model (Figure 13.3) [23–26]. The identification of patients at high risk, cooperation of primary care practitioners and specialists, a focus on social care, and investment in information technology could all improve chronic care [34]. Data from the present study suggest that severe COPD patients with social support could benefit most from home-specialised care.

IMPACT ON EARLY RELAPSES

As alluded to above, patients with severe exacerbations of COPD requiring emergency room or hospital admission show high rates of early relapses after discharge. In developed countries, approximately one-third of these patients used to require re-admission within two months [9, 16–20]. Observational studies on severe exacerbations of COPD [22, 35, 36] indicate that the degree of functional impairment, together with repeated hospital admissions in the previous year, are the two most important factors associated with unplanned hospitalisations. Moreover, repeated hospital admissions are usually associated with poor health-related quality of life (HRQL) [37, 38], accelerated functional decline [39, 40] and increased mortality [41].

We hypothesise that the scenario described above can be partly explained by two complementary factors. Firstly, existing management strategies for COPD patients must be revisited in the light of new modalities of healthcare aiming to overcome the problems associated with fragmented care in chronic patients [23–26]. Secondly, but no less importantly, the pivotal underlying mechanisms that modulate the natural history of the disease are not properly taken into account in the clinical management of these patients. Many studies suggest that factors poorly related to impairment of forced expiratory volume in one second (FEV_1) play an important role in disease outcomes; namely, the association between aerobic capacity (maximum O_2 uptake) and survival [42] and the relationships between poor physical activity and hospitalisation rate [36], let alone the impact of cell oxygenation on the systemic effects of the disease [43].

The study by Hernandez and co-workers [9] confirmed that the high rate of early relapses was a major clinical problem in the management of exacerbated COPD patients. Despite the fact that GOLD recommendations were properly adopted in the two groups of patients, approximately one-third of them showed early relapses as defined in the study. These data further strengthen the idea that reduction of early re-admissions constitutes a relevant target in order to improve a patient's management [23–26]. In this regard, properly evaluated innovative home-based services are a key component of the strategy to prevent relapses [9]. We suggest a prediction model of early relapses (Table 13.3) to be considered in the emergency room assessment of these patients, based on simple variables easily obtainable from the British Thoracic Society (BTS) questionnaire. The high co-linearity among the four BTS variables may reflect the interplay of common underlying physiological disturbances, namely,

Table 13.3 Independent baseline predictors of failure

	<i>OR</i>	<i>95% CI</i>	<i>P-value</i>	<i>OR</i>	<i>95% CI</i>	<i>P-value</i>
FEV ₁ (% predicted)	0.98	(0.955–0.997)	0.02	0.99	(0.96–1.01)	0.23
Previous hospital admissions, 1 yr	1.43	(1.084–1.875)	0.01	1.23	(0.91–1.66)	0.18
Poor general condition				3.72	(1.48–9.34)	0.005
Severe breathlessness				3.07	(1.11–8.47)	0.03
Physical domain (<i>SF-12</i>)				0.96	(0.92–1.00)	0.05

Summary results of the logistic regression analysis: 95% CI = 95% confidence interval; OR = odds ratio. The first column describes the logistic model obtained considering only sociodemographic and clinical data as independent variables. Area under the receiver operating characteristic (ROC) curve = 0.68 and the Hosmer-Lemeshow test = 8.62 (*P* = 0.38). The second column describes the proposed logistic model including all variables. Area under the ROC curve = 0.74 and Hosmer-Lemeshow goodness of fit test = 5.98 (*P* = 0.65).

lung function impairment and systemic effects of the disease. Those COPD patients showing the constellation of predictors alluded to above constitute a high-risk population that may require a specific pattern of care after discharge in order to prevent relapses. Compared to low-risk COPD patients, high-risk patients may need more intensive logistical support and better respiratory nurse accessibility together with some kind of remote home monitoring. It is of note that the predictive factors identified in our study represent an independent confirmation of those documented in recent reports [22, 35] analysing representative samples of severe COPD exacerbations requiring hospital admission in which no specific interventions were carried out. This further supports the results of the current study.

LESSONS LEARNT: THE NEED FOR A HOLISTIC APPROACH

Ageing of the population, together with changes in lifestyle, are central factors in explaining the increasing prevalence of chronic disorders, which are expected to continue to rise in number over the next decades, leading to further ‘dysfunction’ of healthcare systems worldwide [44–47]. It is well accepted that chronic non-communicable diseases represent close to 80% of the burden on healthcare systems in Europe [46], playing an increasingly dominant role on both mortality and disabilities. The urgent need to introduce substantial changes in delivery of care for chronic patients, as well as its articulation with social support services, is widely accepted. In 2002, the WHO launched the Innovative Care for Chronic Conditions initiative formulating basic principles and strategies to enhance the management of chronic patients.

Briefly, changes in lifestyle aimed at disease prevention and promotion of well-being, the empowerment of patients and relatives in the management of their condition, as well as shared care arrangements among the different levels of care are all necessary elements for improving the efficiency of chronic care. There is no doubt that current fragmentation among levels of care [23] and with community services constitute major limiting factors for a practical adoption of the principles formulated in the chronic care model. Moreover, management of comorbidity is a major challenge often overlooked by evidence-based diagnosis and treatment using disease-specific clinical guidelines [47].

CHALLENGES FOR AN EXTENSIVE DEPLOYMENT OF INTEGRATED CARE SERVICES

Several disease-specific randomised controlled trials undertaken in patients with chronic heart failure [48, 49], COPD [9, 10], diabetes [50, 51] and other disease conditions [12, 13]

have consistently shown the potential of integrated care to enhance clinical outcomes while generating cost containment at system level.

Integrated care programmes have traditionally focused on rather advanced disease conditions, tackling the home hospitalisation of patients who would otherwise require conventional hospitalisation. Strategies for prevention of unplanned hospitalisations [10, 11] have also been successfully explored, but financial modalities may preclude their long-term sustainability. As alluded to above, a common problem in all these pilot studies is that disease-specific trials have shown high internal validity, but questionable external validity because of an elevated rate of exclusion [11], mainly due to severe comorbid conditions that can potentially be managed through transversal programmes addressed at frail patients with multiple severe chronic disorders. The second most important exclusion factor, often present in frail patients, is a lack of appropriate social support. As suggested above, there is a strong need to move the focus from the current interest in advanced chronic conditions towards the development of preventive integrated care strategies addressed at the early stages of chronic diseases or even citizens with a high risk of developing chronic disorders. The ultimate aim should not be constrained to management aspects, but mainly to achieving a positive modulation of the prognosis of chronic disorders. However, it should be noted that highly standardised interventions together with the continuous evaluation of results will be required.

In order to face all of these challenges, more and more attention is being paid to the evolution of health systems from a provider-centred perspective to a patient-focused approach. The latter appears essential in order successfully to address the epidemiological changes associated with the ageing of the population and the growing prevalence of chronic disorders worldwide. Organisational adjustments of health systems combined with significant educational changes are urgently needed in order to prepare healthcare professionals for new and evolving roles [52–54].

In this new scenario, a major issue will be the extensive introduction of information and communication technologies (ICT) as enabling tools to facilitate new ways for citizens to access the necessary systems and to effectively promote information sharing across the system among professionals and citizens as well as formal and informal care-givers (Figure 13.5). Whilst the role of ICT in supporting innovative integrated care services is unquestionable, there are several unsolved issues precluding its deployment. Modularity as a form of flexibility to integrate the cluster sites, robustness through redundancy and service grade co-development, and interoperability of the ICT platforms are major elements to be taken into account in order to ensure sustainability.

Facing all of above challenges is essential to achieve a positive impact on the standardisation of the innovative integrated care services needed and to ensure their successful, extensive and sustainable deployment. The final aim is to fully understand the 'ecosystem' in which these care practices will be sustainable and dominant with respect to traditional approaches. Thus, it is primarily concerned with normalisation of service delivery practices and their seamless integration with communication and information technologies. The supporting rationale is that this will favour real implementation in daily practice, with an increase in the number of providers adopting it and thus enlarging the population that has access to the services.

The transitional phase from existing pilot experiences to extensive deployment of health/social services targeting selected groups of citizens requires identification of target services to be validated. They are selected on the basis of the knowledge and experience acquired through small-scale controlled pilot studies showing positive outcomes in terms of efficiency, user satisfaction and cost savings at the system level [9, 11]. Moreover, these services must address the needs of a broad spectrum of health problems, from those affecting citizens at risk or in the early stages of disease to those patients with advanced chronic disorders, namely:

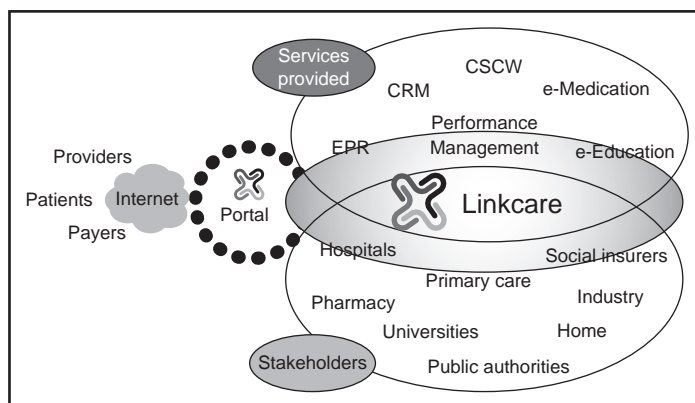


Figure 13.5 Linkcare service provision model. The Linkcare platform (eTEN 517435) aims at delivering ICT support for chronic care (see text for further explanations).

1. Well-being: promoting early diagnosis and healthy lifestyles;
2. Early rehabilitation: enhancement of self-management and improving compliance with prescribed treatments – physical activity and home-based training programmes will be principal components;
3. Enhanced care: support of unplanned hospitalisations addressed at patients with advanced disease and high risk of admissions;
4. Home hospitalisation an early discharge of patients with severe COPD exacerbations; and
5. End-of-life support aimed at improving health-related quality of life at end-stage COPD and to provide support for better interactions among the different individuals involved in patient care.

ICT PLATFORM: THE LINKCARE PROPOSITION

The Linkcare platform (Figure 13.5) aims to support proven innovative services for chronic care – linking hospital care, primary care and home care – thus filling a critical need unmet by today's healthcare systems, to support health professionals and patients, and to pave the way for the implementation of new models of care and better, more affordable chronic care services.

The Linkcare services portfolio includes:

- *Electronic case management module* – Electronic patient record interface with the capability to support integration and communication with the existing customer's systems using industry standard protocols;
- *Customer relationships management (CRM) module* – 'Call-centre' support tools. Core to the Linkcare services is the existence of a single point of access for customers and networked professionals from where different actions can be decided, ordered and transferred or executed. This requires a call-centre supporting advanced CRM features. Furthermore, the specificity of the targeted health services means that some extra capabilities are necessary, such as the link to health information resources (corporate hospital information systems, departmental solutions, etc.);
- *Professionals' mobile support tools* – Most of the services that Linkcare supports are based on the mobility of the professionals providing the service. The tools to be incorporated

into Linkcare should fully support these new work practices, allowing the professional to minimise the need to contact the institution;

- *Patients' mobile support tools* – Similar to the previous point, the potential for deploying healthcare services to patients will depend on the level of monitoring capabilities that Linkcare tools are able to offer. More severe patients will be directly linked to the availability of more continuous, long-term monitoring, along with the possibility of summarising data;
- *Computer-supported cooperative work module including workflow* – Support for modelling the clinical processes at the customer's site, providing the necessary communication and interaction tools to all those involved;
- *Online education and reference access to current content, docs, research, etc.* – Emerging models of care provision maximise the importance of patients and carers as key partners in the management of health conditions. Linkcare should be a comprehensive and trusted repository/broker for information content that can be passively provided (upon the user's will – pull paradigm) or actively suggested (push paradigm, in line with the programme where the patient is currently treated); and
- *Performance monitoring and evaluation module ('control panel/dashboard' and reporting tools)* – A set of decision management tools providing essential information about key indicators of the clinical and business processes, to allow timely intervention for corrective interventions and analytical support to improve actions.

Extensive deployment and sustainability of properly validated integrated care services should be the ultimate goal. As mentioned above, the sustainability of services is stimulated by organisational components, reimbursement factors and technological aspects. The organisational challenge involves changes in the roles of professionals, patients and carers, as well as security issues. All of these components trigger ethical and legal aspects.

The ICT platform supporting the portfolio of services should be modular, scalable and must facilitate organisational interoperability among professionals working with different healthcare providers. The technological platform will generate new means of accessibility for citizens, patients and carers, interconnected healthcare and community services. The ICT platform will also be the basis for future development in two main areas:

1. Knowledge management tools to support decision-making processes; and
2. Convergence of web-based technologies to facilitate innovative interactions.

In summary, it is well accepted that home hospitalisation programmes are not suitable for all patients with severe COPD exacerbations. While some exclusion criteria rely on very strong grounds (mental confusion, low arterial pH, acute chest X-ray film findings, etc.), others, such as arterial oxygenation or level of social support, may require further revision [55] before we are able to define proper clinical guidelines for this specific service. Moreover, we should take into account that elderly COPD patients usually present with several concomitant chronic disorders such that only a patient-oriented approach facing the comorbidity challenge will guarantee successful outcomes. We must also acknowledge that proper management of these patients will only be achieved if all building blocks of the chronic care model are considered in an integrated manner.

SUMMARY

The need to improve delivery of care for chronic patients is generating new modalities of home-based services relying on the empowerment of patients for self-detection of acute episodes, and the implementation of innovative ways of providing accessibility to health

professionals that seem to enhance management of COPD patients. Specifically, home hospitalisation of severe exacerbations in selected COPD patients, as an alternative to conventional hospitalisation, has shown successful outcomes. Home hospitalisation should be considered as part of an integrated strategy aimed at improving the management of chronic patients. These new modalities for chronic care, however, pertain to a relatively novel area requiring continuous evaluation of the innovative services before mature patient-oriented clinical guidelines can be fully consolidated.

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Prevention of acute exacerbations of COPD

F. J. Martinez, J. L. Curtis

INTRODUCTION

Although the topic remains controversial [1], a generally accepted definition of acute exacerbations of COPD (AECOPD) is *'a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD'* [2]. It is important to exclude alternative diagnoses including congestive heart failure, pneumothorax and pulmonary emboli, among others [3–5].

