SPECIAL ARTICLE

Update to the Latin American Thoracic Society (ALAT) Recommendations on Infectious Exacerbation of COPD

ALAT Work Group*

Preamble to the Update

It has been 4 years since the Latin American Thorax Society (ALAT) set up a multidisciplinary working group of experts to draw up the society's first recommendations on the treatment of infectious exacerbations of chronic obstructive pulmonary disease (COPD) and community-acquired pneumonia. The aim of these recommendations,[1,2] which were published in 2001, was to provide an up-to-date review of knowledge concerning the management and treatment of these respiratory infections adapted to the Latin American situation. Until that time, the medical professionals in the region had to consult international recommendations to obtain guidelines for the management of patients with these diseases. For reasons of geographical proximity, the guidelines published by the American Thoracic Society were probably the most well known.[3,4] However, practice and treatment guidelines specific to the Latin American situation are necessary owing to the region's particular patterns of bacterial resistance and different socioeconomic situation. Because of the vast size and great diversity of Latin America, it is difficult to establish guidelines that will be equally useful everywhere, but it is hoped that these documents will serve as a general framework for managing these common conditions. Even within one country we can find differences that are so great that even national guidelines would not necessarily be applicable throughout a whole country.

Over the last 3 years we have witnessed changes in treatment arising from the introduction of new antibiotics. New epidemiological information has also become available, and studies have elucidated the importance of the role of bacteria in COPD exacerbations. Risk factors useful for classifying patients with COPD exacerbations have also been described. The new information available justifies this revision of the recommendations.

The updated version of the ALAT guidelines respects the original text, which has only been modified where new evidence has emerged. This means that the reader can use the new version without referring to the original recommendations.

Introduction

COPD, one of the most common respiratory diseases, is a slowly progressive chronic condition, that can lead to disability and even death. The course of this chronic disease is marked periodically by acute episodes of exacerbation, which are characterized by an increase in the usual symptoms accompanied by purulent expectoration and fever. Most of these exacerbations are caused by infections, which are bacterial in origin in up to 75% or 80% of cases.[5]

Owing to the high prevalence of COPD, a wide range of different medical professionals are involved in providing care, and it is therefore important to draw up and implement guidelines for treating and managing COPD patients both in stable phases of the disease and during exacerbations.[3,6-9] The present recommendations on the infectious exacerbation of COPD have been drawn up by ALAT to provide practice guidelines for the management of patients in the Latin American context. This consensus document focuses exclusively on antibacterial treatment, and does not discuss other pharmacological or nonpharmacological aspects of care.

An evidence-based approach was used to draw up these recommendations, after a review of all the most relevant scientific studies published. The supporting evidence was classified on 3 levels: level I evidence, based on randomized, controlled clinical trials; level II evidence, based on well-designed controlled trials without randomization (including cohort studies, case series, and case control studies); and level III evidence, based on case reports and/or expert opinion. When the treatment recommendations are based on data concerning susceptibility in the absence of clinical observations, the evidence was classified as level III.

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*Members of the ALAT Work Group
Coordinators: J.M. Luna (Guatemala) and J.R. Jardim (Brazil).
Work Group Members: H. López, C.M. Luna, J.A. Mazzei, and D. Stamboulian (Argentina); J.C. Abreu de Oliveira and J. Pereira (Brazil); A. Díaz, C. Lisboa, and F. Saldías (Chile); D. Maldonado and C. Torres (Colombia); S. Martínez Selmo (Dominican Republic); M. Miravitlles, F. Rodríguez de Castro, and A. Torres (Spain); A. Anzueto and J. Ramírez (USA); M. Díaz, R. Pérez Padilla, A. Ramírez, and R. Sansores (Mexico); I. Carrasco (Panama); A. Matsuno (Peru).

Correspondence: Dr. M. Miravitlles.
Servicio de Neumología. Hospital Clínic.
Villarroel, 170. 08036 Barcelona. España
E-mail: marcm@clinic.ub.es

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We hope that these recommendations will be of use to the whole medical community in Latin America and will help improve the management of COPD patients in all branches of the health system.

Definition of COPD and COPD Exacerbations

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is a disease state characterized by airflow limitation that is not fully reversible. Limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[10]

The term COPD encompasses 2 well-defined entities: emphysema and chronic bronchitis.[3] Chronic bronchitis is defined by clinical criteria and is characterized by the presence of cough and expectoration for more than 3 months annually in 2 or more consecutive years when other causes have been ruled out. Pulmonary emphysema is a pathological diagnosis. The condition is characterized by permanent, abnormal enlargement of airspaces distal to the terminal bronchiole accompanied by the destruction of the alveolar walls, in the absence of evident fibrosis.[3] The mechanisms responsible for the airflow limitation are a variable mixture of disease of the small airways (obstructive bronchiolitis) and destruction of the lung parenchyma (emphysema).

The course of the disease can be punctuated by episodes characterized by an acute aggravation of symptoms. These crises are known as exacerbations. Because there are no complementary tests in general use for the diagnosis of exacerbations, diagnosis is based on the presence of a number of symptoms, which include the presence of or an increase in dyspnea, an increase in sputum production, purulent sputum, and other less common symptoms, such as fever or febricula. The presence of a number of these symptoms concurrently can be used to assess the severity of the exacerbation and its possible infectious origin using the criteria described by Anthonisen et al.[11]

Epidemiology of COPD

The prevalence of COPD among people over 50 years old in the general population is estimated to be between 3% and 6% in developed countries, such as the United States of America (USA), which would mean that at least 15 million people suffer from the disease in that country.[12] Some 9% of the Spanish population aged between 40 and 70 have COPD, although only 22% of patients have been diagnosed and are receiving some kind of medical attention.[13] It is important to note that substantial differences in prevalence can exist between different geographical areas, even within one country.[13] A population study carried out in Brazil demonstrated a prevalence of 12.7% for chronic bronchitis in people over 40; the prevalence of COPD could not be ascertained because spirometry was not performed.[14]

It is difficult to obtain reliable statistics on the prevalence of COPD in Latin America because the definition and classification of the disease are in dispute, and this tends to confound the statistics. Moreover, the lack of the necessary data collection infrastructure in some countries gives rise to an information deficit which makes a complete evaluation of the situation regarding COPD difficult. In order to address this problem, ALAT has set up the Latin American Pulmonary Obstruction Project (Proyecto Latinoamericano en Obstrucción Pulmonar or PLATINO). The aim of this project is to assess the prevalence of COPD in various Latin American countries using a common protocol. Until the results of this project are published, the most accessible statistics that can be used in Latin American countries are mortality data. Some countries have official figures that can be used to estimate the extent of the COPD problem in this region. In Mexico, chronic bronchitis and emphysema were together the 13th leading cause of death, with a rate of 9.6 deaths per 100 000 population in 1997. Among the population over 65 it ranked eighth, with 157 deaths per 100 000.[15,16] In Colombia, mortality due to COPD was 15.9 deaths per 100 000 in 1994.[17] In Chile, mortality due to COPD has increased in recent decades, reaching 19.4 deaths per 100 000 population in 1990 (Table 1).[18] In 1999, chronic diseases of the lower airway (mainly COPD) were the seventh leading specific cause of death in both sexes in the Chilean population (Chilean Ministry of Health data from 1999), with a mortality rate of 16.9 per 100 000 population. In the same year, the mortality rate due to chronic diseases of the lower airway was 18.6 deaths per 100 000 population among men and 15.3 per 100 000 among women. In Brazil, COPD was the fourth leading cause of hospitalization in 2002, and the mortality rate was 12.2 per 100 000 population (source: Brazilian Ministry of Health, 2002).

