

COPD guidelines in relation to infections: a critical analysis

Educational aims

- › To define the importance of exacerbations in COPD and chronic bronchitis.
- › To assess current guidelines for the treatment of COPD exacerbations.
- › To outline current antibiotic treatments and treatment periods for exacerbations.

Summary

Chronic obstructive pulmonary disease (COPD) exacerbations have been associated with an increased risk of mortality and currently available therapies for exacerbations show only limited beneficial effects. Bacterial infections caused by pathogens are the predominant cause of acute exacerbations in COPD and chronic bronchitis. Current guidelines suggest a correlation between forced expiratory volume in 1 s (FEV₁) and the type of infecting pathogen and that purulence of sputum is one of the most important factors associated with the presence of a bacterial infection. Antibiotics are recommended for patients with exacerbations and sputum purulence. However, resistance to antibiotics is increasing, especially in southern Europe. To reduce the risk of resistance, shorter treatment periods can be implemented for patients with mild-to-moderate exacerbations.

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Provenance

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Competing interests

None declared

COPD exacerbations

Survival

An exacerbation is defined as an increase in the baseline symptoms of a disease, in the absence of an identifiable cause, according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [1]. In COPD, exacerbations are commonly associated with an increase in dyspnoea, sputum volume, sputum purulence with or without symptoms of upper respiratory infection, increased wheeze and reduced exercise tolerance. Most COPD patients with exacerbations can be managed at home; however, some need to be hospitalised.

An independent link has been found between severe exacerbations of COPD and mortality [2]. This study by SOLER-CATALUÑA *et al.*

[2] demonstrates that an increasing frequency of severe acute exacerbations has a negative prognostic impact on mortality in COPD patients, particularly if the patients require hospitalisation. Figure 1 shows the survival rate of patients according to the frequency of exacerbations. Therefore, a reduction in the number and severity of exacerbations experienced by a COPD patient should be regarded as a priority in the management of these patients.

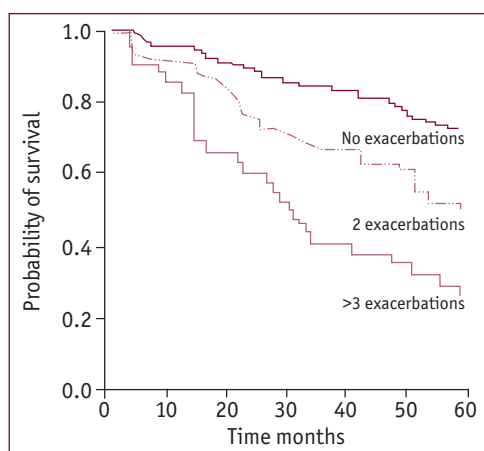
Early therapy and recovery

Currently available therapies for the control of COPD exacerbations, including oral corticosteroids, antibiotics and bronchodilators, appear to have only limited beneficial effects. In addition, COPD patients with exacerbations often delay presentation or do not seek therapy. WILKINSON *et al.* [3] hypothesised that early presentation and intervention of patients with COPD

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B.1.4, B.3, D.3.9, E.1.1

Figure 1

Survival curves of COPD patients with a) no acute exacerbations ($p < 0.001$), b) 1–2 acute exacerbations requiring hospital treatment ($p < 0.001$) and c) > 3 acute exacerbations ($p = 0.07$). Reproduced from [2] with permission from the publisher.



exacerbations would result in a decrease in the severity of exacerbations and hence reduce disease progression. The relationship between symptom recovery time and the delay between the onset of exacerbation and the start of treatment was recorded. The study demonstrated that early treatment of exacerbations with existing therapies shortened recovery time and improved exacerbation-related morbidity and mortality (figure 2).