DEFINITION OF AECOPD

There are two major approaches to defining an AECOPD: symptom-based and event-based. Symptom-based definitions are more frequently used, and are more applicable to patient care. The most popular system-based definitions use the criteria of Anthonisen and colleagues [6], or modifications thereof. Nevertheless, a significant proportion of patients appear to under-report these symptoms to healthcare professionals, even events that lead to significant changes in health status [7]. To circumvent difficulties with quantifying symptom changes, event-based definitions have been utilised, particularly in clinical trials. This approach may capture fewer events. Comparison of a symptom-based definition from daily diary cards to an event-based definition in a large, prospective study of an inhaled steroid/long-acting β -agonist study showed quite weak correlation between the two definitions [8]. Accordingly, intensive investigation continues to develop optimal definitions both for clinical use and research studies [1].

The frequency and severity of exacerbations are quite variable among COPD patients [9]. This variability, in part, reflects the nature of data collection (prospective vs. retrospective), disease severity, medications administered, vaccinations and smoking status [9]. This variability is exemplified by data from a selection of studies that used event-based definitions or daily diary card data (Table 14.1). For example, as noted earlier, reports that define AECOPD by the use of daily diary cards tend to identify more episodes per year [7, 10]. Studies including patients with more severely impaired pulmonary function find a greater annual number of AECOPD, although the various international disease severity classification schemes are associated with a differing relationship between COPD severity and

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Table 14.1 AECOPD rate in selected prospective studies using symptom-based or event-based definitions

<i>Reference</i>	<i>N</i>	<i>FEV₁</i> <i>(% pred)</i>	<i>Definition of AECOPD</i>	<i>Number of AECOPD/yr</i>
Seemungal <i>et al.</i> [10]	70	40	Daily diary cards; modified Anthonisen criteria	2.7/pt/yr
Kanner <i>et al.</i> [17]	5887	75	Patient self report of lower respiratory tract illnesses	0.24 MD visits/pt/yr
Vincken <i>et al.</i> [48]	195 (ipratropium) 356 (tiotropium)	39.4 41.9	Daily diary cards; symptom increase ≥ 3 days	0.96/pt/yr 0.73/pt/yr
Calverley <i>et al.</i> [63]	254 (Bud/For) 257 (Bud) 255 (For) 256 (placebo)	42 44 44 44	Event-based†	1.38/pt/yr 1.60/pt/yr 1.85/pt/yr 1.80/pt/yr
Jones <i>et al.</i> [12]	391 (FP) 359 (FP)	39 62	Event-based†	1.64/pt/yr 0.92/pt/yr
Donaldson <i>et al.</i> [13]	132	38.4	Diary cards; modified Anthonisen criteria	2.52/pt/yr
Decramer <i>et al.</i> [134]	256 (NAC) 267 (placebo)	57 57	Event-based	1.25/pt/yr 1.31/pt/yr
Kardos <i>et al.</i> [68]	487 (SM) 507 (SM/FP)	40.3 40.4	Event-based	1.4/pt/yr* 0.92/pt/yr*
Makris <i>et al.</i> [19]	102	56.4	Daily diary cards	2.85/pt/yr
Seemungal <i>et al.</i> [91]	53 (erythromycin) 56 (placebo)	50.6 49.3	Daily diary cards and event-based	1/pt/yr 2/pt/yr
Zheng <i>et al.</i> [135]	353 (carbocisteine) 354 (placebo)	43.9 45.1	Daily diary cards; modified Anthonisen criteria	1.01/pt/yr 1.35/pt/yr

† = antibiotic or steroid treated; * = moderate (antibiotics and/or steroids) to severe (hospitalisation or emergency room treatment); Bud = budesonide; For = formoterol; FP = fluticasone propionate; SM = salmeterol.

frequency of hospitalisations [11]. In the ISOLDE study there was a clear dichotomy between the annualised exacerbation rates in patients with mild versus moderate–severe airflow obstruction [12]. A separate group has examined 132 patients during three years of follow-up, carefully documenting exacerbations through the use of diary cards [13]. They found that patients with severe COPD (forced expiratory volume in one second [FEV₁] <30% predicted) experienced a higher exacerbation frequency (3.43/yr) than those with moderate COPD (FEV₁ \geq 30% but <80% predicted) (2.68/yr). Interestingly, the annual exacerbation frequency remained constant throughout the period of study, while the time to physiological and clinical recovery from exacerbations grew significantly longer each year.

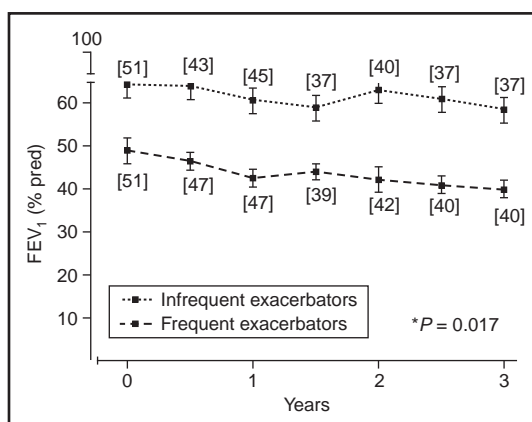


Figure 14.1 FEV₁ (% of predicted) change from baseline over a 3-year study period by total exacerbation status. Values are means with bars representing SE and numbers in brackets reflecting patients with valid readings at each time-point. *Difference in average annual decline rate in FEV₁ (% of predicted) between frequent and infrequent exacerbators, obtained by REM (with permission from [19]).

IMPACT OF AECOPD

AECOPD episodes result in measurable acute deteriorations in pulmonary function [7]. Parker and colleagues examined 20 patients within 72 h of initial symptoms of an AECOPD [14]. A modest improvement in pulmonary function, particularly in lung volumes, was seen over the first two weeks after therapy started. A similar report from another investigative group documented significant improvement in lung volume following treatment of an AECOPD [15]. Most recently, Pinto-Plata and associates noted little intermediate change in FEV₁ during recovery from a hospitalised AECOPD, while inspiratory capacity (IC) improved rapidly [16].

Longitudinal effects of repeated AECOPD have also been reported. Kanner and co-workers confirmed that among smokers, lower respiratory tract infections (LRTI) were associated with additional decline in lung function; those averaging one LRTI per year experienced an additional decline of 7 ml/yr in FEV₁ [17]. However, another group reported a similar decrease in lung function (~8 ml/yr) in patients with frequent exacerbations compared to those with infrequent exacerbations [18]. In a more recent cohort of 102 COPD patients, more frequent exacerbators experienced an additional 1.4% predicted decrease/year than infrequent exacerbators (Figure 14.1) [19]. The totality of these data support that AECOPD have measurable negative short- and long-term impacts on pulmonary function.

Numerous groups have documented the negative implications of AECOPD, which are particularly evident in their effects on health-related quality of life (HRQL) (Table 14.2) [20–22]. Cross-sectional studies have reported reduced HRQL during AECOPD, while longitudinal studies have found that HRQL improves from exacerbation to recovery [20]. The greatest improvement in HRQL after a single episode occurs during the first four weeks, although HRQL continued to improve over 26 weeks [23]. In this study, a recurrence of AECOPD resulted in a markedly attenuated improvement [23]. Other clinical studies have also shown a strong association between the AECOPD frequency, quality of life (QoL) and depression. In the ISOLDE trial, frequent exacerbations were associated with a more rapid decline in the St George's Respiratory Questionnaire (SGRQ) score during the course of the trial. The SGRQ score declined by 2.6 units per year in those patients who experienced at

Table 14.2 Results of selected individual studies examining the impact of AECOPD episodes on quality of life

<i>Reference</i>	<i>N</i>	<i>FEV₁</i>	<i>Major finding</i>
<i>Individual exacerbations</i>			
Doll <i>et al.</i> [135, 136]	207 NHP 163 SGRQ	NA	Worse NHP and SGRQ at AECOPD than at time without exacerbation Number of AECOPD in previous year and exposure to pollution at home associated with worse health status at AECOPD NHP more response to changes with exacerbation
Aaron <i>et al.</i> [137]	66	36.5%	Patients without relapse within 10 days of exacerbation treatment experienced improved CRQ Patients with relapse within 10 days of exacerbation treatment did not experience improved CRP
Andersson <i>et al.</i> [138]	30	30%	Improved SF-36 and SGRQ three months after hospitalisation for exacerbation
Spencer <i>et al.</i> [23]	438	NA	Greatest improvement in SGRQ after exacerbation occurs during first 4 weeks after treatment Subsequent improvement best if no recurrence
<i>Recurrent exacerbations</i>			
Seemungal <i>et al.</i> [10]	70	40%	SGRQ total and component scores worse in the group with frequent exacerbations
Miravitlles <i>et al.</i> [25]	336	33%	Frequent exacerbations had negative effect on SGRQ in patients with moderate COPD (FEV ₁ 35–50% pred)
Spencer <i>et al.</i> [24]	613	50%	Frequent exacerbations were independently associated with worse baseline SGRQ and more rapid deterioration in health status during maximum of 3 years of follow-up
Llor <i>et al.</i> [139]	136	48.7%	Patients with exacerbations experienced worsening health status compared with those not experiencing exacerbations
Quint <i>et al.</i> [140]	169	47%	Patients with an exacerbation rate above the median for the group had worse depression scores and health status
CRP = C-reactive protein; CRQ = Chronic Respiratory Questionnaire; NA = not available; NHP = Nottingham Health Profile; SGRQ = St George's Respiratory Questionnaire.			

least 1 exacerbation compared with only 2.0 units per year for those who did not experience an exacerbation [24]. Similar results were observed when the cohort was divided into those with infrequent exacerbations and frequent exacerbations. Most importantly, a two-year prospective, longitudinal study of 336 COPD patients with severe COPD confirmed that more frequent exacerbations had a deleterious effect on health status [25].

AECOPD are also a major source of healthcare expenditure (Table 14.3) [26]. AECOPD were estimated to result in a total treatment cost of \$1.2 billion in patients ≥ 65 years of age

and \$419 million in those <65 years of age in the US in 1995; these costs were predominantly for hospitalisations [27]. A prospective Spanish study of 2414 COPD patients who had experienced an acute exacerbation noted that 507 patients (21%) relapsed after therapy [28, 29]. Of these, 161 patients required emergency department treatment with 84 requiring hospitalisation; these latter patients accounted for 58% of the total cost. Thus, AECOPD, particularly those that require hospitalisation, result in major healthcare expenditure. It is evident that AECOPD are events that have important negative implications in the natural history of COPD.

INFLAMMATION IN AECOPD

COPD itself has increasingly been accepted to involve lung inflammation, especially in those with severe disease and an emphysematous phenotype [30–33]. However, an exaggerated inflammatory response appears to be the central event of an AECOPD [34–36]. Multiple stimuli can acutely increase airway and parenchymal inflammation, leading to increased bronchial tone, bronchial wall oedema and mucous hypersecretion [37].

The most robust evidence of an augmented inflammatory response comes from analysis of sputum. Both neutrophilic, and in some cases, eosinophilic inflammation have been described. Similarly, a multitude of inflammatory mediators have been implicated, including interleukin-8 (IL-8), leukotriene B₄ (LTB₄), tumour necrosis factor- α (TNF- α), granulocyte-macrophage colony stimulating factor (GM-CSF), the chemokine CCL5 (previously known as regulated upon activation, normal T cell-expressed/secreted [RANTES]), and endothelin-1 (ET-1). Bronchoscopic data, although more limited, have confirmed increased expression of CCL5 in both the surface epithelium and subepithelial mononuclear cells during an acute exacerbation of chronic bronchitis [38]. In addition, increased numbers of neutrophils in AECOPD as well as increases in CXCL5 (ENA-87), CXCL8 (IL-8) and CXCR2 have been documented [39, 40]. Finally, measurable systemic inflammation has been documented during AECOPD, including increased plasma fibrinogen, IL-6, C-reactive protein, and ET-1 [41–44]. Collectively, these data indicate that the majority of exacerbations are associated with an intensified inflammatory response.

PREVENTION OF AECOPD

Given the impact of AECOPD on pulmonary function and health status, minimising the severity of individual episodes and preventing recurrences have become important tenets of COPD therapy [22]. The ability to decrease hospitalisations has become feasible with currently available therapies. We will review the available data for pharmacological and non-pharmacological interventions.

BRONCHODILATORS

A wide variety of bronchodilators have been investigated directly or indirectly for their ability to modulate the number or severity of AECOPD. The main classes include the β -agonists, the antimuscarinics and the methylxanthines.

Long-acting β -agonists (LABA)

LABAs have shown an inconsistent effect in the modulation of AECOPD. Nevertheless, a recent systematic review contrasting two available agents, salmeterol and formoterol, versus placebo demonstrated a beneficial effect [45]. This review documents a similar decrease in AECOPD for both agents (Figure 14.2). It is important to note that AECOPD definition was highly variable among the studies reviewed in [45], and that none of these studies was designed with the primary goal of modulating AECOPD frequency or severity.