In 1990, Christopher et al[19] estimated the incidence of COPD in Latin America to be 40 per 100 000 population, and the prevalence to be 319 per 100 000. These figures were much higher among older age groups, with an estimated prevalence in people aged over 60 of 2880 per 100 000 population for men and 1664 per 100 000 for women.

These figures provide some idea of the extent of the problem, placing COPD just after cardiovascular and neoplastic diseases as a leading cause of death and morbidity. An important point that should be noted is that the prevalence of COPD rises as the life expectancy of

TABLE 1
Number of Deaths per 100 000 Population due to Chronic Obstructive Pulmonary Disease in Various Latin American Countries[18]

Country	Mortality
Argentina	2.3-3.6
Mexico	9.6
Colombia	15.9
Chile	19.4
Brazil	12.2

the population increases because it is a disease that affects older people who have suffered prolonged exposure to the causative agent, most often tobacco smoke.

Risk Factors for COPD

COPD is the result of the presence and action of various risk factors. Although other causes have been identified, smoking is by far the main risk factor for this disease.

Tobacco consumption increased considerably in Latin America during the 1960s and 1970s and until the end of the 1980s. For example, data from Mexico indicate that the prevalence of smoking addiction rose from 25% in 1993 to 27% in 1998.[20] This represents an increase of half a percentage point per year. However, in other countries a slight decline has been reported; in Brazil the prevalence of smoking among men aged 35 declined from 32% in 1989 to 24% in 2002. The available data indicate that the mean prevalence of smoking addiction in Latin America is 37% among men and 20% among women. There is, however, a high degree of variability. For example, in Uruguay, Mexico, Chile, and Peru prevalences of between 40.3% and 66% can be found in certain sectors of the urban male population among the higher socioeconomic groups, while the mean prevalence in these countries is 35.8%, 27%, 32.1%, and 17% respectively (Table 2).[21,22]

One aspect of key importance is the early age of initiation, since most smokers acquire the habit between 13 and 15 years of age. In Guatemala, 25% of adolescents aged 15 smoke,[23] and in Uruguay this figure is 30%. In Brazil, 4.4% of boys and 3% of girls aged between 12 and 17 smoke.[24] Another trend that should be noted is the rise in smoking among young women. The current rise indicates that the prevalence of smoking addiction among men and women will tend to converge within a few years.[21]

Although other factors are less important, some should be mentioned. Air pollution has been observed to be associated with an increase in mortality, particularly among individuals with chronic lung disease. The available evidence demonstrates that COPD can be aggravated by exposure to environmental pollution and in particular the presence of airborne particles. Such exposure provokes the symptoms of exacerbation and leads to an increase in the number of hospital admissions and deaths.[25] There is less evidence to suggest that environmental pollutants alone can actually cause COPD.[26]

Pollution in the home due to the use of wood and other biomasses as a source of energy has, however, been implicated in the pathogenesis of COPD. In some Latin American countries, wood-burning stoves are still used for cooking in rural areas. These appliances give rise to significant smoke pollution inside the home. Epidemiological studies have demonstrated the association between the prevalence of chronic bronchitis and exposure to wood smoke in the home. In Mexico, Pérez Padilla et al[27] demonstrated that people who cooked with wood were 9.7 times more likely to suffer from chronic bronchitis in association with chronic airway obstruction. Moreover, the risk of chronic respiratory disease increased linearly with the number of hours per year the person had spent cooking with a wood stove. Domestic wood smoke exposure has a high potential as a causative agent of chronic lung disease, particularly among women in rural areas, who are the people most directly exposed. Wood smoke contains many toxic and carcinogenic components similar to those found in cigarettes, and it is estimated that 50% of the world's population uses wood for energy. Dennis et al[28] reported similar data for Colombia. Luna and Arango,[29] who studied a group of nonsmoking women in Guatemala with chronic airflow obstruction and chronic bronchitis, observed that 97% of them had a history of over 15 years of exposure to wood smoke and more than 200 hour-years (years of exposure multiplied by average hours of exposure per day). These and other studies carried out in Latin America have made it possible to unequivocally establish the important role played by domestic wood smoke inhalation in the pathogenesis of COPD, especially among nonsmoking women (level I evidence).[27-29]

Another COPD risk factor of variable incidence in various sectors of the population is occupational exposure to smoke and dust, although this factor appears to be unimportant when such exposure is not associated with smoking.[30] Severe respiratory infections in childhood should also be considered. Such infections give rise to greater susceptibility to other agents the individual may be exposed to in later life, such as tobacco smoke, wood smoke, our occupational pollution.[31] In a Brazilian study, low family income, poor schooling, and childhood respiratory infections were, together with smoking, the independent risk factors significantly associated with chronic bronchitis.[14]

In conclusion, it should be taken into account that factors related to the individual, such as nonspecific

TABLE 2
Prevalence of Smoking in Various Latin American Countries[20-24]

Country	Year	Men, %	Women, %
Argentina	1992	39.9	25.4
Bolivia	1992	50.0	21.4
Brazil	2002	28.0	20.0
Chile	1990	37.9	25.1
Colombia	1992	35.1	19.1
Costa Rica	1988	35.1	20.0
Cuba	1990	49.3	24.5
El Salvador	1988	38.0	12.0
Guatemala	1989	37.8	17.7
Honduras	1988	36.0	11.0
Mexico	1998	51.2	18.4
Paraguay	1990	24.1	5.5
Peru	2001	40.3	14.5
Dominican Republic	1990	66.3	13.6
Uruguay	1990	40.9	26.6

bronchial hyperreactivity[32] and gene mutations that code for proteins having a protective effect on the pulmonary region, such as alpha 1-antitrypsin, may also condition an individual's susceptibility to COPD.[33,34]

Etiology of Infectious Exacerbations

COPD is a slowly progressive disease, but its course may be punctuated by sudden crises for various reasons. The most common form of crisis is the so-called exacerbation, which in most cases is caused by infection. Other processes can, however, produce acute respiratory insufficiency in patients with COPD, and it is important to differentiate between the different causes because many of them require specific treatment. The possible causes of acute respiratory insufficiency in COPD patients are shown in Table 3.

