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Cost Effectiveness Analysis of Antibiotic Regimens Used in Outpatient Treatment of Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

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Abstract

Allocation of the resources in health care and finding a way how to prioritize spending within health care systems are hot issue, even in the developed countries. Introduction of new medical products and technologies is one important driver for increased health care costs. COPD is among top five causes of morbidity and mortality worldwide. The aim of this study is to evaluate cost effectiveness of antimicrobial regiments for treatment of acute exacerbation of COPD. Cost effectiveness analysis was performed based on data from two published observational, "real world" studies carried in Institute for occupational Health of Macedonia. Methodology is based on calculation of ICER in as many steps as needed until all exclusion criteria`s are met. All ICER`s are interpreted using cost effectiveness plane. Amoxicillin with clavulanic acid and cefuroxime dominated over other antibiotic regiments. Doxycycline, cefuroxime, cefpodoxime and moxifloxacin are cost-effective alternatives. When deciding, size of the available budget and patient's willingness to pay will be key factors. The results of this study provide data and useful information which antibiotic will give best expected outcomes, with least produced costs.

Keywords: Cost effectiveness; Antibiotics; COPD; ABECB; Macedonia

Classification Code (JEL):

I110 Analysis of Health Care Markets

Introduction

Allocation of the resources in health care and finding a way how to prioritize spending within health care systems are hot issue, even in the developed countries. Introduction of new medical products and technologies is one important driver for increased health care costs [1,2]. These situations highlight need to assess the value of new clinical strategies, to measure the benefits of diagnostic tests, drugs, procedures and medical devices in relation to costs. Various cost effectiveness analysis aim to evaluate such questions in order to inform crucial stakeholders on medical decision and health care policy making [2]. Health economic studies can consider many forms and report a variety of possible outcomes. Usually one or more new strategies or drugs are compared against an existing standard of care with regard to the dual outcomes of clinical effectiveness and cost. Cost effectiveness studies evaluate incremental costs in currency units, while expressing clinical benefits in nonmonetary terms, such as clinical success, avoided deaths, life years gained or quality adjusted life years (QALYs) etc. [3]. When deciding, if ICER is acceptable or not, different points of view need to be considered, for example macroeconomic parameters of the country would dictate what type of threshold might be affordable. Simple cost effectiveness thresholds, based on GDP per capita or benchmark interventions, often fail to evaluate all healthcare system parameters. Results of cost effectiveness analysis should be compared with as many relevant interventions as reasonable in given situation. Decision makers then will have much better position to interpret the results. New framework should be developed for ICER`s in the context of relevant budgets and adopted country setting [4]. One of the budget consuming illnesses is chronic obstructive pulmonary disease (COPD). COPD needs calculation of ICER`s and various cost effectiveness strategies, in order to make budget savings and rational use of resources.

COPD is among top five causes of morbidity and mortality worldwide, according to World Health Organisation (WHO) is 3th leading cause of death and remains frequent and costly disease representing one of the principal demands of the public health worldwide [5]. The exacerbation can be defined as a worsening of the patient`s respiratory symptoms that is beyond normal day-to-day variations and lead to change in medication which consequently changes the course of COPD [6]. Classification of COPD patients according to GOLD criteria is given in Table 1.

Patients Included in the study were from Group A or Group B risk of exacerbations, with probably bacterial etiology of the exacerbation. Respiratory infections account for up to 80% of exacerbations, of which 50–70% are bacterial infections [8]. Investigations with newer medical diagnostic techniques (Bronchoscopic, bacteriologic and serologic) are in favor of arguments that bacteria`s usually do cause acute exacerbations of chronic obstructive pulmonary disease (AECOPD) [9,10]. Patient with exacerbation of COPD can be classified in 4 GOLD groups mild, moderate, severe and very severe,

depending on different criteria, as expected number of exacerbations, hospitalizations, 3-year mortality rate (Table 2).

