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Original article

CEFPODOXIME IN THE OUTPATIENT TREATMENT OF LOWER RESPIRATORY TRACT INFECTIONS

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Abstract

Introduction. According to the recent data, lower respiratory tract infections (LRTIs), i.e. a broad terminology including acute bronchitis (AB), influenza, community-acquired pneumonia (CAP), acute exacerbation of chronic obstructive pulmonary disease (AECOPD), and acute exacerbation of bronchiectasis (AEBX), represent the fourth most common cause of death at global level.

Aim of the study. To assess efficacy and safety of cefpodoxime in the empirical treatment of LRTIs of bacterial origin in an outpatient setting.

Methods. We performed an observational, non-randomized, open-label study (a real life-study) including 126 patients with LRTI of bacterial origin, 59 patients with AECOPD, 32 patients with CAP and 35 patients with AEBX, who met criteria for treatment in an outpatient setting. All study subjects were treated with cefpodoxime 200 mg twice daily, and had intermediate visits at 3, 5, and 7 days (patients with AECB) and at 3, 5, 7, and 10 days (patients with CAP and AEBX) at which their symptoms as well as eventual side effects were evaluated. The treatment was considered to be successful if complete resolution of symptoms or their return to the baseline severity was achieved.

Results. Percentage of clinical success, i.e., complete resolution of clinical symptoms and signs or their return to the baseline severity, varied from 77.9% in patients with AECOPD, 81.3% in patients with CAP to 77.1% in patients with AEBX. Mean time to clinical remission varied from 6.5 ± 0.3 days in patients with AECOPD, 7.8 ± 0.5 days in patients with CAP to 10.7 ± 1.2 days in patients with AEBX. Incidence of side effects during the treatment varied from 10.2% in patients with AECOPD, 12.5% to 8.6% in patients with AEBX. Registered side effects were mild and self-limited and did not require premature discontinuation of the treatment.

Conclusion. Our findings supported the use of cefpodoxime in the treatment of bacterial LRTI due to its high efficacy and good tolerability.

Keywords: bacterial exacerbation, bronchiectasis, cefpodoxime, chronic obstructive pulmonary disease, clinical remission, lower respiratory tract infections, pneumonia, side effects

Introduction

Lower respiratory tract infection (LRTI) is defined as an acute illness (present for 21 days or less), usually with cough as the main symptom, with at least one other respiratory tract symptom (sputum production, dyspnea, wheezing or chest discomfort/pain) and no alternative explanation (e.g. asthma or sinusitis). LRTI is a broad terminology which includes different disease such as acute bronchitis (AB), influenza, suspected and definite community acquired pneumonia (CAP), acute exacerbation of chronic obstructive pulmonary disease (AECOPD), and acute exacerbation of bronchiectasis (AEBX)[1,2,3,4].

AB is defined as an acute illness, occurring in a patient without a chronic lung disease, with symptoms including cough, which may or may not be productive and associated with other symptoms or clinical signs that suggest LRTI and no alternative explanation (e.g. asthma or sinusitis)[1,3].

Influenza is defined as an acute illness, usually with fever, together with presence of one or more headache, myalgia, cough or sore throat[1,3].

CAP is defined as an acute illness with cough and at least on of new focal chest signs, fever longer than 4 days or dyspnea/tachypnea, and without other obvious cause. Depending upon the presence of chest X-ray finding of lung shadowing that is likely to be new, CAP is classified as suspected or definite[5].

AECOPD is defined as an acute worsening of respiratory symptoms in a patient with COPD that requires additional therapy[6].

AEBX is defined as an acute event in a patient with bronchiectasis characterized by a worsening in the patients' baseline dyspnea, and/or cough and/or sputum production beyond day-to-day variability sufficient to warrant a change in management[7].

Majority of the LRTIs are infective, of viral or bacterial origin. In addition, majority of the LRTIs are diagnosed and treated empirically in the outpatient setting.

Antibiotic use is recommended in the LRTIs recognized as bacterial infections[1,8,9,10].