COPD exacerbations occur approximately 2 to 3 times a year in patients with significant obstruction.[35] The most common causes are infections and, in particular, bacterial infections (level II evidence).[1]

Studies carried out using highly specific and sensitive invasive techniques, such as protected bronchial brushing, have demonstrated that the percentage of patients with significant quantities of germs in the lower airways increases during exacerbations, and that there is also an increase in the bacterial load in the same location (level II evidence).[36] Moreover, it has been observed that in many cases exacerbations coincide with the acquisition of a new strain of bacteria against which the host has no acquired immunity.[37] Both of these findings support the importance of the causal role of bacterial infection in exacerbations of COPD. The pathogens most often involved in COPD exacerbations are *Haemophilus influenzae, Moraxella catarrhalis,* and *Streptococcus pneumoniae*.[5,36] Less frequently, other microorganisms, such as viruses or gram negative bacteria, are involved. Other bacteria, such as *Haemophilus parainfluenzae, Chlamydia pneumoniae,* and *Mycoplasma pneumoniae* are currently being detected more frequently in patients with COPD exacerbations, an indication that these pathogens may also play a role in the etiology of such crises. Recent studies have demonstrated that the diverse bacteria involved are distributed in different ways depending on the severity of the individual's COPD; patients with better lung function tend to have exacerbations due to *H influenzae* or *M catarrhalis*, while Gram-negative bacteria, such as *Pseudomonas aeruginosa,* are found together with *H influenzae* in patients with greater obstruction (level II evidence).[38,39] It is important to take these findings into account when deciding on empirical antibiotic treatments for exacerbations. Another phenomenon that is becoming increasingly important is the appearance of mixed infections caused by typical pathogens found in association with atypical microorganisms.[40,41] The repercussion of these mixed infections on antibiotic therapy and their clinical importance is still poorly understood.

TABLE 3
Causes of Respiratory Insufficiency in Patients With Chronic Obstructive Pulmonary Disease

Respiratory causes
Respiratory infections
Inhalation of irritants
Pneumothorax
Pulmonary embolism
Respiratory depression (drugs, alcohol)
Decline in muscle strength
Lung cancer
Non-respiratory causes
Cardiac failure
Ischemic heart disease
Non-respiratory infections
Osteoporotic vertebral collapse
Traumas (ribs, vertebrae)
Gastroesophageal reflux
Malnutrition and myopathy
Anxiety and panic

Empirical antibiotic therapy used to treat patients presenting with exacerbation should provide appropriate coverage for the most common pathogens. The classic treatment for exacerbations used to be first line antibiotics, such as amoxicillin, tetracyclines, and co-trimoxazole. Over the last decade, however, the problem of the emergence of pathogens resistant to traditional antibiotics has taken on greater importance. The most common microorganisms have become increasingly resistant to traditional antibiotics, making the use of new antibiotics essential (level III evidence).

The antibiotic resistance of *H influenzae* is generally due to the production of beta-lactamases. The appearance of beta-lactamase-producing strains increased in the USA from 10% in 1984 to 42% in 1997.[42] Between 85% and 100% of the strains of *M catarrhalis* isolated in Europe and the USA are beta-lactamase-producing. The Sentry program, which monitored 10 hospitals located in various Latin American countries, found that overall 93% of strains of *Moraxella* were beta-lactamase producing.[43]

A more recent problem is the penicillin resistance of some strains of *S pneumoniae*, which is not mediated by beta-lactamase. The resistance of the pneumococcus to penicillin is a growing world wide problem, and the percentage of resistant strains found in the USA went from 3% in 1988 to 32% in 1998.[44] The rate of resistance to penicillin has been found to be in the vicinity of 25% in various Latin American countries, although this finding refers mainly to an intermediate type of resistance characterized by a minimum inhibitory concentration (MIC) of between 0.12 mg/L and 1 mg/L.[43] Researchers in Chile studied 75 strains of *S pneumoniae* isolated in respiratory samples taken from adult patients hospitalized for community-acquired pneumonia and/or COPD exacerbation. They found that 16% of strains were resistant to penicillin, 8% to cefotaxime, and 1.3% to erythromycin. However, no strains of *S pneumoniae* were found with an MIC of more than 4 μg/mL for penicillin.[44]

Resistance to penicillin is occasionally accompanied by cross resistance to macrolides, so that the activity of clarithromycin and azithromycin against the pneumococcus is often diminished in penicillin-resistant strains.[45] This cross resistance is not observed in other antibiotics, such as the quinolones and telithromycin.[46] It is important to note that the problem of penicillin resistance has been growing continually over recent years. In light of this fact, there is some doubt about the use of certain antibiotics traditionally prescribed for COPD exacerbations, such as beta-lactams, oral cephalosporins, and macrolides (level III evidence).

The frequency of antibiotic resistance observed among the most common respiratory pathogens in Latin American countries is shown in Table 4.

TABLE 4
***In Vitro* Comparison of the Activity of Various Antimicrobial Agents Against Respiratory Bacteria in Latin America**

	Sensitivity, %		
	Streptococcus pneumoniae	***Haemophilus influenzae***	***Moraxella catarrhalis***
Penicillin	71.4	–	–
Amoxicillin	85.5	87.2	6.2
Amoxicillin-clavulanic acid	85.5	99.6	100
Cefuroxime	81.2	98.8	99
Cefotaxime	88.9	100	100
Co-trimoxazole	58.1	60.3	96.9
Azithromycin	87.2	100	100
Clarithromycin	86.2	91.7	100
Chloramphenicol	94.0	98.3	100
Tetracycline	74.4	98.3	96.9
Levofloxacin*	99.6	100	100
Moxifloxacin*	99.6	100	100
Telithromycin*	100	98.4	100

Data from the Sentry program[43,44] (234 strains). Or, if asterisked(*), from the PROTEKT program[47] (514 strains) and from López et al.[48]

Diagnosis of Exacerbations

Exacerbations are diagnosed clinically. Patients present with a combination of different symptoms, including development of or increase in dyspnea, increased sputum production, purulent expectoration, and other, more minor symptoms, such as fever or febricula. The typical greenish color of purulent sputum is a good indicator of bacterial infection (level II evidence).[49]

In exceptional cases, additional diagnostic tests are required in patients with COPD exacerbations. When available, microbiological sputum study using Gram stain and culture is indicated in seriously ill patients and cases with a history of prior treatment failure. It should be remembered that sputum samples are susceptible to bacterial contamination so that accurate results can only be obtained when it is possible to obtain a good quality sample representative of the lower airways. Except in the presence of an inflammatory reaction, samples should not be contaminated by oropharyngeal flora. An inflammatory reaction is indicated in the microscopic study by the presence of very few squamous cells and abundant neutrophils. Fewer than 10 squamous cells and more than 25 neutrophils per 10 power field are acceptable limits.[50] The validity of sputum cultures diminishes substantially in patients who have received prior antibiotic treatment.

