Review

The role of antibiotics in Chronic Obstructive Pulmonary Disease

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SUMMARY. Chronic obstructive pulmonary disease (COPD) is the fourth most common cause of death worldwide. Recurrent acute exacerbation of COPD (AE-COPD) are common attributes of its course, and are related to the progress of the disease and its high cost. In the USA, that cost is estimated at $7,757 per exacerbation, mainly due to hospitalization expenses. Patients with repeated acute exacerbations rapidly display reduced lung function and they have a prolonged recovery time and an increased likelihood of suffering from depression or stress, which may consequently lead to a poorer quality of life. Given the fact that almost half of AE-COPD episodes are the outcome of infection, the administration of antimicrobial medication is recommended for patients suffering from exacerbations or severe COPD. In order to administer antibiotics correctly, the risk factors involved in the exacerbation and the choice of the appropriate antibiotics for patients of low and high risk should be taken into consideration. In accordance with the international guidelines, the prophylactic use of antibiotics for patients with COPD is not recommended, although ongoing clinical trials are reevaluating the administration of macrolides as a means of preventing exacerbations, based on their anti-inflammatory properties. *Pneumon 2013, 26(1):84-94.*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) affects millions of people (24,000,000 in the USA alone) and constitutes a major cause of mortality; it is estimated that it will have become the third main cause of death worldwide by 2020. The frequency of COPD in the general population is estimated at 1% in all ages, increasing abruptly to over 10% in people over the age of 40 years[1]. The chronic and progressive course of the disease is usually interspersed by acute exacerbations, which are the most common cause of hospitalization and death in patients with COPD. Acute COPD exacerbations (AE_COPD) diminish the quality of life, accelerate the progression

of the disease and increase the risk of death. In-hospital mortality in patients with COPD is estimated at 10%, and approximately 25% for those admitted to the intensive care unit (ICU)[2]. Accordingto a recent Swedish trial, there is a mortality rate of 69% in the first three years following an exacerbation requiring hospitalization[3].

Despite the plethora of trials and COPD guidelines, there is still no unanimity concerning the management of exacerbations. Infections of the respiratory system may be responsible for 50-60% of acute exacerbations and such episodes are more serious than non-infectious exacerbations, and they have a bad impact on lung function and prolong hospitalization[4]. For these reasons the early administration of the appropriate anti-microbial medication - apart from corticosteroids - is of the utmost importance[5]. Because of the effect exacerbation has on the natural course of the disease, the reduction in the number of exacerbations is a primary goal. COPD and its acute exacerbations are characterized by an increasing inflammatory reaction, and the effect of the prolonged use of antibiotics such as macrolides for the repression of bronchial colonization is still being researched. There have been few correlative studies, which appear to have produced conflicting evidence, although most suggest a possible positive clinical and biological impact from the use of these antibiotics.

This review evaluates the relationship between antimicrobial therapy and the clinical course of COPD.

1. COLONIZATION AND INFLAMMATION IN STABLE COPD

In the cycle of inflammation in COPD, bacterial colonization leads to chronic inflammation and lung damage - a phenomenon known as the "hypothesis of the vicious circle".

It has been demonstrated that the bronchial tree of one in four patients with COPD is colonized by facultative virulent organisms such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*, which are the predominant strains. The production of purulent sputum is an indicator of colonization by infective organisms[6].

The degree of colonization depends on the severity of the disease as indicated by the FEV1% and the continuation of smoking[7,8]. An increase in the bacterial concentration in the bronchi and a change in the bacterial strain are associated with more extensive bronchial inflammation and an acceleration in the reduction of FEV1%[9].

The bronchial colonization is neutrophilic in nature, with interleukine-8 (IL-8) as the main moderator. Chronic bacterial infection can contribute to the lung inflammation in patients with COPD, either as a direct inflammatory irritant or indirectly by altering the host response to tobacco smoke[10]. Failure of antimicrobial treatment to eradicate the bacteria is linked to persistent inflammation, determining their phlegmonous role in the exacerbations. The bacterial concentration increases during exacerbations, and bronchoscopy studies in recent decades have shown this in up to 50% of patients[11]. *In vitro* studies have demonstrated that *H. influenzae* is a pre-inflammatory bacterium, and its strains vary in their capability to cause inflammation. One trial documented the presence of intracellular *H. influenzae* in bronchial mucosal biopsy specimens in 87% of intubated patients with exacerbations, compared with 33% of those with stable COPD and 0% of healthy control subjects[12].

