

Efficacy and Tolerability of Eight Antimicrobial Regimens in the Outpatient Treatment of Exacerbations of Chronic Obstructive Pulmonary Disease

Jordan Minov^{1*}, Jovanka Karadzinska-Bislimovska¹, Tatjana Petrova², Kristin Vasilevska³, Sasho Stoleski¹, Dragan Mijakoski¹, Snezhana Risteska-Kuc¹

¹*Institute for Occupational Health of Republic of Macedonia – WHO Collaborating Center and GA2LEN Collaborating Center, Skopje, Republic of Macedonia;* ²*Department of Pharmacy Practice, Chicago State University, Chicago, IL, USA;* ³*Institute for Epidemiology and Biostatistics, Skopje, Republic of Macedonia*

Abstract

Citation: Minov J, Karadzinska-Bislimovska J, Petrova T, Vasilevska K, Stoleski S, Mijakoski D, Risteska-Kuc S. Efficacy and Tolerability of Eight Antimicrobial Regimens in the Outpatient Treatment of Exacerbations of Chronic Obstructive Pulmonary Disease. *OA Maced J Med Sci*. 2014 Sep 15; 2(3):519-524. <http://dx.doi.org/10.3889/oamjms.2014.093>

Key words: adverse effect; antibiotic; chronic obstructive pulmonary disease; clinical success; exacerbation.

Correspondence: Jordan B. Minov, MD PhD. Department of Cardiorespiratory Functional Diagnostics, Institute for Occupational Health of R. Macedonia – WHO Collaborating Center and GA2LEN Collaborating Center, II Makedonska Brigada 43, 1000 Skopje, Republic of Macedonia. Tel: + 389 2 2639 637, Fax: + 389 2 2621 428. E-mail: minovj@hotmail.com

Received: 24-Jun-2014; **Revised:** 15-Jul-2014; **Accepted:** 16-Jul-2014; **Online first:** 25-Jul-2014

Copyright: © 2014 Minov et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Competing Interests: The authors have declared that no competing interests exist.

BACKGROUND: Bacterial infections are considered as the most important cause of exacerbations in patients with chronic obstructive pulmonary disease.

AIM: To compare the efficacy and tolerability of eight antibiotics empirically administered for outpatient treatment of exacerbations of COPD.

METHODS: We performed an observational study including 343 COPD patients with probable bacterial exacerbation (Group A and Group B COPD patients) managed in an outpatient setting. Eight antibiotic regimens each used 10 days were evaluated: amoxicillin/clavulonic acid, doxycycline, cefuroxime, cefixime, clarithromycin, roxithromycin, ciprofloxacin, and moxifloxacin. All patients were followed up for 30 days, with an intermediate visits at 5, 7 and 10 days at which the duration of symptoms and the side-effects of the drug were evaluated.

RESULTS: The clinical success rate varied from 69.8% with doxycycline to 80.9% with moxifloxacin. The mean time to relief of symptoms varied from 5.6 days with moxifloxacin to 6.3 days with amoxicillin/clavulonic acid. Significant increase of the post-treatment FEV₁ value was registered in all treatment groups. Relapse within the first 20 days was registered in the group receiving doxycycline, clarithromycin, and ciprofloxacin. The prevalence of the adverse events was low varying from 6.7% with cefuroxime to 11.3% with ciprofloxacin.

CONCLUSION: Our findings suggest high clinical success rate and high safety of all studied regimens.

Introduction

Chronic obstructive pulmonary disease (COPD) remains frequent and costly disease representing one of the principal demands of the public health worldwide. Inhaled tobacco smoke and other noxious particles, such as occupational exposures and smoke from biomass fuels, are the most important exogenous factors that influence disease development and progression [1].

The course of COPD can be affected by acute events characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medications, known as exacerbations [1]. These acute episodes, also characterized by increased airway inflammation and physiological deterioration, contribute greatly to the morbidity, the disease progression, and to the overall diminished quality of life in the subjects with COPD [2]. Respiratory infections, environmental and

occupational exposures, discontinuation of the regular treatment, and worsening of the comorbid conditions are considered as causes of exacerbations, but in up to 20% of the cases the cause of exacerbation remains unknown [2, 3].

