Efficacy and Safety of Azithromycine Versus Amoxilline/Clavulanate in Treatment of Acute Exacerbation of Chronic Bronchitis

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Abstract

This study has been done to compare the efficacy, safety, and tolerability of azithromycin and amoxicillin-clavulanate in the treatment of patients with infectious exacerbation of chronic bronchitis(AECB).This study was conducted at Al-Diwaniya Teaching Hospital and included 108 patients from 32 to 80 years of age. Those patients were randomized to receive either azithromycin (500 mg/day for three days, n = 56) or amoxicillin-clavulanate (625 mg two tablets twice daily for seven days, n = 52). The patients were evaluated at the study outset, on day 3-5, on day 7 and at long-term follow-up, day 28 . Based on the clinical evaluation of the signs and symptoms there were no differences between the groups treated with azithromycin or amoxicillin-clavulanate in terms of the percentages of cases in which the outcomes were classified as cure or improvement: 75% vs. 73.2% (p = >0.05) on day ten seven. The results of the present study confirm the efficacy and tolerability of azithromycin for the outpatient treatment of episodes of infectious exacerbation of COPD. In this context, it can be expected that the treatment with azithromycin will promote cure or clinical improvement in most patients, with acceptable toxicity and costs with no significant difference to the amoxicillin-clavulanate.

الخلاصة

هذه الدراسة تمت لمقارنة فعالية العقار(azithromycine) مقارنة بالعقار (amoxillin-clavulanate) من ناحية الكفاءة و التحمل في علاج المرضى المصابين بالنوبات الحادة لالتهاب القصبات المزمن في مستشفى الديوانية التعليمي وقد شملت ١٠٨ مريضا من المرضى المصابين بالنوبات الحادة لالتهاب القصبات المزمن الذين تتراوح أعمارهم مابين ٣٢ و ٨٠ سنة ،كان ٥٦ مريضا ضمن المجموعة الأولى وأعطيت لهم المضاد (azithromycine)، و ٥٢ مريضا في المجموعة الثانية وأعطى لهم المضاد (clavulanate–amoxilline). المرضى الذين شملتهم الدراسة تم تقيمهم سريريا ومختبريا في بداية الدراسة وفي اليوم الثالث وعند نهاية العلاج في اليوم السابع وكذلك في اليوم ٢٨ لغرض المتابعة . واعتمادا على التقييم ألسريري للمرضى تم تقسيم النتائج إلى نجاح أو فشل العلاج .وكانت نسبة الرجال أكثر من نسبة النساء في المجموعتين وكانت أكثر الأعمار بين ٤٠ سنة و ٦٠ سنة كان المدخنون أكثر من الذين أقلعوا عن التدخين . لايوجد فرق بين المجموعة الأولى و الثانية اذ كانت نسبة النجاح في المجموعة الأولى ٧٥% وكانت في المجموعة الثانية ٧٣% . كذلك ليس هناك فرق في نتائج نجاح العلاج بين المدخنين والذين أقلعوا عن التدخين إضافة إلى عدم وجود فرق في نجاح العلاج بين الذكور والإناث . وتبين أن اغلب المضادات الحيوية متشابهة من ناحية الكفاءة لذلك يفضل عند استخدام المضادات الحيوية اختيار الأوسع طيفا والأقل آثارا سلبية والمقبول كلفة .

Introduction

Chronic bronchitis and acute exacerbation of chronic bronchitis (AECB) are common respiratory complaints, accounting for up to 14 million physician visits in the United States [1]. In the United States, the annually treatment coast of AECB has been estimated at greater than $ 1.5 billions [2]. AECB-related feeling of

panic and dread, dependence on medication, reduced self-esteem, and embarrassment about symptoms were identified as factors reducing patients perceived quality of life [3].