There is a correlation between colonization and the increment of inflammatory biomarkers, including tumour necrosis factor α (TNFα), IL-6 and IL-8[13,14], and between the residual bacterial infection of small airways and subsequent AE-COPD[11,15].

A study conducted by Patel and colleagues demonstrated bacterial colonization in the stable disease to be correlated with a high frequency of exacerbations, and increased levels of IL-8 with the microbial load. Colonization thus accelerates the evolution of COPD by increasing the frequency of exacerbations and causing direct damage to the lung tissue[16].

Mechanisms that could possibly lead to a change in inflammation and, consequently, to an exacerbation are: a) a new strain of the bacterial colonization, b) antigen deviation, c) an increment in the bacterial load, and d) a relative increment of pathogens more capable of causing inflammation.

The difficulty lies in knowing whether the same organisms are present before the exacerbation takes place or whether they may actually be its cause, due to the inflammatory reaction that the colonization produces. Bacterial exacerbations were found to be correlated with the emergence of a new strain with significantly larger amounts of elastase that, when released into the airways, can cause greater damage to the lungs and contribute to progressive airway obstruction[10]. In studies of COPD exacerbations new bacterial strains have been isolated from one in three patients[14].

The pathogenetic role of ongoing infection of the

lower airways is also implied by the recent evidence of coexistent bronchiectasis in up to 50% of patients with moderate and severe COPD.

2. THE AETIOLOGY OF COPD EXACERBATIONS

A variety of infectious and virulent irritants can cause an acute increase of bronchial inflammation in COPD, giving rise to an exacerbation. The frequency of acute exacerbations depends on the severity and the duration of the disease.

Respiratory infections cause many of the AE-COPD episodes (50%), most of which are severe, including those derived from viruses (*Rhinovirus spp, Influenza*) and/or bacteria (*H. influenzae, Str. pneumoniae, M. catarhallis, Enterobacteriaceae spp., Pseudomonas spp.*)[4,17,18].

Non-bacterial triggering factors include environmental irritants (e.g., low temperature, air pollution), destabilization of comorbidities, lack of compliance with the prescribed treatment (such as the use of certain drugs and oxygen) and non participation in respiratory rehabilitation programmes. Acidotic stress, which is a feature of AE-COPD, can also contribute to the inflammatory reaction[19].

It has been shown that the microbiological features of the exacerbation are related to the severity of COPD and the number of exacerbations experienced annually. In patients with mild disease *Str. pneumoniae* predominates, while those with greater impairment of lung function show a higher proportion of *H. influenzae and M. catarhallis*[20,21]. *H. influenzae* is the most common pathogen isolated from induced sputum, and is responsible for 35%-50% of acute exacerbations, although some researchers maintain that *Str. pneumoniae* causes 20%.

Sethi and colleagues[22] have shown that during an exacerbation caused by *H. influenzae*, a specific immunoreaction to the infective agent occurs. Defective immune responsiveness and impaired phagocytosis by alveolar machrophages could provide an immunological basis for the persistence of nontypeable *H. influenzae* (NTHi) in the airways of adults with COPD[23]. Other possible mechanisms of colonization include airway epithelial cell invasion, antigenic alteration[24] and biofilm formation[25]. Cigarette smoke induces mucus dysfunction by several mechanisms and ultimately increases mucin production, reduces mucus hydration and decreases mucus clearance, which all might contribute to airway colonization in COPD[28]. NTHi could contribute to COPD progression by inducing neutrophilic influx into the airways, followed by neutrophil necrosis with release of neutrophil elastase and other matrix metalloproteinases and production of oxygen radicals[26]. Its phlegmonous attribute is accompanied by marked increases in inflammatory cytokines (TNFα and IL-6), Th1 cytokines (IFN-γ and IL-12), and the neutrophil chemoattractant KC[27].

In patients with severe airways obstruction, i.e., FEV1<35%, and frequent exacerbations, *Enterobacteriae spp.* and *Pseudomonas aeruginosa* are predominant, as are antibiotic-resistant micro-organisms (MDR). In patients requiring mechanical ventilation, other microorganisms predominate, such as *H. parainfluenzae* and *Ps. aeruginosa*[15].

