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REVIEW

Acute exacerbation of chronic obstructive pulmonary disease and antibiotics: what studies are still needed?

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Acute exacerbation of chronic obstructive pulmonary disease and antibiotics: what studies are still needed? C. Sohy, C. Pilette, M.S. Niederman, Y. Sibille. ©ERS Journals Ltd 2002.

ABSTRACT: The use of antibiotics in acute exacerbations of chronic bronchitis (AECBs) remains the subject of controversy despite considerable medical and socio-economic implications.

First, the contribution of bacterial infection to AECBs is difficult to assess in patients with chronic obstructive pulmonary disease (COPD) who are chronically colonized with respiratory pathogens. In addition, several studies suggest a major role of viral infections in AECBs.

Secondly, it is unlikely that all COPD patients will benefit from antibiotics during AECBs. In particular, the benefit in mild COPD remains uncertain. Unfortunately, the number of studies complying with evidence-based medicine requirements is too small for definite recommendations in AECBs to be drawn up.

Considering the impact of acute exacerbations of chronic bronchitis on chronic obstructive pulmonary disease patients, as well as the community, and the impact of antibiotic therapy on the development of bacterial resistance, there is an urgent need for the design of appropriate multicentric studies to define the usefulness of this type of treatment in acute exacerbations of chronic bronchitis.

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Chronic obstructive pulmonary disease (COPD) represents one of the leading causes of morbidity and mortality (fourth commonest cause of death in the USA). More importantly, epidemiological studies documenting the persistence of tobacco smoking habits predict a rise in the incidence of COPD in the coming decades. Since 1964, >3,400 articles have reported on antibiotics and COPD and volume 17 of the *European Respiratory Journal* (2001) contained three original papers and one review relating to this topic [1–4]. Despite this abundant literature, only a very limited number of studies are suitable for use in the development of guidelines on the place of antibiotics during acute exacerbations of chronic bronchitis (AECBs). This is in striking contrast with the considerable cost encountered worldwide in the treatment of COPD, and particularly in antibiotic treatment during AECBs. Thus, according to a survey carried out in the USA for 1996, the estimated direct annual cost of treatment for COPD was US$14.5 billion, 35% of this relating to medications [5]. More specifically, AECBs account for an annual cost of US$1.6 billion [6]. Considering the medical and socio-economic impact of COPD, and, in particular, that related to acute exacerbations of the disease, it is critical that appropriate and well-designed therapeutic strategies are developed.

During recent decades, guidelines for the clinical management of a series of disorders, including COPD, have been developed. These guidelines should ideally be in agreement with the requirements of evidence-based medicine, *i.e.* driven by good medical practice integrating individual clinical expertize with the best available external clinical evidence from systematic research [7]. In the particular case of COPD, these guidelines appear debatable since major questions regarding the role of infection and the utility of antibiotics in AECBs remain unanswered. Several key issues related to antibiotics in AECBs need to be addressed in order for guidelines to be drawn up. 1) Since it remains unclear to what extent bacterial infection contributes to AECBs, are there tests or clinical or biological markers which could discriminate between bacterial infection and other causes of AECBs? 2) Is the severity of COPD or of the AECB or both critical to the outcome of the exacerbation? 3) Are antibiotics useful in AECBs, and, if so, which antibiotic should be chosen for each patient? 4) Finally, on the basis of which criteria can the decision to treat at home or to hospitalize the patient with an AECB be made?

In the present article, the knowledge accumulated during past decades which is clearly validated and readily available for use in the development of

guidelines is summarized. The issues which remain uncertain and require further studies to be validated are then addressed. The article concludes by tentatively designing the studies (probably large scale multicentric ones) urgently required to provide the clinician with practical guidelines on the use of antibiotics during AECBs.

Diagnosis of acute exacerbations of chronic bronchitis

An exacerbation of chronic bronchitis may be defined as the acute worsening of the clinical symptoms of the disease, *i.e.* breathlessness, wheezing and cough, associated with sputum production and/or sputum purulence. This definition is not so trivial because these symptoms, related to mucus hypersecretion and airflow limitation, represent clinical hallmarks of the disease which aggravate during its natural course. Thus, a first step is to discriminate between symptoms related to the natural course of COPD and those caused by an AECB. It has been reported in the literature that various laboratory findings are associated with clinical "acute exacerbations" of chronic bronchitis (table 1). The study of ANTHONISEN *et al.* [19] proposed defining the presence and severity of AECB on the basis of "cardinal" symptoms: increased breathlessness, sputum production and/or sputum purulence, the presence of one to three of these allowing AECBs to be classified as type III to type I, respectively.

