UPDATED CONSENSUS STATEMENT

Antimicrobial Treatment of Exacerbation in Chronic Obstructive Pulmonary Disease: 2007 Consensus Statement*

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Rationale

In 2002, members of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), the Spanish Society of Chemotherapy (SEQ), the Spanish Society of Emergency Medicine (SEMES), the Spanish Society of General Medicine (SEMG), and the Spanish Society of Rural and General Medicine (SEMERGEN) prepared the second consensus report on the use of antimicrobial agents in exacerbations of chronic obstructive pulmonary disease (COPD).[1] Given the widespread practical interest in that consensus statement, experts from the same societies met 5 years later to prepare an updated statement in the light of literature published in the intervening period. This 2007 Consensus Statement will include new information regarding the significance of purulent sputum in the decision to prescribe antibiotic treatment and changes in the rate of resistance of the main pathogens to previously recommended antimicrobial drugs. It reports on the experience obtained in the last 5 years with the use of fluoroquinolones, the new slow-release formulation of amoxicillin-clavulanic acid, which allows oral administration of high-dose amoxicillin, and the third-generation oral cephalosporins, such as cefditoren, which have a high intrinsic activity against penicillin-resistant strains of pneumococcus.

Magnitude of the Problem

Exacerbation of COPD is a common cause of consultation, both in primary care and hospital departments, and represents 2% of emergency visits,[2] with large seasonal variations. Exacerbations due to infection represent 1.5% of emergencies treated in hospital and 13.7% of the infections, and up to 40% of the patients treated for exacerbations as a result of infection require hospital admission.[3] Four percent of the general population in Europe consults a doctor at least once a year for acute respiratory disease, and 20% of those visits correspond to exacerbations of COPD.[4] In Spain, empiric antibiotic treatment is prescribed in more than 90% of cases of respiratory exacerbation of COPD,[5] although microbiological analysis of sputum is only undertaken in 5% of patients.[6] Penicillins, cephalosporins, and macrolides are the most widely used antibiotics to treat exacerbation of chronic bronchitis and COPD in Spain, followed by quinolones.[5,7,8]

Infections are responsible for 75% of exacerbations of COPD,[9] and half of all infectious exacerbations are due to bacteria, usually *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Chlamydia pneumoniae*.[10] However, *Pseudomonas aeruginosa* may be responsible for exacerbations necessitating mechanical ventilation in patients with severe COPD.[11] Other exacerbations due to infection are caused by viruses, sometimes in association with bacteria, or on occasions by other microorganisms.[4,9,12,13] In exacerbations not due to infection the cause tends to be poorly defined, but exposure to atmospheric pollution, dust, fumes, or smoke, or cessation of habitual treatment for COPD are very likely to be involved in some cases.[14,15]

Severity and Criteria for Hospital Admission in Exacerbation of COPD

The severity of the exacerbation of COPD is dependent upon the degree of functional impairment of the patient in the stable phase of the disease. Consequently, spirometry represents the main tool for assessment of severity. The forced expiratory volume in 1 second (FEV_1), expressed as a percentage of the reference value, is the best indicator of the severity of the patient's disease. FEV_1 offers the advantages of being easy to determine, highly reproducible, and well correlated with disease prognosis.[16] The following classification of disease severity based on FEV_1 is proposed, according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[16]:

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– Mild COPD: FEV_1 greater than 80% of reference
– Moderate COPD: FEV_1 between 50% and 80% of reference
– Severe COPD: FEV_1 between 30% and 50% of reference
– Very severe COPD: FEV_1 less than 30% of reference

These values correspond to postbronchodilator measurement of FEV_1 and in the presence of bronchial obstruction defined by a ratio of FEV_1 to forced vital capacity of less then 70%.

Outpatient Treatment

Outpatient treatment should be the first option in patients with exacerbation of mild or moderate COPD, and even in many cases of severe COPD. Hospital admission is necessary in case of diagnostic uncertainty or unfavorable disease course.[17] Follow-up should be carried out 48 to 72 hours after the initial consultation in all episodes of exacerbation to adjust treatment if the response is inadequate (change of treatment or referral of the patient to hospital).