Chronic bronchitis can be defined clinically as a disorder with expectoration of sputum on most days during at least three consecutive months for more than two successive years, excluding other causes [4]. Chronic bronchitis is present in approximately 85% of patients with COPD [5]. Patients with chronic bronchitis are prone to recurrent exacerbation of their disease. The Global Initiative for Chronic Obstructive Lung Disease (COLD) - a report produced by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO) defines of acute exacerbation chronic bronchitis as an acute increase in symptoms beyond normal day-to-day variation [6]. This generally includes one or more of the following cardinal symptoms:

-Cough increases in frequency and severity.

-Sputum production increases in volume and/or change in character.

-Dyspnea increases.

It is estimated that patients with COPD have, on average, up to three annual episodes of infectious exacerbation [7]. Despite the multifactorial origin of the exacerbation, infection is its principal cause, being responsible for 50 to 80% of the cases [7, 8]. Viral and bacterial infections cause most exacerbations, however [it] has been estimated that as many as 50 to60% of AECB episodes are bacterial in origin [4, 7]. Among these, the most commonly found pathogens are *Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus pneumonia* [8], while atypical bacteria are a relatively uncommon cause [9]. The role of bacterial pathogens in AECB is controversial, but a clearer understanding of their interaction with damaged airways is emerging [10]. Finding a bacterial pathogen within the airways of somebody during an AECB does not necessarily implicate that species as the trigger for the exacerbation [11]. One of the arguments against the importance of bacteria in AECB has been that many patients recover without antibiotic therapy [4]. Up to this point, there have been no characteristic markers separating a bacterial exacerbation from a nonbacterial exacerbation, making the study of potential beneficial effects of antibiotics in AECB very difficult. Anthonisen et al suggested that antibiotics benefit patients with AECB who have a triad of increased sputum volume, sputum purulence and worsening dyspnea[12]. It was only in patients with all the three of these symptoms that antibiotics seemed to have a statistically significant and clinically relevant advantage over placebo[12]. Unfortunately, there are no characteristic physical finding in AECB and no characteristic laboratory or radiographic tests to make the diagnosis of AECB, so the definition of an exacerbation remains problematic. Sputum Gram stain and culture have a very mild role in the investigation of the etiology of AECB because the airways of patients with chronic bronchitis are chronically colonized with bacteria. Objective measurements of lung function are necessary to confirm the presence of air flow obstruction. There is a poor correlation between chronicity of dyspnea and measurement of FEV1 [13]. However, FEV1 remains the best predictor of mortality [14]. There is also evidence that FEV1 is highly predictive of clinical outcomes during AECB [14]. Despite this, there is little evidence to suggest that spirometry has

a role in evaluating an AECB. In addition, it is not clear that there is a correlation between transient falls of lung function and the severity of the exacerbation as defined by Anthonisen criteria [12].

Current guidelines generally recommend ß-lactams and macrolides for the treatment of AECBs[15]. In a retrospective study, the use of third-generation antibiotics (azithromycin, ciprofloxacin and amoxicillin /clavulanic acid) in comparison to that of first-generation antibiotics (amoxicillin, sulfamethoxazole /trimethoprim, erythromycin and tetracycline) was found to be associated with lower rates of treatment failure/hospitalization, longer intervals between exacerbation episodes and (a tendency toward) lower overall treatment costs[14]

Patients and Methods

Patient selection and randomization:

Male and female patients with AECB, as defined by Anthonisen et al. [12], characterized by increased purulent sputum with increased cough and increased dyspnea were eligible to be included in the study. They were between 32 and 80 years of age and they were 15 or more smoking pack per year or they were ex smoking for more than one year and had a history of chronic bronchitis characterized by cough and sputum production for 2 consecutive years and for most days in a consecutive 3-month period in each year. Patients were required to provide a sputum sample and be willing and able to comply with the study protocol. Female patients who were breastfeeding, pregnant or planning to become pregnant (during the study or up to one month after the end of the study) were excluded, and should be using an acceptable method of birth control during the study period. Reasons for exclusion related to underlying disease included clinical and radiological diagnosis of pneumonia, cystic fibrosis, active tuberculosis, radiological and clinical signs of bronchiectasis, active pulmonary malignancy, infectious mononucleosis, known or suspected renal or hepatic impairment (due to the potential for drug-related toxicity in patients with such a condition), including the presence of hepatitis B surface antigen, a complicating disease or infection that would compromise evaluation of the study medication, or an unstable life-threatening or a serious underlying disease.