Chest radiography is not routinely necessary during exacerbations. It is only required when there are clinical symptoms indicative of pneumothorax or pneumonia, such as high fever and prostration, or when patients have not improved despite having received the correct treatment. In such cases, the best course is to obtain a chest radiograph in 2 views, although a posteroanterior projection alone may be useful. It should not be forgotten that a chest radiograph can sometimes reveal a parenchymatous pulmonary lesion indicative of tuberculosis or bronchial carcinoma in patients with COPD, so that in patients who have not had a radiograph prior to the exacerbation this event may provide an opportunity to obtain one.

Serological assays are only of epidemiological value; they contribute to a retrospective diagnosis.

Failure Rate in Exacerbations and the Consequences of Failure

The high prevalence of COPD and the fact that patients with this disease suffer between 2 and 3 exacerbations a year means that the social and economic repercussions of these crises are considerable. The high failure rate in outpatient treatment of exacerbations (which ranges from 13% to 25%) should also be taken into account.[51-57] Failure in the treatment of exacerbations results in a high financial cost generated by hospital admissions, consultations, and additional courses of antibiotics.[56-58] In any evaluation of the overall cost of attending patients with exacerbations, the expense incurred by treatment failure should be taken into account in addition to the cost of the medication prescribed. In a recent study it was observed that treatment failure accounted for 60% of the total expense associated with exacerbations (level II evidence).[58,59] In light of this finding, it is not difficult to appreciate that the use of an effective treatment that reduces the failure

TABLE 5
Risk Factors for Unfavorable Evolution in Exacerbations of Chronic Obstructive Pulmonary Disease (Level II Evidence)[57]

Age >65 years
Severe dyspnea
Significant comorbidity*
More than 4 exacerbations within the prior 12 months
Hospitalization due to an exacerbation during the prior 12 months
Use of systemic corticosteroids in the last 3 months
Use of antibiotics in the last 15 days
Malnutrition

*Heart disease, insulin-dependent diabetes mellitus, renal or hepatic insufficiency.

rate will probably be a cost-effective option.

A number of personal characteristics related to a patient's history and situation increase the risk of failure when treating exacerbations (level II and level III evidence).[51,53,55-57,60-66] These factors are listed in Table 5.

The basic aim of treatment is to obtain improvement or total remission of symptoms. However, several trials have shown that remission of symptoms is not always accompanied by effective eradication of the pathogen that caused the exacerbation.[67,68] This persistence of pathogens in the lower airways, a phenomenon basically due to the presence of *H influenzae*, may be accompanied by an inflammatory response.[69-72] Finding lower airway *H influenzae* has also been associated with a deterioration of pulmonary function[69] and a shorter symptom-free interval between exacerbations (level II evidence).[68,73,74] Levels of inflammatory markers found in the bronchial secretions of COPD patients colonized by *H influenzae* are significantly higher than those observed in patients with a similar degree of respiratory obstruction who are not colonized (level II evidence).[69] Furthermore, it has been observed that patients with persistent colonization have more frequent exacerbations[74] (level II evidence), and the presence of more frequent exacerbations is linked to an acceleration in lung function decline (level II evidence).[75] Moreover, bronchial colonization *per se* has been observed to be associated with a greater decline in lung function in patients with severe COPD.[76] The eradication of colonizing microorganisms is justified whenever possible for all of the above reasons, in addition to improving the patients' symptoms.[77,78]

Treating Infectious Exacerbations of COPD

These recommendations focus on treating the infectious exacerbation of COPD. However, it should be remembered that the treatment of exacerbations should also include other therapeutic measures, including in particular the concomitant administration of oral corticosteroids for 7 to 15 days,[79,80] an increase in the bronchodilator dose, and the administration of oxygen in the case of hypoxemia. Early identification of the patients who will require hospital treatment is important. These patients should be transferred to the nearest hospital for specialized care. Table 6 shows a list of the indications for the hospitalization of patients with COPD exacerbations.[3,60]

TABLE 6
Indications for the Hospitalization of Patients With Exacerbation of Chronic Obstructive Pulmonary Disease[3]

Poor response to outpatient treatment
Inability to walk, eat, or sleep because of dyspnea
Inadequate home care
Serious comorbidity (congestive heart failure, decompensated diabetes mellitus , cardiac ischemia, etc)
Altered mental state: confusion or lethargy
Severe hypoxemia or hypercapnia
Respiratory muscle fatigue (paradoxical abdominal motion)
Need for invasive or noninvasive assisted ventilation

From earlier studies we know that for an exacerbation to be considered of probable bacterial origin it must be associated with 2 or more of the symptoms described by Anthonisen et al:[11] increased dyspnea, increased sputum production, and/or sputum purulence (level III evidence). The greenish color or purulent appearance of sputum is probably the most indicative sign of bacterial bronchial infection (level II evidence).[49] In this respect, it is important to stress that patients with acute bronchitis, that is, individuals with no chronic airflow obstruction and no underlying chronic bronchial disease, who present with acute bronchial symptoms, such as a productive or nonproductive cough, should not be given antibiotics, especially if the expectoration is mucoid.[9,49] In young people without risk factors, the majority of these cases of acute bronchitis are viral in origin and self-limiting (level I evidence).[81] However, classic trials that studied the antibiotic treatment of exacerbations have shown that the course of the exacerbation in patients with bronchial obstruction (COPD) who present with 2 or more of the symptoms listed above evolves more favorably in those treated with antibiotics than in controls receiving placebo (level I evidence).[11,82] Moreover, it has recently been reported that the rate of relapse is lower in patients treated with antibiotics.[51] Finally, a meta-analysis has demonstrated the significant beneficial effect of antibiotics as compared to placebo on both the cure rate and on the time required to recover from the exacerbation.[83]

In order to achieve this beneficial effect, the best available treatment for bronchial infection in COPD patients must be selected. In this context, it is important to understand the pharmacokinetics and pharmacodynamics of the antimicrobial agents. In the case of antibiotics that have a time-dependent bactericidal action and a minimal or moderate postantibiotic effect (beta-lactams, macrolides, and oxazolidinones), the most useful predictor of therapeutic efficacy is the period of time during which serum concentrations are higher than the MIC. The following variables have been found to be associated with antibacterial efficacy in the case of drugs that are classified as concentration-dependent and have a prolonged postantibiotic effect (aminoglycosides, fluoroquinolones, and ketolides): the area under the concentration-time curve of the antibiotic in relation to the MIC, also known as the area under the inhibitory curve (AUIC); and the maximum concentration/MIC ratio or inhibitory quotient. The AUIC represents both the time of exposure and the maximum concentration attained by the antimicrobial agent in the place of infection. It can, therefore, also be used to predict the effectiveness of time-dependent antibiotics with a prolonged elimination half-life and postantibiotic effect (azithromycin,

TABLE 7
Classification of Chronic Obstructive Pulmonary Disease (COPD), Causative Agents of Exacerbations, and Recommended Outpatient Antibiotic Treatment (Level II Evidence)*