The role of atypical microorganisms in AE-COPD continues to be a subject for debate. A study conducted by Diederen and colleagues[29] using PCR technique in sputum to define atypical pathogens during exacerbations and stable COPD failed to detect any differences. Later studies, however, have linked the presence of organisms such as *Chl. pneumoniae, Legionella spp.* and *Mycoplasma pneumoniae* to AE-COPD[17,30], *Chl. pneumoniae* identified as the main cause in 4-34%[30]. (Percentages vary, possibly on account of the differences between serological methods used to detect infections caused by *Chl. pneumoniae*, the diversity of the patients with COPD included in the studies and the frequency of these infections in patients with stable disease.)

M. pneumoniae is detected only in a minority (1-14%) of patients with AE-COPD[17,31].

The viruses incriminated most frequently are rhinoviruses and respiratory syncytial virus (RSV), adenoviruses and influenza viruses, which are present in 30% of AE-COPD and can cause the typical inflammatory reaction of such exacerbations[32]. It has been demonstrated that rhinoviral infection of the bronchial epithelium can result in the expression of many pre-inflammatory genes, and the inflammatory process in COPD is increased in patients with human RSV (HRSV) infection[10,14]. In a study by Quint and colleagues, a correlation was found between high concentrations of interferon-γ and protein-10 in the serum of patients with COPD and the bacterial load of rhinovirus in their sputum[33].

Recent studies have also demonstrated that co-infection by viruses and bacteria is present in approximately one quarter of the exacerbations in hospitalized patients and they these cases are characterized by greater clinical severity[8]. One study showed that 45.7% of patients with COPD with exacerbation due to *H. influenzae* had previously had an acute viral infection[10]. Infections due to

HRSV, parainfluenza, and influenza viruses and rhinovirus increase bacterial adhesion to epithelium cells. A significant correlation between viral load and the concentrations of inflammatory markers has been identified, and patients with rhinoviral and *H. influenzae* infection present an increment in both the viral load and the levels of IL-6[34].

3. MICROBIOLOGICAL DIAGNOSIS IN COPD EXACERBATIONS

The degree of airway inflammation is estimated by culture of the sputum and bronchoalveolar lavage (BAL) or bronchial biopsy. The possible pathogen bacterium can be isolated from the BAL specimen, and the cell population of the airways can be estimated, both qualitatively and quantitatively. Markers of inflammation can be measured in the patient's cells or tissues, such as IL-6, IL-8, MPO and TNFα. As far as the diagnosis of AE-COPD is concerned, the European Respiratory Society (ERS)[35] suggests the following diagnostic procedures:

Culture of the sputum or endotracheal suction sample (in mechanically ventilated patients) should be conducted as an optimal alternative to bronchoscopy in validating the range of possible virulent microorganisms.

Regardless of the bacterial or viral nature of the inflammation, neutrophilic cells are increased in the sputum during exacerbations compared to the stable disease, while eosinophilic inflammation may be observed in patients with viral, bacterial or mixed infections. The aetiology of AE-COPD may possibly determine the type and the magnitude of the inflammatory reaction.

The problem in determining the bacterial origin of the exacerbation in a patient with COPD is that the bacterial growth in sputum cultures cannot exclude the possibility of plain airway colonization, which is not a clear indication for antibiotic treatment[17]. Unfortunately, sputum culture has important limitations, such as underestimation of NTH i colonization, in contrast to detection by polymerase chain reaction (PCR) methods[35].

The evolution of diagnostic methods will help to solve these problems. Novel methods include the culture of lung secretions sampled during bronchoscopic procedures, molecular epidemiological studies on pathogenic bacteria, and the specification of the response to antibiotic treatment[36,37].

In addition, studies on the variants of surface antigen have shown that the emergence of a new bacterial strain with which the host patient had not been infected in the past doubles the risk of a future AE-COPD[19].

One field of recent research concerns the measurement of the infection index of bacterial inflammation during AE-COPD. Increases in serum levels of fibrinogen, IL-6 and C-reactiver protein (CRP) in parallel with the state of systemic inflammation have been described throughout exacerbations[38,39].

According to recent studies, procalcitonin (PCT) and CRP could aid in the selection of those patients who would be most likely to benefit from antibiotic treatment. One of these studies indicated that CRP was superior to PCT as an indicator of bacterial presence and constitutes a valuable asset in the selection of patients for treatment with antibiotics[40]. In agreement with this, Soler and colleagues[41] state that therapeutic strategy guided by purulence of the sputum permits the reduction of antibiotics in COPD patients without purulent sputum, and also that CRP, but not PCT, can be a useful parameter in the diagnosis of bacterial COPD exacerbations.