The use of certain concomitant medications was prohibited, including current or scheduled receipt of systemic corticosteroids at a dose of >10 mg/day of prednisone or equivalent, the commencement of mucolytic therapy, concomitant renal tubular secretion inhibitors, allopurinol, or abuse of drugs or alcohol. Patients were not included in the study if they had been treated with any other systemic antibacterial within 7 days prior to study entry. Patients were excluded from the study if they had a known or suspected hypersensitivity to penicillin or other ß-lactam antibacterial, a history of amoxicillin-clavulanate-associated cholestatic jaundice or hepatic dysfunction.

This study was conducted at Al-Diwanyia Teaching Hospital and private clinic in our city and included 108 patients from 32 to 80 years of age.**108** Patients who fulfilled the study entry criteria were randomized approximately (1:1) to receive either oral amoxicillin-clavulanate at 1000/125 mg (given as two 500 /125-mg tablets) twice daily for 7 days or an oral Azithromycine 500 mg daily for 3 days. **Group A** (n=56) received an azithromycine 500 mg as a single oral dose for three days. **Group B** (n=52)

received an oral amoxicillin-clavulanate as two tablets of Augmentine (500 /125-mg) twice daily for 7 days**.**

Patient assessment: Patients were required to attend the clinic four times for assessment at screening (day 0), on therapy (days 3 to 5), at the end of therapy (days 7), and at long-term follow-up (days 28 to 35). Patients who withdrew from the study prematurely were asked to return for a safety follow-up visit (days 28 to 35).

The patients considered for inclusion in the study were evaluated in the initial medical visit, during which clinical histories were taken, complete physical examinations were performed, laboratory tests were done including complete blood picture, ESR, renal function tests, liver enzymes and function tests , simple chest X rays were taken, spirometry was performed (for some patients), and purulent sputum (recently expectorated) was submitted to microbiological analysis.

Lung function test results and recorded symptoms were assessed according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria [6] and were used to categorize a patient's severity of disease. Sputum samples were obtained at screening prior to the first dose of study medication and, where possible, at the end of therapy. If the patient was a clinical success at the previous visit, a sample was also obtained, if possible, at the test-of-cure. Sputum samples were evaluated by Gram stain for purulence, defined as <10 squamous epithelial cells and >25 leukocytes per x100 microscopic field. A sputum sample had to be purulent to be considered valuable for routine culture. Valuable samples cultured will be done by a laboratory of Al-Diwanyia Teaching Hospital for the presence of aerobic bacteria.

Then, on therapy, visit assessment included measurement of vital signs (temperature, pulse rate, and respiration rate), a blood sample for hematology and clinical chemistry evaluation, and urinalysis. Vital signs were also recorded at each subsequent visit.

In the second and third examinations, the clinical response of the patients was classified as cure, improvement or treatment failure. Cure was defined as the resolution of the signs and symptoms of acute exacerbation, reverted to the usual pattern for each patient. Improvement was defined as the disappearance of fever, with incomplete resolution of the other signs and symptoms, without the need for additional antibiotics. Treatment failure was defined as the lack of resolution of signs and symptoms or the need for further use of antibiotics. The primary evaluation of treatment efficacy was based on the percentage of patients who presented cure or improvement. The secondary parameters of efficacy were the evaluations of signs and symptoms and the results of microbiological evaluations.

Safety assessment. All adverse events reported by the patients, or observed by the examiners, over the course of the study, were recorded. The incidence of serious adverse events, defined as any events that resulted in death, hospitalization, prolongation of hospitalization, persistent/significant incapacitation, or risk to the life of the patient, was also analyzed. Cases in which the treatment was discontinued, whether due to its inefficacy or to related adverse events, were evaluated.