Group A-Low risk, Less symptoms Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation); and/or 0–1 exacerbations per year and no hospitalization for exacerbation and CAT score <10 or mMRC grade ≥0–1	**Group B-Low risk, More symptoms** Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation); and/or 0–1 exacerbations per year and no hospitalization for exacerbation and CAT score ≥10 or mMRC grade ≥2
Group C-High risk, Less symptoms Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation); and/or ≥2 exacerbations per year or ≥1 with hospitalization for exacerbation and CAT score <10 or mMRC grade 0–1	**Group D-High risk, More symptoms** Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation); and/or ≥2 exacerbations per year or ≥1 with hospitalization for exacerbation and CAT score ≥10 or mMRC grade ≥2
GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease; CAT: COPD Assessment Test; mMRC: Modified British Medical Research Council Questionnaire	

Table 1: Patient groups according to GOLD classification [7].

GOLD	Exacerbations	Hospitalizations	3 year mortality
Spirometry levels	**(per year)**	**(per year)**	
GOLD 1: Mild	?	?	?
GOLD 2: Moderate	0.7–0.9	0.11–0.2	11%
GOLD 3: Severe	1.1–1.3	0.25–0.3	15%
GOLD 4: Very severe	1.2–2.0	0.4–0.54	24%
GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease; TORCH: Towards a Revolution in COPD Health Study; UPLIFT: Understanding Potential Long-term Impacts on Function with Tiotropium Study; ECLIPSE: Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points Study			

Table 2: Risk in COPD: Placebo limb data from TORCH, UPLIFT and ECLIPSE [11-13].

Management of AECOPD has great importance, since exacerbations have serious negative impact on patient's quality of life, lung function and socioeconomic costs [14]. Prevention, early detection and treatment have great importance in the management of the disease. Outpatient treatment of the exacerbations of COPD exclude "huge" expenses as hospital care, drug and medical devices costs, use of Intensive Care Units (ICU), daily activities of the medical personal etc. Improved clinical outcomes and overall lower costs (Especially by minimizing hospital admissions and preventing respiratory failure) can be achieved if the treatment is directed toward resistant pathogens with potent bactericidal drugs. Further studies that will examine role of the antibiotics should determine, if new therapies have significant clinical, quality of life and economic advantages over older antimicrobial agents [15]. Evaluation of disease–free interval as outcome, evaluation of multiple therapies, assessing the impact of current and future antibiotic resistance and measurement of costs direct and indirect, can help health care organizations in making evidence based decisions regarding cost-effective management of AECOPD [16].

The aim of this study is to evaluate cost effectiveness of eight antimicrobial regiments used for outpatient treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD), as recommended by Sanford guide for empirical selection of antimicrobial therapy in acute bacterial exacerbation of chronic bronchitis (ABECB) [17]. The results of this study will provide us data and useful information, which antibiotic will give best expected outcomes, with least produced costs.

Materials and Methods

Cost effectiveness analysis was performed based on data from two published observational, "real world" studies carried out in the Institute for Occupational Health of R. Macedonia, Skopje–WHO Collaborating Center and GA2LEN Collaborating Center, and published in 2014 [7,18]. In total 333 outpatients classified as Group A or Group B COPD with an exacerbation of probably bacterial etiology, met criteria's for including in the examination, of which 182 males and 151 females, aged 35 to 78 years, with characteristic of the subjects included in the study presented on the Table 3.

Variable	Study subjects (n=333)
Males	182 (55.9%)
Females	151 (44.1%)
Mean Age (years)	48.7 ± 10.4
Mean duration of COPD	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%)

Table 3: Characteristics of the study subjects included in the study.

Patients including criterion was the presence of a probable bacterial exacerbation according to the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) classification that can be managed on outpatient basis, given in Table 1. Exacerbation was defined by the patient's symptoms, using criteria described by Anthonisen et al. [19]. 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 were followed up to 30 days, with an intermediate visits at 5, 7 and 10 days, at which were examined about duration of symptoms and the side effects of the drug. The treatment of exacerbation was considered to be successful if cure or clinical improvement was achieved and registered by the examiners. 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. After establishment of the diagnosis, exacerbation was managed ambulatory, with the antibiotic treatment given through per oral route of administration.