Respiratory infections account for up to 80% of exacerbations, of which bacterial infections are involved in around 50-70% of exacerbations [4]. Although the role of bacterial infection in acute exacerbations of COPD has been debated for many years, the investigations with newer research techniques (bronchoscopic, bacteriologic, and serologic studies) bolster the arguments that bacteria do cause exacerbations [5, 6]. Respiratory infections account for up to 80% of exacerbations, of which bacterial infections are involved in around 50-70% of exacerbations [4]. The predominant bacteria recovered from the lower airways in patients with chronic bronchitis (CB) and COPD exacerbations are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Atypical bacteria, e. g. *Mycoplasma pneumoniae* and *Chlamidia pneumoniae*, are implicated in up to 10% of exacerbations, whereas viral infections, e. g. influenza and parainfluenza viruses, rhinovirus and adenovirus, cause up to 30% of episodes of infectious exacerbations [7, 8]. On the other hand, studies in patients with COPD exacerbations have showed that the severity of the disease may be an important determinant of the type of microorganism. Namely, in mild exacerbations *Streptococcus pneumoniae* is predominant and as forced expiratory volume in one second (FEV₁) declines *Haemophilus influenzae*, and *Moraxella catarrhalis* become more frequent, whereas *Pseudomonas aeruginosa* and other enteric bacteria usual appear in patients with severe airway inflammation. The diagnosis of an exacerbation relies exclusively on the clinical presentation of the patient complaining of an acute change of symptoms (baseline dyspnea, cough, and/or sputum production) that is beyond normal day-to-day variation [1].

The criteria of Anthonisen [9] are still the most important classification system to identify patients likely to be infected with bacterial pathogens based on presentation of clinical symptoms [10, 11]. A type I exacerbation was defined as a patient presenting with increased dyspnea, sputum volume and purulence. A type II exacerbation referred to a patient with two of these symptoms, while a type III exacerbation occurred when a patient had only one symptom with evidence of fever or upper airways infection.

According to the actual version of Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) [1], antibiotics should be given to patients with type I exacerbation (Evidence B); with type II exacerbation, if increased purulence of sputum is one of the two symptoms (Evidence C); as well as in patients who require mechanical ventilation (invasive or noninvasive) (Evidence B). The recommended length of antibiotic therapy is usually 5-10 days

(Evidence D).

The goals of treatment for COPD exacerbations are to minimize the impact of the current exacerbation, as well as to prevent the development of subsequent exacerbation. Depending on the severity of an exacerbation and/or the severity of the underlying disease, an exacerbation can be managed in an outpatient or inpatient setting. More than 80% of exacerbations can be ambulatory treated with antibiotics. Potential indications for hospital management of the exacerbation include marked increase in symptoms intensity (e.g., sudden development of resting dyspnea), severe underlying COPD, onset of new physical signs (e.g., cyanosis, peripheral oedema), failure to respond to initial medical management, presence of serious comorbidities (e.g., heart failure, newly occurring arrhythmias), etc [1, 12].

The present study aims to evaluate efficacy and safety of eight antibiotic regimens in the outpatient treatment of probable bacterial exacerbations in the COPD patients.

Material and Methods

An observational study including 343 outpatients classified as Group A and Group B COPD patients with an exacerbation of probably bacterial etiology, 192 males and 151 females, aged 35 to 78 years. All participants were informed about the study and their written consent was obtained.

The study was carried out in the period December 2012 – March 2013 at the Institute for Occupational Health of R. Macedonia, Skopje – WHO Collaborating Center and GA²LEN Collaborating Center. The study of the effects of various antimicrobial regimens on the clinical course of exacerbations of CB and COPD carried out by Miravittles et al [13] was used as a model.