Acute exacerbations of chronic bronchitis

Aetiology

Chronic bronchitis and acute exacerbations are both associated with COPD. Chronic bronchitis is defined as a cough present for ≥ 3 months for two consecutive years. Exacerbations may be caused by respiratory viruses or bacteria: typically, 25% are caused by viruses, 26% by bacteria and 27% by a combination of the two; 22% have no ascertainable cause. Therefore, bacterial infections are the predominant cause of acute exacerbations of chronic bronchitis (AECB). A Gram stain of sputum, > 2 exacerbations within the previous year, and purulence of sputum, are used as evidence for the presence of bacteria. A strong correlation has been shown between failure to eradicate

bacterial infection and clinical failure rate, demonstrating that treatment of bacterial infections plays a key role in the clinical outcome [4].

The most common bacterial pathogens isolated in AECB patients are *Haemophilus influenzae*, *H. parainfluenza*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*. The presence of these bacteria can depend on the severity of airway disease: more virulent organisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* have been found in patients with more severe AECB. Nonpathogenic bacteria also appear to play a role in the aetiology of AECB.

P. aeruginosa is more commonly isolated in recently hospitalised patients compared with other pathogens; this could largely be due to the fact that it is associated with more severe exacerbations. Several risk factors have been associated with the presence of *P. aeruginosa* including the use of antibiotics within the previous 3 months, especially in those who have not been vaccinated against influenza [5]. FEV1 $< 50\%$ predicted has also been associated with a very high risk of *P. aeruginosa* in patients with acute exacerbations of COPD [6]. In addition, colonisation or previous isolation of *P. aeruginosa* during an exacerbation increases the risk of a subsequent infection. A large clinical study is still needed to determine the real role of *P. aeruginosa* in AECB.

Treatment with antibiotics

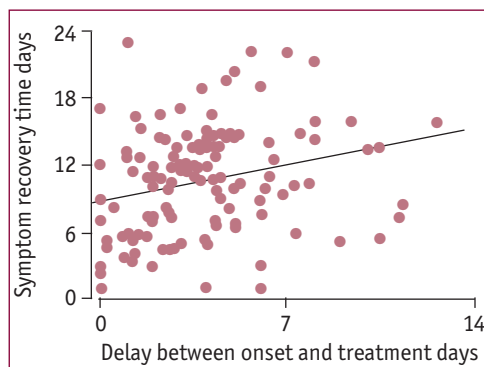
The majority of studies available on the use of antibiotics for the treatment of exacerbations are very old. A large proportion of these studies show some benefit for the use of antibiotics for exacerbations, although some showed no benefit [7]. Most of the more recent positive information available for antibiotics in AECB comes from a study by NOUIRA *et al.* [8] in 2001. The NOUIRA *et al.* [8] study states that antibiotics are a vital therapy for patients with severe exacerbations on mechanical ventilation however, patients with mild-to-moderate exacerbations may not benefit from antibiotics because they have a high spontaneous remission rate.

Parameters used to predict specific microorganisms

The meaning of mild, moderate and severe disease is not well defined in acute exacerbations of COPD (AECOPD), in contrast with the situation in community-acquired pneumonia. Guidelines

Figure 2

Effect of early treatment on the recovery of exacerbation symptoms. Patient mean recovery time against patient treatment delay (i.e. time from onset of exacerbations to initiation of therapy) in 108 patients. Regression coefficient 0.42 days per days, delay; 95% confidence interval 0.19–0.65; $p < 0.001$. Reproduced from [3] with permission from the publisher.



suggest that the type of infecting microorganism can be predicted by the severity of the disease in terms of FEV₁; however, FEV₁ is not always available. Microorganisms have been divided into three categories according to FEV₁ severity (table 1) [9]. It is not yet known whether this system will be useful in clinical practice in an emergency department because, to date, no studies have addressed the issue.

The ERS has divided patients into three groups according to their COPD severity [10].

- Group A: mild with comorbidities.
- Group B: moderate to severe without risk factors for *P. aeruginosa*.
- Group C: moderate to severe with risk factors for *P. aeruginosa*.

Each group has been assigned different microorganisms that could be involved in the infection, for example group A are most commonly infected with *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* and group B with all those in group A plus Enterobacteriaceae, *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus* and *Enterobacter*.