Several studies have described, during AECBs, increases in levels of inflammatory parameters, such as airway neutrophils (and their granule products myeloperoxidase (MPO) and elastase) or eosinophils; the neutrophil chemoattractants interleukin (IL)-8 and leukotriene (LT) B_4 in sputum; markers of oxidative stress (reactive oxygen and nitrogen species) in exhaled air and breath condensate; and C-reactive protein (CRP) in serum, and plasma leakage of large proteins into airway secretions (table 1) [10, 12, 15–18]. These inflammatory cells and mediators, which are already present in the stable state of COPD, further increase during exacerbations, including in patients with severe airflow limitation [8]. However, no clear-cut values distinguishing between the exacerbated and stable state are readily available since most previous studies have been cross-sectional [8, 9, 11, 13, 14, 20], limiting the conclusions that can be drawn. In addition, it is not known whether some AECBs may occur in the absence of increased airway inflammation, and/or whether changes in inflammatory features can occur in chronic bronchitis patients without clinical impact. Therefore, prospective longitudinal studies are required to follow both clinical and biological parameters before, during and after AECBs. The preliminary longitudinal study of AARON *et al.* [21] evaluated changes in the concentrations of tumour necrosis factor-α, IL-8 and MPO in sputum from 14 severe COPD patients (baseline forced expiratory volume in one second (FEV_1) 37% of the predicted value) who experienced an AECB. An increase in sputum tumour necrosis factor-α and IL-8, but not MPO, levels was confirmed in these patients during the exacerbation as compared to their stable state, and returned to baseline levels 1 month later.

Table 1. – Inflammatory factors related to acute exacerbations of chronic bronchitis

	Factor	Sampling	[Refs.]
Systemic response	C-reactive protein	Blood	[8, 9]
Leukocytes	Neutrophils and/or eosinophils	Sputum	[10, 11]
		Blood?	[12]
		Bronchial biopsy?	[13]
Mediators	IL-8, LTB_4	Sputum	[8, 14]
	MPO, elastase		[14, 15]
	IL-6		[14]
Markers of oxidative stress	ROIs, RNIs	Breath condensate, exhaled air	[16, 17]
	Plasma TEAC	Blood	[17, 18]
	Glutathione	ELF	[17, 18]

IL: interleukin; LTB_4: leukotriene B_4; MPO: myeloperoxidase; ROI: reactive oxygen intermediate; RNI: reactive nitrogen intermediate; TEAC: Trolox-equivalent anti-oxidant capacity; ELF: epithelial lining fluid.

Although severity of inflammation has been associated with severity of airflow limitation in stable COPD [13], only one study [22] has suggested that severity of AECB relates to severity of increased airway inflammation. Parameters other than airway inflammation such as hypercapnia and/or pulmonary hypertension, low body mass index, and a limited 6-min walking distance have been described as predictors of severity of AECB or hospitalization due to AECB [23]. Thus the severity of an AECB seems closely related to the severity of the disease in its stable state, suggesting that severe COPD itself often implies severe (and/or frequent) exacerbations. This assumption has been integrated into the Canadian guidelines [24], in which the number of exacerbations of bronchitis a year (<4 or >4) is a factor in the classification of disease severity, and is supported by three lines of evidence. First, current tobacco smoking represents a risk factor for both acute and chronic bronchitis [25, 26]. Similarly, it is thought that viral and bacterial infections, which may be responsible for AECBs, also play an important role in the pathophysiology of COPD. Secondly, it has been shown that sputum IL-6 levels, which increase during AECBs, remain elevated in COPD patients who suffer frequent exacerbations even when measured in the stable state [14]. Thirdly, in addition to reducing the quality of life, AECBs are associated with a more rapid decline in lung function and lower survival than in the stable state [27–29]. Thus improving management of COPD may require better definition of AECBs through a better understanding of its determinants.