	FEV_1	Most Common Pathogens	Recommended Treatment
Slight COPD without risk factors	>50%	*H influenzae* *M catarrhalis* *S pneumoniae* *C pneumoniae* *M pneumoniae*	Amoxicillin-clavulanic acid† Cefuroxime Azithromycin/clarithromycin
Slight COPD with risk factors‡	>50%	*H influenzae* *M catarrhalis* PRSP	The same as above plus moxifloxacin/gatifloxacin/levofloxacin Telithromycin
Moderate COPD	35%-50%	*H influenzae* *M catarrhalis* PRSP Enteric bacteria	Moxifloxacin/gatifloxacin/levofloxacin Telithromycin Amoxicillin-clavulanic acid†
Severe COPD	<35%	*H influenzae* PRSP Enteric bacteria *P aeruginosa*	Moxifloxacin/gatifloxacin/levofloxacin Ciprofloxacine if *Pseudomonas* is suspected Amoxicillin-clavulanic acid† (if allergic to quinolones)§

*PRSP indicates penicillin-resistant *S pneumoniae*.
†Other more inhibiting beta-lactams available in Latin America are amoxicillin/sulbactam and ampicillin/sulbactam; ‡the risk factors are shown in Table 5; §intravenous treatment may sometimes be necessary in patients with suspected or confirmed infection by gram negative bacteria, including *Pseudomonas*. In this case piperacillin-tazobactam, imipenem or cefepime can be administered.

tetracyclines, and streptogramins). A dose regimen that ensures high levels of the antibiotic not only at the focus of infection but also in areas that are normally colonized may impede or delay the phenomenon of resistance selection. This result is more easily achieved if antibiotics with concentration-dependent bactericidal effect are prescribed in such as way as to ensure an inhibitory quotient of between 8 and 10 or an AUIC greater than 100, except in the case of certain microorganisms, such as pneumococcus, for which an AUIC of more than 30 is sufficient. The objective of a dose regimen for antibiotics with time-dependent bactericidal effect should be to obtain serum concentrations that exceed the MIC of the pathogen for over 40% of the period between doses.[84]

For the purpose of establishing treatment guidelines, we will classify patients into 3 groups according to the stage of their underlying disease using the criteria shown in Table 7. This classification is based on spirometric values, basically forced expiratory volume in 1 second (FEV_1), because in a recent multicenter study it was observed that patients with an FEV_1 less than 50% of predicted were significantly more likely to suffer from exacerbations caused by *H influenzae*, and that infections caused by *P aeruginosa* did not occur in patients with an FEV_1 of over 1700 mL.[39]

Since spirometry is not easily available in certain care settings,[85,86] other signs can be used to provide information regarding the severity of a patient's condition and to facilitate the classification of condition by severity. This list of signs and symptoms is shown in Table 8. The cutoff points for moderate and severe COPD are 60 and 70 years of age respectively. These cutoff points are lower than those used in many developed countries and have been chosen taking into account the lower life expectancy in many Latin America countries (level III evidence).

TABLE 8
Clinical Characteristics Relating to Severity (Level II Evidence)

Properties	Slight	Moderate	Severe
Age, years	<60	60-70	>70
Baseline dyspnea	Considerable effort	Medium effort	Slight effort
Current smoker	No	Yes	Yes
Comorbidity*	No	Yes	Yes
Domiciliary oxygen	No	No	Yes
Exacerbations during the previous 12 months	<4	>4	>4
Hospitalizations during the previous 12 months	0	1	>1
Use of antibiotics during the preceding 15 days	No	Yes	Yes

*Presence of ischemic heart disease, cor pulmonale, renal or hepatic failure, or insulin-dependent diabetes mellitus.

When an exacerbation occurs in patients with moderate or severe COPD, treatment with the new quinolones, which are active against pneumococcus, is justified because of the high probability of encountering penicillin-resistant strains of pneumococci (level III evidence). These new fluoroquinolones that are active against pneumococci are levofloxacin, moxifloxacin, and gatifloxacin. Although all 3 are active against this bacteria, the MIC 90s reveal the more potent intrinsic activity of moxifloxacin against *S pneumoniae* as compared to the other new fluoroquinolones.[46,87]

Since the bacteria have been observed to be quite sensitive to chloramphenicol, this agent could serve as an alternative in countries or areas where it is difficult to acquire fluoroquinolones. However, we must bear in mind the difficulty of administering 4 daily doses and the potential adverse events associated with chloramphenicol.

TABLE 9
Antibiotics Used Routinely in the Treatment of Respiratory Infections

Antibiotics	Dosage	Days of Treatment
Amoxicillin-clavulanic acid*	875/125 mg/12 h	
	500/125 mg/8 h	10 days
Cefuroxime axetil	500 mg/12 h	10 days
Clarithromycin OD	500 mg/12 h	
	Once daily	10 days
Azithromycin	500 mg the first day, then 250 mg/day	5 days
Telithromycin	800 mg/day	5 days
Moxifloxacin	400 mg/day	5 days
Gatifloxacin	400 mg/day	7 days
Levofloxacin	500 mg/day	7 days
Ciprofloxacin	750 mg/12 h	10-15 days

*Other more inhibiting beta-lactams available in Latin American are amoxicillin-sulbactam and ampicillin-sulbactam.

Conversely, resistance to co-trimoxazole is very high, and the use of this antimicrobial agent is not advisable.

Telithromycin is a new ketolide antibacterial agent with potent activity against *S pneumoniae*, even against strains resistant to both penicillin and macrolides. However, its activity against *H influenzae* is similar to that of azithromycin.[88] In one published trial telithromycin was shown to be as effective as amoxicillin-clavulanic acid in the treatment of exacerbations of chronic bronchitis.[89] Its indication as an alternative to quinolones is justified in patients with risk factors for resistant microorganisms (level III evidence). Its use is pending approval by health authorities in various countries, including the USA.

In severe cases of COPD where the patient has an FEV_1 of less than 35% of predicted, the possibility that *P aeruginosa* might be the cause of the exacerbation should not be ruled out.[38,39,90] Oral ciprofloxacin is the treatment of choice for patients presenting with risk factors for *Pseudomonas*, such as bronchiectasis, chronic bronchial suppuration, or a prior positive sputum culture for this pathogen (level III evidence).

The recommended treatment protocols for the principal antibiotics used to treat COPD exacerbations are shown in Table 9.