Guidelines for antibiotic therapy in AECOPD

The following guidelines have been set by organisations concerning the use of antibiotics for AECOPD.

- Canadian Thoracic Society: "...antibiotics should only be considered for use in patients with purulent exacerbations" [11].
- Global Initiative for Chronic Obstructive Lung Disease: "Antibiotics are only effective...with worsening dyspnoea and cough...also increased sputum volume and purulence" [12].
- ATS: "May be initiated in patients with altered sputum characteristics" [13].
- National Institute for Health and Clinical Excellence: "Antibiotics should be used to treat exacerbations of COPD associated with a history of more purulent sputum" [14].

To monitor antibiotic therapy in hospitalised patients with AECOPD, the ERS recommends that sputum cultures or endotracheal aspirates should be used [10]. Procalcitonin has also been suggested as a means of monitoring bacterial infection because procalcitonin levels increase rapidly in the presence of infection. The efficacy and safety of procalcitonin guidance for reducing antibiotic prescriptions in patients with AECOPD

Table 1. Microorganisms categorised by the severity of FEV₁

FEV ₁ <100% pred	FEV ₁ <50% pred	FEV ₁ <30% pred
<i>Streptococcus pneumoniae</i>	<i>Haemophilus influenzae</i>	Enterobacteriaceae
<i>Streptococcus</i> spp.	<i>Moraxella catarrhalis</i>	<i>Pseudomonas aeruginosa</i>
<i>Staphylococcus aureus</i>	<i>Haemophilus parainfluenza</i>	
% pred: % predicted.		

has been studied in a recent trial [15]. The findings demonstrated that guidance with procalcitonin levels reduces the exposure to antibiotics by an absolute risk reduction of 31.5% in AECOPD patients after presentation to the emergency department.

Sputum cultures

All the above guidelines suggest that exacerbations and purulence of sputum are the most important factors for the presence of a bacterial infection. If purulence of sputum and exacerbations are present guidelines strongly recommend the use of antibiotics. In a recent study, sputum purulence was defined as a change in sputum colour from uncoloured to yellow-green monitored by the patient [16]. The study was carried out in 40 patients with severe exacerbations of COPD requiring hospitalisation; none of the patients had prior antibiotic treatment. A strong relationship was found between the self-reported observation of purulence and the presence of a bacterial infection (odds ratio 27.2). This simple parameter may help to identify patients to receive antibiotics.

To perform an adequate study on the usefulness of sputum cultures in AECOPD, sputum samples from all exacerbated patients who need hospitalisation would be required; however, if the resistance is known and the subject of the study is clinical routine, a subpopulation of patients would be sufficient. Patients who could benefit from having a bacterial culture from their sputum and a sensitivity pattern to antibiotics are those who have a potential risk of infection with multidrug-resistant microorganisms. This group of patients is generally the more severely infected population, who are more commonly infected with *P. aeruginosa*, have an FEV₁ <30% and have received antibiotics in the previous month.

How to deal with nonresponsive patients

The issue of nonresponsiveness is controversial because although it is known that there is a 20% chance of treatment failure for AECOPD, there

are no clear guidelines on what to do when a patient is not responsive to initial antibiotics. The ERS guidelines state that noninfectious causes of failure, for example inadequate medical treatment, embolisms and cardiac failure, should be evaluated. An antibiotic change with good coverage against *P. aeruginosa* and *S. pneumoniae*, is also recommended with subsequent adjustment of new antibiotic treatments according to microbiological results. However, currently there are no studies to support these recommendations. Studies exist on the rate of failure, but there are none examining interventions that are required in non-responsive patients, with an increased length of hospital stay and an increase in mortality.

Are the current recommendations useful for all European countries?