Outpatient treatment should be optimized with the use of high-dose short-acting bronchodilators. The use of oral corticosteroids to treat exacerbation of mild or moderate COPD is not always necessary, although they should be continued during exacerbations in patients receiving inhaled corticosteroids as part of their maintenance treatment. However, when improvement is not observed at follow-up, addition of oral corticosteroids is advisable. The recommended dose is 0.5 mg/kg/d in a single morning dose for 7 to 10 days. Continuation of treatment for more than 14 days does not lead to improvement and is associated with a higher incidence of adverse effects.[18]

Inpatient Treatment

It is recommended that exacerbations in patients with very severe COPD be assessed in hospital (Table 1). If information is unavailable on the patient's respiratory function during the stable phase of the disease, the level of dyspnea should be used as an estimate of severity. If the patient has dyspnea of grade 3 or above (Table 2),[19] COPD should initially be considered as severe or very severe.

High doses of bronchodilators are required in cases of exacerbation of very severe COPD, meaning that it may be necessary to use a nebulizer to administer the drugs. It is also advisable to administer systemic corticosteroids from the outset. This treatment will be maintained for 3 or 4 days and then progressively reduced. In exacerbations that do not respond to initial bronchodilator treatment, it may be advisable to administer intravenous aminophylline, although its efficacy is subject to debate.[20] If the patient displays respiratory failure, adequate tissue oxygenation should be maintained by oxygen therapy with the minimum inspired oxygen fraction necessary to achieve a PaO_2 of at least 60 mm Hg (or an oxygen saturation >90%) without it generating a significant reduction (<7.3) in arterial blood pH.

TABLE 1
Criteria for Inpatient Assessment in Exacerbations of COPD

Very severe COPD
Any degree of severity of COPD with:
Severe associated comorbidity
Rapid breathing (>30 breaths/min)
Use of accessory muscles
Decompensated cor pulmonale
Cyanosis
Clinical signs of hypercapnic encephalopathy
Impossibility of disease management at home
Requirement to rule out other diseases
Lack of improvement in a follow-up appointment for the exacerbation

TABLE 2
Dyspnea Scale[a]

Level	Definition
0	Absence of a sensation of dyspnea except on intensive exercise
1	Dyspnea with rapid walking or walking up a shallow gradient
2	Inability to follow the pace of others of a similar age while walking on the flat due to difficulty breathing, or a need to stop and rest when walking on the flat at the individual's own pace
3	Need to stop and rest after walking 100 m or within a few minutes when walking on the flat
4	Dyspnea prevents the patient from leaving the house or appears with simple activities such as dressing

[a] Based on Mahler et al.[18]

Criteria for Hospital Admission

Patients with exacerbation of COPD should be assessed in hospital if no improvement is seen in the first 12 hours, with persistent deterioration of blood gas values and symptoms of severe dyspnea. In-hospital mortality is 10% in patients admitted for exacerbation of COPD,[21] and therefore, in these cases, all available therapeutic options should be employed to achieve clinical improvement. It is essential to monitor patients in the emergency department observation ward to assess their condition in the first 24 to 48 hours before deciding to discharge them or admit them definitively.[22]

Hospital discharge can be considered when there is clinical improvement that achieves something close to the patient's baseline. Even if this is not achieved, discharge can be considered if the symptoms and blood gas values are stabilized and the patient is able to manage his or her disease at home, even in case of persistent hypoxemia or hypercapnia.

Treatment with systemic corticosteroids should be reduced gradually and then withdrawn following discharge. A follow-up appointment 2 weeks after discharge is recommended since the condition worsens during this period in a quarter of all patients.[23] The presence of hypercapnia at discharge necessitates careful monitoring of the patient, since it carries with it a high risk of death in the following months.[21,24]

Recommendations for the Microbiological Diagnosis of COPD Exacerbations

The microorganisms implicated in exacerbation of COPD vary according to the severity of the obstruction[25,26] and the antibiotic treatment that the patient has received previously.[27] Mild or moderate obstruction (FEV_1 >50%) is mainly associated with *S pneumoniae*, *H influenzae*, and *M catarrhalis*. The same microorganisms, particularly *H influenzae*, tend to be implicated along with common enterobacteria (*Escherichia coli*, *Klebsiella pneumoniae*) in severe (FEV_1, 30%-50%) or very severe (FEV_1 <30%) obstruction.[25,26] If the patient has received antibiotic treatment in the last 3 months or on 4 or more occasions in the last year, there is an increased probability that the mucus also contains *P aeruginosa*[27] and occasionally enterobacteria with added resistance (production of broad-spectrum β-lactamases). In general, patients with exacerbations requiring antibiotic treatment on 4 or more occasions within a 1-year period tend to have a high degree of airflow limitation (FEV_1 <50%).