Prevention of COPD and its Exacerbations

It is obvious that the most effective way to prevent COPD is to avoid the risk factors. In certain cases the physician should actively engage in the task of ensuring that the patient gives up harmful habits, such as smoking. In other circumstances, preventative action is very difficult, such as in the case of environmental pollution and even when the problem is domestic wood smoke pollution. Other factors, such as those related to the patients' genes, cannot be modified. Vaccinations are another way of preventing the morbidity associated with COPD. Of these, we should make particular mention of vaccination against influenza, which should be administered every year to patients with COPD following the World Health Organization recommendations and targeting the strains specified by this institution (level I evidence).[91] This is particularly important in countries with seasonal climate change where there are flu epidemics. Administration of the 23-valent pneumococcal vaccine is also recommended (level I evidence). This vaccine is administered to COPD patients in a single dose.[92]

Other purportedly preventative measures, such as the *H influenzae* vaccine and the administration of oral vaccines with inactivated germs, have not been shown to be effective in patients with COPD. Likewise, no evidence supports a role for the administration of other pharmacological therapies—such as vitamins—in the prevention of exacerbations or has demonstrated that such treatments have any effect on the natural course of the disease.

Controversial Issues

Our understanding of the infectious exacerbation of COPD is continually evolving, making necessary a constant process of revision of the guidelines in order to incorporate new scientific evidence into clinical practice. Some of the new information is still speculative and new studies will change our knowledge further. In this context, it is worth mentioning the influence of chronic bacterial airway colonization on the evolution of COPD and exacerbation frequency. As mentioned, very recent studies indicate that bacterial colonization is linked to a higher exacerbation frequency and produces an acceleration in lung function decline, at least in patients with severe COPD. New studies of large groups of COPD patients are needed to confirm the effects of colonization in these patients.

Since we do not have quick, economical methods for diagnosing the bacterial etiology of exacerbations, treatment is nearly always empirical. With respect to treatment, it is not clear whether the etiology of slight exacerbations is bacterial. The hypothesis that slight exacerbations may have a viral etiology, which is subsequently complicated by bacterial superinfection, is interesting. If the hypothesis were true, antibiotic treatment would be indicated. The theory has not, however, been demonstrated.

The term clinical cure is probably excessively ambiguous and subjective for use in evaluating the results of antibiotic therapy and does not facilitate comparison of the efficacy of different drugs. New parameters of treatment efficacy should be studied, such as quality of life or time free of symptoms. Alternatively certain biochemical parameters of bronchial inflammation could be used as markers.

These and other aspects of the disease are currently the focus of intense research, which in the near future will certainly provide answers to some of the questions we ask ourselves when we are treating a patient with exacerbated COPD.

Conclusion

COPD is a very common disease that affects between 6% and 12% of the population over 40 years of age. Its association with tobacco is clear although in Latin America other risk factors, such as wood smoke, are also present. Exacerbations are the most common reason why these patients consult a doctor, and treatment of their crises must be as energetic as possible in order to combat the high rate of treatment failure, which ranges from 14% to 26%. When prescribing antibacterial treatment, physicians must take into account the prevalence of causative pathogens, sensitivity patterns, and the antibiotics available in each geographical area. Patients suffering from acute bronchitis who present without signs of bacterial infection will recover without sequelae and do not require antibiotic treatment. Patients with moderate to severe COPD or with risk factors for failure should receive antibiotics prescribed empirically. In such cases the physician should prescribe an agent active against the most common pathogens in the area; moreover it should be an antibiotic that is not affected by the resistance patterns of the predominant local bacterial strains.

The objectives of the treatment of COPD exacerbations should be clinical cure in the greatest number of patients and the most complete eradication of bacteria possible.

REFERENCES

1. Grupo de Trabajo de la Asociación Latinoamericana del Tórax (ALAT). Recomendaciones ALAT sobre neumonía adquirida en la comunidad. Arch Bronconeumol 2001;37:340-8.
2. Grupo de Trabajo de la Asociación Latinoamericana del Tórax (ALAT). Recomendaciones ALAT sobre exacerbación infecciosa de la EPOC. Arch Bronconeumol 2001;37:349-57.
3. Celli BR, Snider GL, Heffner J, Tiep B, Ziment I, Make B, et al. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995; 152:S77-S120.
4. American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Am J Respir Crit Care Med 2001;163:1730-54.
5. Miravitlles M. Epidemiology of chronic obstructive pulmonary disease exacerbations. Clin Pulm Med 2002;9:191-7.
6. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, et al. ERS consensus statement. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). A consensus statement of the European Respiratory Society (ERS). Eur Respir J 1995;8:1398-420.
7. British Thoracic Society. BTS guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997;52(Suppl 5): 4-28.
8. Barberà JA, Peces-Barba G, Agustí AGN, Izquierdo JL, Monsó E, Montemayor T, et al. Guía clínica para el diagnóstico y el tratamiento de la enfermedad pulmonar obstructiva crónica. Arch Bronconeumol 2001;37:297-316.
9. Balter MS, Hyland RH, Low DE, Renzi PM, Braude AC, Cole PJ, et al. Recommendations on the management of chronic bronchitis. A practical guide for Canadian physicians. Can Med Ass J 1994; 151(Suppl):7-23.
10. Pauwels RA, Buist AS, Calverley PMA, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. Am J Respir Crit Care Med 2001;163:1256-76.
11. Anthonisen NR, Manfreda J, Warren CPW, Hershfield ES, Harding GKM, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106: 196-204.
12. Mannino DM, Brown C, Giovino GA. Obstructive lung disease deaths in the United States from 1979 through 1993. An analysis using multiple-cause mortality data. Am J Respir Crit Care Med 1997;156:814-8.
13. Sobradillo V, Miravitlles M, Gabriel R, Jiménez-Ruiz CA, Villasante C, Masa JF, et al. Geographical variations in prevalence and underdiagnosis of COPD. Results of the IBERPOC multicentre epidemiological study. Chest 2000;118:981-9.
14. Menezes AMB, Victoria CG, Rigatto M. Prevalence and risk factors for chronic bronchitis in Pelotas, RS, Brazil: a population-based study. Thorax 1994;49:1217-21.
15. Sansores R, Pérez-Padilla JR. Enfermedad pulmonar obstructiva crónica. Un problema mundial, un enfoque en México. México DF: Piensa Ed., 1997.
16. INEGI, SSA/DGEI. Estadísticas vitales. Mortalidad, Estados Unidos Mexicanos, 1997. México, DF: INEGI, SSA/DGEI, 1998.
17. Maldonado D, Bolívar F, Caballero A, Casas A, Roa J, Salgado C. Sociedad Colombiana de Neumología y Cirugía de Tórax. Recomendaciones para el diagnóstico y manejo del paciente con enfermedad pulmonar obstructiva crónica (EPOC). Rev Colombe Neumol 1997;9(Supl):1-39.
18. Report number 12681-CH. Chile. The adult health policy change. Human resources operation division. Country department. Latin America and the Caribbean Region. Document of the World Bank. 10 November, 1994.
19. Christopher J, Murray L, López A. Global health statistics. Harvard School of Public Health, editor. Harvard University Press. Maryland: World Health Organization, 1997.
20. Secretaría de Salud. Dirección General de Epidemiología. Instituto Mexicano de Psiquiatría. Encuesta Nacional de las Adicciones, tabaco. México, DF: SSA, 1993.
21. Department of Health and Human Services. Centers for Diseases Control. Smoking and health in the Americas. USA. Atlanta: DHHS publication number CDC 92-8420, 1992.
22. Farías Alburquerque C, Vega Huaman R, Gamboa Aboado R, Pinillos Ashton L, Diouff MA. Plan nacional para prevención y control del tabaquismo en el Perú 2001-2005. Comisión Multisectorial Permanente de Lucha Antitabáquica-COLAT Perú. Ministerio de Salud. Organización Panamericana de Salud. Lima, 2001.
23. Arango L, Luna J, Martínez G, Flores M. Tabaquismo en Guatemala. Boletín OPS 1990;2:6-9.
24. Carlini EA, Galduróz JC, Noto AR, Nappo SA. I levantamento domiciliar sobre o uso de drogas psicotrópicas no Brasil. São Paulo: CLR Balieiro Editores Ltda, 2002.
25. Ostro B, Sánchez JM, Aranda C, Eskaland G. Air pollution and mortality: results from a study in Santiago, Chile. J Exp Environ Epidemiol 1996;6:97-114.
26. Tashkin DP, Detals R, Simmonds M, Liu H, Coulson AH, Sayre J, et al. The UCLA population studies of chronic obstructive respiratory diseases. Impact of air pollution and smoking on annual change in forced expiratory volume in one second. Am J Respir Crit Care Med 1994;149:1209-17.
27. Pérez-Padilla R, Regalado J, Vadel S, Pare P, Chapela R, Samons R, et al. Exposure to biomass smoke and chronic airway diseases in Mexican women. Am J Respir Crit Care Med 1996; 154:701-6.
28. Dennis RJ, Maldonado D, Norman S, Baena E, Martínez G. Wood smoke exposure and risk for chronic obstructive airways disease among women. Chest 1996;109:115-9.
29. Luna J, Arango L. Bronquitis crónica secundaria a la exposición al humo de leña. Archivos Unidad Pulmonar. Hospital Roosevelt. Revista de Medicina Interna de Guatemala 1996;3:16-20.
30. Hendrick DJ. Occupation and chronic obstructive pulmonary disease (COPD). Thorax 1996;51:947-55.
31. Shaheen SO, Barker DJP, Shiell AW, Crocker FJ, Wield GA, Holgate ST. The relationship between pneumonia in early childhood and impaired lung function in late adult life. Am J Respir Crit Care Med 1994;149:616-9.
32. Hodgins P, Henneberger PK, Wang M-L, Petsonk EL. Bronchial responsiveness and five-year FEV_1 decline: a study in miners and