Including criterion was the presence of a probable bacterial exacerbation in Group A and Group B COPD patients according to the combined COPD assessment [1], i.e. in patients with mild or moderate COPD according to the GOLD 2010 classification [14], which can be managed on outpatient basis. Diagnosis of the exacerbation was defined by the patient's symptoms, using the criteria described by Anthonisen et al. [9]. Probable bacterial etiology was established when the exacerbation was Anthonisen type I or type II if increased purulence of sputum was one of the two 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.

Excluding criterions were bacterial exacerbations in Group C and Group D COPD patients, patients with exacerbation type III or type II if increased purulence of sputum was not one of the two

symptoms, patients with asthma, cystic fibrosis, malignancy or pneumonia, patients with known hypersensitivity to certain antibiotic and/or patients who fulfilled criteria for hospitalization.

After the diagnosis was established, the exacerbations were managed with antibiotics. Eight antibiotic regimens each used 10 days were evaluated: amoxicillin/clavulonic acid 875 mg/125 mg twice daily in 42 patients (12.2%), doxycycline 100 mg twice daily initially, then once daily in 43 patients (12.5%), cefuroxime 250 mg twice daily in 44 patients (12.8%), cefixime 400 mg once daily in 43 patients (12.5%), clarithromycin 500 mg twice daily in 42 patients (12.2%), roxithromycin 150 mg twice daily in 43 patients (12.5%), ciprofloxacin 500 mg twice daily in 44 patients (12.8%), and moxifloxacin 400 mg once daily in 42 patients (12.2%). Each antibiotic regimen was administered to the next patient who met including criterion in the mentioned cyclic order if there was no contraindication (i.e. known hypersensitivity) for its use. The patients were advised to continue the regular treatment of stable COPD, as well as to use short-acting bronchodilators when needed.

All patients were followed up for 30 days, with an intermediate visits at 5, 7 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, FEV₁, FEV₁/FVC, MEF₂₅, MEF₅₀, MEF₇₅, and MEF₂₅₋₇₅) 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 time to relief of the symptoms and of the mean FEV₁ 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.

The percentage of clinical success (i.e. clinical cure or resolution of the symptoms) was similar in the eight groups, varying from 69.8% with doxycycline to 80.9% with moxifloxacin (Figure 1).

Table 1: Characteristics of the study subjects.

Variable	Study subjects (n = 343)
Males	192 (55.9%)
Mean age (years)	48.7 ± 10.4
Mean duration of COPD (years)	10.9 ± 5.7
Patients Group A*	147 (42.9%)
Patients Group B*	196 (57.1%)
Type I exacerbation **	157 (45.8%)
Type II exacerbation **	186 (54.2%)
Increase in dyspnea	262 (76.4%)
Increase in sputum volume	239 (69.7%)
Increase in sputum purulence	297 (86.6%)
Current smokers	79 (23.0%)
Pack-years smoked	12.9 ± 5.8
Ex-smokers	108 (31.5%)
Passive smokers	84 (24.4%)

Numerical data are expressed as a mean value with standard deviation; the frequencies as a number and percentage of examinees with certain variable. COPD: chronic obstructive pulmonary disease. * Patients are classified following combined COPD assessment according to the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) updated 2011 [1]. ** Type of exacerbation is defined according to the Anthonisen et al. [9] classification.

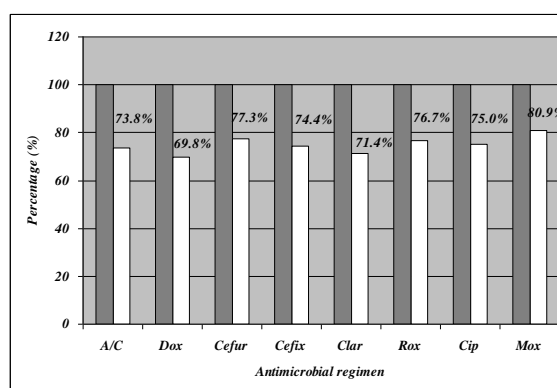


Figure 1: Clinical response to the antibiotic treatment in the eight groups. A/C: amoxicillin/clavulonic acid; Dox: doxycycline; Cefur: cefuroxime; Cefix: cefixime; Clar: clarithromycin; Rox: roxithromycin; Cip: ciprofloxacin; Mox: moxifloxacin.