Characteristics of used antibiotics (ATC code, dose and dose interval) and distribution of included patients is given in Table 4. Additionally every patient received regular treatment for stable COPD and bronchodilators when needed. There are few constrains on what measure of effectiveness is used in the cost effectiveness studies, although some measures have more appeal than others. Changes in life

expectancy generally trump other outcomes and form focus on many health economic studies. Effects of the treatment are measured using single outcome, usually in "natural" units (life years gained, deaths avoided, heart attacks avoided etc.), but in outcome patients we could easily measure effect with "numerical" unit as days of treatment, with consideration of adverse effects ratio. Overall clinical success of the treatment will be calculated from clinical success, corrected with the adverse effects coefficient. Adverse effects of the patients were carefully followed on defined visits on 5, 7 or 10 days from the treatment. All adverse effects reactions were documented, but no adverse reactions that required discontinuing of the treatment were registered.

Costs for the treatment are seen differently, from various aspects of view. In economics view, the notion of cost is based on the value that would be gained from using resources elsewhere referred as opportunity cost. It is essential to distinguish between direct costs and indirect, as well as the intangibles, which are often consequences of the treatment and should be included in the cost profile. Since patients included in the study are outpatient treated, most costs for different therapeutic regiments for the treatment on COPD are not taken into consideration. Variety of the treated patients is represented by the different antimicrobial regimens that are used for the treatment of bacterial exacerbations of chronic obstructive pulmonary disease. Direct costs for the antimicrobial treatment are main cost factors in the study. Indirect costs are not taken into consideration, since ambulatory treatment does not offer valuable data for indirect costs evaluation.

Direct costs are calculated on the basis of daily defined dose of the antibiotics. Daily defined dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults. DDD is assigned with ATC code of the drug and it is assigned per route for administration. It should be emphasized that DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. DDD provide us with fixed unit of measurement independent of price and dosage form enabling the researcher to assess trends in drug consumption and to perform comparison between population groups [20]. To calculate cost of the treatment for antibiotic regimens used to treat acute exacerbations of COPD, we will take cost for the antibiotics from reference price list of the maximum prices of the drugs and medicines in Macedonia [21].

Antibiotic	ATC Code	Dose	Dose interval	No of patients	Percentage of total patients
Amoxicillin/ Clavulanic acid	J01CR02	875 mg/125 mg	12 h	42	12.6%
Doxycycline	J01AA02	100 mg	24 h	43	12.9%
Cefuroxime	J01DC02	250 mg	12 h	44	13.2%
Cefixime	J01DD08	400 mg	24 h	43	12.9%
Clarithromycin	J01FA09	500 mg	12 h	42	12.6%
Cefpodoxime	J01DD13	200 mg	12 h	33	9.9%
Ciprofloxacin	J01MA02	500 mg	12 h	44	13.2%
Moxifloxacin	J01MA14	400 mg	24 h	42	12.6%
ATC: Anatomic Therapeutic Chemical Classification					

Table 4: Used antibiotic, ATC code, dose and interval of dosing, no. of patients on antibiotic and percentage of total patients in the study.

Methodology of the study is based on calculation of ICER, in as many steps as needed until all exclusion criteria's are met. All calculated ICER are interpreted using cost effectiveness plane. ICER is calculated using mathematical formula, as follows:

$$ICER = \frac{(C_1 - C_0)}{(E_1 - E_0)}$$

Where ICER is incremental cost effectiveness ratio, C_1 is cost of new drug, C_0 is cost of standard treatment, E_1 is efficacy of new drug and E0 is efficacy of the standard treatment. An important tenet, which needs clarification at the start of every cost effectiveness analysis, is that while calculation of ICER each relevant strategy should be compared with the next best alternative based on the economic concept of opportunity costs [22].