4. CRITERIA FOR ANTIBIOTIC TREATMENT

The antibiotic treatment of COPD and the exacerbations of chronic bronchitis has been subject to debate for many years. The main reasons for the discussion are the difficulties in determining the bacterial aetiology and the differentiation between colonization and a new infection.

It is recognized that the administration of antibiotics without a clear indication of infection leads to the increase of microbial resistance to them. For this reason only those patients who have exacerbations that are definitely of bacterial origin should be treated. In spite of this recommendation, in a multicentre study in 360 hospitals in the USA, antibiotic treatment was administered to 85% of 69,820 patients hospitalized for AE-COPD[42]. The gold standard examination in diagnosis and isolation of the microbial pathogen is sputum culture.

The study of Anthonisen and colleagues[43] study demonstrated the positive effect of antibiotic treatment in non-hospitalized patients suffering from AE-COPD. The researchers grouped patients in 3 categories based on their symptoms, namely increased dyspnoea, increased quantity of sputum and increased purulence of the sputum, in an attempt to recognize possible infectious exacerbations.

Class I included patients who met all three of the above criteria, while Class II and Class III included patients with two criteria or just one criterion respectively.

This clinical stratification has continued to be used in guidance to this day, since studies over the last decade have showed a clear correlation between purulent spu-

tum and bacterial presence[44,45]. In a study conducted by Stockley and colleagues the presence of green-coloured sputum was found to have 94.4% sensitivity and 77% specitivity in detecting a high bacterial load in AE-COPD. In addition, it was observed that when the antibiotic treatment diminished the bacterial load, the colour of the sputum turned back to white[46].

Currently, therefore, antibiotic treatment is recommended for patients with AE-COPD who are in Class I on the Anthoninsen scale patients and to those in Class II with an increase of purulent sputum. It has been found that the greatest benefit of antimicrobial therapy is achieved when it is administered early during the course of the exacerbation, which suggests that antibiotics accelerate the reduction of symptoms.

In addition, antibiotic treatment is recommended for patients with severe exacerbation who require invasive or non-invasive mechanical ventilation. In a study conducted on mechanically ventilated patients, it was shown that lack of antibiotic administration was associated with to an increased incidence of in-hospital infections and higher mortality[11].

5. STRATIFICATION OF PATIENTS FOR ANTIBIOTIC TREATMENT AND TYPE OF TREATMENT

The major clinical goals in treating AE-COPD include achievement of a more rapid resolution of symptoms, postponement of the next exacerbation and prevention of early relapse.Although antibiotic treatment in exacerbations diminishes the microbialload in the airways, and therefore the inflammatory load of the exacerbation, the administration of the antibiotic has a substantial effect on the degree of colonization in the stable phase. If the colonization decreases after the first course of antibiotic treatment, then the degree of microbial load can increase the profit from antibiotics in future exacerbations, with a mechanism not yet completely defined.

For the initial empirical treatment, a stratification approach is recommended in the choice of antibiotic, which will take into consideration the risk factors for a bad outcome of the exacerbation and the likelihood of infection by a multi-resistant strain of pathogen[10,37]. In this context, patients at high risk of a bad outcome are suitable candidates for aggressive initial antibiotic treatment, with a view to amelioration of the overall outcome of the exacerbation.

The appropriate choice of antibiotic treatment in coping with AE-COPD should be based on the following parameters regarding the possible bad outcome of the disease:

- the severity of COPD, established by FEV1%, and a history of more than three exacerbations during the preceding twelve months
- the age of the patient (< or > 65years)
- the presence of significant comorbidities (diabetes mellitus, liver cirrhosis, chronic renal failure or heart disease)
- the risk of infection by *Ps. aeruginosa* (the isolation of which during an exacerbation increases the mortality[47]). The risk factors which should be examined for this are tabulated in Table 1.

In a recent study conducted in hospitalized patients with AE-COPD, Garcia-Vidal and colleagues[48] identified the following risk factors for pseudomonal infections: BODE index (i.e., BMI, airway obstruction, inhalation and exercise capability), number of hospitalizations over the preceding year, treatment with oral steroids and previous isolation of *Ps. aeruginosa*.

The guidelines of the Global Strategy for Diagnosis, Management, and Prevention of COPD (GOLD guidelines)[18], recommend antibiotic treatment in every exacerbation (regardless of the severity) that causes increased dyspnoea, increase in the quantity of sputum and purulent sputum.