Role of bacteria in acute exacerbations of chronic bronchitis

Various potential causes of AECBs have been identified. Once an intercurrent cardiopulmonary event has been excluded (such as cardiac failure,

pulmonary embolism, pleural effusion or pneumothorax), an infectious aetiology is often suspected. Air pollution and temperature are also potential causes of AECBs [30], but are difficult to assess at the level of the individual patient. Among infectious causes, viral infections might be responsible for almost half of AECBs, as reported in a recent serological study [31]. However, in the same study, evidence for combined viral and bacterial infections has been observed in 30% of AECBs. This might be related to the possibility that viral infection may promote a secondary bacterial infection [32], through mechanisms most probably involving epithelial damage [33].

Bacteria are considered a major aetiological factor in AECBs, at least from an empirical point of view. Three lines of evidence support the idea that bacteria may cause AECBs. First, a positive sputum culture for potentially pathogenic micro-organisms is observed in $\geqslant$50% of AECBs [28, 34, 35], especially those accompanied by sputum purulence. Secondly, the presence of bacteria in airway secretions is associated with increased airway inflammation [22], and antibiotic treatment of AECBs results in a decrease in the levels of some inflammatory parameters during AECBs [8]. Thirdly, antimicrobial therapy can improve clinical outcome in AECBs [19, 36]. However, each of these arguments has limitations. Thus, a positive culture for potentially pathogenic micro-organisms is also observed in almost half of stable chronic bronchitis [37], and is thought to represent colonization of COPD airways. Quantification of the bacterial load (number of colony-forming units) might be useful for discrimination between colonization and infection [38]. Various defence mechanisms are impaired in COPD, and this could favour persistence of bacteria in the airways. These include defects in epithelial and mucociliary function [39] and secretion of neutralizing immunoglobulins [40, 41], as well as defective phagocyte and natural killer cell activities [42]. However, a high bacterial load in the airways, especially of *Pseudomonas aeruginosa* and *Haemophilus influenzae*, may elicit an inflammatory response even in the clinically stable state, and independent of disease severity [43]. Finally, >50% of AECBs (even of type I) resolve spontaneously [19] and the observed benefit of antibiotic treatment might be related, in some cases, to its additive anti-inflammatory effect, especially with macrolides [44].

Nevertheless, although it remains difficult to prove a cause/effect relationship, it is likely that the proliferation and/or tissue invasion of bacteria in the airways (related notably to the acquisition of virulence factors) may induce an AECB. Some findings thought to be preferentially related to bacterial AECBs, as opposed to AECBs due to other causes are listed in table 2 [45–51]. Unfortunately, regarding the diagnosis of AECB itself, follow-up studies are not available and conclusions from the existing literature are therefore largely biased. In the longitudinal study of AARON *et al.* [21], the limited number of patients with documented infection (one with bacterial and two with viral AECBs) did not permit representative findings. With regard to this distinction, as well as that between bacterial colonization and infection, future studies should be designed to identify new tools (blood and sputum markers) to improve the management of AECBs. Thus an evidence-based strategy for defining which exacerbated COPD patients are infected and will clearly benefit from antibiotics is lacking.

Antibiotics in acute exacerbations of chronic bronchitis

Data from randomized studies

Conclusions from randomized studies were addressed in the meta-analysis of SAINT *et al.* [36] in 1995. This meta-analysis traced 239 reports on

Table 2. – Clinical, inflammatory and microbiological findings related to bacterial acute exacerbations of chronic bronchitis (AECB)

	Finding	Observations	[Refs.]
Clinical	Presence of the three cardinal symptoms	May be a predictor of response to antibiotics	[19]
	Sputum purulence	Correlates with MPO concentration and bacterial load	[9, 35, 43]
	Fever	Might be unusual in bacterial AECBs, but frequent during viral infections	[45]
Inflammatory	Blood leukocytosis (neutrophilia)	Not or poorly documented; interference of oral steroids	[12]
	Sputum neutrophilia	Increases during AECBs, not validated in longitudinal studies	[10]
	Increased sputum neutrophil elastase	Possibly biased *via* its correlation with the severity of AECBs	[22]
Microbiological	Sputum bacteriology (Gram stain, culture)	Positive in half of stable COPD patients (colonization); bacterial load $>10^6$ cfu·mL^{-1} (or $>10^5$ for *Streptococcus pneumoniae*); protected brush specimens more accurate but less feasible in routine practice	[38, 46–50]
	Serology (strongly positive or $\geqslant$4-fold titre increase)	Mainly "retrospective" diagnosis; chronic carriage may also be associated with high antibody titres	[31, 51]