Results were expressed as mean and standard deviation. Chi-square test were used for statistical analysis and $P < 0.05$ considered significance.

Results

Table (1): presents the fifty six patients of group A , forty two patients of them are male and represent 75% and fourteen patients are female; compared with the sex distribution of group B that represent about 71% of male. The predominance of male in both groups might reflect the increase in the prevalence of chronic bronchitis in male patients than female.

Table 2 demonstrates the distribution of the age group among the patients of both groups. It's clearly appears that most patients of both groups are between 40-60 years age, 70% and 75% in group A and B respectively .

Table 3 show the smoker patients in group A and the effect of smoker on the improvement of AECB. 57% of patients are current smokers while the remainder are ex smoker since one year or more. By using Chi square the P value is > 0.05 that is no significance in improvement between smoker and ex smoker patients who using oral azithromycine.

Table 4 shows the distribution of smokers and ex smokers and its effect on the improvement in group B. 59% of patients are still smokers and 41% patients are ex smoker. Also by using Chi square the P value is > 0.05 that is no significance in improvement between smoker and ex smokers in patients using oral amoxicillin-clavulanate drug.

Table 5 shows the effect of gender on the improvement of the AECB in both groups. This table shows no significant effect of gender on the improvement of disease among those taking the drug.

Table (6): 62 patients will do the pulmonary function tests(PFT), thirty seven patients of group A and the remainder from group B. All those patients show impairment in the PFT. Fifty one of them: twenty two patients from group A and twenty nine from group B, repeated the test at the end of therapy visit, forty-two of them show improvement more than 10% of the baseline FEV1 while the remainder nine patients show improvement less than 10%.

Table 7 demonstrates the result of sputum culture in both groups. About 40% of samples isolate *Streptococcus pneumonia*,30% show *staphylococcus aurous,* 25% isolate *H. influenza* and 5% isolate gram negative. Unfortunately the Bacteriological Department in our laboratory had limited ability in isolation many types of bacteria in sputum samples, as well as many sputum samples were contaminated with oral Candida. for these reasons the result of these samples cannot be taken seriously .

Table1 Sex in both groups.

Sex	Male	Female	Total
Group A	42(75%)	14(25%)	56
Group B	37(71.2)	15(28.8)	52
Total	79(73%)	29(27%)	108

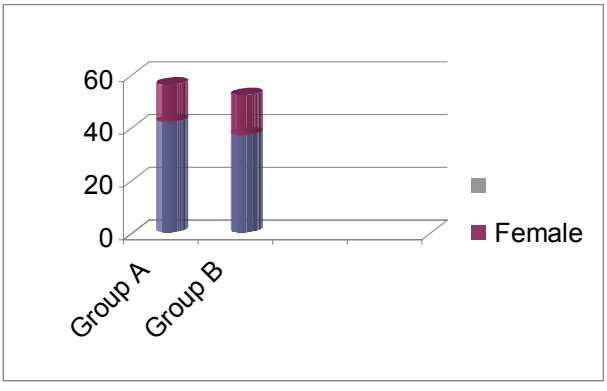

Table 2 The distribution of patients according to age.

Age	<40	40-49	50-60	>60
Group A	8	16	23	9
Group B	6	20	19	7
Total	14	36	42	16

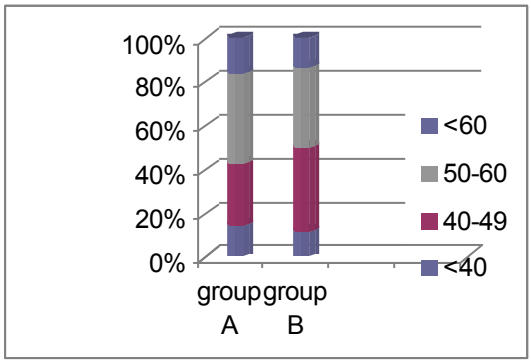

Table 3 The improved patients in smokers and ex smokers n group A.