A meta-analysis recently included in the Cochrane Library confirms these findings, showing that in AE-COPD with increased cough and sputum purulence, antibiotic use reduces the risk of short-term mortality by 77% and decreases the risk of treatment failure by 53%[49].

Table 2 presents the classification of AE-COPD compounded with the most common pathogens in each group, and the suggested treatment, and is a variant of the European Guidelines[35]:

- In **Group A** the combination of **amoxicillin and clavulanic acid** is appropriate in high doses (875/125mg

TABLE 1. Risk factors for infection by Pseudomonas aeruginosa[28]

• recent hospitalization [A3]
• frequent (>4 times annually) or recent (during the last 3 months) administration of antibiotics [A3]
• severe disease (FEV1 <30%)
• use of oral corticosteroids (>10mg prednisone daily during the last two weeks) [A3]

TABLE 2. Microorganisms and empirical antibiotic treatment in chronic obstructive pulmonary disease (COPD)

Groups	Severity of COPD	Microorganism	Oral Treatment		Parenteral Treatment
A	Mild COPD with no co-morbidities	*H. influenzae, S. pneumoniae, M. catharallis, M. pneumoniae, C. pneumoniae*	Amoxicillin-clavulanic acid	Macrolide Levofloxacin Moxifloxacin	
B	Mild-severe COPD with no risk factors for *Ps. aeruginosa*	Group A and *Enterobacteriacacae, K. pneumoniae, E. coli, Proteus, Enterobacter etc.*		Levofloxacin Moxifloxacin Cefditoren	Amoxicillin-clavulanic acid, *2nd and 3rd* generation cephalosporines, Levofloxacin, Moxifloxacin
C	Mild-severe COPD with risk factors for *Ps. aeruginosa*	Group B and *Ps. aeruginosa*	Ciprofloxacin		Ciprofloxacin or b-lactamic active against *Ps.aeruginosa* +/- Aminoglycosides

per sample) to obtain efficacy against strains of *Pneumonococcus* resistant to penicillin[50,51].

New fluoroquinolones (**levofloxacin** and **moxifloxacin**) act against strains of *H. influenzae* and *Str. pneumoniae*.

Due to the high level of resistance of Streptococcus pneumonia (30-50%) to macrolides in Europe, they are not generally recommended[52,53](Table 2).

- Patients in **Group B** can be treated with oral **amoxicillin-clavulanic acid (**high doses of amoxicillin**)** or with quinolones (**levofloxacin** and **moxifloxacin**) given the fact that these are active against Gram (-) bacilli other than *Ps. aeruginosa*. Non-antipseudumonal third generation cephalosporines such as **ceftriaxone** or **cefotaxime**, should be considered for this group as a single drug therapy.
- In **Group C**, oral antipseudomonal treatment is recommended with **levofloxacin** or **ciprofloxacin** in high doses (750mg/12h) due to the resistance (>30%) of *Ps. aeruginosa* strains to the drug[54]. The results of the GLOBAL and MOSAIC studies demonstrate that the *in vitro* microbiological superiority of fluoroquinolones, especially **moxifloxacin**, translates into greater *in vivo* effectiveness in treating patients with AE-COPD[55].

The administration of anti-pseudomonal b-lactamic antibiotics (**cefepime**, **piperacillin-tazobactam**, **imipenem** or **meropenem**) is parenteral. The addition of aminoglycosides (**tobramycin** or **amikacin**) can be effected in the first three to five days.

About 10-20% of patients with moderate to severe AE-COPD do notrespond to the initial empirical treatment. In these cases, the infection may be caused by tolerant microorganisms such as MRSA, *Ps.aeruginosa, Acinetobacterbaumanii* or to a fungus (e.g. *Aspergillus fumigatus*) that cannot be dealt with by the initial form of treatment. In such a case, a new sputum culture will help to determine the second choice of antibiotic treatment.

DURATION OF THERAPY

Clinical trials have shown equal or, in some cases, better efficacy of high doses of quinolones given for a short duration, as opposed to the usual treatment of AE-COPD based on the clinical and bacteriological results[8,55,56].

In a comparative study, 369 patients with severe AE-COPD were treated with either 750mg pd of levofloxacin for five days or amoxicillin-clavulanic acid 875/125mg bid for ten days. Most of the patients in the levofloxacin group had a greater decrease in purulent sputum production (57.5% vs 35.6%, P<0.006) and coughing (60.0% vs 44.0%, P<0.045) compared to the amoxicillin-clavulanic acid group[57].