MPO: myeloperoxidase; COPD: chronic obstructive pulmonary disease; cfu: colony-forming units.

antimicrobial therapy and AECBs published 1955–1994. Only nine studies involving 1,101 episodes of AECB met the criteria of randomized *versus* placebo. The analysis supports a small but significant beneficial effect of antibiotic treatment in the outcome of AECBs. However, it remains uncertain whether this benefit is clinically and/or financially relevant. The only objective measurement in six of the nine studies was peak expiratory flow rate (PEFR), which improved significantly in patients treated with antibiotics; the mean benefit was 10.75 $L \cdot min^{-1}$. Interestingly, as stated by the authors, "this antibiotic based improvement is small but could be clinically significant especially in COPD patients with low baseline PEFR and in hospitalized patients". Nevertheless, the authors also point out that these data should be interpreted with caution considering the heterogeneity of the population analysed, which included in- and outpatients, the various antibiotics used for various durations, and, particularly, the different inclusion and outcome criteria defined in each study. A more recent meta-analysis supports the use of antibiotics in AECBs, especially for patients with more severe exacerbation [52]. However, as stated by the authors themselves, most of the studies showing benefit of antibiotics in AECBs were performed before the emergence of bacterial resistance, in particular to β-lactams and macrolides. Thus, although early studies showed no difference in outcome, regardless of antibiotic choice, it is likely that different therapies may lead to different outcomes at the current time given the high frequency of antibiotic-resistant pathogens in AECB patients.

Among randomized placebo-controlled studies, the study of ANTHONISEN *et al.* [19], published in 1987, is still considered a key reference in this field. Patients were divided into three groups according to symptoms (increased dyspnoea, increased sputum production and increased sputum purulence). Group I included patients presenting with the three symptoms, group II those with two symptoms and group III those with only one. In this study, 173 patients with moderate-to-severe COPD (mean FEV_1 33.9±13.7% pred (mean± SD)) were followed 1982–1984 and, during this period, a total of 362 episodes of AECB were recorded. The results, based on both resolution of symptoms and return to baseline PEFR, demonstrated a beneficial effect of antibiotics. The authors noted two additional observations, namely, first, that 55% of AECBs resolved spontaneously (disappearance of symptoms within 21 days) in the placebo group and, secondly, that systemic corticosteroids (used equally in 43% of placebo- and antibiotic-treated patients) did not account for the benefit obtained in the group treated with antibiotics. There was no significant difference according to which antibiotic was used; however, antibiotic resistance was uncommon at the time of the study. In addition, the benefit from antibiotics was most striking in group I patients, and this benefit was marginal in group II and absent in group III. This supports the theory that antibiotics are more useful in patients presenting with a combination of increased dyspnoea and purulent sputum production, at no cost of side-effects, which were similar in the two groups (placebo and antibiotic-treated).

Most publications reporting on randomized placebo-controlled studies only consider some of the key issues relating to AECBs. For instance, despite the suggestion that antibiotics could be of benefit in more severely ill patients (the aged, severe COPD and/or severe exacerbation, and the presence of comorbidity factors), no study systematically randomized all of these parameters. Moreover, concomitant therapy (such as corticosteroids) was often overlooked and, if criteria were proposed to define AECBs, chest radiography was not systematically performed and, therefore, pneumonia cannot formally be excluded. Another important issue is that most studies did not separate hospitalized and nonhospitalized patients. In addition, the types of antibiotics used in the trials did not cover the spectrum of the majority of bacteria currently recovered from sputum during AECBs. Furthermore, the same bacteria are often present in the sputum of COPD patients both during and between episodes of AECB. Finally, there is no consensus as to which criteria should be used to evaluate the success of therapy in either short- or long-term assessment. Alongside the very few randomized placebo-controlled studies found in the literature, there are numerous randomized double-blind studies comparing two antibiotics in the treatment of AECBs. Most studies comparing two antibiotics tend to demonstrate that the antibiotics used are of similar clinical efficacy and safety (table 3) [53–61]. However, these studies have other drawbacks which prevent them from being used in the development of guidelines (table 4). First, the inclusion criteria vary considerably from one study to another. Some studies defined an acute exacerbation only on clinical bases (such as the criteria of ANTHONISEN *et al.* [19]), whereas others used microbiological criteria, generally qualitative estimates (one study included only patients with documented pneumococci in their sputum) [60]. Moreover, patients with an exacerbation who received antibiotics during the week prior to the episode were generally excluded from the studies; conversely, those who had stopped taking antibiotics >1 week before the exacerbation could be enrolled. This all serves to illustrate the difficulty in defining a clear relationship between bacterial infection and AECB and in comparing different studies.