The mean time to complete resolution of the symptoms or its return to the baseline severity varied from 6.2 days with amoxicillin/clavulonic acid to 5.7 days with moxifloxacin. The difference in the mean time to relief of symptoms between the eight groups was statistically non-significant (Figure 2).

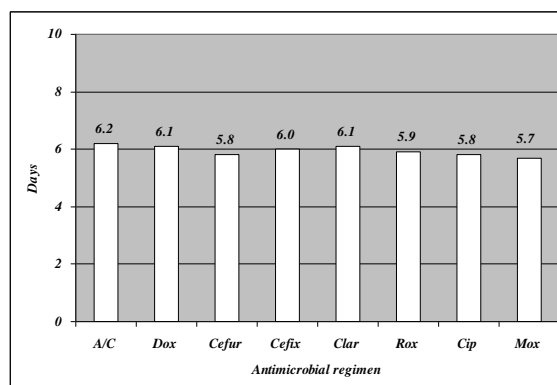


Figure 2: Mean time to relief of the symptoms in the eight groups. A/C: amoxicillin/clavulonic acid; Dox: doxycycline; Cefur: cefuroxime; Cefix: cefixime; Clar: clarithromycin; Rox: roxithromycin; Cip: ciprofloxacin; Mox: moxifloxacin.

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

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

Antimicrobial regimen	Increased dyspnea (days)	Increased expectoration (days)	Purulence of expectoration (days)
Amoxicillin/clavulonic acid	5.3 ± 1.1	5.1 ± 1.2	4.4 ± 1.6
Doxycycline	5.0 ± 1.4	4.8 ± 1.6	4.5 ± 1.7
Cefuroxime	5.0 ± 0.7	4.7 ± 1.4	4.3 ± 1.1
Cefixime	5.2 ± 1.5	4.7 ± 2.0	4.2 ± 1.3
Clarithromycin	5.0 ± 1.4	4.8 ± 1.7	4.4 ± 1.4
Roxithromycin	4.9 ± 1.8	4.7 ± 1.1	4.3 ± 1.5
Ciprofloxacin	4.8 ± 1.7	4.6 ± 1.1	4.1 ± 1.6
Moxifloxacin	4.8 ± 1.1	4.5 ± 1.4	4.1 ± 1.2

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 FEV₁ value was observed in all treatment groups (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)	P-value
Amoxicillin/clavulonic acid	62.3 ± 5.8	67.1 ± 7.4	.041
Doxycycline	60.9 ± 4.7	68.1 ± 5.8	.037
Cefuroxime	61.8 ± 5.9	67.2 ± 4.7	.043
Cefixime	59.4 ± 6.3	66.1 ± 4.9	.039
Clarithromycin	61.2 ± 5.0	67.8 ± 5.1	.046
Roxithromycin	58.3 ± 7.1	68.2 ± 4.3	.026
Ciprofloxacin	60.2 ± 5.6	66.6 ± 6.9	.035
Moxifloxacin	58.9 ± 6.8	67.1 ± 5.7	.029

FEV₁: forced expiratory volume in 1 second; % pred: % of predicted value.

Relapse during a 20 days follow-up period in the patients with remission of the symptoms was registered in the group receiving doxycycline, clarithromycin, and ciprofloxacin (2.3%, 2.4%, and 2.2%, respectively). In the other treatment groups there was not any case with relapse of the exacerbation in the follow-up period.

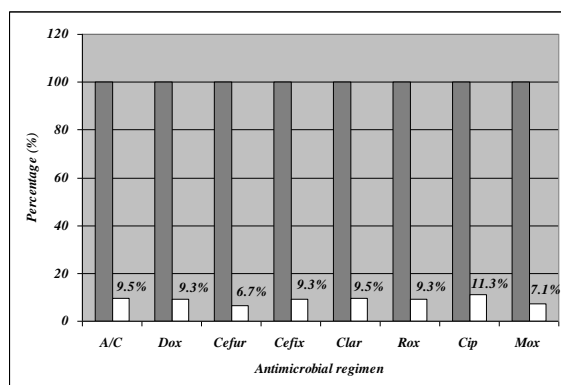


Figure 3: Prevalence of the side-effects during the treatment in the eight groups. A/C: amoxicillin/clavulonic acid; Dox: doxycycline; Cefur: cefuroxime; Cefix: cefixime; Clar: clarithromycin; Rox: roxithromycin; Cip: ciprofloxacin; Mox: moxifloxacin.