Type of pat. gr. A	improved	Not improved	total
Smoker	22	10	32
Ex smoker	19	5	24
Total	41	15	56

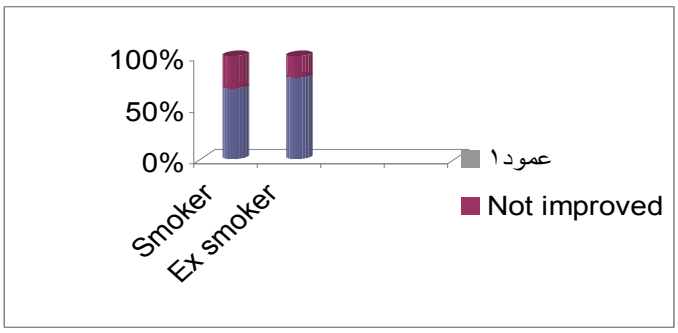

Table 4 The improved patients in group B.

Type of pat. Gro. B	Improved	Not improved	total
smoker	21	10	31
Ex smoker	18	3	21
Total	39	13	52

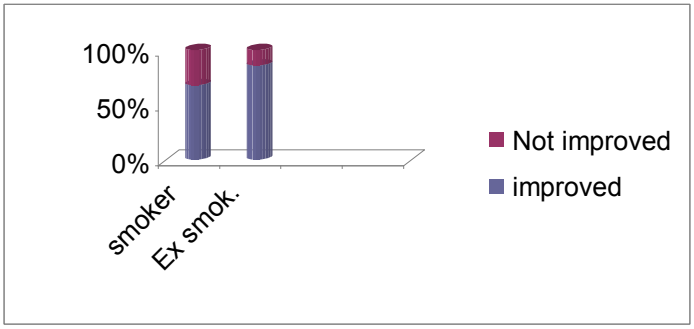

Table 5 The distribution of improved patients according to sex.

	Sex	improved	Not imp.
Group A	Male	31	11
	Female	10	4
Group B	Male	29	8
	female	10	5

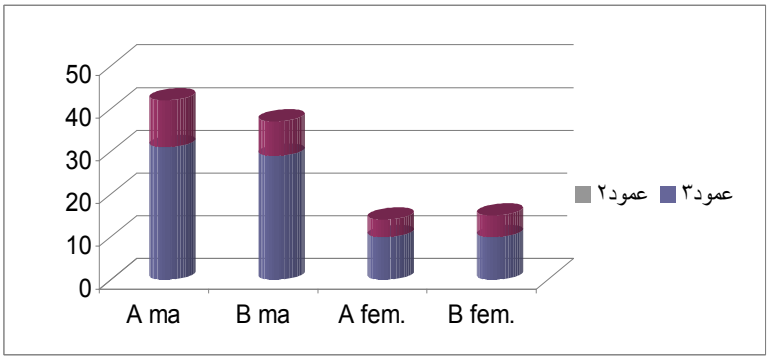

Table 6 The PFT in both groups.

Group	FEV1 increased >15%	FEV1 increased 10-15%	FEV1 increased <10%	Total
Group A	8	10	4	22
Group B	16	8	5	25
Total	24	18	9	51

Table 7 The result of sputum culture.

Type of patients	Strep pneumo.	Staph aurous	H influenz	Gram negative
Group A	23	16	14	3
Group B	20	14	15	3
Total	43	30	29	6

Discussion

In this randomized, double-blind, parallel group study, azithromycine 500 mg daily for 3 days was at least as effective clinically in the treatment of AECB as amoxicillin-clavulanate 625 mg, two tablets given twice daily for 7 days. Both treatments had high rates of clinical success at all endpoints.