Results can be visualized on two dimensional plot referred as "cost effectiveness plane" where standard of care defines the coordinates of the graph [23]. All examined interventions will locate themselves to the right or to the left of the Y axis, if they are more or less effective than the current standard of care. Also above or below of the X axis, if they are more or less costly. If new intervention is clinically superior and cost saving, the intervention is referred as "dominant" strategy, and if opposite then intervention is "dominated" strategy. Only few of new technologies will be part from these two scenarios, most expected scenario is that new technologies will improve clinical results but at increased cost.

Every step of ICER calculations has excluding position, where dominated alternatives are excluded from further considerations. When new drug is clinically superior and cost saving, it is referred to as economically "dominant" strategy, if opposite clinical inferior and/or more costly, then the strategy is "dominated". But few new drugs will fall into some of these categories, most common scenario is that new drugs improves the clinical result, but at increased cost.

Results

The pharmacoeconomic evaluation included medical results for 333 examined outpatients. All included patients were ambulatory treated, classified as Group A or Group B COPD with an exacerbation of probably bacterial etiology, the characteristic of the subjects included in the study were presented on the Table 3 [7,18].

Daily defined doses (DDD) of the used antibiotics, calculated costs per DDD according to the price list of unique prices for medicines issued by the ministry of health are on Table 5. Clinical success of the treatment is estimated by the physicians included in the process of evaluation, average days of treatment are calculated from all included patients.

Adverse effects of the patients were carefully followed and the prevalence varied from 6.7% to 11.3%, but no serious adverse effects that require discontinuation of the treatment were registered. Gastrointestinal manifestations (Nausea, vomiting, epigastric pain and diarrhea), headache and dizziness were most frequent adverse events. Still ratio of adverse effects must be taken in consideration when calculating overall effectiveness (E). We calculate clinical effectiveness (E) by dividing clinical success (CS) with ratio of adverse events (AE).

Incremental cost effectiveness ratio (ICER) is calculated for every of the eight regiments used in the treatment of the acute bacterial exacerbations of the chronic obstructive pulmonary disease, and results are given in the Table 6. All results for ICER`s of used

antimicrobial regimens are interpreted using cost effectiveness plane on Figure 1.

Negative ICER score for Amoxicillin/Clavulanic and Cefuroxime means that these two antibiotics have improvement to the effectiveness with reduction in costs, and are dominant alternatives over other antibiotics previously used for the treatments. So alternatives that are more expensive and less effective (Ciprofloxacin and cefixime) are excluded from the further calculations and ICER`s are recalculated for the rest six antibiotic choices (Table 7).

Antibiotic	DDD (mg)	Cost per DDD (C)	Clinical Success (CS)	Average days of treatment (DT)	Adverse events (AE)	Calculated effectiveness (E)
Amoxicillin/ Clavulanic acid	400	17.375	73.8%	6.2	9.5%	67.40%
Doxycycline	1000	4.596	69.8%	6.1	9.3%	63.86%
Cefuroxime	400	26.829	77.3%	5.8	6.7%	72.45%
Cefixime	500	68.918	74.4%	6.0	9.3%	68.07%
Clarithromycin	100	23.764	71.4%	6.1	9.5%	65.21%
Cefpodoxime	1000	90.000	81.8%	5.8	9.1%	74.98%
Ciprofloxacin	500	31.870	75.0%	5.8	11.3%	67.39%
Moxifloxacin	400	148.619	80.9%	5.7	7.1%	75.54%

ATC: Anatomic Therapeutic Chemical Classification; DDD: Defined Daily Dose

Table 5: DDD, cost of the treatment per DDD, clinical success of every used antibiotic, average days of treatment, adverse effects and calculated effectiveness.