Table 14.3 Estimates of costs for AECOPD in selected studies

<i>Study</i>	<i>Country</i>	<i>Total medical resource utilisation/patient or /exacerbation episode</i>	<i>Distribution of costs</i>	<i>Additional data</i>
Pechevis <i>et al.</i> [141]	France	FF3289/episode	60% for hospitalisation	
Grasso <i>et al.</i> [142]	US	\$8482/year	64% for hospitalisation	Higher comorbidity associated with greater costs
Niederman <i>et al.</i> [27]	US	\$5497/exacerbation hospitalisation in >65 yrs of age \$5561/exacerbation hospitalisation in <65 yrs of age		Outpatient costs much lower
Ward <i>et al.</i> [143]	US	\$6574/patient	\$1609/hospitalisation	
Strassels <i>et al.</i> [144]	US	\$6469/patient	\$4430/hospitalisation	68% hospitalisation related
Miravittles <i>et al.</i> [145]	Spain	\$159/exacerbation	\$58.70 in patients without relapse \$477.50 in patients with initial treatment failure	Hospitalisation generated 58% of total cost
Andersson <i>et al.</i> [146]	Sweden	€3136/exacerbation	€2106/year	67% of total cost reflected hospitalisation; much higher in severe COPD
Miravittles <i>et al.</i> [147]	Argentina	\$329/exacerbation	\$118 cost of failure	35.8% of total cost reflected failure
Miravittles <i>et al.</i> [147]	Brazil	\$211/exacerbation	\$102 cost of failure	48.3% of total cost reflected failure
Miravittles <i>et al.</i> [147]	Colombia	\$98/exacerbation	\$28 cost of failure	28.6% of total cost reflected failure
Miravittles <i>et al.</i> [147]	Ecuador	\$177/exacerbation	\$105 cost of failure	59.3% of total cost reflected failure
Miravittles <i>et al.</i> [147]	Mexico	\$215/exacerbation	\$109 cost of failure	50.7% of total cost reflected failure
Miravittles <i>et al.</i> [147]	Peru	\$302/exacerbation	\$90 cost of failure	29.8% of total cost reflected failure

Table 14.3 (continued)

<i>Study</i>	<i>Country</i>	<i>Total medical resource utilisation/patient or /exacerbation episode</i>	<i>Distribution of costs</i>	<i>Additional data</i>
Miravittles <i>et al.</i> [147]	Venezuela	\$283/exacerbation	\$136 cost of failure	48.0% of total cost reflected failure
Halpern <i>et al.</i> [26]	US	\$4120/patient	\$2891/hospitalisation	Severe COPD associated with significantly higher costs
Miravittles <i>et al.</i> [29]	Spain	\$1876/patient	\$821/hospitalisation	43.8% of costs were hospitalisation related
Detournay <i>et al.</i> [148]	France	€4366/year	~25% related to exacerbations	>1/3 related to hospitalisations – increased with disease severity
Oostenbrink <i>et al.</i> [149]	Netherlands & Belgium	€720/exacerbation	€555/hospitalisation	More severe exacerbation more costly (€4007) than moderate (€579) and mild (€86)
Monte <i>et al.</i> [150]	US	\$288/exacerbation	51% for initial visit/diagnostics	

Long-acting antimuscarinics (LAMA)

By contrast with LABAs, much more consistent data support the ability of LAMAs to decrease AECOPD frequency and severity, as described in two recent systematic reviews [46, 47]. Interestingly, the direction and magnitude of the effect in both systematic reviews were similar. Figure 14.3 illustrates the beneficial effect of tiotropium, the prototypical and first available LAMA. Importantly, a similar effect has been noted in a blinded, double-dummied comparison with the short-acting antimuscarinic ipratropium [48]. The varying nature of an AECOPD definition could create difficulty in interpretation. As such, many of these studies have also shown a beneficial effect of tiotropium on AECOPD-related hospitalisation (Figure 14.4). In comparison to ipratropium and salmeterol the direction of benefit using tiotropium persisted, although statistical significance was not reached [46].

Most reassuring is the large, prospective Veterans Affairs (VA) study of Niewoehner and colleagues [49]. This large study directly compared tiotropium to placebo, with the co-primary endpoints being the proportion of patients experiencing an AECOPD or COPD-related hospitalisation. Compared to placebo, tiotropium reduced AECOPD frequency while resulting in a trend towards reduced hospitalisations; exacerbation days and both unscheduled medical visits and duration of antibiotic treatment for AECOPD were also decreased. Pre-defined *post hoc* comparisons provided additional important insight (Figure 14.5). Statistical comparisons were limited due to smaller sample sizes although the direction of benefit was similar in the majority of the comparisons. Not unexpectedly, the magnitude of effect seemed

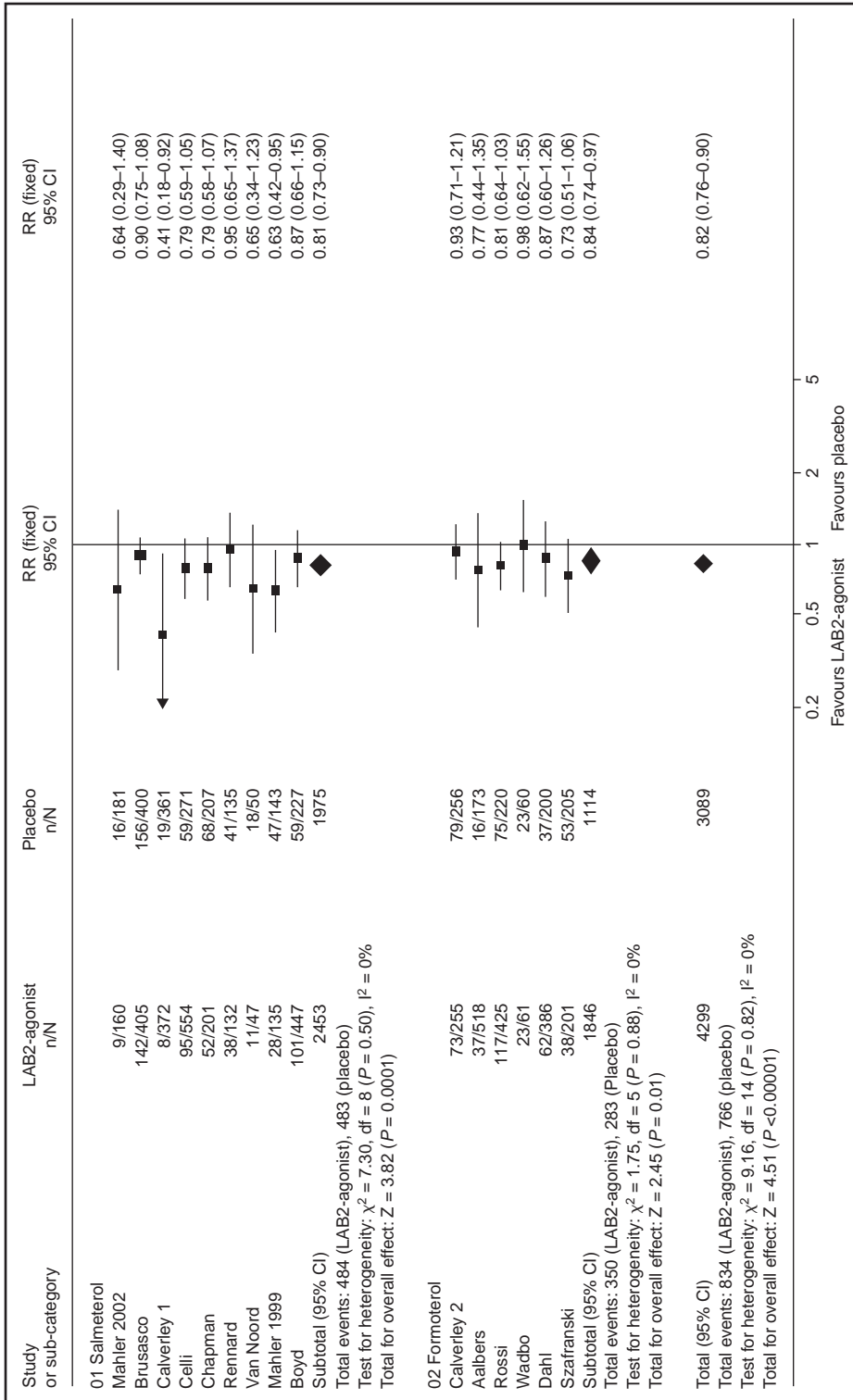


Figure 14.2 Systematic review of LABAs vs. placebo in preventing AECOPD (with permission from [45]).

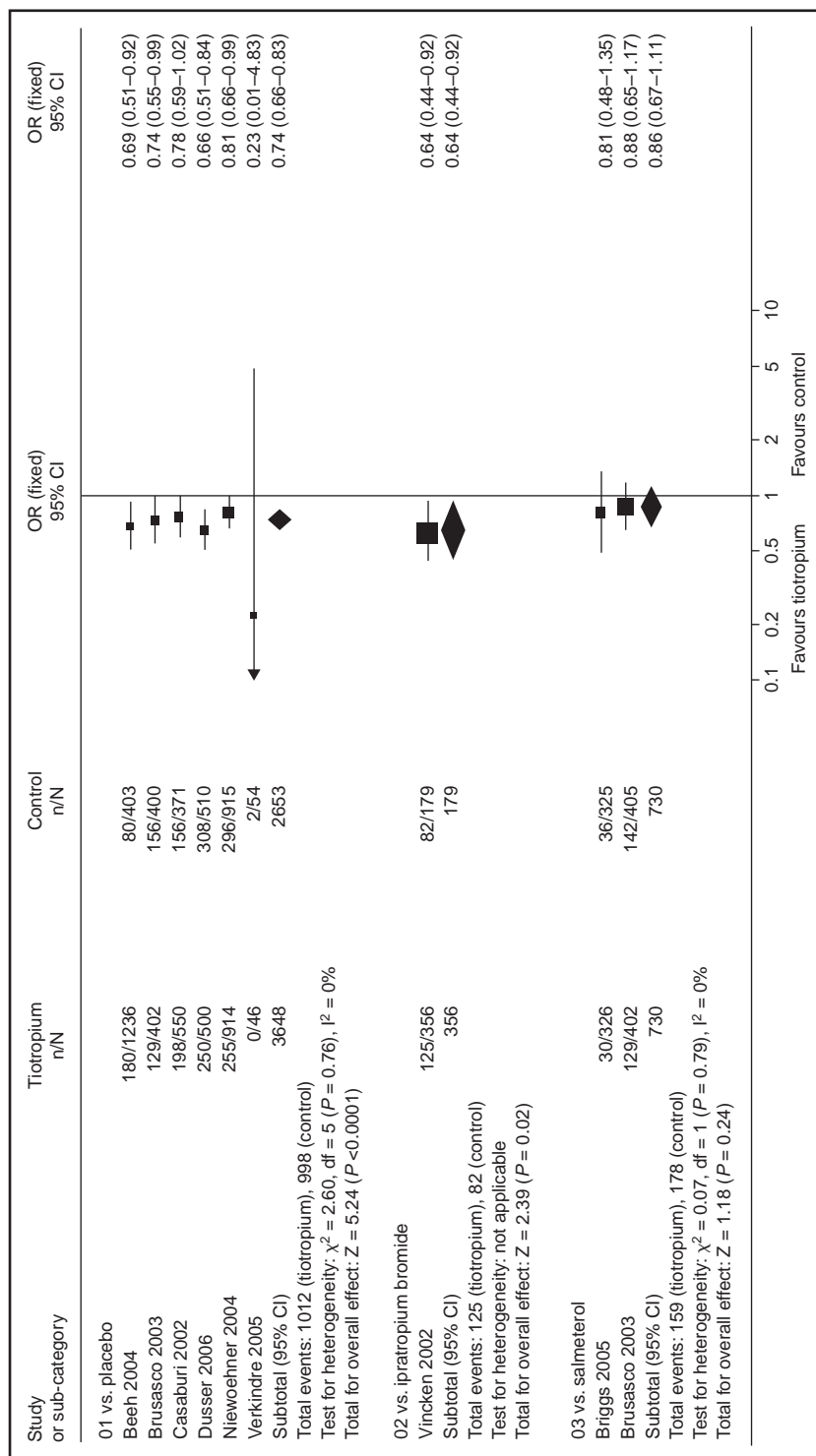


Figure 14.3 Systematic review of the long-acting antimuscarinic tiotropium vs. placebo, ipratropium and salmeterol in preventing AECOPD (with permission from [46]).

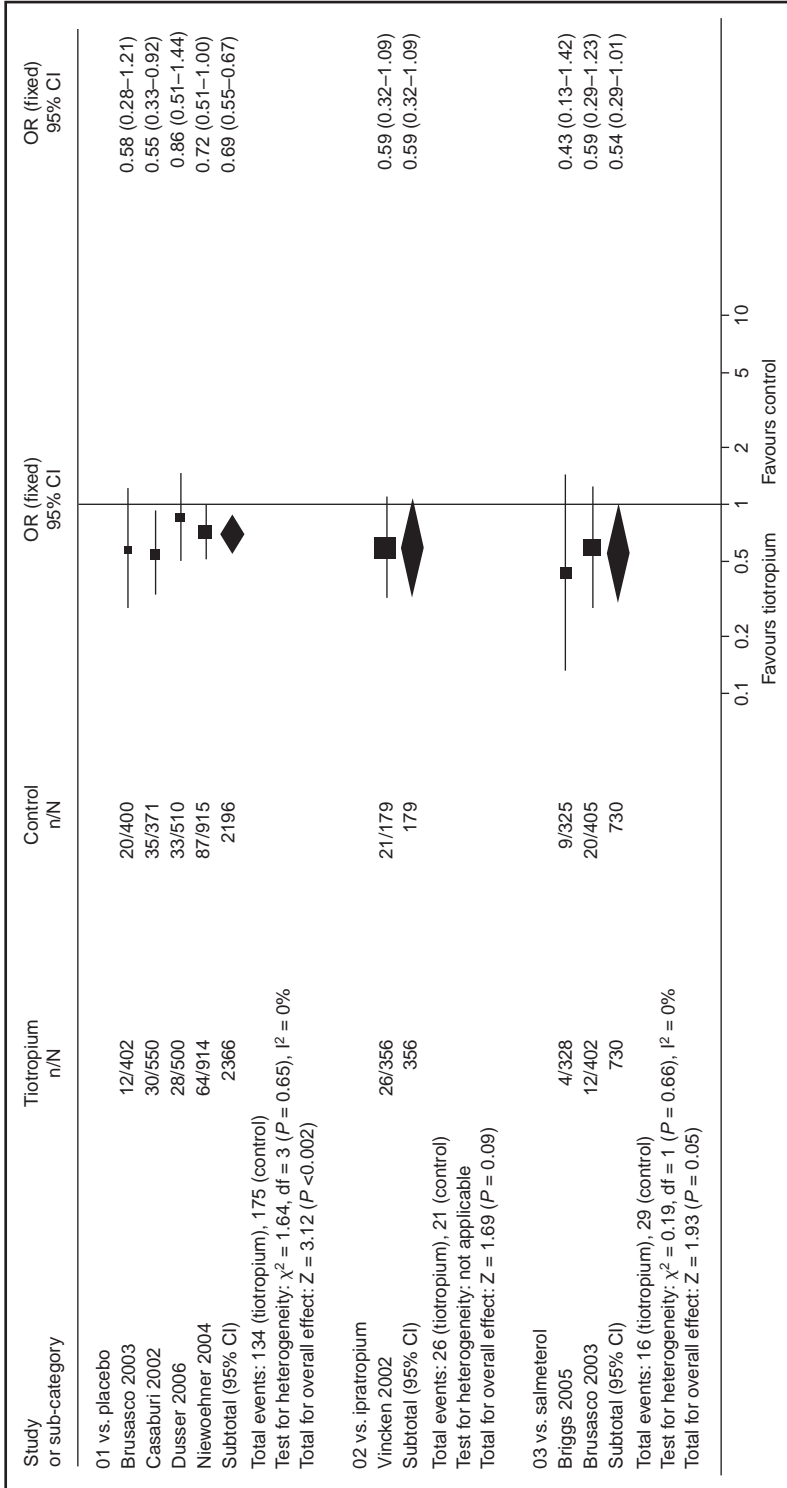


Figure 14.4 Systematic review of long-acting antimuscarinic tiotropium vs. placebo, ipratropium and salmeterol in preventing AECOPD-related hospitalisations (with permissio from [46]).