In most studies, including placebo-controlled randomized studies, patients are not randomized for treatments other than antibiotics (*e.g.* bronchodilators, physical therapy, mucolytic agents and sometimes even systemic corticosteroids). It remains to be proven that these treatments do not influence the outcome of AECBs. Despite the suggestion that antibiotic treatment could be of clinical and economic benefit in moderate-to-severe COPD patients and those who present with >4 episodes of AECB in the preceding year [62], many studies did not report initial lung function testing prior to antibiotic treatment. It is therefore difficult to estimate the severity of the fixed airflow limitation in these patients. Moreover, few studies evaluated the correlation between clinical improvement and bacteriological cure during AECB

Table 3. – Outcome parameters in acute exacerbations of chronic bronchitis in randomized double-blind studies comparing different antibiotic regimens

First author [Ref.]	Subjects n	Antibiotic regimen	Clinical response	Bacteriological response	Lung function	Tolerability
CHODOSH [53]	208	CPF 500 mg *b.i.d*, 14 d *vs* CFXAX 500 mg *b.i.d*, 14 d	sim.	CPF (96%)> CFXAX (82%)**	ND	sim.
GOTFRIED [54]	527	CLM 500 mg *b.i.d*, 10 d *vs* GTF 400 mg *o.d.*, 5 d *vs* GTF 400 mg *o.d.*, 7 d	sim.	sim.	ND	sim.
GEORGOPOULOS [55]	395	AMX 1 g *b.i.d*, 10 d *vs* AMX 500 mg *t.i.d*, 10 d	sim.	sim.	sm. imp. FEV_1, sim.	sim.
ADLER [56]	620	CLM, ER 2×500 mg *o.d.*, 7 d *vs* CLM, IR 500 mg *b.i.d*, 7 d	sim.	sim.	ND	sim.
FILE [57]	600	AMX/CA 500 mg *t.i.d*, 7 d *vs* GMF 320 mg *o.d.*, 5 d	sim.	sim.	ND	sim.
MCADOO [58]	469	CFB 400 mg *o.d.*, 5–15 d *vs* AMX/CA 500 mg *t.i.d*, 5–15 d	sim.	sim.	ND	CFB fewer GI side-effects
LANGAN [59]	566	AMX 500 mg *t.i.d*, 7–10 d *vs* GPF 400 mg *o.d.*, 7–10 d *vs* GPF 600 mg *o.d.*, 7–10 d	sim.	sim.	ND	GPF 600 mg less tol. (GI)
ZUCK [60]	97	CFXAX 250 mg *b.i.d*, 8 d *vs* CFX 200 mg *b.i.d*, 8 d	CFXAX> CFX	CFXAX> CFX[#]	ND	sim.
SHAH [61]	832	CFXAX 250 mg *b.i.d*, 7–10 d *vs* LVF 250 mg *o.d.*, 7–10 d	sim.	sim.	ND	sim.

[#]: bacteriological eradication of *Streptococcus pneumoniae*. CPF: ciprofloxacin; CFXAX: cefuroxime axetil; CLM: clarithromycin; GTF: gatifloxacin; AMX: amoxicillin; CA: clavulanic acid; GMF: gemifloxacin; CFB: ceftibuten; GPF: grepafloxacin; CFX: cefixime; LVF: levofloxacin; *vs*: *versus*; d: days; ER: extended release; IR: immediate release; sim: similar; ND: not determined; sm. imp.: small improvement; FEV_1: forced expiratory volume in one second; GI: gastrointestinal; tol.: tolerated. **: p=0.01.

follow-up. As illustrated in table 3, except for one study suggesting a different clinical and bacteriological outcome according to the antibiotic used [60] and another supporting only different bacteriological outcome [53], all studies showed an equivalent response regardless of the antibiotic used. Unfortunately, the follow-up in these studies was generally short and none of them took into consideration the cost or the cost/efficacy.