Short duration treatment with moxifloxacin was studied in 936 patients with AE-COPD, with a clinical effect comparable to that of long duration treatment with clarithromycin: 89% responded to a five-day treatment with moxifloxacin, compared with 91% responding to a ten-day treatment with clarithromycin[58].

In addition, short term courses of treatment are associated with better tolerance and safety and fewer side effects

than those of longer duration. In the case of severe COPD with a high risk of infection with *Ps aeruginosa*, schemes of short term therapy are not considered appropriate.

6. RESPONSE TO ANTIBIOTIC TREATMENT

Most patients with AE-COPD are treated with, in addition to the classic treatment with bronchodilators and corticosteroids, some form of antibiotics, but the benefit of antibiotic treatment is a matter for debate, because at least one-third of exacerbations are not infective.

Daniels and colleagues[60] explored the effects of antibiotic treatment with **doxycycline** in addition to corticosteroids in AE-COPD. Their results indicated that add-on treatment with doxycycline is associated with a higher clinical and bacterial success rate and a greater reduction in symptoms 10 days after admission.

In other studies showed that compared with a placebo, the use of antibiotics for AE-COPD reduced treatment failure by 46% (RR:0.54)[2,56,61,62], but there has been a significant heterogeneity in results across studies. Classification of studies according to patient type (in-patient vs. out-patient) attenuated the heterogeneity. Antibiotics were shown to significantly reduce treatment failures when administered to patients who were hospitalized, but not when used in out-patients. It is possible that antibiotics prevent in-hospital infection, especially in patients requiring endotracheal intubation and invasive mechanical ventilation.

Three clinical trials demonstrated that in-hospital mortality was reduced by 78% when antibiotics were administered during the initial phase of hospitalization COPD[2].

The latest publication in the field is of a retrospective cohort study of 84,621 patients with AE-COPD hospitalized in 413 acute care facilities throughout the USA[63]. It was found that in patients who were treated with antibiotics for at least two days, the risk of intubation, mortality and the risk of readmission were all lower than in patients who did not take antibiotics.

A review of studies showed that systemic administration of corticosteroids reduced treatment failure not only during hospitalization (a calculated reduction of 46%), but also in the outpatient treatment of AE-COPD, whereas antibiotics reduced treatment failure by 46% and improved survival only in hospitalized patients[2].

Further clinical trials are needed to determine the role of antibiotics in the treatment of AE-COPD[43].

7. COMMUNITY ACQUIRED PNEUMONIA IN COPD

COPD is a frequent comorbidity in patients hospitalized with community acquired pneumonia (CAP), which may be explained mainly by the altered local and systemic immunity associated with this condition.

The TORCH study[64] confirmed the overall risk of CAP

TABLE 3. Guidelines of the Canadian Thoracic Society (CTS) for the treatment of chronic obstructive pulmonary disease [59]

Group	Definition	Risk factors	Oral Treatment
A	Simple Chronic Bronchitis	No. of annual exacerbations <4, lack of heart disease, FEV1 >50%	Macrolide (azithromycin, clarithromycin) or new cephalosporine Doxycycline Amoxicillin, TMP-SMX
B	Complex Bronchitis	Age >64years No. of annual exacerbations <4, Heart disease, Chronic treament with steroids, Acute exacerbation the last three months, FEV1 <50%	Fluoroquinolones or Amoxicillin-clavulanic acid
C	Purulent Complex Bronchitis (with risk factors for *Ps. aeruginosa)*	Chronic purulent sputum, Chronic treatment with steroids, Antibiotic administration more than four times annually, FEV1 <35%	Antibiotic treatment according to bacilli-culture results, Ciprofloxacin against *Ps. aeruginosa*

in patients using inhaled corticosteroids (ICS). A meta-analysis of eleven studies reached the same conclusion, and they all confirmed the overall risk of CAP from the combination of long active bronchodiolators (LABAs) with ICS, with an OR:1.83[65]. This risk does not appear to apply to budesonide, although the reason for this difference is unclear.

