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Efficacy and Tolerability of Various Antimicrobial Regimens in the Treatment of Exacerbations of Chronic Bronchitis and Chronic Obstructive Pulmonary Disease in Outpatients

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Abstract

Objective. To compare the efficacy and tolerability of different antibiotics empirically administered for exacerbations of chronic bronchitis and chronic obstructive pulmonary disease (COPD).

Methods. We performed an observational, non-randomized, open-label study including 226 outpatients with exacerbations of chronic bronchitis and mild or moderate COPD, 123 males and 103 females, aged 24 to 81. All patients were followed up for 30 days, with an intermediate visits at 5 and 10 days at which they were asked about the duration of symptoms (increased expectoration, increased dyspnea and/or presence of purulent sputum) and the side-effects of the drug. Five antibiotic regimens were evaluated: amoxicillin/clavulanic acid 875 mg/125 mg twice daily for 10 days, cefuroxime 250 mg twice daily for 10 days, cefixime 400 mg once daily for 10 days, clarithromycin 500 mg twice daily for 10 days, and ciprofloxacin 500 mg twice daily for 10 days.

Results. The clinical success rate, defined as a complete resolution or a return of the symptoms to the baseline severity, in the groups receiving amoxicillin/clavulanic acid, cefuroxime, cefixime, clarithromycin, and ciprofloxacin was 68.9%, 75.0%, 73.5%, 72.7%, and 77.1%, respectively. The mean time to relief of symptoms varied from 6.8 days with amoxicillin/clavulanic acid to 6.1 days with cefuroxime. Relapse within the first month was registered in the group receiving clarithromycin and ciprofloxacin (3.1% and 2.6%, respectively). The prevalence of the adverse events varied from 10.4% with ciprofloxacin, following by 8.9% for amoxicillin/clavulanic acid, 7.5% for cefixime, 6.8% with clarithromycin to 6.1% with cefuroxime.

Conclusion. Our findings suggest high efficacy and safety of all studied regimens in the treatment of exacerbations of chronic bronchitis and COPD.

Introduction

Chronic bronchitis and chronic obstructive pulmonary disease (COPD) are common, costly, and preventable diseases representing one of the principal demands of the public health worldwide. According to the European Lung White Book (1), the prevalence of clinically relevant COPD varies in European countries from 4 to 10% of the adult population. The most important aetiological factor for chronic bronchitis and COPD is active smoking. Results of the recent Finnish study (2) indicate that chronic bronchitis occurs in more than two fifths of smokers, and half of these

cases go on to develop COPD.

The course of chronic bronchitis and COPD can be affected by episodes of acute worsening of respiratory symptoms, increased airway inflammation, and physiological deterioration, known as exacerbations (3). Two types of exacerbations can be distinguished, one bacterial and the other nonbacterial that has therapeutic implications (4). Respiratory infections account for up to 80% of exacerbations, of which bacterial infections are involved in around 50-70% of exacerbations (5). *Haemophilus influenzae* is the most frequent bacterial pathogen associated with exacerbations, followed by *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa*. Atypical bacteria, principally *Mycoplasma pneumoniae* and *Chlamidia pneumoniae*, are implicated in up to 10% of exacerbations. Viral infections, particularly influenza and parainfluenza viruses, rhinovirus and adenovirus, may cause up to 30% of episodes of infectious exacerbations (6, 7). The causes of non-infective exacerbations may be environmental exposures, discontinuation of the regular treatment, and worsening of the comorbid conditions. In around 20% of the cases the cause of exacerbation remains unknown (3).

It has been known for many years that the presence of at least two of the three cardinal symptoms of exacerbation criteria (8): increased sputum, increased dyspnea, and change in the colour of sputum) indicates bacterial aetiology of the exacerbation. It was indicated that the presence of green (purulent) sputum as opposed to white (mucoid) sputum is one of the best and easiest methods of predicting a high bacterial load in respiratory tract secretions and the need for antibiotic therapy (9).