Another important issue considered in randomized studies concerns the decision to treat in an ambulatory setting or to hospitalize patients during an AECB. In the recent study of SKWARSKA *et al.* [63], it was deduced that there was no significant difference between patients treated at home and at hospital regarding readmission and quality of life. Satisfaction of offered service was also good and the cost was, as expected, much lower in the out- compared to the inpatient group. Adequate follow-up at home, including regular visits by a nurse and/or physician, was part of the ambulatory treatment. Without this close follow-up, it is uncertain whether the outcome at home would be satisfactory. It is also important to stress that more than half of the initial 1,006 patients were excluded from the study because the severity of the exacerbation required hospitalization.

Data from nonrandomized studies

In several studies, follow-up of various parameters (clinical, lung function and microbiological) in

Table 4. – Characteristics of some randomized double-blind studies comparing different antibiotic regimens

First author [Ref.]	Follow-up	Wash-out* weeks	AECB definition	Bacteriological parameters	Lung function		Other treatment	Cost
					Before AECB	Follow-up		
CHODOSH [53]	9 months	NR	A+B+C+E	GS	ND	ND	ND	ND
GOTFRIED [54]	21–28 days	1	A+B+C	QC	ND	ND	Yes but not studied	ND
GEORGOPOULOS [55]	28–35 days	4	2 of A, B, C, E (±D)	GS	$PEFR+FEV_1$	$PEFR+FEV_1$	ND	ND
ADLER [56]	12 months	3	A+C+D+E	GS	ND	ND	Steroids excluded	ND
ZUCK [60]	30–40 days	1	C+D	GS+QC	ND	ND	ND	ND
SHAH [61]	21–28 days	NR	A+B+C+E	GS	$PEFR+FEV_1$	ND	ND	ND

NR: not reported as an inclusion criterion; A: increased dyspnoea; B: increased sputum volume; C: increased sputum purulence; D: fever; E: increase of cough; GS: Gram stain and culture; QC: quantitative culture; ND: not determined; PEFR: peak expiratory flow rate; FEV_1: forced expiratory volume in one second. *: time without antibiotic before inclusion in study.

AECBs was used to define the subgroups of COPD patient who would most benefit from antibiotics. Unfortunately, these studies were generally non-randomized or retrospective and therefore their conclusions are of limited value. However, some useful trends could be identified. An important factor to consider in antibiotic treatment of AECB is the presence or absence of patient characteristics which increase the morbidity associated with COPD. More specifically, age >65 yrs, comorbid diseases such as cardiac or renal failure, alcoholism and diabetes clearly influence the outcome of AECBs. In a prospective study, BALL *et al.* [45] identified a previous history of cardiopulmonary disease and more than three AECBs during the preceding year as representing a major risk factor for recurrence of AECB, as well as for hospitalization. The most predictive factor for the use of antibiotics in AECBs was the combination of a history of cardiopulmonary disease and >4 AECBs during the past year. The same findings were also made by DEWAN *et al.* [64] in a retrospective study. They estimated that the choice of antibiotic had little impact on the outcome of treatment. By contrast, factors such as FEV_1 <35% pred, home oxygen therapy, number of exacerbations within the last 24 months, and previous history of pneumonia, sinusitis or chronic use of oral corticosteroids (prednisone >5 $mg \cdot day^{-1}$ for >3 months) clearly influenced the outcome of AECBs.

However, ADAMS *et al.* [65] obtained different results. In a retrospective study of 173 COPD patients (veterans), factors such as age, severity of the underlying pulmonary disease, comorbidity factors such as diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, renal insufficiency, liver disease, cancer and cerebrovascular accident, and the severity of symptoms (based on the criteria of ANTHONISEN *et al.* [19]) did not predict the frequency or severity of the AECB. In contrast, these authors noted that patients receiving certain antibiotics had a lesser tendency to relapse within the next 14 days, compared to those getting no antibiotic therapy. There was no bacteriological evaluation to select antibiotics or information about compliance with treatment. All of these findings should be further studied on a larger scale in randomized multicentric studies and used in the development of guidelines to define subgroups of COPD patients benefitting from antibiotic treatment during AECBs.