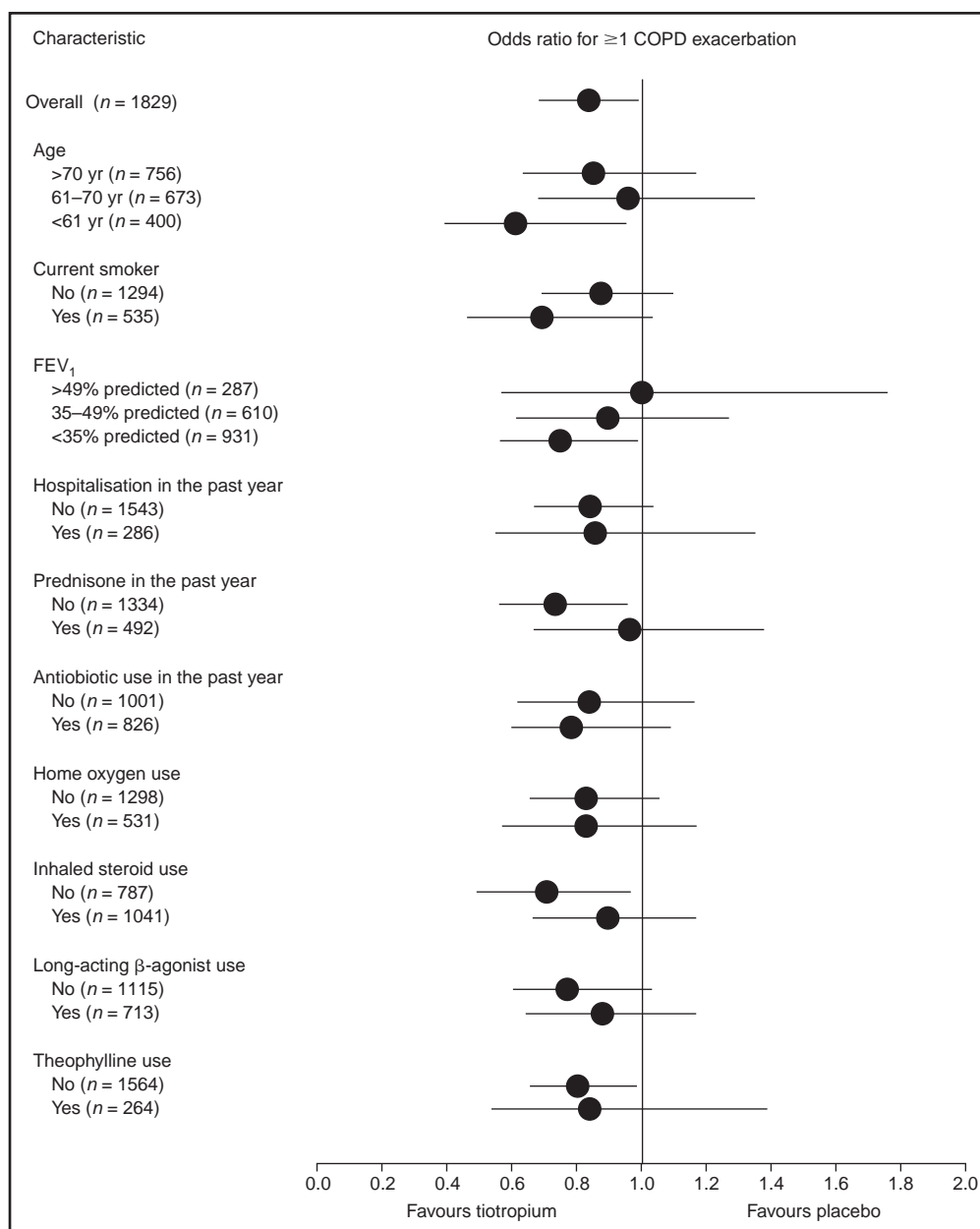


Figure 14.5 Odds ratios and 95% CIs for reduction in first AECOPD with tiotropium as stratified according to selected baseline characteristics (with permission from [49]).

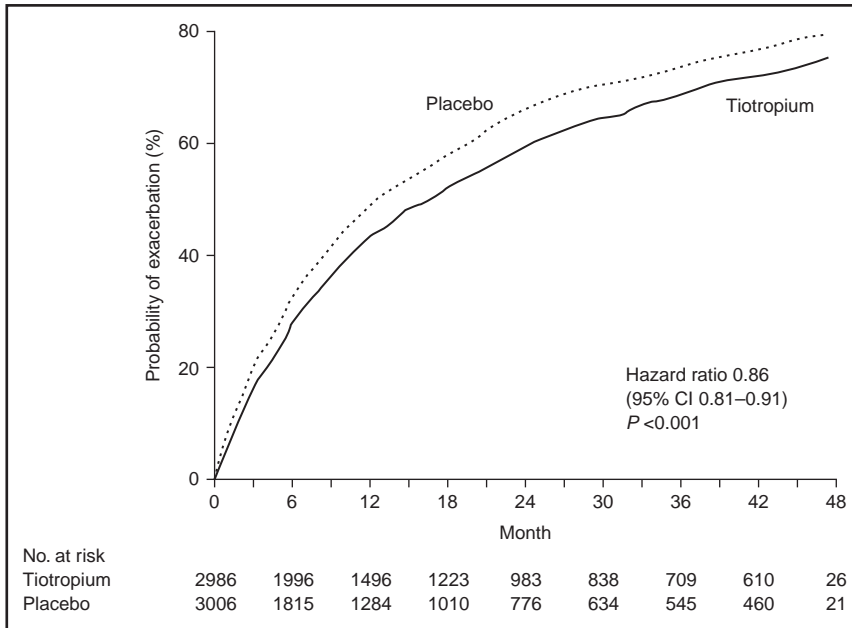


Figure 14.6 Kaplan–Meier curves showing the cumulative incidence estimate of the probability of COPD exacerbation with tiotropium or placebo therapy in the UPLIFT study. The numbers of patients who continued to receive a study drug (including those at 30 days after the last dose) are listed for each time-point, with the study period truncated at 48 months. All patients who received at least one dose of a study drug were included in the analysis. *P*-values were calculated with use of the log-rank test (with permission from [53]).

higher in patients with lower FEV₁ at baseline, a group at higher risk of subsequent events. Similarly, in patients using inhaled corticosteroids (ICS) at baseline the magnitude of tiotropium benefit seemed attenuated.

A subsequent, large multicentre study compared the effect of tiotropium versus placebo on the co-primary endpoint of AECOPD and airflow obstruction [50]. Tiotropium delayed the time to first exacerbation, and decreased both the number of acute exacerbations and the number of AECOPD days. Importantly, this benefit was also seen in patients using ICS. Although published data are limited, the combination of tiotropium and LABA/ICS appears to yield incremental benefits in physiology, symptoms and health status [51, 52]; the short-term nature of these studies did not allow a robust assessment of the impact on AECOPD. Most recently, the results of the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) were published [53]. A total of 5993 patients with COPD (mean FEV₁ 39% predicted) were randomised to four years of therapy with tiotropium or placebo. Even though nearly two-thirds of patients were also taking a LABA and or an ICS, a prespecified secondary analysis confirmed a prolongation in time to COPD exacerbation with tiotropium therapy (hazard ratio [HR] 0.86; 95% confidence interval [CI] 0.81–0.91) (Figure 14.6).

INHALED CORTICOSTEROIDS (ICS)

Given the presence of inflammation in COPD, especially during AECOPD, and the known benefit of steroids in asthmatics [54], ICS have frequently been used in clinical practice to treat patients with COPD. Nevertheless, the efficacy of corticosteroid therapy in COPD remains controversial [55–58]. ICS have not generally been felt to improve pulmonary

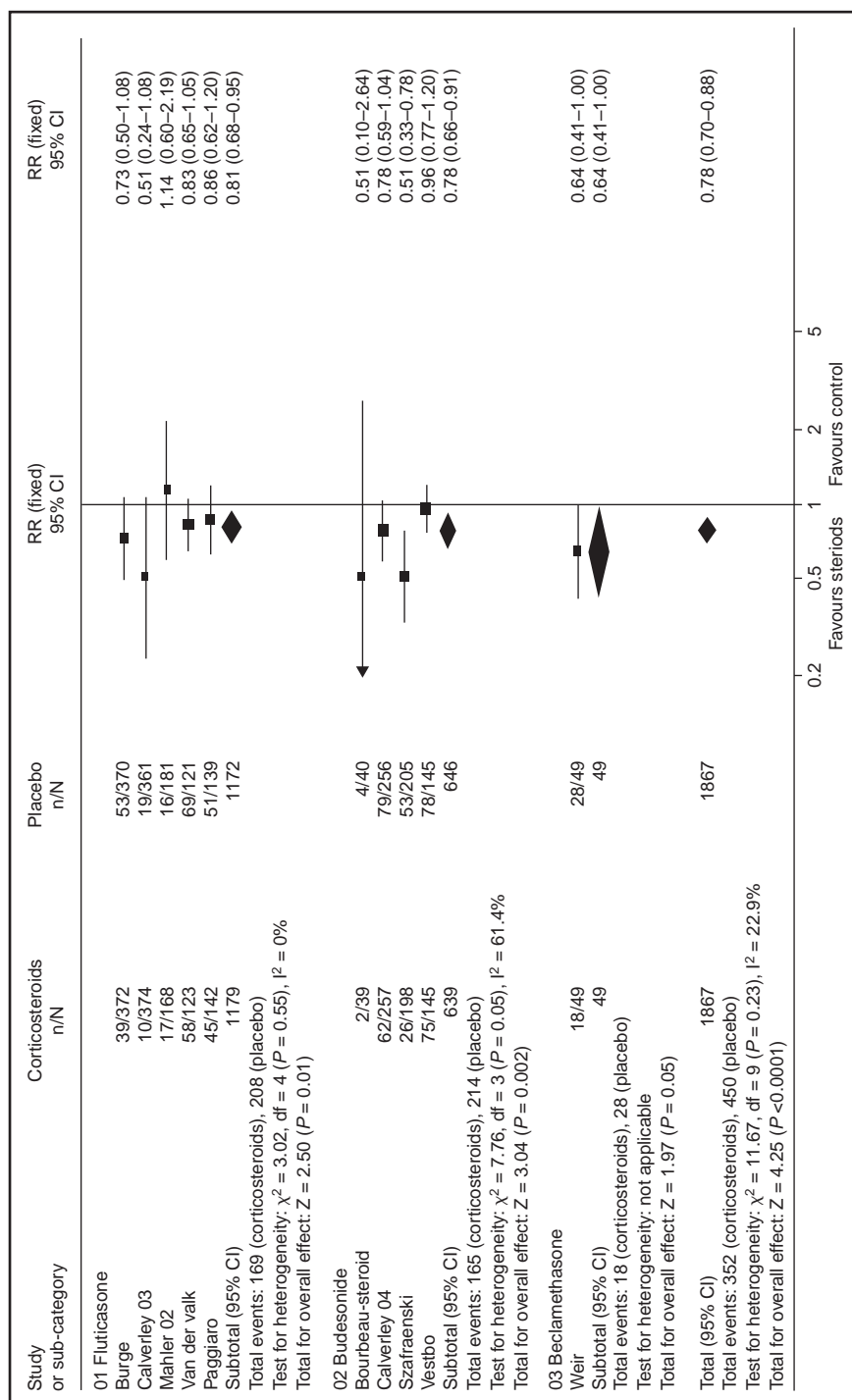


Figure 14.7 Systematic review of various ICS vs. placebo in preventing AECOPD (with permission from [45]).

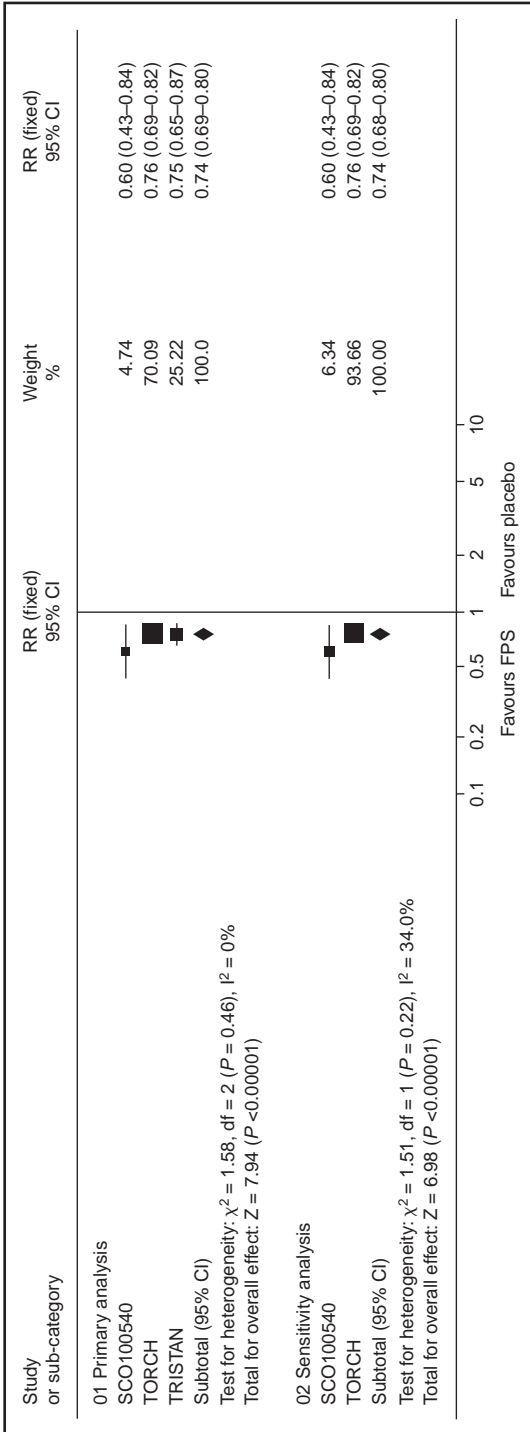


Figure 14.8 Pooled rate ratios for combination fluticasone and salmeterol and placebo and salmeterol combination (with permission from [66]). FPS = fluticasone propionate/salmeterol combination.