Antibiotic	C	E	ΔC	ΔE	ICER
Doxycycline	4,596	0,6386	4,596	0,6386	7,2
Clarithromycin	23,764	0,6521	19,168	0,0135	1419,9
Ciprofloxacin	31,87	0,6739	8,106	0,0218	371,8
Amoxicillin/ Clavulanic acid	17,375	0,6740	-14,495	0,0001	-144950,0
Cefixime	68,918	0,6807	51,543	0,0067	7693,0
Cefuroxime	26,829	0,7245	-42,089	0,0438	-960,9
Cefpodoxime	90	0,7498	63,171	0,0253	2496,9
Moxifloxacin	148,619	0,7554	58,619	0,0056	10467,7

C: Cost; E: Efficacy; ΔC: Difference in Costs; ΔE: Difference in Efficacy; ICER: Incremental Cost Effectiveness Ratio

Table 6: Incremental cost effectiveness ratios (ICERs).

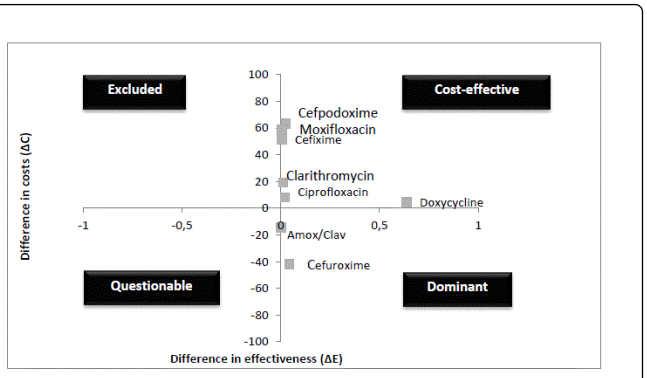

Figure 1: Cost effectiveness plane for the eight antibiotic regiments used for the treatment of acute bacterial exacerbations of chronic obstructive pulmonary diseases ABECOPD.

Antibiotic	C	E	ΔC	ΔE	ICER
Doxycycline	4,596	0,6386	4,596	0,639	7,2
Clarithromycin	23,764	0,6521	19,168	0,014	1419,9
Amoxicillin/Clavulanic acid	17,375	0,674	-6,389	0,022	-291,7
Cefuroxime	26,829	0,7245	9,454	0,051	187,2
Cefpodoxime	90	0,7498	63,171	0,025	2496,9
Moxifloxacin	1,48,619	0,7554	58,619	0,006	10467,7

C: Cost; E: Efficacy; ΔC: Difference in Costs; ΔE: Difference in Efficacy; ICER: Incremental Cost Effectiveness Ratio

Table 7: Exclusion of more costly and less effective antibiotics.

Again new ICER calculation, showed that treatment of acute bacterial exacerbations of COPD with amoxicillin/clavulanic acid have more success with less cost, over treatment exacerbations with clarithromycin, therefore we exclude clarithromycin from further calculations and make new ICER calculation for the other five antibiotics (Table 8).

ICER`s from the last calculation showed that Amoxicillin/ Clavulanic acid is dominated by Cefuroxime as it is shown that Cefuroxime is more effective and costs less to produce an additional unit of effect, so the dominated alternative is excluded and the ICER`s are recalculated for the last time, for the remaining four antibiotics (Table 9).

The results from the last ICER calculation after eliminating all dominated alternatives are shown on the Figure 2. All four antibiotics regimens doxycicline, cefuroxime, cefpodoxime and moxifloxacin are located at cost-effective segment of the cost effectiveness plane, and they are alternatives for empirical treatment of acute bacterial exacerbations of chronic obstructive pulmonary diseases. Out of eight studied antibiotic treatments two antibiotics (Amoxicillin/Clavulanic acid and Cefuroxime) were marked as dominant treatment (Less cost but more effective) and other six antibiotic treatments were more effective but more costly, as expected.