Cefpodoxime is an oral, third generation cephalosporin antibiotic for the treatment of various mild to moderate susceptible infections. It is an extended-spectrum, semi-synthetic bactericidal cephalosporin antibiotic that inhibits bacterial cell wall synthesis and it has activity against some beta-lactamases, both penicillinases and cephalosporinases.

Cefpodoxime is active against most Gram-positive bacteria, including *Staphylococcus aureus* (methicillin-susceptible strains, including those producing penicillinases), *Staphylococcus saprophiticus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae* (excluding penicillin-resistant isolates), as well as against most Gram-negative bacteria, such as *Haemophilus influenzae* (including beta-lactamase producing isolates), *Moraxella catarrhalis*, *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus mirabilis*, and *Neisseria gonorrhoeae*, but not against *Pseudomonas aeruginosa*, *Enterococcus*, and *Bacteroides fragilis*. In addition, atypical bacteria, i.e. *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Chlamydophila psittaci, Legionella* spp., etc., are sensitive to antibiotics other than β-lactams such as macrolides, tetracyclines or fluoroquinolones which are concentrated intracellularly and which is the usual site of replication of these pathogens. Due to its broad antibacterial spectrum, cefpodoxime is used in the treatment of a wide range of infections, including infections of the upper and

lower respiratory tract, urinary tract infections, and skin infections. It also finds use as an oral continuation therapy when intravenous cephalosporins (e.g. ceftriaxone) are no longer necessary for continued treatment.

Results from several studies have indicated that cefpodoxime is fairly well-tolerated, with diarrhea and nausea as the most common adverse events occurring in around 10% of the cefpodoxime-treated patients[11-15].

Aim of the study

The aim of the study was to evaluate efficacy and tolerability of cefpodoxime in the empirical treatment of LRTI in an outpatient setting. The present study is a continuum of our investigations of efficacy and tolerability of various antimicrobial regimens in outpatient treatment of respiratory tract infections[16-18].

Methods

Study design and setting

An observational, non-randomized, open-label study (a real life-study) was carried out in the period January 2020 – March 2021 at the Institute of Occupational Health of R. North Macedonia, Skopje.

Study population

The study included 126 patients with LRTI of bacterial origin, 59 patients with AECOPD (37 males and 22 females, aged 46 to 74 years), 32 patients with CAP (17 males and 15 females, aged 29 to 71 years) and 35 patients with AEBX (19 males and 16 females, aged 37 to 73 years), who met criteria for treatment in an outpatient setting. Patients with AB were not included in the study as almost 90% of the cases with AB are related to viruses, such as adenovirus, coronavirus, parainfluenza, influenza, and rhinovirus, and less than 10% to bacteria, such as *Bordetella pertussis*, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*[19, 20].

All participants were informed about the study and their written consent was obtained. In addition, all included patients had neither positive epidemiological evidence for Covid-19, nor positive clinical findings or positive molecular test to SARS-CoV-2.

Diagnosis of bacterial LRTI

According to the current recommendations, diagnosis of bacterial LRTI in all included patients was established by its clinical signs, i.e., microbiological investigations were not performed [6-8].

Bacterial AECOPD was defined by presence of three cardinal symptoms (increase in dyspnea, sputum volume and sputum purulence) or by two cardinal symptoms if increased sputum purulence was one of the two symptoms[6,21].

Bacterial CAP was defined by its radiological confirmation in clinically suspected patients. According to the current recommendations, microbial etiology of CAP is changing, and there is an increased recognition of the role of viral pathogens. Bacterial pathogens often coexist with viruses and there is no diagnostic test accurate enough or fast enough to determine that CAP is due solely to a virus at the time of presentation so it should be treated empirically for possible bacterial infection or coinfection[8,22].

An exacerbation requiring antibiotics in patients with bronchiectasis was defined by deterioration of three or more of the following symptoms for at least 48 hours: cough, sputum volume and/or consistency, sputum purulence, breathlessness and/or exercise tolerance, fatigue and/or malaise, and hemoptysis, when a clinician determined that changes in bronchiectasis treatment were required[23,24].