The GOLD guidelines recommend antimicrobial therapy for patients showing signs and symptoms of bacterial infection[24]. This study was not, therefore, designed to evaluate the benefit of antimicrobial therapy versus no antimicrobial therapy in AECB but rather to compare the efficacy of the azithromycine versus amoxicillin-clavulanate in cases where antimicrobial therapy would be considered appropriate and in line with currently accepted guidelines.

In this study, patients were required to be at least in middle age group and had history of smoker or ex smoker. These criteria were selected to ensure that patients recruited had a profile most consistent with underlying chronic bronchitis, thus increasing the chance of an infection that was bacterial in origin. All patients had criteria of chronic bronchitis with history of at least two episodes of exacerbation.

Both groups had male predominance and this was compatible to other studies, this might reflect the high incidence of smokers habit among male than female, especially in our country.

Although the improvement in both groups was more in ex smoker patients, but there is no statistically significance in improvement between smokers and ex smokers and this might reflect that the airways of patients with chronic bronchitis are chronically colonized with bacteria. The cessation of smoking is essential in the treatment of AECB because the smoking can cause further impairment in cilliary function.

Approximately 60 % of patients in the present study who do pulmonary function test had an FEV1

of > 50%. This would suggest that patients recruited in this study were moderately severely ill, and thus more likely to respond to treatment. After the use of antimicrobial therapy the improvement in FEV1 was most likely because of reduction of inflammatory changes and edema of bronchial mucosa with improvement of airways narrowing.

Clinical response rate, defined as the percentage of patients who achieved cure or improvement of the signs and symptoms of the infectious exacerbation condition, was similar in the two groups and comparable to the results obtained in other studies with a similar chronic bronchitis which have many of these characteristics. Azithromycin is a broad-spectrum macrolide antibiotic, indicated for the pathogens design. Similarly, there were no significant differences in other parameters of efficacy or in the toxicity attributed to the treatment.

Various factors must be considered when choosing antibiotics for the treatment of patients with infectious exacerbation of AECB[16]. Noteworthy among these factors are the spectrum of action, the expected rate of bacterial resistance, convenient dosage schedule and adequate penetration into respiratory secretions. Various antibiotics are used in the treatment of infectious exacerbation of most commonly implicated in community-acquired respiratory infections. In an international study, in which the rates of in vitro resistance to various antibiotics were compared among respiratory pathogens, the results of the samples from Brazil revealed that S. pneumoniae and H. influenzae presented, respectively, 95% and 100% sensitivity to azithromycin[17]. The administration of azithromycin for three days guarantees adequate antibiotic levels for up to ten days. This pharmacokinetic property makes azithromycin an antibiotic with a quite satisfactory dose schedule. In addition, azithromycin presents excellent penetration into respiratory secretions[18].

A meta-analysis comprising fourteen randomized studies in which azithromycin and amoxicillin were compared showed that the two present similar efficacy, and that the incidence of adverse events was lower among individuals receiving amoxicillin, with or without clavulanic acid. The efficacy of azithromycin has been shown to be equivalent to that of other classes of antibiotics, including moxifloxacin, levofloxacin and pivampicillin, as well as to that of other macrolides, including roxithromycin, clarithromycin and dirithromycin[19].

In a retrospective study, the use of third-generation antibiotics (azithromycin, ciprofloxacin and amoxicillin/clavulanic acid) in comparison to that of first-generation antibiotics (amoxicillin, sulfamethoxazole/trimethoprim, erythromycin and tetracycline) was found to be associated with lower rates of treatment failure/hospitalization, longer intervals between exacerbation episodes and (a tendency toward) lower overall treatment costs[20].

The results of the present study confirm the efficacy and tolerability of azithromycin for the outpatient treatment of episodes of infectious exacerbation of COPD. In this context, it can be expected that the treatment with azithromycin will promote cure or clinical improvement in most patients, with acceptable toxicity and costs. Taking these characteristics into consideration, in addition to the convenient dosage schedule offered by azithromycin, we can considere the use of this drug one of the treatments of

choice for patients with infectious exacerbation of COPD[18-20].