Antibiotic	C	E	ΔC	ΔE	ICER
Doxycycline	4,596	0,6386	4,596	0,639	7,2
Amoxicillin/Clavulanic acid	17,375	0,674	12,779	0,035	361,0
Cefuroxime	26,829	0,7245	9,454	0,051	187,2
Cefpodoxime	90	0,7498	63,171	0,025	2496,9
Moxifloxacin	148,619	0,7554	58,619	0,006	10467,7

C: Cost; E: Efficacy; ΔC: Difference in Costs; ΔE: Difference in Efficacy; ICER: Incremental Cost Effectiveness Ratio

Table 8: Exclusion of more costly and less effective antibiotics.

Antibiotic	C	E	ΔC	ΔE	ICER
Doxycycline	4,596	0,6386	4,596	0,6386	7,2
Cefuroxime	26,829	0,7245	22,233	0,086	258,8
Cefpodoxime	90	0,7498	63,171	0,025	2496,9
Moxifloxacin	148,619	0,7554	58,619	0,006	10467,7

C: Costs; E: Efficacy; ΔC: Difference in Costs; ΔE: Difference in Efficacy; ICER: Incremental Cost Effectiveness Ratio

Table 9: Exclusion of dominated antibiotic.

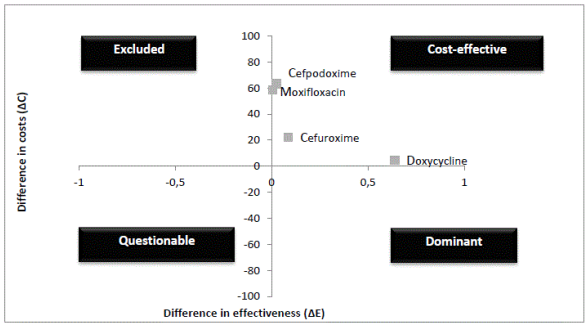

Figure 2: Cost effectiveness plane for the four antibiotic regiments used for the treatment of acute bacterial exacerbations of chronic obstructive pulmonary diseases that meet cost effectiveness criteria with the final ICER calculation.

Discussion

Cost effectiveness research is meant to be a source of unbiased information for medical decision making and policy setting, for use in broad applications such as the development of clinical guidelines or reimbursement policy. They provide us information`s for effects, costs and consequences of choices that would not be apparent through assessment of clinical outcomes. However the information obtained from cost effectiveness analysis are not final decision tool, advice is every patient to be considered at individual level. The more explicit use of cost effectiveness analysis is usually prevented by many barriers and obstacles, such as political obstacles, willingness to pay for the treatment, available budget resources etc. Often there are valid concerns about accuracy and transparency of data interpreted in the cost effectiveness analysis, so even the best studies are subject to different limitations. Despite all limitations we believe that cost effectiveness analysis will continue to grow in importance, as scientific and clinical researches develop new technologies and medicines. There for we encourage science to obtain more and more cost effectiveness analysis in other to bridge this issues in policy making.

Outpatient treatment of acute bacterial exacerbations of COPD is often acute treatment where good treatment decisions must be made fast and prompt. Since COPD is major problem concerning a lot of patients, huge amount of time and resources are invested in preventing, diagnosing and cure patients with this life threating disease. Acute bacterial exacerbations require fast interventions since every exacerbation is only a progressive route to the final result of the illness, and that is very often death to the patient. Antibiotic choice must be in line with actual antibiotic protocols for the treatment of acute bacterial exacerbations of COPD, supported with the laboratory and diagnostic test tools, such as blood analysis or microbiologically testing, and we must be aware of microbial resistance situation of the region, prior history of the patients and many other factors.