Recent studies demonstrated that patients with chronic bronchitis and COPD experience a mean of two exacerbations per year, of which around 90% are ambulatory treated with antibiotics, and up to 10% require hospital treatment (10). Indications for hospital admission for exacerbation are marked increase in intensity of symptoms, severe background COPD, onset of new physical signs (e.g. cyanosis, peripheral edema), failure of exacerbation to respond to initial medical management, significant co-morbidities, and diagnostic uncertainty (11).

The present study aims to define the clinical course of outpatients with exacerbation of chronic bronchitis or of COPD comparing five different antimicrobial regimens.

Patients and Methods

We performed an observational, non-controlled, open-label study including 226 outpatients with exacerbation of chronic bronchitis and mild or moderate COPD, 123 males and 103 females, aged 24 to 81. The study was carried out between October 2007 and December 2008 at the Institute for Occupational Health of R. Macedonia, Skopje – WHO Collaborating Center and GA^{2}LEN Collaborating Center. The study of the effects of various antimicrobial regimens on the clinical course of exacerbations of chronic bronchitis and COPD carried out by Miravittles et al (12) was used as a model.

Including criterion was the presence of a probable bacterial exacerbation of chronic bronchitis or of mild and moderate COPD. Chronic bronchitis was defined as a productive cough for at least 3 months per year for 2 consecutive years (13). COPD was defined and classified as a mild COPD ($FEV_1/FVC < 0.70$; $FEV_1 > 80\%$ predicted) and moderate COPD ($FEV_1/FVC < 0.70$; $50\% < FEV_1 < 80\%$ predicted) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (11). Diagnosis of the exacerbation was defined by the patient's symptoms, using the criteria described by Anthonisen et al (8). Probable bacterial aetiology was established when the exacerbation was Anthonisen type I (presence of all three cardinal symptoms) or type II (presence of two cardinal symptoms). All patients underwent clinical examination, spirometry, blood gas measurements, ECG, and laboratory analysis. Chest X-ray was performed in a part of the patients by indications.

Patients with exacerbations of severe COPD ($FEV_1/FVC < 0.70$; $30\% < FEV_1 < 50\%$ predicted) or of very severe COPD ($FEV_1/FVC < 0.70$; $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ plus chronic respiratory failure), patients with asthma, cystic fibrosis, malignancy or pneumonia, patients with known hypersensitivity to certain antibiotic, and/or patients who fulfilled criteria for hospitalization were excluded.

After diagnosis of the exacerbation, the antibiotic treatment administered was amoxicillin/clavulonic acid 875 mg/125 mg twice daily for 10 days in 45 patients (19.9%), cefuroxime 250 mg twice daily for 10 days in 49 patients (21.7%), cefixime 400 mg once daily for 10 days in 40 patients (17.7%), clarithromycin 500 mg twice daily for 10 days in 44 patients (19.5%), and ciprofloxacin 500 mg twice daily for 10 days in 48 patients (21.2%). The patients were advised to use short-acting b_2 agonist when needed. Regular treatment of the moderate COPD patients with long-acting bronchodilator, as well as appropriate treatment of the

patients with accompanied diseases, was continued.

All patients were followed up for 30 days, with an intermediate visits at 5 and 10 days at which they were asked about the duration of symptoms and the side-effects of the drug. The course of exacerbation was evaluated as a function of the resolution of the symptoms and the treatment was considered to be successful if cure or clinical improvement was achieved. The cure was defined as complete resolution of the cardinal symptoms, whereas the clinical improvement was defined as return of the symptoms to the baseline severity. In addition, spirometric parameters (FVC, FEV_1, FEV_1/FVC, MEF_{50}, MEF_{25}, and MEF_{25-75}) at the first visit and at the end of the treatment were compared. Relapse rates were registered during a 20 days follow-up period in the patients with remission of the symptoms.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 for Windows. Chi-square test was used for testing difference in the prevalence. Comparison of the mean spirometric values was performed by independent-samples *t*-test. A *P*-value less than 0.05 was considered as statistically significant.