Another important factor influencing the need for specific therapies is the severity of the underlying airway disease. Thus, severe fixed airflow limitation, which might be associated with a greater number of exacerbations per year, also influences the outcome of AECBs. This might be related to the different microbiological flora found in airway secretions from such patients. Several studies [46, 47, 66, 67] have shown that *P. aeruginosa*, *Enterobacter* spp. and *H. influenzae* are the bacteria predominantly recovered in the sputum of COPD patients with an FEV_1 of <35 [46] or <50% pred [47]. These retrospective studies in COPD patients document a correlation between lung function test results and the strain of bacteria isolated from sputum during the AECB. Patients with less severe lung function defects yielded primarily *Streptoccocus pneumoniae* and nonpathogenic bacteria. These results are in agreement with those of SOLER *et al.* [66], who observed Gram-negative bacteria and *H. influenzae* in 44 and 33%, respectively, of AECBs requiring mechanical ventilation (in contrast with only 11% with *S. pneumoniae*), probably because severity of AECB was largely due to the severity of the pre-existing airflow limitation. MIRAVITLLES *et al.* [47] noticed, in addition, that *H. influenzae* was more often cultured from the sputum of actively smoking patients. Other authors [49, 50] have also identified current tobacco smoking as associated with a high risk of airway colonization by *H. influenzae*. These data appear to offer some direction for the antibiotic treatment of AECB on the basis of lung function test results and smoking habits.

Blood and sputum characteristics could also provide some useful therapeutic direction. In a prospective study, STOCKLEY *et al.* [15] evaluated the colour of sputum in order to stratify COPD patients during AECBs and to define which patients would benefit from antibiotic treatment. They divided their population into two groups according to sputum colour: mucoid AECB (sputum colour grades 1 and 2) and purulent AECB (colour grades 3–8, *i.e.* yellow to green). They concluded that green purulent sputum was 94% sensitive and 77% specific for high concentrations of bacteria and could be a useful criterion in initiating antibiotic treatment. This study also showed that all patients with mucoid and clear sputum resolved their episode of AECB without antibiotic. The same authors also assessed the potential relationship between the colour of sputum and serum CRP levels in COPD patients during AECBs. Serum CRP level was increased when sputum was purulent, whereas this parameter tended to normalize with sputum clearing. If patients with purulent sputum require antibiotics, the question remains which antibiotic to use and which pathogen to target. Another study suggested that CRP level was a marker of AECB but not necessarily of bacterial infection [68]. However, this study included a low number of COPD patients, bacterial infection was defined on the basis of qualitative bacteriological tests on sputum alone and antibiotic treatment was not standardized.

The mode of treatment of patients with an AECB and, notably, the decision to treat the patient at home or in hospital has important clinical and economic implications. A recent prospective study investigated the feasibility and efficiency of supported discharge with nurse supervision at home [3]. This study suggested that supported discharge allows significant reduction of the length of hospital stay without an increased rate of rehospitalization and contributes to optimizing the use of hospital resources. Nevertheless, this study suffers from several limitations such as the low number of patients studied, exclusion of those with severe AECB, and absence of evaluation of impact on quality of life, compliance with treatment and cost. Moreover, there was no precise definition of AECB or information about chest radiography to exclude pneumonia. Another study illustrated that, in addition to the decision to hospitalize a patient with

Table 5. – Potential indications for antibiotic treatment in acute exacerbations of chronic bronchitis (AECB)

Factors	Observations	[Refs.]
Disease severity stage III ($FEV_1 \leqslant 35\%$ pred)	High prevalence of positive culture for Gram-negative bacteria	[46, 47, 66, 67]
Comorbidity factors including the elderly, cardiac or renal disease, alcoholism, systemic corticotherapy, diabetes	Increased mortality of AECB	[10]
Recent previous course(s) of antibiotic and/or previous hospitalization	Increased risk of β-lactamase-producing bacteria	[46, 66]
Current cigarette smoking	High prevalence of *Haemophilus influenzae*	[34]

FEV_1: forced expiratory volume in one second.