References

1.Grossman, R. F. 1997. Guidelines for the treatment of acute exacerbations of chronic bronchitis. Chest 112(Suppl. 6):310S-313S.

2.Niederman, M. S., J. S. McCombs, A. N. Unger, A. Kumar, and R. Popovian. 1999. Treatment cost of acute exacerbation of chronic bronchitis. Clin. Ther. 21:576-591.

3.Nicolson, P., and P. Anderson. 2000. The patient's burden: physical and psychological effects of acute exacerbations of chronic bronchitis. J. Antimicrob. Chemother. 45:25-32.

4. definition and classification of chronic bronchitis for clinical and epidemiological purposes. A report to the Medical Research Council by their Committee on the Aetiology of Chronic Bronchitis. Lancet 1965;1:775-9.

5. Oswald NC, Harold JT, Martin WJ. Clinical pattern of chronic bronchitis. Lancet 1953;2265:639-643.

6. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Executive summary 2006. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Available from http://www.goldcopd.org. (Accessed August 31, 2007).

7. Brunton S, Carmichael BP, Colgan R, Feeney AS, Fendrick AM, Quintiliani R, et al. Acute exacerbation of chronic bronchitis: a primary care consensus guideline. Am J Manag Care. 2004;10(10):689-96.

8. Update to the Latin American Thoracic Society (ALAT) Recommendations on Infectious Exacerbations of COPD. Arch Bronconeumol. 2004;40:315-25.

9. McNamara, MJ, Phillips, IA, Williams, OB. Viral and Mycoplasma pneumoniae infections in exacerbations of chronic lung disease. Am Rev Respir Dis 1969; 100:19.

10. Cosio M, Guerassimov A. Chronic obstructive pulmonary disease . Inflammation of small airways and lung parenchyma . . Am J Respi Crit Care Med 1999; 160(Suppl):S21-5.

11. Gump DW, Phillips CA, Forsyth BR, Mclntosh K, Lamborn KR, Stouch WH. Role of infection in chronic bronchitis. Am Rev Respire Dis 1976;113:465-74.

12. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med. 1987;106(2):196-204.

13. Wolkove N, Dajczman E, Colacone A, Kreisman H. The relationship between pulmonary function and dyspnea in obstructive lung disease. Chest 1989;96:1247-51.

14. Niewoehner D, Collins D, Erbland M. Relation to FEV1 to clinical outcome during exacerbation of chronic obstructive pulmonary disease. The department of Veterans Affairs Cooperative Study Group. Am J Respi Crit Care Med 2000;161:1201-5.

15.Pauwels, R. A., A. S. Buist, P. M. Calverley, C. R. Jenkins, and S. S. Hurd. 2001. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/W.H.O. Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. Am. J. Respir. Crit. Care Med. 163:1256-1276.

16. Dever LL, Shashikumar K, Johanson WG Jr. Antibiotics in the treatment of acute exacerbations of chronic bronchitis. Expert Opin Investig Drugs. 2002; 11(7):911-25.

17. Thornsberry C, Sahm DF. Resistance in respiratory tract pathogens: an international study 1997-1998. J Chemothe. 2000;12 (Suppl 4):16-20.

18. Baldwin DR, WiseR, Andrews JM, Ashby JP, Honeybourne D. Azithromycin concentrations at the sites of pulmonary infection. Eur Respir J. 1990; 3(8):886-90. 19. Amsden GW, Baird IM, Simon S, Treadway G. Efficacy and safety of azithromycin vs levofloxacin in the outpatient treatment of acute bacterial exacerbations of chronic bronchitis. Chest. 2003;123(3):772-7.

20. Destache CJ, Dewan N, ODonohue WJ, Campbell JC, Angelillo VA.Clinical and economic considerations in the treatment of acute exacerbations of chronic bronchitis.J Antimicrob Chemother.1999;43 Sup A:107- 13.