nonminers. Am J Respir Crit Care Med 1998;157:1390-6.
33. Sandford AJ, Weir TD, Paré PD. Genetic risk factors for chronic obstructive pulmonary disease. Eur Respir J 1997;10:1380-91.
34. Miravitlles M, Vidal R, de Gracia J. Enfisema por déficit de alfa-1-antitripsina. Situación actual y nuevas perspectivas para el tratamiento. Arch Bronconeumol 1992;28:296-302.
35. Miravitlles M, Mayordomo C, Artés M, Sánchez-Agudo L, Nicolau F, Segú JL, on behalf of the EOLO Group. Treatment of chronic obstructive pulmonary disease and its exacerbations in general practice. Respir Med 1999;93:173-9.
36. Monsó E, Ruiz J, Rosell A, Monterola J, Fiz J, Morera J, et al. Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. Am J Respir Crit Care Med 1995;152:1316-20.37. Sethi S, Evans N, Grant BJB, Murphy T. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. N Engl J Med 2002;347:465-71.
38. Eller J, Ede A, Schaberg T, Niederman MS, Mauch H, Lode H. Infective exacerbations of chronic bronchitis. Relation between bacteriologic etiology and lung function. Chest 1998;113:1542-8.
39. Miravitlles M, Espinosa C, Fernández-Laso E, Martos JA, Maldonado JA, Gallego M, and Study Group of Bacterial Infection in COPD. Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. Chest 1999;116:40-6.
40. Lieberman D, Lieberman D, Shmarkov O, Gelfer Y, Ben-Yaakov M, Lazarovich Z, et al. Serological evidence of *Legionella* species infection in acute exacerbation of COPD. Eur Respir J 2002; 19:392-7.
41. Mogulkoc N, Karakurt S, Isalska B, Bayindir U, Celikel T, Korten V, et al. Acute purulent exacerbation of chronic obstructive pulmonary disease and *Chlamydia pneumoniae* infection. Am J Respir Crit Care Med 1999;160:349-53.
42. Richter SS, Brueggemann AB, Huynh HK, Rhomberg PR, Wingert EM, Flamm R, et al. A 1997-1998 national surveillance study: *Moraxella catarrhalis* and *Haemophilus influenzae* antimicrobial resistance in 34 US institutions. Intern J Antimicrob Agents 1999;13:99-107.
43. Guzmán-Blanco M, Casellas JM, Sader HS. Bacterial resistance to antimicrobial agents in Latin America. The giant is awakening. Infect Dis Clin North Am 2000;14:67-81.
44. Soler T, Salamanca L, Arbo G, Molina E. Susceptibilidad in vitro de cepas de *Streptococcus pneumoniae* aisladas de infecciones de las vías aéreas inferiores en el Instituto Nacional del Tórax (INT). Rev Med Chil 2002;130:304-8.
45. Felmingham D, Gruneberg RN. The Alexander Project 19961997: latest susceptibility data from this international study of bacterial pathogens from community-acquired lower respiratory tract infections. J Antimicrob Chemother 2000;45:191-203.
46. Wise R, Honeybourne D. Pharmacokinetics and pharmacodynamics of fluoroquinolones in the respiratory tract. Eur Respir J 1999;14: 221-9.
47. Felmingham D. Evolving resistance patterns in community-acquired respiratory tract pathogens: first results from the PROTEKT Global Surveillance Study. J Infect 2002;44(Suppl A):3-10.
48. López H, Sader H, Amábile C, Pedreira W, Muñoz Bellido JL, García Rodríguez JA, y Grupo MSP-LA. Actividad in vitro de moxifloxacino frente a patógenos respiratorios en Iberoamérica. Rev Esp Quimioterap 2002;15:325-34.
49. Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. Chest 2000;117:1638-45.
50. Murray PR, Washington JA. Microscopic and bacteriologic analysis of expectorated sputum. Mayo Clin Proc 1975;50;339-44.
51. Adams SG, Melo J, Luther M, Anzueto A. Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. Chest 2000;117:1345-52.
52. MacFarlane JT, Colville A, Guion A, MacFarlane RM, Rose DH. Prospective study of aetiology and outcome of adult lower respiratory tract infections in the community. Lancet 1993;341: 511-4.
53. Ball P, Harris JM, Lowson D, Tillotson G, Wilson R. Acute infective exacerbations of chronic bronchitis. Q J Med 1995;88:61-8.
54. Huchon GJ, Gialdroni-Grassi G, Léophonte P, Manresa F, Schaberg T, Woodhead M. Initial antibiotic therapy for lower respiratory tract infection in the community: a European survey. Eur Respir J 1996;9:1590-5.
55. Dewan NA, Rafique S, Kanwar B, Satpathy H, Ryschon K, Tillotson GS, et al. Acute exacerbation of COPD. Factors associated with poor treatment outcome. Chest 2000;117:662-71.
56. Miravitlles M, Murio C, Guerrero T, on behalf of the DAFNE Study Group. Factors associated with relapse after ambulatory treatment of acute exacerbations of chronic bronchitis. A prospective multicenter study in the community. Eur Respir J 2001;17:928-33.
57. Miravitlles M. El fracaso en el tratamiento de las agudizaciones de la enfermedad pulmonar obstructiva crónica. Factores de riesgo e importancia clínica. Med Clin (Barc) 2002;119:304-14.
58. Miravitlles M, Murio C, Guerrero T, Gisbert R, on behalf of the DAFNE study group. Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. Chest 2002;121: 1449-55.
59. Miravitlles M, Murio C, Guerrero T, Gisbert R, on behalf of the DAFNE study group. Costs of chronic bronchitis and COPD. A one year follow-up study. Chest 2003;123:784-91.
60. Murata GH, Gorby MS, Kapsner CO, Chick TW, Halperin AK. A multivariate model for predicting hospital admissions for patients with decompensated chronic obstructive pulmonary disease. Arch Intern Med 1992;152:82-6.
61. Antonelli Incalzi R, Fuso L, de Rosa M, Forastiere F, Rapiti E, Nardecchia B, et al. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. Eur Respir J 1997;10:2794-800.
62. Prescott E, Lange P, Vestbo J. Chronic mucus hypersecretion in COPD and death from pulmonary infection. Eur Respir J 1995; 8:1333-8.
63. Landbo C, Prescott E, Lange P, Vestbo J, Almidal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160:1856-61.
64. Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:158-64.
65. Miravitlles M, Guerrero T, Mayordomo C, Sánchez-Agudo L, Nicolau F, Segú JL, on behalf of the EOLO Study Group. Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis. Respiration 2000;67:495-501.
66. Connors AF Jr, Dawson NV, Thomas C, Harrel FE Jr, Desbiens N, Fulkerson WJ, et al. Outcomes following acute exacerbation of severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996;154:959-67.
67. Wilson R, Kubin R, Ballin I, Deppermann KM, Bassaris HP, Leophonte P, et al. Five day moxifloxacin therapy compared with 7 day clarithromycin therapy for the treatment of acute exacerbations of chronic bronchitis. J Antimicrob Chemother 1999;44:501-13.
68. Chodosh S, Schreurs A, Siami G, Barkman HW, Anzueto A, Shan M, et al. The efficacy of oral ciprofloxacin vs. clarithromycin for the treatment of acute bacterial exacerbations of chronic bronchitis. Clin Infect Dis 1998;27:730-8.
69. Soler N, Ewig S, Torres A, Filella X, González J, Xaubet A. Airway inflammation and bronchial microbial patterns in patients with stable chronic obstructive pulmonary disease. Eur Respir J 1999;14:1015-22.
70. Crooks SW, Bayley DL, Hill SL, Stockley RA. Bronchial inflammation in acute bacterial exacerbations of chronic bronchitis: the role of leukotriene B_4. Eur Respir J 2000;15:274-80.
71. Bhowmik A, Seemungal TAR, Sapsford RJ, Wedzicha JA. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. Thorax 2000;55:114-20.
72. Bresser P, Out TA, van Alphen L, Jansen HM, Lutter R. Airway inflammation in nonobstructive and obstructive chronic bronchitis with chronic *Haemophilus influenzae* airway infection. Am J Respir Crit Care Med 2000;162:947-52.
73. Anzueto A, Rizzo JA, Grosman RF. The infection-free interval: its use in evaluating antimicrobial treatment of acute exacerbation of chronic bronchitis. Clin Infect Dis 1999;28:1344-5.
74. Patel IS, Seemungal TAR, Wilks M, Lloyd-Owen SJ, Donaldson GC, Wedzicha JA. Relationship between bacterial colonisation