AECB, adequate antibiotic treatment should be prescribed [69]. Thus, in a retrospective study reviewing >100 admissions for AECB, antibiotic treatment was optimal in <50% of cases with overuse of dual therapy. Although limited to one hospital, this study probably reflects the misuse of antibiotics in many other institutions.

Discussion

Several factors such as environmental exposures and viral or bacterial infections have been linked to the acute worsening of COPD patients. What proportion of AECBs are caused by bacterial infection remains largely uncertain and therefore the place of antibiotics is still being debated. This represents a crucial medical and economic problem since the prevalence of COPD around the world is quite high ($\geqslant$800,000 cases in France and >4% of the population in the USA) and continues to rise [70, 71]. Therefore, criteria for determining which COPD patients will clearly benefit from antibiotics during AECBs are urgently needed. Only a few studies devoted to this topic have defined a clear strategy according to evidence-based medicine criteria. Thus, on the basis of one meta-analysis reviewing placebo-controlled randomized antibiotic studies in the treatment of AECBs, recommendations should consider that antibiotic treatment may have a beneficial effect on the outcome particularly in patients with severe AECB. By contrast with other diseases such as community-acquired pneumonia, the major problem with guidelines in AECB is that the pre-existing COPD status varies considerably from one patient to another. The degree of airflow and gas exchange impairment, as well as the presence of comorbidity factors, is likely to influence the outcome of the AECB.

In COPD patients with severe airflow obstruction, current knowledge favours the use of antibiotics, especially when comorbidity factors are present (table 5). However, in this group of patients, studies should be addressed at determining whether hospitalization is required and which type of antibiotic (broad- or narrow-spectrum) should be prescribed. In this context, it is important to consider the increasing frequency of antibiotic resistance in the key pathogens causing exacerbations, and the fact that these organisms are not likely to respond to traditional antibiotic choices. Further studies are needed to document whether there is benefit in the use of newer therapies in patient populations that are complex or likely to contain resistant organisms. However, preliminary data support the concept that certain therapies may be of benefit in certain patients, particularly in prolonging the disease-free interval and preventing hospitalization [72].

It remains unclear whether patients with mild-to-moderate COPD require antibiotics during AECBs. Therefore, in these patients, a large-scale double-blind placebo-controlled study testing first-line antibiotics should be initiated. This study should not only evaluate the clinical and functional outcome (both short- and long-term) but also the benefit in terms of cost, quality of life and socioeconomic aspects. In addition, inflammatory blood and sputum markers, as well as microbiological (including quantitative

Table 6. – Parameters to consider in the design of future studies on antibiotic treatment in acute exacerbations of chronic bronchitis (AECBs)

- Prospective randomized study
- Inclusion of large numbers of COPD patients
- Clear definition of AECB
  - (criteria of ANTHONISEN *et al.* [19]?)
- Consider chronic COPD treatment (corticosteroids, mucolytic agents, bronchodilators, physical therapy)
- Consider delay of prior antibiotic treatment
- Determine subgroups of patients
  - Severity of COPD
  - Severity of AECB
  - Number of exacerbation in the past year
  - Comorbidity factors (cardiovascular or renal diseases, smoking, alcoholism)
- Define parameters
  - Clinical
  - Functional
  - Bacteriological (Gram stain and culture with quantitative analysis)
  - Biological (CRP, leukocytosis, *etc.*)
- Establish short- and long-term evaluation during follow-up
- Use standardized antibiotic treatment
  - (first- and second-line)
- Use standardized additional treatment
- Evaluation of compliance with treatment
- Evaluation of quality-of-life score using questionnaire
- Evaluation of economic impact
  - of both disease and treatment
- Criteria for hospitalization and discharge

COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein.

estimates) parameters, should be included in the evaluation and follow-up. Particular attention should be paid to compliance with treatment, side-effects and emergence of antibiotic resistance.

To conclude, it is obvious that further studies are mandatory to clarify the place of antibiotics in acute exacerbations of chronic bronchitis. Considering the medical and socioeconomic impact of this problem, it is the authors′ hope that a nonprofit organization such as the European Respiratory Society will take on the challenge of designing studies to address the issues listed in table 6 and also provide the physician with appropriate guidelines.

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