The impact of the pre-existent COPD on the outcome of CAP remains obscure. Some retrospective studies on patients with COPD have identified a higher risk of mortality[66], while others have found no differences[67]. The recent study of the author (AL) concluded that COPD does not constitute a risk factor for death from CAP[68]. Factors that could diminish the mortality rate of CAP in patients with COPD include prior modification of the immune response to pathogenic bacteria, the limitation of airway inflammation and the use of oral corticosteroids for the treatment of the simultaneous AE-COPD.

8. PROPHYLACTIC ANTIMICROBIAL TREATMENT

The recent ERS guidelines do not advise the prophylactic use of antibiotics in COPD[35].

Studies on this issue were begun in the 1950s and 1960s and have produced equivocal results[69]. A meta-analysis of studies on prophylactic antibiotics, which included nine studies conducted before 1970, found that the probability of a participant suffering an exacerbation during the course of the study was reduced, but not significantly so, with the use of prophylactic antibiotics[59,60,61]. It must be pointed out that many of the participants had a rather mild type of COPD compared to the patients who would be considered candidates for receiving preventive treatment today.

Clinical trials with antibiotics in patients with AE-COPD have documented long time periods between exacerbations in patients in whom it was possible to eradicate the bronchial pathogen. This suggests that patients in whom eradication of bacteria was achieved required a longer time to reach the threshold of bacterial load necessary for recurrence of exacerbation those who were cured of the exacerbation, but in whom the bacteria persisted after antibiotic treatment[59]. This hypothesis would also explain why patients with acute exacerbations may be clinically cured, even without the eradication of pathogenic bacteria.

For this reason, there has been renewed interest in recent years in studying the potential benefit of prophylactic antibiotics in patients with COPD in the stable phase.

Macrolides are antibiotics that are used preventively for the reduction of inflammation in cystic fibrosis (CF). *In vitro* studies have shown that erythromycin reduces the inflammatory response to HRV[62]. Jang and colleagues have also indicated that clarithromycin reduces the HRV load in type A549 infected lung epithelial cells[63].

It has also been demonstrated that macrolids reduce neutrophilic activity by limitating the production of oxidases[64], and reduce bacterial adherence through their bactericidal activity[65,66], and they are effective against *Chlamydia*[24].

Studies exploring their ability to prevent AE-COPD via to their immune-modulatory and anti-inflammatory properties, rather than their antibacterial action[61], have presented conflicting results.

Two of these studies, lasting 3 months[67] and 1 year[48] respectively, showed no changes in the bronchial bacterial flora. The study of Wedzicha and colleagues[78], in which erythromycin was administered in a dose of 250mg twice daily for 1 year, showed a significant reduction by 35% in both the frequency of exacerbations and their duration (13 vs 9 days) compared with a placebo.

Albert and colleegues[67] recently published the results of a prospective randomized trial of azithromycin (250mg/day for a year) in the prevention of AE-COPD. Azithromycin reduced the number of exacerbations per year by up to 27%, improving the quality of life, although 5% of the patients suffered hearing loss. A higher prevelance of macrolide-resistent bacteria in the nasopharyngeal irrigation of the patients was also found.

The risk of microbial resistance associated with long-term use of azithromycin in patients with COPD should be considered part of the risk-benefit ratio of this treatment.

Another antibiotic that has been studied in the treatment of stable COPD is moxifloxacin, because of its antibacterial effectiveness. In the study of Sethi and colleagues[80], an intermittent pulsed five day-therapy with moxifloxacin every eight weeks was associated with a reduction of up to 20% in the risk of AE-COPD, compared to patients who received no antibiotic. Treatment with moxifloxacin was effective in eradicating bacteria from the airways, but the new strains of bacteria that colonize were present again 8 weeks after treatment with antibiotics. These results suggest that to be effective, treatment should be repeated in cycles of 8 weeks at least.

CONCLUSION

Frequent acute exacerbations contribute substantially to the morbidity and the mortality from COPD. Current evidence suggests that antibiotics may be a reasonable option for the treatment of severe exacerbations, characterized by an increased volume of purulent sputum, which require hospitalization, or exacerbations that do not improve despite treatment with systemic corticosteroids. Short-term antibiotic therapy in AE-COPD is at least as effective as traditional standard therapy in clinical success and microbiological eradication rates. Currently, the use of prophylactic antibiotics, mainly macrolides, in COPD is not recommended due to the debate surrounding their effectiveness, the risk of side effects and the potential development of bacterial resistance. Ongoing studies show the long term use of azithromycin to be associated with a significant decrease in the frequency of AE-COPD and an improvement in the quality of life.

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