The prevalence of the adverse events during the treatment varied from 6.7% with cefuroxime to

11.3% with ciprofloxacin with no statistical difference between the groups (Figure 3).

In any group there was not serious adverse effect that required discontinuation of the treatment. Gastrointestinal manifestations (nausea, vomiting, epigastric pain, and diarrhoea), followed by headache and dizziness were the most frequent adverse events (Table 4).

Table 4: The most frequent adverse effects during the treatment in the eight groups.

Antibiotic regimen	Gastrointestinal manifestations (%)	Headache (%)	Dizziness (%)
Amoxicillin/clavulonic acid	9.5	4.7	/
Doxycycline	9.3	2.3	2.3
Cefuroxime	4.5	2.2	/
Cefixime	4.6	/	2.3
Clarithromycin	9.5	/	/
Roxithromycin	9.3	/	2.3
Ciprofloxacin	11.3	2.2	2.2
Moxifloxacin	7.1	4.7	/

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

Discussion

Exacerbations of COPD have serious negative impact on patient quality of life, lung function, and socioeconomic costs so their prevention, early detection, and prompt treatment have a great importance in the management of the disease. The total of COPD-related expenses for outpatients care in the European Union countries is € 4.7 billion per year [15]. 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 [16].

In the present study we compared the efficacy and tolerability of eight antibiotic regimens empirically administered for outpatient treatment of exacerbations of Group A and Group B COPD patients. The choice of the antimicrobial regimens was done in accordance to the actual recommendations [1, 14, 17]. The diagnosis of exacerbation was based on the presence of clinical symptoms and lung function measurements without microbiological evaluation of the sputum. 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 [3, 18].

Examined subjects were divided in eight 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 [19, 20].

The regional pattern of resistance to

respiratory pathogens has a great impact on the choice of appropriate antibiotic regimen for treatment of acute exacerbations of COPD. 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% [5, 21, 22]. Second-generation macrolides are considered to be the first-line treatment by Canadian Guidelines [23], 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, actual guidelines [14, 25] recommend use of some older antibiotics (e.g. trimethoprim/ sulfamethoxazole and tetracycline) for which ten years ago by some authors [26] has been suggested not to be used in the treatment of exacerbations of chronic bronchitis and COPD. 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 results were obtained in our previous study on efficacy and safety of five antimicrobial regimens (amoxicillin/clavulonic acid, cefuroxime, cefixime, clarithromycin, and ciprofloxacin) in the outpatient treatment of exacerbations of CB and COPD [27]. Similar effects of amoxicillin/clavulonic acid, cefuroxime, clarithromycin, and moxifloxacin were reported by the MOSAIC study [28], the IMPAC study [29], and the MAESTRAL study [30]. Similar results were also reported by Siempos et al. [31] in the meta-analysis of effectiveness of amoxicillin/clavulonate, macrolides, and quinolones in the treatment of acute exacerbations of CB. In the present study we found low proportion of the subjects with adverse events in all treatment groups similarly to the results of studies reviewed [32-34].

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 favor 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. The strength of the study is the number of antibiotic regimens studied, as well as the studying of only exacerbated subjects with COPD, not exacerbated subjects with both CB and COPD.

In conclusion, in an observational study of efficacy and tolerability of eight antibiotic regimens (amoxicillin/clavulonic acid, doxycycline, cefuroxime, cefixime, clarithromycin, roxithromycin, ciprofloxacin, and moxifloxacin) in the outpatient treatment of the exacerbations in Group A and Group B COPD patients 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 tolerability of all treatment options. Our findings suggest that each of the examined options should be considered as a first choice antibiotic in the outpatient treatment of the exacerbations in Group A and Group B COPD patients.