Table 14.4 Effect of salmeterol and fluticasone on health status, pulmonary function and exacerbations (with permission from [67])

<i>Secondary endpoint</i>	<i>Salmeterol/ fluticasone vs. placebo (95% CI)</i>	<i>Salmeterol/ fluticasone vs. salmeterol (95% CI)</i>	<i>Salmeterol/ fluticasone vs. fluticasone (95% CI)</i>
Moderate/severe exacerbations* (rate ratio)	0.75 (0.69–0.81) <i>P</i> <0.0001	0.88 (0.81–0.95) <i>P</i> = 0.002	0.91 (0.84–0.99) <i>P</i> = 0.024
* Moderate = antibiotics and/or systemic corticosteroids; severe = hospitalisation.			

function when used longitudinally in COPD but they favourably affect HRQL [58]. Several systematic reviews have suggested that ICS decrease AECOPD risk [45, 59–61]. Results of ten studies (Figure 14.7) show an aggregate relative risk for AECOPD of 0.78 (95% CI 0.70–0.88); there was no suggestion that any single corticosteroid agent was superior [45]. It should be noted that this topic remains controversial, with suggestions that the methodological approach taken in analysis may overestimate the putative benefits [62].

COMBINATION LABA/ICS AND ADDITION OF LABAs

Combining ICS and LABAs appears to provide additive benefit compared with the individual components [63–65]. A recent meta-analysis [66] of results from several multi-arm trials (Figure 14.8) disclosed that an absolute risk reduction in exacerbations was seen with combination therapy compared to placebo (RR 0.74; 95% CI 0.69–0.80). A subgroup analysis by Calverley indicated that therapeutic effectiveness varied by severity of obstruction; the RR reduction for combination therapy compared to placebo was 39% for all enrollees compared with only 10% for those with FEV₁ >50% of predicted [64].

The results of a sentinel study have recently been published. The TOWARDS a Revolution in COPD Health (TORCH) trial randomised 6112 subjects to therapy with fluticasone 500 µg, fluticasone 500 µg/salmeterol 50 µg, salmeterol 50 µg or placebo. Although all-cause mortality contrasting combination therapy with placebo was the primary endpoint, AECOPD frequency and severity were key secondary endpoints. Table 14.4 enumerates the results of each treatment arm on AECOPD [67]. It is evident that the greatest effect on AECOPD frequency was attributed to combination therapy. Additional prospective, controlled studies with AECOPD modulation as the primary endpoint have provided additional insight into the effects of combining an ICS with a LABA. Kardos and colleagues randomised 994 patients with moderate to severe airflow obstruction and a previous history of repeated AECOPD to fluticasone/salmeterol 500/50 µg bid or salmeterol 50 µg bid for 44 weeks; the primary endpoint was the number of moderate (requiring a change in medical therapy) and severe (requiring emergency department treatment or hospitalisation) exacerbations in each group [68]. The results are shown in Table 14.5. It is evident that the number and severity of AECOPD were ameliorated by the addition of an ICS to a LABA; the magnitude of decrease was a 35% decrease in the rate of moderate to severe episodes. A separate multicentre group randomised 782 patients (mean FEV₁ 33% predicted) with a history of previous exacerbation and moderately severe COPD to fluticasone (250 µg bid) plus salmeterol or salmeterol plus placebo [69]. The primary endpoint, the annual rate of moderate to severe exacerbations, was favourably impacted (Table 14.5). It is evident that the magnitude of improvement in exacerbation was remarkably similar in both studies strongly supporting that an ICS adds incremental benefit in exacerbation reduction when combined with a LABA.

Table 14.5 Impact of adding fluticasone to salmeterol on AECOPD in moderate to severe COPD patients with a history of repeated exacerbations (adapted with permission from [68, 69])

<i>AECOPD</i>	<i>Fluticasone/salmeterol</i>	<i>Salmeterol</i>
<i>Fluticasone 500 µg*</i>		
Number of moderate to severe AECOPD	334	464
Annualised rate of moderate to severe AECOPD	0.92	1.4
Treatment ratio for comparison (95% CI)	0.65 (0.57–0.76)	
Number of AECOPD requiring oral steroids	58	139
<i>Fluticasone 250 µg†</i>		
Patients with >1 moderate/severe AECOPD	211	230
Total number of moderate/severe AECOPD	368	432
Annualised rate of moderate to severe AECOPD	1.06	1.53
Treatment ratio for comparison (95% CI)	0.695 (0.58–0.83)	
Number of AECOPD requiring oral steroids	231	289
* Adapted from [68].		
† Adapted from [69].		

Table 14.6 Impact of adding fluticasone to salmeterol on AECOPD in moderate to severe COPD patients with a history of repeated exacerbations (adapted with permission from [70])

<i>Analysis</i>	<i>Tiotropium + placebo</i>	<i>Tiotropium + salmeterol</i>	<i>Tiotropium + fluticasone/salmeterol</i>
<i>Primary analyses</i>			
Patients with >1 AECOPD (%)	98 (62.8)	96 (64.8)	87 (60.0)
<i>Absolute risk reduction compared with tiotropium plus placebo, % points (95% CI)</i>		-2.0 (-12.8–8.8)	2.8 (-8.2–13.8)
<i>Secondary analyses</i>			
Mean exacerbations/patient-year	1.61	1.75	1.37
<i>Incidence rate ratio compared with tiotropium plus placebo (95% CI)</i>		1.09 (0.84–1.40)	0.85 (0.65–1.01)
Hospitalisations for AECOPD	49	38	26
<i>Absolute risk reduction compared with tiotropium plus placebo, % points (95% CI)</i>		0.83 (0.54–1.27)	0.53 (0.33–0.86)
All-cause hospitalisations	62	48	41
<i>Absolute risk reduction compared with tiotropium plus placebo, % points (95% CI)</i>		0.83 (0.57–1.21)	0.67 (0.45–0.99)

Combination of tiotropium with ICS/LABA has been studied to a lesser extent. Unfortunately, the contribution of tiotropium addition to an ICS/LABA combination cannot be teased from the data presented in the UPLIFT report [53]. A direct comparison was studied by a multicentre, Canadian consortium which randomised 449 patients with moderate or severe COPD to one year of tiotropium plus placebo, tiotropium plus salmeterol, or tiotropium plus fluticasone/salmeterol; the primary endpoint was the proportion of patients who experienced an AECOPD that required treatment with systemic steroids or antibiotics [70]. Table 14.6 enumerates the primary and secondary analyses. It is evident that the primary

analysis was negative although an alternative presentation of the data (time to first exacerbation) trended towards significance (HR 0.80; 95% CI 0.60–1.08; $P = 0.15$). Interestingly, several relevant secondary endpoints were significant (Table 14.6). It is likely that the study was underpowered to document a clear benefit of combination therapy.

A comparison of fluticasone/salmeterol versus tiotropium has recently been reported [71]. This investigative group randomised 1323 COPD patients to two years of therapy with fluticasone/salmeterol 500/50 μg bid versus tiotropium 18 μg daily; the primary endpoint was healthcare utilisation exacerbation rate [71]. The modelled annual exacerbation rate was 1.28 in the fluticasone/salmeterol group compared with 1.32 in the tiotropium group (RR 0.967; 95% CI 0.836–1.119). It is evident that both therapeutic approaches exhibited similar effect on the primary endpoint.

THEOPHYLLINE

Methylxanthines have been used to treat respiratory disorders for many decades [72], but the use of theophylline has decreased over the past decade [73]. This change in practice pattern reflects the controversy regarding the benefits of theophylline [74, 75], the availability of alternative bronchodilator regimens [76] and theophylline's narrow therapeutic spectrum [74]. In COPD, theophylline is a weak bronchodilator, with improvement in FEV₁ ranging from 10–21% [75], although this improvement is generally similar to that achieved with β -agonists [77, 78]. When theophylline is administered in combination with LABAs, statistically significant additive effects have been observed [75, 78–80]. The bronchodilatory effect of theophylline is most often achieved with prolonged administration [75]. Importantly, tolerance to this agent is limited. In one study comparing the efficacy of adding theophylline to salmeterol, 150/1185 screened patients were unable to tolerate theophylline during a wash-in period and 30 additional patients were unable to achieve therapeutic theophylline levels [78]. Data regarding the effect of theophylline on AECOPD are limited. In combination with salmeterol, fewer exacerbations were noted than in patients treated with theophylline alone or salmeterol alone in one study [78].

ANTIMICROBIALS

The role of antimicrobial therapy in the prevention of AECOPD remains unclear. Numerous controlled trials were reported several decades ago with a more recent Cochrane meta-analysis suggesting that antibiotic administration reduced the rate of AECOPD [81]. The most promising data are with macrolides, agents with broad-ranging immunomodulatory effects *in vitro* and *in vivo* and diverse actions suppressing microbial virulence [82–84]. Beneficial effects of macrolides have been demonstrated in a variety of chronic respiratory disorders [82], including COPD. A small, open-label, controlled trial suggested that erythromycin (200–400 mg/day) for twelve months decreased the risk and frequency of experiencing a common cold and subsequent AECOPD [85]. A small, placebo-controlled trial suggested that two weeks of low-dose clarithromycin therapy improved sputum inflammatory markers [86], although a second, longer study did not confirm these findings [87]. Gomez and colleagues treated 54 severe COPD patients with azithromycin 500 mg daily for three days every 21 days from September through May [88]. In comparison to a similar, retrospective group of untreated COPD patients, azithromycin-treated patients experienced fewer exacerbations and fewer hospitalisations per year. It is notable that during AECOPD, the azithromycin-treated group experienced infection with macrolide non-susceptible *Streptococcus pneumoniae*. Similarly, in cystic fibrosis patients starting azithromycin maintenance therapy, colonisation with macrolide-resistant staphylococcus increased from 10% to 83% within one year and to 100% in the third year of therapy [89]. The most compelling results favouring chronic macrolide therapy come from a recent, placebo-controlled, randomised trial of 250 mg bid erythromycin for

one year in 109 patients with moderately severe COPD and the ability to produce sputum; the primary endpoints were exacerbation rate and sputum inflammation [90]. The rate ratio for exacerbation with macrolide therapy compared with placebo was 0.648 (95% CI 0.489–0.859). Interestingly, no difference was seen in sputum or systemic inflammatory parameters; the impact on antimicrobial resistance was not systematically reported. Thus, these studies, although suboptimally designed and underpowered, suggest that a beneficial response may be seen with chronic macrolide prophylaxis in high-risk COPD patients, albeit with the potential of driving antimicrobial resistance. A much larger, optimally designed multicentre study, supported by the National Heart, Lung and Blood Institute (NHLBI), is now underway to better define the results of this therapeutic approach.

VACCINATIONS

Influenza is an important cause of lower respiratory tract infections, particularly during the winter months. Epidemiological studies have shown that COPD patients are at increased risk of hospitalisation during influenza outbreaks [91]. A meta-analysis of 20 cohort studies of influenza vaccination in elderly subjects confirmed a 56% reduction in respiratory illness and 50% reduction in hospitalisation [92]. In a large, multiseason cohort study, patients with chronic lung disease who had undergone influenza vaccination experienced a 52% reduction in hospitalisations [93]. Randomised controlled data in COPD patients are more limited. A meta-analysis of controlled trials confirmed that influenza vaccination was associated with a reduction in AECOPD, particularly those three or more weeks after vaccination (Figure 14.9) [94]. As such, influenza vaccine has been routinely recommended in COPD patients.

A polyvalent vaccine has been shown to be effective in preventing pneumococcal bacteraemia [95]. Antibody titres increase after vaccination in COPD patients, even those treated with chronic oral steroids [96, 97]. A single-blind, randomised, non-placebo-controlled trial of the 23-valent vaccine confirmed that vaccination was associated with decreased community-acquired pneumonia caused by pneumococcus or of unknown aetiology [98]. Although a meta-analysis of available randomised controlled trials did not suggest a treatment effect in COPD patients, its evidence base was quite limited [99]. Despite these somewhat conflicting data, pneumococcal polysaccharide vaccination has been recommended for COPD patients aged 65 years and older [100, 101].

The additive role of combined influenza and pneumococcal vaccination has been studied to a limited extent. A two-year retrospective cohort study among elderly members of a staff-model managed care organisation examined clinical outcomes associated with influenza and pneumococcal vaccination [102]. Pneumococcal vaccination was associated with a lower risk of pneumonia hospitalisation (RR 0.57; 95% CI 0.38–0.84) and death (RR 0.71; 95% CI 0.56–0.91). During the influenza season, the benefits of pneumococcal and influenza vaccinations were additive (RR 0.28; 95% CI 0.14–0.58) for the number of hospitalisations for pneumonia or influenza among persons who had received both vaccinations. A more recent, open-label study compared influenza and pneumococcal vaccination in 191 patients with chronic lung disease (32.9% with COPD) [103]. Overall, the number of patients experiencing an infectious exacerbation was significantly lower in those receiving both vaccines; an additive effect was significant only in COPD patients.