Bronchoscopy confirms these findings and, in patients with mild exacerbation who do not require hospital admission, it has been shown that close to half the group of patients with COPD have high concentrations of bacteria and that *H influenzae* (nontypeable and noncapsulated), *S pneumoniae*, and *M catarrhalis* are the predominant microorganisms.[28] However, in patients who require mechanical ventilation, the frequency of these bacteria is lower and other microorganisms such as *Haemophilus parainfluenzae* and *P aeruginosa* predominate.[11,29]

The microorganisms that are normally identified in exacerbations are often resistant to routinely used antibiotics. Up to 40% of *H influenzae* strains and more than 90% of *M catarrhalis* strains produce β-lactamases, and as a result, antibiotics such as ampicillin and amoxicillin can be ineffective.[30] Pneumococci are also often resistant to penicillin and macrolides. In Spain, the rates of penicillin resistance in *S pneumoniae* are around 40%, while the rate of resistance to macrolides is close to 30%.[31] It has recently been demonstrated that in patients with community-acquired pneumonia a minimum inhibitory concentration (MIC) of penicillin for the pneumococcus of at least 4 mg/L, or at least 2 mg/L for cefotaxime, can have prognostic implications for the patient.[32]

Finally, it should be noted that an appreciable percentage of patients (between 10% and 20%) with moderate or severe exacerbation do not respond to initial empiric treatment and require the antibiotic to be changed.[33,34] In these cases, the infection can be caused by *Staphylococcus aureus*, *P aeruginosa*, or an atypical microorganism not covered by the initial regimen; consequently, microbiological assessment will be of use in choosing an appropriate second-option antibiotic. Given the bacteriological complexity of the exacerbations in some patients with COPD, which are sometimes due to microorganisms that are difficult to treat, along with the possibility that the microorganisms responsible are resistant to routinely used antibiotics, it is advisable to obtain an etiologic diagnosis in some groups of patients with exacerbation of COPD.

The established recommendations are as follows:

1. Patients who do not require hospital admission do not tend to display the risk factors mentioned, and therefore, it is recommended that they be treated empirically without a requirement for microbiological diagnosis.

2. In patients who require hospitalization, those at risk of infection with less common microorganisms (*P aeruginosa*) or antibiotic-resistant strains should be identified. Thus, if the patient was treated with antibiotics in the previous 4 months, was receiving long-term corticosteroid treatment, had more than 4 exacerbations in the previous year, or had very severe airflow obstruction (FEV_1<30%), a sample of respiratory secretions should be obtained for microbiological analysis.

3. In the case of patients with COPD who need to be admitted to an intensive care unit, whether or not mechanical ventilation is necessary, it is always advisable to obtain microbiological diagnosis. The reasons are twofold: on the one hand, these patients also tend to present the risk factors mentioned, and on the other, the severity of the exacerbation means that antibiotic treatment must be as tailored as possible to the microorganism responsible.

4. In those patients in whom the exacerbation responds poorly to empiric treatment, as indicated by the persistence of the main signs and symptoms of the exacerbation 72 hours after initiation of treatment, it is advisable that microbiological diagnosis be sought.

Types of Sample

Blood. Most patients with exacerbation of COPD tend not to have bacteremia, and it is therefore unnecessary to obtain blood samples for culture. This should be reserved for patients with fever and those admitted to intensive care units for severe exacerbation.

Samples from the airways. It should be taken into consideration that many patients with exacerbation of COPD will have received one or more doses of antibiotics before samples are obtained, and this can have a significant effect on the sensitivity of the method. Taking this into account, the following samples can be obtained from the airways:

– SPUTUM. Obtaining sputum samples for Gram staining and culture is the simplest available technique. According to the scale published by Murray and Washington,[35] samples are valid if they contain predominantly polymorphonuclear leukocytes and few squamous epithelial cells. The sample obtained will be used for Gram staining and culture in standard media. It is recommended that obtaining sputum samples only be considered in patients admitted to hospital with one of the risk factors mentioned earlier.