and the frequency, character, and severity of COPD exacerbations. Thorax 2002;57:759-64.
75. Donaldson GC, Seemungal TAR, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002; 57:847-52.
76. Wilkinson TMA, Patel IS, Wilks M, Donaldson GC, Wedzicha JA. Airway bacterial load and FEV_1 decline in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2003;167:1090-5.
77. Stockley RA. Role of bacteria in the pathogenesis and progression of acute and chronic lung infection. Thorax 1998;53:58-62.
78. Miravitlles M. Exacerbations of chronic obstructive pulmonary disease: when are bacteria important? Eur Respir J 2002;20(Suppl 36):9-19.
79. Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gros NJ, Light RW, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. N Engl J Med 1999;340:1941-7.
80. Davies L, Angus RM, Calverley PMA. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Lancet 1999;354:456-60.
81. Evans AT, Husain S, Durairaj L, Sadowski LS, Charles-Damte M, Wang Y. Azithromycin for acute bronchitis: a randomised, double-blind, controlled trial. Lancet 2002;359:1648-54.
82. Allegra L, Grassi C, Grossi E, Pozzi E, Blasi F, Frigerio D, et al. Ruolo degli antibiotici nel trattamento delle riacutizzazioni della bronchite cronica: risultati di uno studio italiano multicentrico. Ital J Chest Dis 1991;45:138-48.
83. Saint S, Bent S, Vittinghoff E, Grady D. Antibiotics in chronic obstructive pulmonary disease exacerbations: a meta-analysis. JAMA 1995;273:957-60.
84. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1-12.
85. Miravitlles M, Murio C, Guerrero T, Segú JL. Tratamiento de la bronquitis crónica y la EPOC en atención primaria. Arch Bronconeumol 1999;35:173-8.
86. Kesten S, Chapman KR. Physician perceptions and management of COPD. Chest 1993;104:254-8.
87. Miravitlles M. Moxifloxacin: an antibiotic designed for use in the community. Eur Respir Rev 2000;10:161-9.
88. Odenholt I, Lowdin E, Cards O. Pharmacodynamics of telithromycin in vitro against respiratory tract pathogens. Antimicrob Agents Chemother 2001;45:23-9.
89. Aubier M, Aldons PM, Leak A, McKeith DD, Leroy B, Rangaraju M, et al. Telithromycin is as effective as amoxicillin/clavulanate in acute exacerbations of chronic bronchitis. Respir Med 2002;96:862-71.
90. Soler N, Torres A, Ewig S, González J, Celis R, El-Ebiary M, et al. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. Am J Respir Crit Care Med 1998;157:1498-505.
91. Nichol KL, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. Ann Intern Med 1999;130:397-403.
92. Centers for Disease Control and Prevention. Prevention of pneumococcal disease. Recommendations of the Advisory Committee of Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 1997;46:1-24.