PULMONARY REHABILITATION AND COMPREHENSIVE DISEASE MANAGEMENT

Pulmonary rehabilitation improves exercise capacity, exertional breathlessness, and health status in COPD patients [104–106], with these benefits noted across a wide spectrum of COPD disease severity [105]. Importantly, pulmonary rehabilitation has been reported to be associated with an almost two-fold reduction in AECOPD frequency [107] and reduced healthcare utilisation [108]. Long-term maintenance of pulmonary rehabilitation is crucial in

order to maintain benefits [107, 109–111] and is most effective when programmes include telephone contacts and intermittent supervised sessions [112].

Preliminary data suggest that comprehensive intervention at discharge from a hospitalisation for AECOPD significantly reduces such risk factors for AECOPD re-admission as timed walking distance, functional status and symptoms [113–116]. Two partly retrospective studies reported impressive declines in number of hospital-days during the year after rehabilitation compared with the previous year [115, 116]. Congruent physiological and functional improvements were seen in two small controlled trials of pulmonary rehabilitation immediately after AECOPD hospitalisation [117, 118]. In fact, a systematic review of six trials including 230 patients found improved risk of subsequent hospital admissions (RR 0.26; 95% CI 0.12–0.54) and mortality (RR 0.45; 95% CI 0.22–0.91) [119].

Simple post-discharge interventions, such as ensuring timely follow-up, also decrease AECOPD re-admissions [120]. However, programmes to teach patients enhanced skills can improve their ability to participate in their own disease management [121], in part by facilitating access to healthcare professionals [122]. A systematic review of self-management programmes found improved patient recognition, self-initiation of action, and use of antibiotics for severe exacerbations, but did not show improved healthcare utilisation or mortality [123]. Contrasting results were seen in a multicentre Canadian consortium, which examined a comprehensive patient education programme in patients with advanced COPD hospitalised for an AECOPD at least once in the previous year [121]. Patients receiving education (weekly visits by a trained healthcare professional over a 2-month period with monthly telephone follow-up) had decreases in AECOPD-related and all-cause hospital admissions, emergency visits and unscheduled physician visits, compared with those managed with 'usual care'. This cohort continued to show statistically and clinically relevant reductions in all-cause hospitalisations and all-cause emergency room visits over 2-year follow-up [124]. However, another study found no difference in health status, symptom scores, exercise capacity or exacerbations between a usual care group and self-management intervention group [125]. Reasons for the difference in results are not readily apparent. Additional investigation, possibly incorporating nurse-administered chronic disease management [122], is needed to determine whether such an approach could decrease a patient's likelihood of a subsequent AECOPD.

NOVEL THERAPEUTIC APPROACHES

Given the role of inflammation in COPD pathogenesis, and AECOPD in particular, it is not surprising that aggressive investigation is ongoing to modulate this inflammatory process. The agents that seem most promising are the new generation of selective phosphodiesterase (PDE) inhibitors targeting PDE₄ [126]. Although only weak bronchodilators, PDE₄ inhibitors appear to be potent anti-inflammatory agents, blocking release of IL-8 and TNF- α . Two agents, roflumilast (Daxas®, Altana) and cilomilast (Ariflo®, Glaxo SmithKline) are in advanced stages of development [127]. A phase III double-blind, randomised, placebo-controlled study of roflumilast in 1411 COPD patients confirmed reduced AECOPD frequency and improved health-related symptom scores (Figure 14.10a) [128]. A decrease in the overall mean number of AECOPD per patient was noted, particularly in mild events. A more recent study examined the effect of 500 μ g daily of roflumilast compared to placebo in 1513 patients with severe to very severe COPD [129]. The overall AECOPD rate was low in both groups and the effect of roflumilast was less impressive; *post hoc* analyses suggested a decrement in exacerbation rate in a subgroup of patients with very severe COPD and high exacerbation rate. Very preliminary results of two subsequent 1-year studies confirmed an improvement in FEV₁ and decrease in exacerbation rate in this population.* A 24-week study of cilomilast

* http://www.nycomed.com/en/Menu/Media/News+releases/PR_Daxas_081028.htm

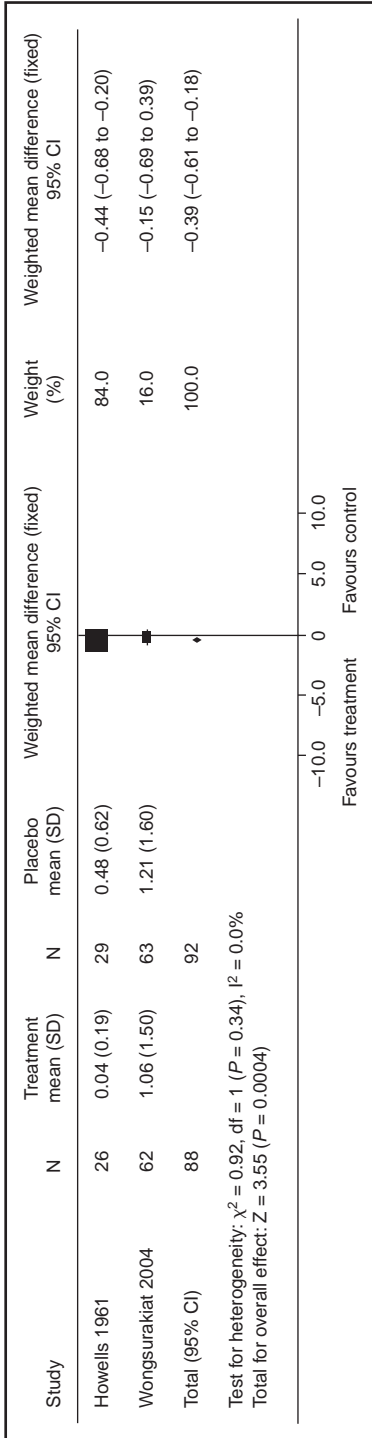


Figure 14.9 Systematic review comparing the effect of influenza vaccine on preventing late AECOPD (after 3–4 weeks) (with permission from [94]).

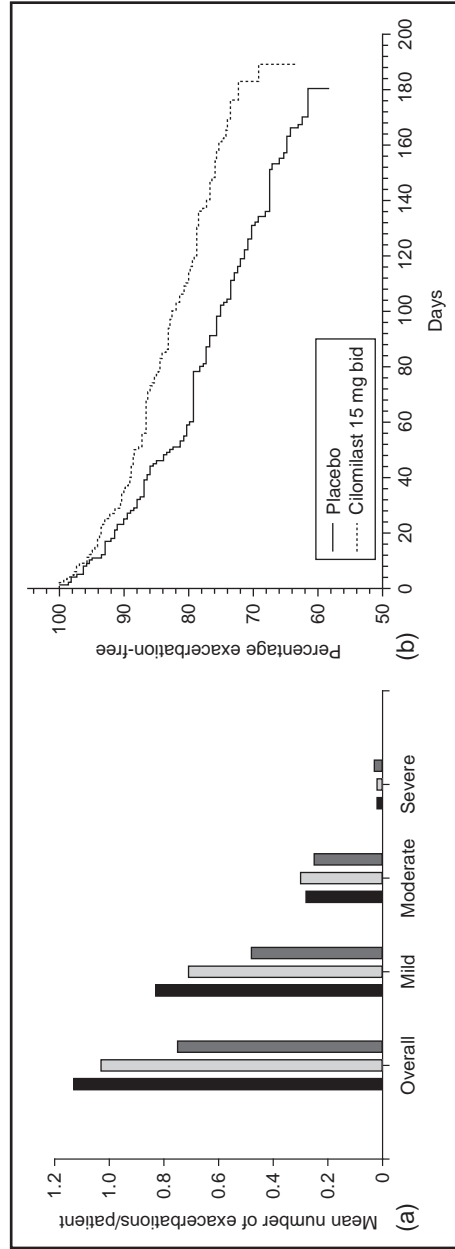


Figure 14.10 (a) The impact of roflumilast at two doses (250 μg , 500 μg) and placebo on the mean number of AECOPD, as well as on mild, moderate or severe episodes. With permission from [128]. (b) Kaplan-Meier estimates of exacerbation-free survival over 24 weeks of treatment with either cilomilast or placebo ($P = 0.008$) (with permission from [130]).

therapy also resulted in a decreased exacerbation rate and improved health status compared with placebo (Figure 14.10b) [130]. It is clear that additional investigation is required to assess the role of these novel agents on attenuating the inflammatory response in COPD and its associated exacerbations.

Additional approaches to ameliorating AECOPD frequency and severity continue to be investigated. The immunomodulatory agent OM-85 BV has been examined for its potential effect in preventing AECOPD. A systematic review identified 13 trials involving 2066 individuals; no consistent evidence of benefit was noted [131]. Most recently, 273 patients with mild COPD or chronic bronchitis were randomised at the time of an AECOPD to OM-85 or placebo; a decrease in the number of subsequent AECOPD was the primary endpoint [132]. The authors confirmed a 29% decrease in the mean number of episodes, particularly in patients with a history of current or past smoking. Additional investigation is required to better define the role of this immunostimulant.

The role of mucolytics in the treatment of COPD has remained controversial. A recent systematic review of 26 randomised, controlled trials suggests a decrease in exacerbations by up to 0.8 exacerbations/year, with a greater effect in those with more severe COPD [94]. Two large studies have recently reported conflicting results on mucolytic therapy. The Bronchitis Randomized on NAC Cost-Utility Study (BRONCUS) did not confirm a reduction in exacerbation rate during three years of N-acetylcysteine therapy compared to placebo [133]. In contrast, in a study of 709 subjects, the PEACE study found significant reductions in AECOPD (RR 0.75; 95% CI 0.62–0.92) in those randomised to 1500 mg carbocysteine for one year, as compared to placebo [134].

SUMMARY

AECOPD are important events, which are associated with an intensified inflammatory process. More importantly, recurrent or severe episodes are associated with negative effects on pulmonary function and quality of life, and with major healthcare expenditure. Increasingly, the paradigm in COPD therapy has shifted, extending management from symptom improvement to preventing or ameliorating the severity of AECOPD. There are numerous currently available therapeutic options proven to have a positive effect on AECOPD frequency. In addition, combining some classes of these agents appears to have additional benefit. Further investigation is required to better define the timing or number of these agents in individual COPD patients.

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15

Novel therapeutic targets for acute COPD exacerbation

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INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are characterised by periods of acute worsening of respiratory symptoms beyond the day-to-day variation of a patient's symptoms and usually require a change in therapy [1]. Management of exacerbations aims at optimising air flow by bronchodilation, reducing inflammation, treating infection, providing supportive care including ventilation and oxygen and minimising non-respiratory related symptoms including anxiety and sleep disturbances that accompany exacerbations [2]. Current pharmacological therapies have a modest effect in treating and preventing exacerbations and thus there is a great need for novel interventions. In this chapter, we will discuss a variety of novel pharmacological agents currently in clinical development that aim to prevent or treat COPD exacerbations (Table 15.1) [3].

BRONCHODILATORS

Bronchodilators play an important role in the prevention and treatment of acute exacerbations of COPD. Their acute use during exacerbations improves symptoms and lung function, and prevents or reverses respiratory failure.

Short-acting bronchodilators, which include β_2 -adrenoceptor agonists and anticholinergic bronchodilators, are the initial treatment of choice during an exacerbation. The delivery of short-acting bronchodilators during an acute exacerbation can be achieved using metered dose inhalers (MDI), dry powder inhalers (DPI) or nebulisers. A recent systematic review failed to reveal any evidence of superiority of one delivery system over the other [4]. However, nebulisation therapy has traditionally been the preferred method of delivery of bronchodilators during an acute exacerbation in the emergency department. Several studies suggest that the use of long-acting β_2 -adrenoceptor agonists and long-acting anticholinergic bronchodilators can prevent exacerbations [5–8]. A recent four-year large multicentre randomised clinical trial compared tiotropium to placebo in patients with stable COPD. COPD exacerbations were reduced by 25% in subjects taking tiotropium compared to placebo. However, the use of long-acting bronchodilators for the treatment of acute exacerbation has not been extensively evaluated and is not currently recommended [9].

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Table 15.1 Pharmacological agents in clinical development with their possible role in reducing COPD exacerbations

<i>Group</i>	<i>Type</i>	<i>Agent</i>
Anti-inflammatory agents	PDE4 inhibitors	Cilomilast Roflumilast
	NF- κ B inhibitors	I κ κ inhibitor
	IL-10	rhuIL-10
	Adhesion molecules blocker	TBC1269
	MAP-kinase inhibitor	SD-282; SB239063
	Resveratrol Curcumin	Resveratrol Curcumin
Mediator antagonists	LTB4 inhibitors	BAYx1005
	LTB4 antagonists	LY293111 SB225002
	Chemokine inhibitors	IL-8 blocking antibody SB225002
	TNF- α inhibitors	Infliximab Etanercept
Anti-oxidants	Anti-oxidants	N-acetylcysteine
Protease inhibitors	Neutrophil elastase inhibitor	FR901277 Desulfated heparin
Muco-active agents	Osmotic agents	Hypertonic saline Mannitol
	P _{2Y2} agonist	INS37217
	Exocytosis inhibitors	MANS peptide
	EGF inhibition	Gefitinib
	Calcium-activated chloride channel inhibitor	Talniflumate
	Retinoic acid antagonist	RO415253

Because of its rapid onset of action and high intrinsic efficacy [10], formoterol may prove effective in the management of acute exacerbation and a few small studies have demonstrated its beneficial effects in such situations when used alone [11–13] or when combined with other agents such as other bronchodilators or inhaled corticosteroids [14, 15]. Recently, two nebulised formulations of formoterol (arformoterol and racemic formoterol) were approved in the United States for use in stable patients with COPD [16]. Although these agents are currently only approved for the maintenance therapy of COPD, their role in treating acute exacerbations of COPD in the emergency department or hospital setting deserves future evaluation. Several novel bronchodilators are currently in development and although most are intended for maintenance therapy, they may have significant effect in reducing the frequency of acute exacerbations of COPD (Table 15.2).