All eight antibiotics included in the study meet all this previous criteria's. From pharmacoeconomic point of view amoxicillin with clavulanic acid and cefuroxime, when empirically chosen, showed dominance over other six antibiotic regiments that could be used for treatment for acute exacerbations of COPD, with less cost and more effectiveness at the end of the treatment. Further ICER calculations showed us that doxycycline, cefuroxime, cefpodoxime and moxifloxacin, are also cost-effective alternatives over other antibiotics used for treatment of these indication. When deciding, which antibiotic to choose for the treatment of acute exacerbations of COPD, factors as availability of the medication, available budget resources and willingness to pay for the treatment, should be taken into consideration? This study results provide data and useful information for decision makers, when choosing which antibiotic treatment will give best expected outcomes for the patient with acute bacterial exacerbation of COPD, with the least produced costs to patient and to the society.

Conflict of Interest's Statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

1. Bodenheimer T (2005) High and rising health care costs. Part 2: technologic innovation. Ann Intern Med 142: 932-937.
2. Cohen D, Reynolds M (2008) Interpreting the results of Cost effectiveness studies. J Am Coll Cardiol 52: 25.
3. Gafni A, Birch S (2006) Incremental cost effectiveness ratios (ICERs): the silence of lambda. Soc Sci Med 62: 2091-2100.
4. Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S (2015) Thresholds for the cost effectiveness of interventions: alternative approaches. Bull World Health Organ 93: 118-124.

5. World Health Organization (WHO) (2016) Media Centre, Fact sheets.
6. Minov J, Karadzinska BJ, Petrova T, Vasilevska K, Stoleski S, et al. (2014)Efficacy and tolerability of eight antimicrobial regimens in the outpatient treatment of exacerbations of chronic obstructive pulmonary disease. Maced J Med 7: 519-524.
7. Global Strategy for the Diagnosis (2016) Management and Prevention of Chronic Obstructive Pulmonary Disease: 2016 update.
8. Ball P, Chodosh S, Grossman R, Tillotson G, Wilson R (2000) Causes, epidemiology and treatment of bronchial infections. Infect Med 17: 186-198.
9. Sethi S, Evans N, Grant BJ, Murphy TF (2002) New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. N Engl J Med 347: 465-471.
10. Sethi S, Wrona C, Grant BJ, Murphy TF (2004) Strain specific immune response to Haemophilus influenza in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 169: 448-453.
11. Jenkins CR, Jones PW, Calverley PM, Celli B, Anderson JA, et al. (2009) Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. Respir Res 10: 59.
12. Decramer M, Celli B, Kesten S, Lystig T, Mehra S, et al. (2009) Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. Lancet 374: 1171-1178.
13. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, et al. (2010) Suceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 363: 1128-1138.
14. Anzueto A (2010) Impact ofexacerbations on COPD. Eur Res Rev 19: 113-118
15. Grossman R (1998) The value of antibiotics and the outcomes of antibiotic therapy in exacerbations of COPD. Chest J 113: 249-255.
16. Saint S, Flaherty KR, Abrahamse P, Martinez FJ, Fendrick AM (2001) Acute exacerbation of chronic bronchitis: disease-specific issues that influence the cost effectiveness of antimicrobial therapy. Clinical Therap 23: 499-512.
17. Gilbert D, Chambers H (2015) The Sanford Guide to antimicrobial therapy (45th edn.).
18. Minov J, Karadzinska BJ, Vasilevska K, Stoleski S, Mijakoski D (2014) Efficacy and tolerability of cefpodoxime in the outpatient treatment of exacerbations of chronic obstructive pulmonary disease. VOX Medici 2: 519-524.
19. Anthonisen NR, Manfreda J, Warren CPW, Hershfield ES, Harding GKM, et al. (1987) Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 106: 196-204.
20. WHO Collaborating Center for Drug Statistics Methodology (2016) The Anatomical therapeutic chemical (ATC) classification system, the Defined daily dose (DDD).
21. https://lekovi.zdravstvo.gov.mk/maxprices/0
22. Gold MR, Siegel JE, Russell LB, Weinstein MC (1996) Cost effectiveness in health and medicine. New York, NY: Oxford University Press.
23. Black W (1990) The CE Plane A graphic representation of cost effectiveness. Med Decis Making 10: 212-214.