– BRONCHIAL ASPIRATES. In intubated, mechanically ventilated patients, a simple aspirate obtained through the orotracheal tube is equivalent to sputum samples obtained

in nonventilated patients. In this case, the technique has been validated with quantitative cultures in comparison with reference techniques, such as use of a protected brush catheter, and the agreement was found to be excellent.[11] In principle, given the ease with which they are obtained and their good diagnostic yield, these are the samples of choice in intubated patients.

– BRONCHOSCOPIC SAMPLES. From a microbiological point of view, samples obtained with a protected brush catheter best reflect the presence of bronchial infection, as a result of the segmental nature of the exploration. Generally, a microorganism should be considered the cause of the bronchial infection when the colony count is at least 100 colony forming units (CFU) per milliliter,[11,25] although some authors recommend a cutoff of 1000 CFU/mL.[28] In patients with exacerbation of COPD, this technique should be reserved for intubated patients, although there is no evidence that it has a greater diagnostic yield than bronchial aspirates, and it may also be indicated in some patients who require hospital admission and do not respond to initial treatment. Bronchoalveolar lavage should not be used in patients with exacerbation of COPD.

Indications and Regimens for Empiric Antimicrobial Treatment in Exacerbations of COPD

Antibiotic treatment of episodes of exacerbation of COPD aims to reduce the density of the bacterial population in bronchial secretions.[36] Consequently, in the event of any exacerbation, defined as a worsening of the baseline condition (cough, expectoration, or dyspnea), the indication for antibiotic treatment is dependent on the presence of truly purulent sputum[37,38] or changes in its properties (color, opacity, viscosity, or adhesiveness), which tend to be associated with increased purulence.

There are currently 4 families of available antibiotics for which the spectrum of antimicrobial activity encompasses the 2 main microorganisms implicated in exacerbations of COPD: penicillins, cephalosporins, fluoroquinolones, and macrolides/ketolides.

Among the penicillins, association of amoxicillin with clavulanic acid, administered orally at a dose of 875/125 mg every 8 hours, and the slow-release formulation at 2000/125 mg every 12 hours produce a serum concentration that remains above the MIC of 90% of strains (MIC_{90}) of *S pneumoniae* and *H influenzae* isolated in recent years in Spain for more than 50% of the interdose interval.[39] However, the concentration in bronchial secretions might be insufficient for optimal efficacy against strains with an MIC_{90} of 2 mg/L or more. Fortunately, the current prevalence of such strains is low and only limits the use of oral amoxicillin-clavulanic acid in exacerbations of severe COPD, in which parenteral use should be considered along with other therapeutic options.

The oral cephalosporins that are active against both *S pneumoniae* and *H influenzae* include cefuroxime, cefpodoxime, and cefditoren. Of those, cefditoren is the most active in vitro, with MIC_{90} values similar to the third-generation parenteral cephalosporins such as cefotaxime and ceftriaxone, 2 to 4 times lower than cefpodoxime, and 8 to 16 times lower than cefuroxime.[40,41] Although cefditoren is many times more active than amoxicillin-clavulanic acid, in practice the pharmacokinetic and pharmacodynamic parameters of the 2 antibiotics are similar if a dose of 400 mg every 12 hours for cefditoren is compared with a dose of 2000/125 mg every 12 hours of the slow-release formulation of amoxicillin-clavulanic acid.[42] The bioavailability of amoxicillin is linear over a wide dosage range, and consequently, the amount administered in a single dose can be increased to achieve a serum concentration above that of cefditoren, thereby compensating for its lower intrinsic activity. Both cefixime and ceftibuten should be ruled out as options for the treatment of respiratory tract infections because, although they are highly active against *H influenzae*, they show almost no activity against *S pneumoniae*, even against penicillin-sensitive strains.[39,42]

Of the fluoroquinolones, both levofloxacin and moxifloxacin are active against almost 100% of *S pneumoniae* and *H influenzae* strains and achieve concentrations in bronchial secretions that are several times higher than the MIC for these microorganisms.[43,44] That, coupled with their rapid concentration-dependent bacteriocidal effect, makes them potentially the most effective options for the treatment of exacerbations of severe or very severe COPD.[44,45] Moxifloxacin is 4 to 8 times more active than levofloxacin against *S pneumoniae*. Although the serum concentration of levofloxacin is greater than that of moxifloxacin, to achieve an area below the curve similar to that of moxifloxacin, levofloxacin should be administered at a dose of 500 mg every 12 hours or 750 mg daily.[46] Moxifloxacin has been shown to extend the exacerbation-free period beyond that achieved with the use of antibiotics considered as gold-standard treatments (amoxicillin, cefuroxime, or clarithromycin). The MOSAIC study demonstrated that patients treated with moxifloxacin had a symptom-free period of 132 days, compared with 118 days in the control group (P=.03).[47] This effect was attributed to greater eradication of bacteria, especially compared with macrolides.[47,48]