NOVEL ANTIBIOTICS

Antibiotics may improve outcomes in exacerbations of COPD [17]. Patients who present with dyspnoea and increased sputum volume and/or purulence or patients who require mechanical ventilation mostly benefit from a 3–7 day course of oral or parenteral antibiotics

Table 15.2 Novel bronchodilators in clinical development

<i>Products in late-phase development</i>	<i>Products in early-phase development</i>
<ul style="list-style-type: none"> - Ultra-LABAs <ul style="list-style-type: none"> - Indacaterol - Carmoterol - LAMAs <ul style="list-style-type: none"> - Acclidinium - Combination therapy <ul style="list-style-type: none"> - ICS / LABA <ul style="list-style-type: none"> - Budesonide + formoterol* - Mometasone + indacaterol - Mometasone + formoterol - LABA / LAMA / ICS combination 	<ul style="list-style-type: none"> - Ultra-LABAs <ul style="list-style-type: none"> - GSK 159797, 597901, 159802, 642444, 678007 - LAMAs <ul style="list-style-type: none"> - NVA 237 (glycopyrrolate) - GSK 656398 - GSK 233705 - LAS 35201 - Combination therapy <ul style="list-style-type: none"> - Carmoterol + tiotropium - Salmeterol + tiotropium - Indacaterol + NVA 237 - Others
<p>* Approved for asthma in the USA; ICS = inhaled corticosteroid; LAMA = Long acting antimuscurinic (anticholinergic); Ultra-LABA = once-a-day long-acting beta-2-adrenoceptor agonist.</p>	

[18–20]. The causative organism implicated in the exacerbation is often difficult to identify. Sputum is often not diagnostic, based on the fact that many of these patients' airways are already colonised with several different bacteria. Furthermore, blood cultures are usually negative. However, the choice of antibiotics is usually based on the severity of COPD: patients with mild to moderate COPD are mostly susceptible to infection with *Haemophilus influenzae*, *Streptococcus pneumoniae* or *Moraxella catarrhalis*, while patients with severe COPD, those with prior hospitalisation and those with past use of frequent antibiotics may be infected with resistant organisms and other Gram-negative organisms such as *Pseudomonas* [20, 21]. Thus, in mild to moderate exacerbation, oral β -lactam antibiotics, tetracycline, trimethoprim-sulfamethaxazole and macrolides are recommended. In more severe disease, the use of broad-spectrum antibiotics such as fluoroquinolones, β -lactam/ β -lactamase inhibitors and second or third generation cephalosporins should be considered [1, 22]. Several new antibiotics are now available or are in development for use in the management of acute COPD exacerbation. Most new antibiotics are modifications of existing structures, suggesting that every effort should be made to conserve the sensitivity of current antibiotics by using them appropriately [23].

The frequency of acute exacerbation of COPD is higher in patients whose lower airways are colonised with bacteria [24]. Thus, it is postulated that the eradication of bacterial colonisation may reduce the frequency of exacerbations. Several trials have evaluated the effects of intermittent prophylactic antibiotic administration in preventing COPD exacerbations. In a systematic review of eleven trials conducted before 1970, prophylactic antibiotics were shown to have a small but statistically significant effect in reducing the days of illness due to exacerbations of chronic bronchitis [25]. However, these trials mostly evaluated the effect of continuous prophylactic antibiotic therapy over a few months. In a more recent trial, more patients receiving gemifloxacin over 26 weeks remained exacerbation free compared with those receiving clarithromycin [26]. A large trial investigating the prophylactic intermittent use of moxifloxacin in COPD patients who had at least two COPD exacerbations in the preceding year demonstrated a 25% reduction in COPD exacerbation rate. *Ad hoc* analysis of this study revealed that patients with mucopurulent sputum gained the most benefit from prophylactic use of antibiotics [27].

An alternative to the administration of prophylactic antibiotic to prevent acute exacerbation of COPD is the administration of oral vaccines such as whole-cell non-typeable *H. influenzae* vaccine (NTHi) and other multicomponent vaccines using killed bacterial extracts. However, these vaccines are not recommended by current clinical guidelines, as many of the primary trials on which they are based are small and methodologically flawed. Further trials are needed before the use of these oral vaccines can be considered as part of the routine clinical management of patients with COPD [28].

Viral infections play a major role in COPD exacerbation, however with the diagnostic tools currently available to make an accurate diagnosis, it is usually difficult to differentiate between viral and bacterial infections based on clinical features alone. More rapid diagnostic approaches are therefore needed to guide practitioners in the use of more appropriate antibiotics or antiviral treatments.

As both viral and bacterial infections play a major role in COPD exacerbation, several studies have evaluated the preventive value of using various vaccines. Influenza vaccine is recommended in patients with COPD to reduce influenza [22]. A recent study demonstrated that COPD exacerbation was significantly lower in COPD subjects who received combined vaccination with 23-valent pneumococcal vaccine and influenza vaccine against pneumonia compared to influenza vaccine alone [29]. OM-85 BV, an immunomodulatory agent from detoxified bacterial extract, has also been used in multiple studies for prevention of COPD exacerbations. However, a recent meta-analysis concluded that consistent evidence across multiple important outcomes which clearly demonstrates clinical benefit does not exist [30].

NOVEL ANTI-INFLAMMATORY AGENTS

COPD is characterised by chronic inflammation of the airways and the lung parenchyma [31]. The levels of inflammatory cytokines in induced sputum and blood correlate with the incidence of COPD exacerbation [32]. Further, airway inflammation intensifies during acute exacerbation of COPD [33]. Thus, it is reasonable to speculate that effective anti-inflammatory agents, especially those that may reduce neutrophil recruitment or activation, will reduce the rate of COPD exacerbations. Several novel anti-inflammatory agents are currently in development and may play a role in reducing the rate of COPD exacerbation.

CORTICOSTEROIDS

The use of systemic corticosteroids, while discouraged in stable COPD, plays a major role in the management of acute exacerbation of COPD. Systemic corticosteroid therapy improves various outcomes including lung function, symptoms and oxygenation and reduces treatment failure and length of hospital stay in patients with severe or very severe forced expiratory volume in one second (FEV₁) reduction [34–36]. The maximum benefit from these agents is obtained during the first two weeks of therapy and a longer duration of therapy or the use of doses larger than 40–60 mg of prednisone per day do not confer any additional benefits.

The maintenance use of inhaled corticosteroids has been shown in several trials to decrease the incidence of acute COPD exacerbations by 12–25% depending on the severity and the definition used [22, 37]. This effect is more pronounced in patients with more severe disease and those with a history of recurrent exacerbations [38]. The reduction of exacerbation frequency was also described with the use of a fixed combination of inhaled corticosteroid/long-acting β_2 -adrenoceptor agonist; fluticasone/salmeterol and budesonide/formoterol where the reduction in the frequency of exacerbation was more pronounced than the use of inhaled corticosteroids alone [8, 39–41]. In a recently published, large multicentre study, treatment with fluticasone/salmeterol combination therapy for

three years resulted in a 25% reduction in the annual rate of moderate to severe exacerbation of COPD compared with placebo ($P < 0.005$) [8]. Furthermore, two more recent US clinical trials compared fluticasone/salmeterol (250/50 μg bid) to salmeterol (50 μg bid). Fluticasone/salmeterol combination, compared to salmeterol, reduced the rate of moderate to severe COPD exacerbation by 30% during the 1-year study follow-up [42]. Furthermore, another randomised 2-year clinical trial compared fluticasone/salmeterol (500/50 μg bid) to tiotropium [43]. Rates of COPD exacerbations did not differ between the two study arms. However, the fluticasone/salmeterol arm had a lower rate of systemic steroid-requiring exacerbation episodes while subjects on tiotropium had fewer antibiotic-requiring exacerbations [43].

PDE-4 INHIBITORS

The cyclic nucleotides, adenosine monophosphate AMP (cAMP) and guanosine mono-phosphate (cGMP), are intracellular second messengers that suppress the activity of inflammatory cells and mediate the relaxation of airway smooth muscle through the activation of protein kinase A and B. However, both cyclic nucleotides are unstable due to the presence of the phosphodiesterase enzymes (PDEs), which hydrolyse and degrade them. Amongst the PDE isoenzymes, PDE-4 is highly selective for cyclic AMP and represents the major cyclic AMP metabolising enzyme in all immunocompetent cells. Inactivation of cAMP by PDE-4 results in a pro-inflammatory cascade. PDE-4 is expressed in many airway cells involved in the pathogenesis of COPD, including neutrophils, macrophages, T cells and endothelial cells. Thus, PDE-4 inhibitors have a broad spectrum of anti-inflammatory effects and may play a therapeutic role in COPD. Several selective PDE-4 inhibitors are under study at this time [44]. Trials with cilomilast in COPD reported a reduction in inflammatory markers in bronchial biopsies (i.e. CD8+ T cells and CD68+ macrophages) and modest improvement in FEV₁, quality of life and reduction in COPD exacerbation [45–47]. Roflumilast, another orally delivered, potent and selective PDE-4 inhibitor is currently under investigation (phase III trials) for the treatment of COPD. In a large clinical trial of 1411 COPD patients, roflumilast significantly and dose-dependently reduced the total number of exacerbations (mild, moderate and severe) per patient ($P = 0.0029$). Compared with placebo, patients treated with roflumilast 500 μg experienced 34% fewer exacerbations [48]. In a subsequent large multicentre 1-year study, roflumilast decreased exacerbations of COPD in those patients with severe disease [49]. Thus, available data suggest that PDE-4 inhibitors may have a role in reducing COPD exacerbations. Further clinical trials are ongoing to evaluate these effects. The use of PDE-4 inhibitors during an acute exacerbation of COPD has not been evaluated.

NF- κ B INHIBITORS

The nuclear factor (NF)- κ B family plays a major role in control of both innate and adaptive immunity. NF- κ B proteins are present in the cytoplasm in association with inhibitory proteins that are known as inhibitors of NF- κ B (I κ Bs) [50]. NF- κ B is activated in macrophages and epithelial cells of COPD patients. It regulates expression of chemokines like IL-8, TNF- α and other inflammatory cytokines, and some of the metalloproteinases [51, 52]. Several approaches, including inhibition of the enzymes that degrade I κ Bs (such as I κ B kinase or IKK) may have some effect in COPD exacerbations. An inhibitor of IKK decreased release of chemokines from alveolar macrophages [53]. However, in an elastase-induced model of airway inflammation, IKK inhibitor did not reduced the inflammatory cell burden [54].

INTERLEUKIN-10

IL-10 is an anti-inflammatory cytokine that inhibits the secretion of several chemokines, TNF- α and matrix metalloproteinase 9 (MMP-9), and increases the release of the tissue inhibitors of MMPs (TIMPs), the endogenous inhibitors of MMPs [54]. Recombinant IL-10 is currently under evaluation for chronic inflammatory diseases like inflammatory bowel disease. One drawback of IL-10 is its haematological side-effects such as asymptomatic and reversible anaemia and thrombocytopenia [55]. The role of IL-10 in airway neutrophilic inflammation is not known.

ADHESION MOLECULE BLOCKERS

Adhesion molecules play a major role in recruitment of the inflammatory cells to the lungs [56]. E-selectin on endothelial cells interacts with neutrophils. A selectin blocker, TBC1269, inhibits neutrophil adhesion to endothelial cells [57]. Inhibition of neutrophil recruitment to airways may reduce inflammation and mucus hypersecretion and reduce COPD exacerbation [56]. However, one possible problem with adhesion molecule blockers is that impaired neutrophil recruitment may result in increased susceptibility to infection [51]. A recent study using the inhaled selectin blocker, bimosiamose, (TBC1269) in subjects with mild asthma attenuated the allergen-induced late asthmatic reaction [58]. Further studies are needed to assess value of these agents in COPD.

p38 MITOGEN-ACTIVATED PROTEIN (MAP) KINASE INHIBITORS

The p38 MAP kinase pathway has a major role in increased expression of cytokines involved in COPD like IL-8, TNF- α , and metalloproteinases. p38 MAP kinase may mediate the increased inflammation during exacerbation and thus inhibitors of this kinase may play a major role in reducing exacerbation intensity and frequency. Inhibitors of p38 MAP kinase exhibit a broad range of anti-inflammatory effects in conditions such as arthritis and other joint diseases, septic shock and myocardial injury [59]. SB-239063, an inhibitor of p38 MAP kinase, blocked the release of inflammatory cytokines from alveolar macrophages [60] and reduced neutrophilia and cytokine release induced by cigarette smoke in a mouse model [61, 62]. Another inhibitor of p38 MAP kinase (SD-282) improved IL-1 β -induced impairment of β -adrenoceptor-mediated bronchodilation *in vivo* [63]. However, safety and long-term efficacy data for these inhibitors are not currently available and their role in COPD is unknown. In addition, the effects of such a broad-spectrum anti-inflammatory agents may prove to be toxic and this needs further exploration [51].

RESVERATROL

Resveratrol (3,5,4'-trihydroxystilbene) is a polyphenolic molecule found in the skins of red fruits such as grapes, and is one of the compounds in red wine extract that exhibits a range of biological activities [64]. It has antioxidant, antineoplastic and anti-inflammatory properties [65]. Resveratrol inhibited both basal and stimulated cytokine release by bronchoalveolar lavage (BAL) fluid macrophages from cigarette smokers and patients with COPD [66]. Resveratrol's antioxidant properties may play a role in treatment of COPD, however, the identification of its mechanisms of action and its role in COPD requires further study [67].

CURCUMIN

Curcumin, a derivative of turmeric, is commonly used as a spice, flavouring agent, food preservative, colouring agent or for decoration. There is growing evidence, however, to sug-

gest it has a significant anti-inflammatory effect by suppressing NF- κ B [68, 69]. The role of curcumin in COPD is not clear but is currently being evaluated at our centre.

MEDIATOR ANTAGONISTS

Several chemotactic factors for neutrophils exist and the levels of these factors are increased during exacerbations. Over the last two decades, many of the inflammatory mediators that are increased in COPD have been identified. Currently, several mediator antagonists are under investigation for their potential therapeutic role.

LEUKOTRIENE B₄ INHIBITORS

LTB₄, a key chemoattractant of neutrophils, reduces neutrophil chemotactic activity of COPD sputum in the stable state [70]. Antagonists of the two subtypes of LTB₄ receptor (LY29311 [71] and SB201146 [72]) have been shown to inhibit sputum-induced neutrophil chemotaxis. Inhibitors of LTB₄ synthesis (e.g. BAYx1005) produce a modest reduction in sputum LTB₄ concentration [73]. The clinical efficacy of LTB₄ inhibition preventing acute exacerbation of COPD is unknown.