Resistance to antibiotics among common respiratory infections has risen dramatically in recent years. The ERS recommends the administration of macrolides, tetracyclines, amoxicillin and levofloxacin for the treatment of mild exacerbations and second-generation cephalosporins for more severe exacerbations. In some countries in the south of Europe, penicillin-resistant *S. pneumoniae*, which is common in patients with mild exacerbations, has a high likelihood of reduced susceptibility to antibiotic classes including macrolides, cephalosporins, tetracyclines and trimethoprim-sulphamethoxazole. This is a significant problem because it causes clinical failure. Penicillin-resistant bacterial strains have shown a high level of resistance to the macrolides including the newer agents. A large cohort study of pneumococcal pneumonia patients showed that mortality was significantly associated to high levels of penicillin resistance, even when using the third-generation cephalosporin cefotaxime [17]. Therefore, it is important to tailor antibiotic treatment according to the pattern of resistance in each country.

Antibiotic considerations

Levofloxacin and moxifloxacin are third-generation quinolones that are recommended for the treatment of mild and moderate-to-severe COPD without the risk of *P. aeruginosa*. A comparison of levofloxacin 500 mg once daily for 7 days and moxifloxacin 400 mg once daily for 5 days in AECB patients demonstrated that the two quinolones were very similar in terms of clinical success and microbiological eradication [18].

The MOSAIC study examined the effectiveness of moxifloxacin with standard antibiotic therapy in AECB [19]. Results showed that moxifloxacin was superior to standard antibiotic in clinical cure, bacteriological eradication and long-term outcomes, but equivalent in clinical success. A 6-month open-label trial in AECOPD patients studied the success of levofloxacin against standard therapy [20]. The study found lower numbers of hospitalisations (12% versus 27%), a similar number of exacerbations (33 versus 41) and similar infection-free survival intervals (112 versus 101 days) between the levofloxacin and standard antibiotic group, respectively.

A meta-analysis including 12 randomised controlled trials compared the safety and effectiveness of first- and second-line antibiotics in the treatment of AECOPD [21]. The meta-analysis concluded that the administration of first-line antibiotics was associated with lower treatment success compared with second-line agents. No differences were found in regard to mortality, microbiological outcomes and safety between the two arms. These results are interesting, because in some countries the use of quinolones is being restricted in favour of first-line antibiotics.

Cefditoren (CDTR) is an oral third-generation cephalosporin that acts by inhibiting the synthesis of the bacterial wall. CDTR is a β -lactam with the lowest minimum inhibitory concentration values against respiratory pathogens; it is active against *S. pneumoniae* including strains with diminished susceptibility to penicillin. CDTR has the potential to be used as a secondary antibiotic treatment in addition to the current therapeutic armamentarium.

Can short treatment periods be used?

Evidence from several studies has confirmed that it is possible to use short treatment periods for antibiotics. For example, a study that compared levofloxacin 750 mg once daily for 3 days against azithromycin once daily for 5 days in uncomplicated patients showed that results were comparable between the two therapies in terms of microbiological eradication and clinical success [22]. In addition, complicated patients were randomised to receive levofloxacin 750 mg once daily for 5 days or amoxicillin 875 mg/clavulanate 125 mg twice daily for 10 days and again the results were comparable between the treatment arms.

Therefore, the length of antibiotic treatment can be reduced in these patients.

A meta-analysis was designed to assess whether courses of antibiotics ≤ 5 days are as effective as longer conventional treatment in AECOPD patients [23]. A total of 21 studies with 10,698 patients aged ≥ 18 years old were included. Patients were divided into those treated ≤ 5 days and those treated > 5 days with antibiotics. Several antibiotic treatments were used, with some studies comparing two different antibiotics.

No difference in clinical or bacteriological cure was noted between the two treatment strategies at early follow-up in mild-to-moderate AECOPD. Furthermore, when dividing the patients according to treatment with cephalosporins, macrolides or quinolones no differences were found in clinical cure with either ≤ 5 or > 5 days of therapy.

In conclusion, it is clear that shorter treatment periods are as effective as longer conventional treatment periods, at least in mild-to-moderate AECOPD patients.

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