Finally, macrolides (erythromycin, azithromycin, and clarithromycin) can be considered as possible oral treatments. In Spain, around 30% of *S pneumoniae* strains are resistant to all macrolides,[49] having MIC values well above the concentrations that can be achieved in serum and bronchial secretions. Furthermore, most strains of *H influenzae* are resistant to erythromycin and clarithromycin. To some extent, it is possible that the benefit observed in vivo with the use of macrolides in exacerbations of mild or moderate COPD is linked to their potential anti-inflammatory effect. The macrolides should be considered as an alternative treatment valid for cases in which β-lactam or fluoroquinolone antibiotics cannot be used due to allergy or other factors. Telithromycin is a ketolide that, unlike the macrolides, exhibits bacteriocidal activity against almost all *S pneumoniae* strains. Like azithromycin, it is also active against a large number of *H influenzae* strains.[50] However, the recent description of cases of sometimes severe hepatotoxicity have led to it being ruled out as a first-choice option.[51]

TABLE 3
Classification of Patients With COPD and Empiric Antibiotic Treatment Regimens Recommended for Exacerbations According to the Most Likely Microorganisms Responsible

Group	Definition	Most Likely Risk Factors	Probable Microorganisms	Antibiotic	Treatment Alternatives	Duration,[d]
I	COPD with FEV_1 >50% (mild or moderate)	No comorbidity[a]	*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*	Amoxicillin-clavulanic acid[b]	Cefditoren[c]	5-7
		Comorbidity[a]	*H influenzae*, *S pneumoniae*, enterobacteria	Moxifloxacin, levofloxacin[d]	Amoxicillin-clavulanic acid[d]	5-7
II	COPD with FEV_1 ≤50% (severe or very severe)	No risk of *Pseudomonas aeruginosa* infection[a]	*H influenzae, S pneumoniae,* enterobacteria	Moxifloxacin, levofloxacin[d]	Amoxicillin-clavulanic acid[d]	5-7
		With risk of *P aeruginosa* infection[a]	As above plus *P aeruginosa*	Levofloxacin, ciprofloxacin	β-lactam antibiotic with activity against *P aeruginosa*[e]	10

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second.
[a]See criteria for comorbidity and risk factors in the main text.
[b]Doses of at least 875/125 mg every 8 hours (see main text).
[c]Dose of 400 mg every 12 hours (see text). Other alternatives are fluoroquinolones and macrolides (azithromycin or clarithromycin).
[d]Consider parenteral administration in patients who require hospital admission.
[e]Cefepime, ceftazidime, piperacillin-tazobactam, imipenem, or meropenem.

The choice of the most appropriate antibiotic from among those that are potentially useful for the treatment of exacerbations of COPD should be based both on assessment of the sensitivity profile of the most likely responsible microorganisms and the severity of the case. Thus, initial empiric antibiotic treatment in a patient with mild or moderate COPD and no comorbid conditions, and who is not expected to suffer more than 1 or 2 exacerbations per year, can be undertaken with a reasonable safety margin with antibiotics that are active in most pneumococcus or *Haemophilus* species isolates that are currently prevalent in the community. In contrast, in exacerbations in patients with severe or very severe COPD, or in whom there are risk factors for treatment failure, it is advisable to choose antibiotics that display maximal activity against the causative microorganism and that have a rapid bacteriocidal effect.