CHEMOKINE INHIBITORS

There are a number of chemokines and cytokines that play important roles in mediating inflammation in COPD and are therefore potential therapeutic targets. Chemokines are cytokines capable of causing selective leukocyte recruitment by acting on specific members of the chemokine receptor family [74]. Chemokines are synthesised by different cells including leukocytes, endothelial and epithelial cells, smooth muscle cells and fibroblasts. Four groups of chemokines (CC, CXC, C_m and CX₃C [fractalkine]) have been described [75]. Each chemokine receptor binds specific members of one family and is therefore named accordingly as CXCR, CCR, XCR and CX₃R. Neutrophils express CXCR1 and 2, monocytes have CCR2 and lymphocytes (CD8+) have CXCR3. CXCL8 or IL-8 is a strong neutrophil chemoattractant: IL-8 level is elevated in COPD and correlates with neutrophil count in induced sputum and disease severity [76]. An antibody against IL-8 is effective in reducing neutrophilic inflammation in animal models and in clinical trials for COPD [77]. Furthermore, a CXCR2 antagonist (SB225002) has been developed and is undergoing clinical trial. It is predicted to be useful in reducing and treating exacerbations [78–80]. However, chemokine pathways exhibit a degree of redundancy, so inhibiting any one element may not be effective. The results of a phase II clinical trial with an IL-8 inhibitor suggest a beneficial effect on reducing dyspnoea in stable patients with COPD [81]. Beeh and colleagues investigated the effect of combining an anti-IL-8 antibody with an LTB₄ antagonist, and found that the combination effect was not significantly greater than the effect of either single agent given alone [72].

TNF- α INHIBITORS

A further addition to the list of therapeutic targets is TNF- α , which induces IL-8 via nuclear factor kappa B (NF- κ B). TNF- α is elevated in the sputum of patients with COPD, especially those with muscle wasting. A role in susceptibility to COPD for the polymorphism of the TNF- α gene is suggested. TNF- α is normally synthesised as a precursor in a membrane-bound form. With stimulation, the precursor is converted to pro-TNF- α that is finally converted to active TNF- α by a membrane-bound metalloproteinase called TNF- α converting enzyme (TACE) [75]. Humanised monoclonal TNF antibodies (infliximab and adalimumab), humanised soluble recombinant tumour necrosis factor receptor (etanercept) and TACE

may exert beneficial effects in airway inflammation of COPD [82]. The use of humanised monoclonal antibodies (infliximab) and soluble TNF- α receptors (etanercept) is currently being investigated [71, 83]. However, a recently published prospective study using infliximab in stable COPD patients failed to reveal any beneficial effects for this agent when used over six months [84]. Furthermore, the long-term safety of this agent was questioned in this study, as the incidence of malignancy was higher in the treated patients compared with placebo. Another study of infliximab in patients with COPD did not show significant effects on airway inflammation, lung function, resting energy expenditure or quality of life [85].

ANTIOXIDANTS

Oxidative stress is elevated during COPD exacerbations and acts as an amplifying mechanism for inflammation [69]. This suggests that anti-oxidants may play an important role in preventing and treating exacerbations. The use of N-acetylcysteine (NAC), to provide intracellular cysteine for the production of the endogenous antioxidant glutathione is one of several treatment options under investigation. Initial research suggests that oral NAC reduces the number of exacerbations in COPD [86], but a more recent randomised controlled trial failed to show that the addition of NAC to treatment with corticosteroids and bronchodilators can modify the outcome in acute exacerbations of COPD [87]. However, when patients not treated with inhaled corticosteroids were analysed, a significant reduction was noted.

PROTEASE INHIBITORS

An imbalance between proteases and anti-proteases is proposed as the mechanism of tissue damage in COPD. Elastin may be the most important target for these enzymes, because there is a loss of elasticity in the lung parenchyma in patients with emphysema and elastin cannot be regenerated in an active form [75]. Therefore, small molecules that can inhibit these proteases may have a role in future COPD treatment. Neutrophil elastase and MMP-9 are the possible targets for such therapy. Small molecules inhibiting neutrophil elastase will be tested in clinical trials. The non-selective inhibitor of MMP-9 has significant side-effects, however, the more selective inhibitors may play a role in COPD management [51]. Sivelestat (ONO-5046) is a competitive inhibitor of human neutrophil elastase under study for pulmonary fibrosis and idiopathic interstitial pneumonia [88]. Its role in COPD is not yet clear. In an acute neutrophilic inflammatory model in rats, sivelestat significantly weakened the lung injury [89]. FR901277, a natural agent isolated from the culture filtrate of *Streptomyces resistomicificus* that shows potent inhibitory activity against human leukocyte elastase ameliorated elastase-induced emphysema in male golden Syrian hamsters [90, 91]. In addition to the agents mentioned above, it has been shown that heparin inhibits neutrophil elastase [92] and a form of desulfated heparin is entering into clinical trial for treatment of acute exacerbations of COPD.

MUCOREGULATORS

Mucus hypersecretion in the small and large airways is one of the characteristics of COPD and plays a major role in COPD exacerbations, hospitalisation and COPD mortality [93–97]. Several classes of medications are currently in development that specifically target mucus hypersecretion [71, 98].

AGENTS THAT IMPROVE MUCOCILIARY CLEARANCE

There is a renewed interest in improving mucociliary clearance by increasing airway surface liquid. Several of these agents have been tested in cystic fibrosis. Patients with cystic fibrosis responded to nebulised 7% hypertonic saline with improvement in lung function and reduction in exacerbation rate [99–100]. In another study, hypertonic saline acutely increased mucociliary clearance in patients with moderate to severe COPD [101]. Mannitol significantly increased mucociliary clearance in subjects with asthma, bronchiectasis and cystic fibrosis [102]. Future trials are required to evaluate the effect of the above agents in reducing the frequency of COPD exacerbation. P_{2Y2} purinoceptors, via interaction with adenosine triphosphate (ATP) and uridine 5' triphosphate (UTP), increase mucin and water secretion in airways [103]. A P_{2Y2} agonist may increase the airway water secretion and thus increase mucociliary clearance [104].

EXOCYTOSIS INHIBITORS

Myristoylated alanine-rich C kinase substrate (MARCKS) mediates the movement of mucin granules to the apical membrane of secretory cells. Instillation of N-terminal domain of MARCKS prevented goblet cell secretion in a mouse model of asthma [105]. However, the use of this agent has not yet been tested in COPD.

INHIBITION OF MUCIN SYNTHESIS AND GOBLET CELL METAPLASIA

Epidermal growth factor receptor plays a critical role in mucus hypersecretion resulting from various insults including exposure to cigarette smoke and Gram-positive bacteria [106]. Gefitinib, an inhibitor of epidermal growth factor receptor is under clinical evaluation for different malignancies [104]. Its role in COPD is unknown. Calcium-activated chloride channels are important in mucus secretion from goblet cells [107, 108]. Talmiflumate is an inhibitor of the channel and may exert a mucoregulatory effect in COPD [109]. Retinoic acid may also have an important role in mucin expression and mucus hypersecretion [103]. A retinoic acid antagonist (RO-41-5253) is currently in development and may have a mucoregulatory role [110].

SUMMARY

Acute exacerbation of COPD is a major cause of morbidity, hospitalisation, mortality and healthcare costs. Several currently approved pharmacological agents reduce the frequency of COPD exacerbations. However, recent insights into the inflammatory pathways in COPD have led to the identification of several novel targets of therapy, allowing the potential development of new pharmacological agents. Several such agents are currently being studied and if effective and safe may provide a vast new armamentarium for the future prevention and therapy of acute exacerbation of COPD.

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Abbreviations

ABC	Antibiotics, bronchodilators and corticosteroids
ADP	adenosine diphosphate
AECB	acute exacerbation of chronic bronchitis
AECOPD	acute exacerbation of COPD
AM	alveolar macrophage
AMP	adenosine monophosphate
APACHE II	Acute Physiology And Chronic Health Evaluation
ARF	acute respiratory failure
ATP	adenosine triphosphate
ATS	American Thoracic Society
AUC	area under the curve
BAL	broncho-alveolar lavage
BCAA	branched-chain amino acid
BD	bronchodilator
BMI	body mass index
BNP	brain natriuretic peptide
BODE	Body mass index, airflow Obstruction, Dyspnoea and Exercise
BRONCUS	Bronchitis Randomized on NAC Cost-Utility Study
BTS	British Thoracic Society
C-AECB	complicated AECB
cAMP	adenosine 3',5'-cyclic monophosphate
CAP	community-acquired pneumonia
CI	confidence interval
cGMP	cyclic guanosine monophosphate
C_{\max}	maximum concentration
CO ₂	carbon dioxide
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CPE	clinical probability estimate
Cr	creatinine
CRM	customer relationship management
CRP	C-reactive protein
CRQ	Chronic Respiratory Questionnaire
CTS	Canadian Thoracic Society
DALY	disability adjusted life-year
ΔFEV_1	change in FEV ₁
DIT	diet-induced thermogenesis
DNA	deoxyribonucleic acid
DPH	dynamic pulmonary hyperinflation
DPI	dry powder inhaler
ECG	electrocardiogram

ECOPD	exacerbation of COPD
ECP	eosinophil cationic protein
ED	emergency department
EE	energy expenditure
EELV	end-expiratory lung volume
<i>erm</i>	erythromycin ribosomal methylase
ERS	European Respiratory Society
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ET-1	endothelin-1
FBC	formoterol–budesonide
FEF	forced expiratory flow
FEV ₁	forced expiratory volume in one second
FFM	free fat mass
FiO ₂	fraction of inspired oxygen
FM	fat mass
FRC	functional respiratory capacity
FVC	forced vital capacity
GLOBE	Gemifloxacin Long-Term Outcomes in Bronchitis Exacerbations
GM-CSF	granulocyte–macrophage colony stimulatory factor
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GRO- α	growth-related oncogene-alpha
Hb	haemoglobin
HbO ₂	oxyhaemoglobin
HH	home hospitalisation
HIV	human immunodeficiency virus
HMPV	human metapneumovirus
HRQL	health-related quality of life
IBERPOC	Epidemiological study of chronic obstructive pulmonary disease in Spain
IC	inspiratory capacity
ICAM-1	intracellular adhesion molecule-1
ICCC	Innovative Care for Chronic Conditions
ICS	inhaled corticosteroid
ICT	information and communication technology
ICU	intensive care unit
IgA	immunoglobulin A
I κ B	inhibitor of NF- κ B
IL	interleukin
IMP	inosin monophosphate
ISOLDE	Inhaled Steroids in Obstructive Lung Disease in Europe (study)
i.v.	intravenous
LABA	long-acting β -agonist
LAMA	long-acting anti-muscarinic
LOS	lipooligosaccharide
LRTI	lower respiratory tract infection
LTB ₄	leukotriene B ₄
MAP	mitogen-activated protein
MARCKS	myristoylated alanine-rich C kinase substrate
MBL-2	mannose binding lectin 2
MDI	metered dose inhaler
<i>mef</i>	macrolide efflux pump
MIC	minimum inhibitory concentration

MIGET	multiple inert gas elimination technique
MMP-9	matrix metalloproteinase 9
MPC	mutant prevention concentration
MPO	myeloperoxidase
MRC	Medical Research Council
mRNA	messenger ribonucleic acid
MV	mechanical ventilation
NAC	N-acetylcysteine
NE	neutrophil elastase
NF	nuclear factor
NF- κ B	nuclear factor kappa B
NHLBI	National Heart, Lung and Blood Institute
NHP	Nottingham Health Profile
NIV	non-invasive ventilation
NPPV	non-invasive positive pressure ventilation
NTHi	non-typeable <i>H. influenzae</i> (vaccine)
NT-proBNP	N-terminal prohormone brain natriuretic peptide
OMP	outer membrane protein
OR	odds ratio
PaCO ₂	arterial carbon dioxide tension
PaO ₂	arterial oxygen tension
PB	protein breakdown
PBP	penicillin binding protein
PCr	phosphocreatinine
PCR	polymerase chain reaction
PD	pharmacodynamic
PDE	phosphodiesterase
P _{di}	transdiaphragmatic pressure
PEACE	Preventive Effect on Acute Exacerbation of COPD
PEEPi	positive end-expiratory pressure
PEFR	peak expiratory flow rate
P _{ga}	gastric pressure
PK	pharmacokinetic
PMN	polymorphonuclear leukocyte
PO ₂	partial pressure of oxygen
P _{oes}	oesophageal pressure
P _{pl}	total pleural pressure
PS	protein synthesis
PSV	pressure support ventilation
PvO ₂	mixed venous oxygen pressure
QALY	quality-adjusted life year
QoL	quality of life
RANTES	regulated upon activation, normal T cell-expressed and secreted
REE	resting energy expenditure
RNA	ribonucleic acid
ROC	receiver operating characteristic
RR	relative risk
RSV	respiratory syncytial virus
SaO ₂	arterial oxygen saturation
SARS	severe acute respiratory syndrome
SCTA	spiral computed tomographic angiography
SGRQ	St George's Respiratory Questionnaire

SIT	serum inhibitory titre
SLPI	secretory leukoprotease inhibitor
SOLDQ	Seattle Obstructive Lung Disease Questionnaire
SP-A	surfactant protein A
sPAP	systolic pulmonary artery pressure
SP-D	surfactant protein D
SpO ₂	peripheral saturation of oxygen (measured by pulse oximetry)
TACE	TNF- α converting enzyme
TDI	Transition Dyspnoea Index
TIMP	tissue inhibitor of MMP
TLC	total lung capacity
TLR	toll-like receptor
TNF- α	tumour necrosis factor-alpha
TORCH	Towards a Revolution in COPD Health
U-AECB	uncomplicated AECB
UPLIFT	Understanding Potential Long-Term Impacts on Function with Tiotropium
UTP	uridine 5' triphosphate
VA	(US Department of) Veterans Affairs
VA/Q	alveolar ventilation/perfusion ratio
VAS	visual analogue scale
V _T	tidal volume
WBC	white blood cell
WHO	World Health Organization
WOB	work of breathing

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