Results

The characteristics of the study subjects is shown Table 1.

Table 1: Characteristics of the study subjects.

Variable	Study subjects (n = 226)
Males	123 (54.4%)
Mean age (years)	45.4 ± 10.8
Mean duration of chronic bronchitis/COPD (years)	10.4 ± 6.3
Type I exacerbation *	98 (43.4%)
Type II exacerbation *	128 (56.6%)
Increase in sputum volume	197 (87.2%)
Increase in dyspnea	167 (73.9%)
Increase in sputum purulence	203 (89.8%)
Active smokers	74 (32.7%)
Pack-years smoked	36 ± 19
Ex-smokers	24 (10.6%)
Passive smokers	63 (27.9%)
Patients with co-morbidities	76 (33.6%)
Arterial hypertension	43 (19.0%)
Peptic ulcer	21 (9.2%)
Diabetes mellitus type 2	14 (6.2%)

Numerical data are expressed as a mean value with standard deviation; the frequencies as a number and percentage of examinees with certain variable.
* Type of exacerbation is defined according to the Anthonisen et al. (8) classification.

The percentage of clinical success (i.e. clinical cure or improve of the symptoms) was similar in the five groups, varying from 68.9% with amoxicillin/clavulonic acid to 77.1% with ciprofloxacin (Figure 1).

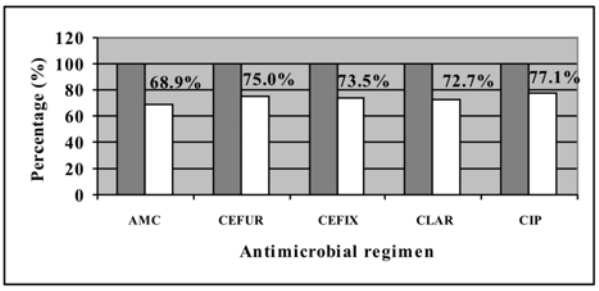

Figure 1: Clinical response to the antibiotic treatment in the five groups. AMC: amoxicillin/clavulonic acid; CEFUR: cefuroxime; CEFIX: cefixime; CLAR: clarithromycin; CIP: ciprofloxacin.

The mean time to complete resolution of the symptoms or its return to the baseline severity was 6.8 days with amoxicillin/clavulonic acid, 6.1 days with cefuroxime, 6.4 days with cefixime, 6.4 days with clarithromycin, and 6.5 days with ciprofloxacin. The difference in the mean time to relief of symptoms between the five groups was statistically non-significant (Figure 2).

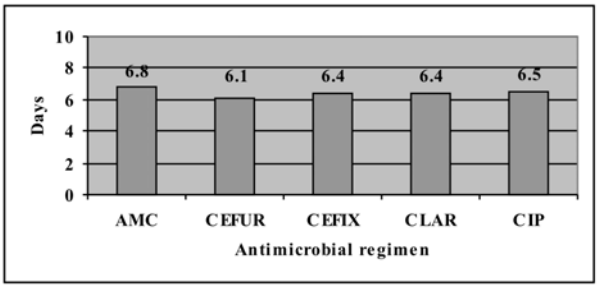

Figure 2: Mean time to relief of the symptoms in the five groups. AMC: amoxicillin/clavulonic acid; CEFUR: cefuroxime; CEFIX: cefixime; CLAR: clarithromycin; CIP: ciprofloxacin.

Similar results were observed on comparison of the time to resolution or to return to the baseline severity of the certain symptoms in the different treatment groups (Table 2).

Table 2: Days to resolution or to return to the baseline severity of the certain symptoms.

Antibiotic regimen	Increased expectoration (days)	Purulence of Expectoration (days)	Increased dyspnea (days)
Amoxicillin/clavulonic acid	5.2±2.5	4.4±2.2	5.6±2.6
Cefuroxime	4.7±2.4	4.2±1.9	5.0±2.4
Cefixime	4.9±2.1	4.2±2.3	5.2±2.5
Clarithromucin	5.0±2.7	4.5±2.4	5.3±2.6
Ciprofloxacin	4.6±2.4	4.1±2.4	5.2±2.7

Data are expressed as a mean value with standard deviation.