The results of clinical trials with amoxicillin-clavulanic acid (2000/125 mg),[52] cefditoren,[53] levofloxacin,[54] moxifloxacin,[47,55] and telithromycin[56] indicate that these antibiotics can be used in the treatment of exacerbations of COPD using regimens lasting 5 days. The following criteria allow patients with exacerbated COPD to be classified into 2 groups (Table 3): *a)* severity of COPD, based on the value of FEV_1; *b)* presence or absence of significant comorbidity (diabetes mellitus, liver cirrhosis, chronic renal insufficiency, or heart disease); and *c)* risk of involvement of *P aeruginosa* in the exacerbation (established based on a history of having received antibiotic treatment in the previous 3 months or on more than 4 occasions in the previous year). Group 1 includes exacerbations of mild or moderate COPD (FEV_1 >50%), and group 2, those involving severe or very severe COPD (FEV_1 ≤50%). Patients in group 1 can in turn be subdivided according to the presence or absence of risk factors for failure, and those in group 2 according to the presence or absence of risk factors for *P aeruginosa* infection. In group 1, antibiotic treatment directed against *H influenzae* and *S pneumoniae* can be provided with amoxicillin-clavulanic acid administered at a dose of 875/125 mg every 8 hours for 7 days. The slow-release 2000/125 mg formulation administered every 12 hours for 5 days has been shown to be equivalent to an 875/125 mg dose every 8 hours for 7 days.[52] In patients who cannot be prescribed amoxicillin due to penicillin allergy (nonanaphylactic) or other causes, the alternative is cefditoren administered at a dose of 400 mg orally every 12 hours for 5 days, or secondly, a macrolide (azithromycin or clarithromycin). Most studies of cefditoren for the treatment of exacerbations of chronic bronchitis have used a dose of 200 mg every 12 hours.[53] However, the sensitivity of the *S pneumoniae* strains that are currently prevalent in Spain makes it advisable to use a dose of 400 mg every 12 hours.

Patients in group 1 in whom risk factors are present and those in group 2 without evidence of *P aeruginosa* infection can be treated with moxifloxacin (400 mg/d for 5 to 7 days) or levofloxacin (500 mg every 12 to 24 hours for 7 days) orally. In this group of patients, amoxicillin-clavulanic acid at a dose of 2000/125 mg every 12 hours is considered an alternative. If hospital admission is necessary, parenteral treatment should be considered with levofloxacin (500 mg every 12 hours), amoxicillin-clavulanic acid (1-2 g every 6-8 hours), cefotaxime (1-2 g every 8 hours), or ceftriaxone (1 g every 12-24 hours). Parenteral treatment with a cephalosporin can be followed by oral cefditoren. Finally, patients in group 2 who meet the criteria to be considered at risk of *P aeruginosa* infection can be treated with high oral doses of ciprofloxacin or levofloxacin. However,

given that the current rate of resistance of *P aeruginosa* to both fluoroquinolones is greater than 30%,[57] culture of a respiratory sample should be requested prior to initiation of treatment. The pharmacodynamic parameters (area beneath the concentration–time curve above the MIC) of levofloxacin against *P aeruginosa* are similar to those of ciprofloxacin at maximum doses of both antibiotics.[58]

In severe cases, it is necessary to initiate parenteral antibiotic treatment with a β-lactam that is active against *P aeruginosa* (cefepime, ceftazidime, piperacillin-tazobactam, imipenem, or meropenem), alone or, preferably, in combination with an aminoglycoside (tobramycin or amikacin) for the first 3 to 5 days. Levofloxacin or ciprofloxacin can replace aminoglycosides if there are contraindications for their use and the strain is susceptible. Table 3 shows a summary of the empiric treatment regimens recommended for each of the groups of COPD patients described. Table 4 shows the dose, interval, and main precautions for the administration of antibiotics to treat exacerbations of COPD.

Prevention of Infectious Exacerbations of COPD

One of the main objectives of the treatment of COPD is to prevent exacerbations. Patients experience a great deal of anguish around these episodes and ask to be able to avoid them with preventive pharmacological treatment.[59] There are various treatment strategies aimed at preventing exacerbations (Table 5).[60] In accordance with the objectives of this statement, we will review those associated with the prevention of exacerbations due to infection.

Traditionally, vaccination has represented a useful option for the prevention of certain infectious diseases. In the case of COPD, anti-pneumococcus and anti-influenza vaccines have the potential to prevent exacerbations.