Ethical Approval

The Ethical Committee of the Institute of Occupational Health of Republic of Macedonia, Skopje – WHO Collaborating Center and GA²LEN Collaborating Center gave approval for performing the study and publishing the results obtained (03-133/2-03.2013).

Authors Participations

JM participated in the study design, writing the protocol, data collection, managing the analyses of the study, and writing all versions of the manuscript. JKB participated in the study design, writing the protocol, managing the analyses of the study, as well as writing all versions of the manuscript. TP managed the literature searches and participated in the managing the analyses of the study. KV performed the statistical analysis and participated in the managing of the analyses of the study. SS, DM and SRK participated in the data collection. All authors read and approved the final manuscript.

References

1. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2011 Update. Available at: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf (30.10.2012).
2. Bhowmik A, Seemungal TA, Sapsford RJ, Wedzicha JA. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax*. 2000; 55: 114-120.
3. Miravittles M, Niederman M. Lectures in Respiratory Tract Infections: Acute Exacerbations of Chronic Bronchitis. London: Science Press Ltd, 2004: p. 7-8.
4. Ball P, Chodosh S, Grossman R, Tillotson G, Wilson R. Causes, epidemiology, and treatment of bronchial infections. *Infect Med*. 2000; 17: 186-198.
5. Sethi S, Evans N, Grant BJB, Murphy TF. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 2002; 347: 465-471.
6. Sethi S, Wrona C, Grant BJB, Murphy TF. Strain specific immune response to *Haemophilus influenzae* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2004; 169: 448-453.
7. Miravittles M. Epidemiology of chronic obstructive pulmonary disease exacerbations. *Clin Pulm Med*. 2002; 9: 191-197.
8. Ball P. Epidemiology and treatment of chronic bronchitis and its exacerbations. *Chest*. 1995; 108: 43S-52S.
9. Anthonisen NR, Menfreda J, Warren CP, Herschfield EG,