The values of spirometric parameters at the end of the treatment improved in all groups. Statistical

difference of the pre- and post-treatment FEV_1 value was observed in the group receiving cefuroxime, clarithromycin, and ciprofloxacin, whereas in the groups with amoxicillin/clavulonic acid and with cefixime the difference just missed statistical significance (Table 3).

Table 3: Comparison of the mean FEV1 value at the first visit and at the end of the treatment in the five groups.

Antibiotic regimen	Pre-treatment FEV_1 (% pred)	Post-treatment FEV_1 (% pred)	Significance*
Amoxicillin/clavulonic acid	73.4	76.1	$P > 0.05$ ($P = 0.09$)
Cefuroxime	71.6	77.2	$P < 0.05$
Cefixime	72.3	75.1	$P > 0.05$ ($P = 0.07$)
Clarithromycin	71.8	76.4	$P < 0.05$
Ciprofloxacin	70.9	76.6	$P < 0.05$

FEV_1: forced expiratory volume in 1 second; % pred: % of predicted value.
*Compared by independent-samples *t*-test.

Relapse during a 20 days follow-up period in the patients with remission of the symptoms was registered in the group receiving clarithromycin and ciprofloxacin (3.1% and 2.6%, respectively). In the other treatment groups there was not any case with relapse of the exacerbation in the follow-up period.

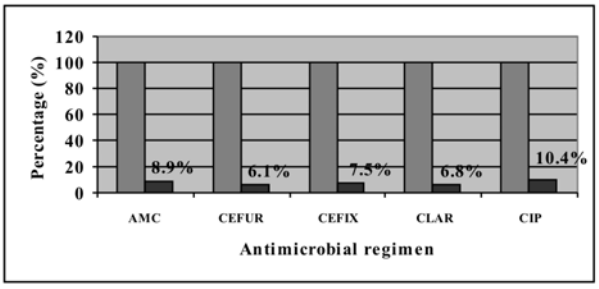

Figure 3: Prevalence of the side-effects during the treatment in the five groups. AMC: amoxicillin/clavulonic acid; CEFUR: cefuroxime; CEFIX: cefixime; CLAR: clarithromycin; CIP: ciprofloxacin.

The prevalence of the adverse events during the treatment varied from 10.4% with ciprofloxacin to 6.1% with cefuroxime with no statistical difference between the groups (Figure 3).

In any group there was not serious side-effect that required discontinuation of the treatment.

Table 4: The most frequent side-effects during the treatment in the five groups.

Antibiotic regimen	Gastrointestinal manifestations (%)	Headache (%)	Dizziness (%)	Pruritus (%)
Amoxicillin/clavulonic acid	8.9	/	2.2	4.4
Cefuroxime	6.1	2.0	/	/
Cefixime	5.0	5.0	/	2.5
Clarithromucin	4.6	6.8	/	/
Ciprofloxacin	10.4	2.1	6.2	2.1

Data are expressed as a percentage of patients with certain adverse event.

Gastrointestinal manifestations (nausea, vomiting, epigastric pain, diarrhoea), headache, dizziness, and pruritus were the most frequent adverse events (Table 4).

Discussion

Chronic bronchitis and COPD represent a major economic burden for all European countries, as well as a major threat to the quality of life of individuals. The total of COPD-related expenses for outpatients care in the European Union countries is € 4.7 billion per year (14). Exacerbations of chronic bronchitis and COPD are of major importance of their prolonged detrimental effects on patients, the acceleration in disease progression and high healthcare costs. There is still debate about how exacerbations should be defined and graded, and their mechanisms are not well understood. The routine treatment of exacerbations with antibiotics remains controversial but there is no doubt that antibiotics are of benefit with exacerbations of a bacterial origin (15).