The anti-pneumococcus vaccine has been shown to be effective in preventing pneumococcal pneumonia and invasive pneumococcal disease in adults, including those aged over 65 years.[61] Consequently, the US Centers for Disease Control recommend vaccination in individuals aged over 65 years and those at greater risk of pneumococcal infection, including patients with chronic respiratory diseases.[62] In the same risk groups, repeat vaccination is indicated at least 6 to 8 years after initial vaccination. Studies undertaken in Spain have shown that the anti-pneumococcus vaccine is effective for the prevention of death due to pneumonia in individuals over the age of 65 years.[63] Specifically, in patients with COPD it was effective in reducing the incidence of pneumonia in patients younger than 65 years and in those with severe airflow obstruction.[64] These findings justify systematic anti-pneumococcus vaccination in patients with COPD.

Various studies have shown that viral infections also play an important role in COPD.[9,12,65] There is evidence that inactivated influenza virus vaccine administered intramuscularly is effective in reducing the frequency of exacerbations in patients with COPD,[66] and annual administration of the vaccine is therefore recommended.

Orally administered lyophilized bacterial extracts have been marketed for some years as immunomodulators designed to improve symptoms and prevent exacerbations. A recent systematic review analyzed the results of 13 randomized placebo-controlled clinical trials.[67] The authors of the review noted that the majority of the trials were of low methodological quality and did not

TABLE 4
Dose, Interval, and Precautions for the Administration of Antibiotics to Treat Exacerbations of COPD

Antibiotic	Dose, Interval, and Route of Administration	Precautions
Amoxicillin-clavulanic acid	875/125 mg po every 8 h 2000/125 mg PO every12 h 1-2/0.2 g IV every 6-8 h	Administration with food delays absorption. Administration with allopurinol can produce exanthems
Cefditoren	400 mg PO every 12 h	Bioavailability increases significantly if administered with food and is reduced if administered with antacids
Ciprofloxacin	750 mg PO every 12 h 400 mg IV every 8 h	Intestinal absorption is reduced if administered with preparations containing aluminum, iron, magnesium, zinc, or calcium, or with sucralfate
Levofloxacin	500 mg PO or IV every 12 to 24 h	Intestinal absorption is reduced if administered with preparations containing aluminium, iron, magnesium, zinc, or calcium, or with sucralfate
Moxifloxacin	400 mg PO every 24 h	Intestinal absorption is reduced if administered with preparations containing aluminium, iron, magnesium, zinc, or calcium, or with sucralfate
Azithromycin	500 mg PO every 24 h	
Clarithromycin	500 mg PO every 12 h	
Ceftazidime	2 g IV every 8 h	
Cefepime	2 g IV every 8 h	
Piperacillin-tazobactam	4/0.5 g IV every 6 h	
Imipenem	0.5-1 g IV every 6-8 h	
Meropenem	0.5-1 g IV every 6-8 h	

Abbreviations: COPD, chronic obstructive pulmonary disease; IV, intravenous; PO, orally.

TABLE 5
Strategies to Reduce the Frequency of Exacerbations

With demonstrated efficacy
Stopping smoking
Optimizing treatment in the stable phase of COPD
Treatment with inhaled corticosteroids in patients with FEV_1<50%
Anti-influenza and anti-pneumococcus vaccination
Antibiotic treatment to eradicate infection in exacerbations
Treatment with oral corticosteroids in exacerbations
Pulmonary rehabilitation
Health education, self-care plan for the disease
Of questionable efficacy
Immunomodulators
Antioxidants
Mucolytics

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second.

conclusively demonstrate an effect in terms of prevention of exacerbations. The only significant effect that was found was a reduction in the severity of symptoms and a mean reduction of 3 days in the length of the exacerbations, although the poor quality of the studies means that these results should be treated with caution.

Of more interest is the use of AM3, an immunomodulator that is capable of partially restoring the cytotoxic capacity of natural killer cells and increasing the phagocytic capacity of circulating macrophages and neutrophils, all of which are affected in COPD. In a recent double-blind randomized clinical trial in patients with COPD, there was a slight, nonsignificant reduction in the percentage of exacerbations in patients treated with AM3 over a 6-month follow-up period, accompanied by a significant improvement in quality of life.[68] More extensive studies with longer follow-up periods will be required to demonstrate the efficacy of this treatment in the prevention of exacerbations of COPD.

Bronchial infection is one of the most important processes in the natural history of COPD. Identification of the mechanisms underlying the interaction between the host and the microorganisms involved should help to design more effective strategies to combat colonization and infection in patients with COPD, and in this way to improve the prognosis of such a common disease.

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