- Harding HK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med.* 1987; 106 (2): 196-204.
10. Woodhead M, Blasi F, Ewig S, Huchon G, Leven M, Orqvist A, Schaberg T, Torres A, van der Heijden G, Verheij TJM. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J.* 2005; 26: 1138-1180.
 11. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J.* 2004; 23 (6): 932-946.
 12. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, Bruce M, Lomas DA, Agusti A, MacNee W, Calverley P, Rennard S, Wouters EFM, Wedzicha JA for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med.* 2010; 363: 1128-1138.
 13. Miravittles M, Llor C, Naberan K, Cots JM, Molina J. Effect of various antimicrobial regimens on the clinical course of exacerbations of chronic bronchitis and chronic obstructive pulmonary disease in primary care. *Clin Drug Invest.* 2004; 24 (2): 63-72.
 14. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2010 Update. Available at: <http://www.goldcopd.org/Guidelines/guideline-2010-gold-report.html> (30.10.2012).
 15. Andersson F, Borg S, Jansson S-A, Jonsson AC, Ericsson A, Prütz C, Rönmark E, Lundbäck B. The costs of exacerbations in chronic obstructive pulmonary disease (COPD). *Respir Med.* 2002; 96: 700-708.
 16. Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. *Eur Respir J.* 2007; 29: 1224-1238.
 17. Balter MS, La Forge J, Low D, Mandell L, Grossman RF. Canadian guidelines for the management of acute exacerbations of chronic bronchitis. *Can Respir J.* 2003; 10: 3B-32B.
 18. 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: 1638-1645.
 19. Minov J, Karadzinska-Bislimovska J, Vasilevska K, Stoleski S. Smoking status in exposed and unexposed workers. *Mak Med Pregled.* 2006;60 (68):128.
 20. Minov J, Karadzinska-Bislimovska J, Vasilevska K, Risteska-Kuc S, Stoleski S. Exposure to environmental tobacco smoke in the workplace in Macedonia: Where are we now? *Arh Hig Rada Toksikol.* 2008; 59: 103-109.
 21. Pérez-Trallero E, Fernández-Mazarrasa C, García-Rey C, Bouza E, Aguilar L, García-de-Lomas J, Baquero F; Spanish Surveillance Group for Respiratory Pathogens. Antimicrobial susceptibilities of 1,684 *Streptococcus pneumoniae* and 2,039 *Streptococcus pyogenes* isolates and their ecological relationships: results of a 1-year (1998-1999) multicenter surveillance study in Spain; Spanish Surveillance Group for Respiratory Pathogens. *Antimicrob Agents Chemoter.* 2001; 45: 3334-3340.
 22. Doern GV, Pfaller MA, Kugler K, Freeman J, Jones RN. Prevalence of the antimicrobial resistance among respiratory tract isolates of in North America: 1997 results from the SENTRY Antimicrobial Surveillance Program. *Clin Inf Dis.* 1998; 27: 764-770.
 23. Snow V, Lascher S, Mottur-Pilson C. Evidence base for management of acute exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med.* 2001; 134: 595-599.
 24. Garcia JA, Baquero F, Garcia de Lomas J, Aguilar L. Antimicrobial susceptibility of 1,422 *Haemophilus influenzae* isolates from respiratory tract infections in Spain: results of a 1-year (1996-1997) multicenter surveillance study in Spain; Spanish Surveillance Group for Respiratory Pathogens. *Infection.* 1999; 27: 265-267.
 25. Hunter MH, King DE. COPD: Management of acute exacerbations and chronic stable disease. *Am Fam Physician.* 2001; 64 (4): 603-613.
 26. Blondeau JM, Tillotson GS. Antimicrobial susceptibility patterns of respiratory pathogens - a global perspective. *Semin Respir Infect.* 2000; 15: 195-207.
 27. Minov J, Karadzinska-Bislimovska J, Petrova T, Vasilevska K, Risteska-Kuc S, Stoleski S, Mijakoski D. Efficacy and tolerability of various antimicrobial regimens in the treatment of exacerbations of chronic bronchitis and chronic obstructive pulmonary disease in outpatients. *Maced J Med Sci.* 2009; 2(2): 115-120.
 28. Wilson R, Allegra L, Huchon G, Izquierdo JL, Jones P, Schaberg T, Sagnier PP; MOSAIC Study Group. Short-term and long-term outcomes of moxifloxacin compared to standard antibiotic therapy for the treatment of acute exacerbations of chronic bronchitis. *Chest.* 2004; 125: 953-964.
 29. Miravittles M, Zalacain R, Murio C, Ferrer M, Alvarez-Sala JL, Masa JF, Vereá H, Ros F, Vidal R; on behalf of the IMPAC Study Group. Speed of recovery from acute exacerbations of chronic obstructive pulmonary disease after treatment with antimicrobials: a results of a two-years study. *IMPAC Study Group. Clin Drug Invest.* 2003; 23: 439-450.
 30. Wilson R, Anzueto A, Miravittles M, Arvis P, Alder J, Haverstock D, Trajanovic M, Sethi S. Moxifloxacin versus amoxicillin/clavulanic acid in outpatient acute exacerbations of COPD: MAESTRAL results. *Eur Respir J.* 2012;40(1):17-27.
 31. Siempos II, Dimopoulos G, Korbila JP, Manta K, Falagas ME. Macrolides, quinolones and amoxicillin/clavulonate for chronic bronchitis: meta-analysis. *Eur Respir J.* 2007; 29 (6): 1127-1137.
 32. Perry CM, Brogden RN. Cefuroxime Axetil. A review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs.* 1996; 52 (1): 125-156.
 33. Destache CJ, Dewan N, O'Donohue WJ, Campbell JC, Anquillo VA. Clinical and economic considerations in the treatment of acute exacerbations of chronic bronchitis. *J Antimicrob Chemoth.* 1999; 43: 107-113.
 34. Sethi S. Moxifloxacin for the treatment of acute exacerbations of chronic obstructive pulmonary disease. *Clin Infect Dis.* 2004; 39 (7): 987-989.