In the present study we compared the efficacy and tolerability of different antibiotics empirically administered for exacerbations of chronic bronchitis and COPD. The choice of the antimicrobial regimens was done in accordance to the actual recommendations (15-18).

The diagnosis of exacerbation was based on the presence of clinical symptoms and lung function measurements without microbiological evaluation of the sputum. The role of sputum evaluation in determining the aetiology of exacerbation is questionable because the airways and upper respiratory tract of patients with chronic bronchitis and COPD are chronically colonized with bacteria, and thus, the finding of a particular organism does not necessarily imply a causal relationship to the exacerbation (4). On the other side, a positive sputum culture by standard techniques occurs in approximately 50% of patients with exacerbation because saliva is often cultured instead of the secretions produced in the bronchial tree (19). According to the actual recommendations, sputum analysis should be reserved for patients with frequent exacerbations and for chronic purulent sputum in whom the presence of more virulent and/or more resistant bacteria is likely (4, 9).

Examined subjects were divided in five groups balanced in all their demographic, clinical, and functional characteristics, as well as in the severity of the exacerbations. We found a large proportion of active and passive smokers among examined subjects that

was similar to its prevalence in adults documented in our previous studies (20). We also found a low prevalence of ex-smokers that suggested insufficient smoking cessation activities taking into account that active smoking is the major risk factor for chronic bronchitis and COPD.

There is a number of regional/national guidelines for the management of exacerbations of chronic bronchitis and COPD due to the considerable national, regional, and local variations in the resistance of the respiratory pathogens. For example, prevalence rates of beta-lactamase production of up to 40% for penicillin-resistant *Streptococcus pneumoniae* have been reported in Spain and in the USA, and 58% in the Hungary, although in other countries, such as Germany and the UK, the prevalence rates are less than 5% (21, 22, 23). Second-generation macrolides are considered to be the first-line treatment by Canadian and British Guidelines (17, 18), whereas the Spanish authors (24) observed low efficacy of these agents due to the high rates of resistance (up to 35%) shown by *Haemophilus influenzae.* On the other hand, many studies indicated an increasing prevalence of resistance of the respiratory pathogens to the older antibiotics (e.g. ampicillin, erythromycin, trimethoprime/sulfamethoxasole, tetracycline) with a general suggestion that they should not be more used in the treatment of exacerbations of chronic bronchitis and COPD (25). Results from the present study indicated high clinical success rate and time-course of the recovery that did not differ significantly between examined treatment options. Similar effects of amoxicillin/clavulonic acid, cefuroxime, and clarithromycin were reported by the MOSAIC study (26) and the IMPAC study (27). Both studies indicated similar clinical cure rate but significantly shorter mean time to relief of symptoms in the subjects with exacerbations of chronic bronchitis/COPD treated with moxifloxacin (a new fluoroquinolone still not registered in R. Macedonia) as compared to the treatment with amoxicillin, cefuroxime, and clarithromycin (the MOSAIC study) or with amoxicillin/clavulonic acid, cefuroxime, clarithromycin, and azithromicin (the IMPAC study). In the present study the proportion of the subjects with adverse events was low in all treatment groups similarly to the results of studies reviewed (28, 29).

The present study had some limitations. The results should be viewed with caution, since the study was neither blinded nor randomised and, it is, therefore, subject to possible selection bias in favour of one treatment or another. On the other hand, relatively small number of the subjects in the different treatment groups could have certain implications on the data obtained and its interpretation. Relapses between days 10 and 30 appeared to be very infrequent due to the short time of observation.

In conclusion, in an observational, non-randomised, open-label study of efficacy and tolerability of different antibiotic options (amoxicillin/clavulonic acid, cefuroxime, cefixime, clarithromycin, and ciprofloxacin) in the treatment of exacerbations of chronic bronchitis and COPD we found high clinical success rate, as well as similar time to relieve the symptoms of all regimens studied. Low incidence of adverse events indicated high safety of all treatment options. Our findings suggest that each of the examined options should be considered as a first choice antibiotic in the treatment of exacerbations of chronic bronchitis and COPD in outpatients.

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