Study protocol

All study subjects underwent clinical examination, spirometry, blood gas measurements, ECG, and laboratory analysis. Chest X-ray was performed in a part of the patients by indications. Classification of smoking status was done by the World Health Organization (WHO) recommendations[25]. The Body Mass Index (BMI) as a measure of body fat based on height and weight that applies to adult population was determined in all study subjects by computed calculation using BMI calculator[26].

After the diagnosis of AECOPD, CAP or AEBX was established all patients were empirically treated with cefpodoxime.

Patients with AECOPD were treated 10 days with cefpodoxime 200 mg twice daily *per os*. They were advised to continue the regular treatment of stable COPD, as well as to use short-acting bronchodilators when needed.

Patients with CAP were treated 14 days with cefpodoxime 200 mg twice daily *per os*.

Patients with AEBX were treated 14 days with cefpodoxime 200 mg twice daily *per os*. Those with regular treatment for bronchiectasis were advised to continue it.

All study subjects had intermediate visits at 3, 5, and 7 days (patients with AECB) and at 3, 5, 7, and 10 days (patients with CAP and AEBX) at which their symptoms as well as eventual side effects of cefpodoxime were evaluated.

The course of LRTI was evaluated as a function of the resolution of the symptoms and the treatment was considered to be successful if complete resolution of symptoms or their return to the baseline severity was achieved. According to the current recommendations, in patients with CAP whose symptoms resolved after the given treatment, follow-up chest X-ray was not performed. Treatment of cepodoxime was stopped two days after resolution of the clinical symptoms and signs. Treatment failure was considered if the clinical symptoms and signs did not improve or got worse as it was noted at each intermediate visit or was not resolved at the end of the treatment[6,10,22].

Statistical analysis

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 of relief of symptoms and of mean FEV_1 values was performed by independent-samples *t*-test. A *P*-value less than 0.05 was considered as statistically significant.

Results

Demographic and other characteristics of the study subjects is shown Table 1.

Table 1. Demographics of the study subjects

Characteristics	Patients with AECOPD (n = 59)	Patients with CAP (n = 32)	Patients with AEBX (n = 35)
M/F ratio	1.7	1.1	1.2
Mean age (years)	58.3 ± 10.8	45.3 ± 9.7	56.1 ± 11.4
BMI	26.1 ± 2.3	25.4 ± 1.8	26.4 ± 1.7
Smoking status			
Current smokers	18 (30.5%)	12 (37.5%)	12 (34.3%)
Ex-smokers	7 (11.9%)	2 (6.3%)	5 (14.3%)
Passive smokers	14 (23.7%)	7 (21.9%)	9 (25.7%)
Comorbidities			
Arterial hypertension	11 (18.6%)	5 (15.6%)	8 (22.8%)
DM type 2	6 (10.2%)	3 (9.4%)	5 (14.9%)
IHD	5 (8.5%)	2 (6.2%)	3 (8.6%)
Osteoarticular disease	8 (13.5%)	4 (12.5%)	6 (17.1%)
Peptic ulcer	5 (8.5%)	3 (9.4%)	3 (8.6%)

Numerical data are expressed as a mean value with standard deviation; the frequencies as a number and percentage of examinees with certain variable.

AECOPD: exacerbation of chronic obstructive pulmonary disease; CAP: community-acquired pneumonia; AEBX: exacerbation of bronchiectasis; M: male; F: female; BMI: Body Mass Index; DM: diabetes mellitus; IHD: ischemic heart disease.

Percentage of clinical success, i.e., complete resolution of clinical symptoms and signs or their return to the baseline severity, varied from 77.9% (46/59) in patients with AECOPD, 81.3% (26/32) in patients with CAP to 77.1% (27/35) (Figure 1). As clinical symptoms and signs did not improve in some intermediate visit, cefpodoxime was discontinued prematurely in 16 patients (eight patients with AECOPD, three patients with CAP and five patients with AEBX, respectively) and the treatment was continued with another antibiotic (macrolide or fluoroquinolone). There was not any hospitalized patient due to the current LRTI.

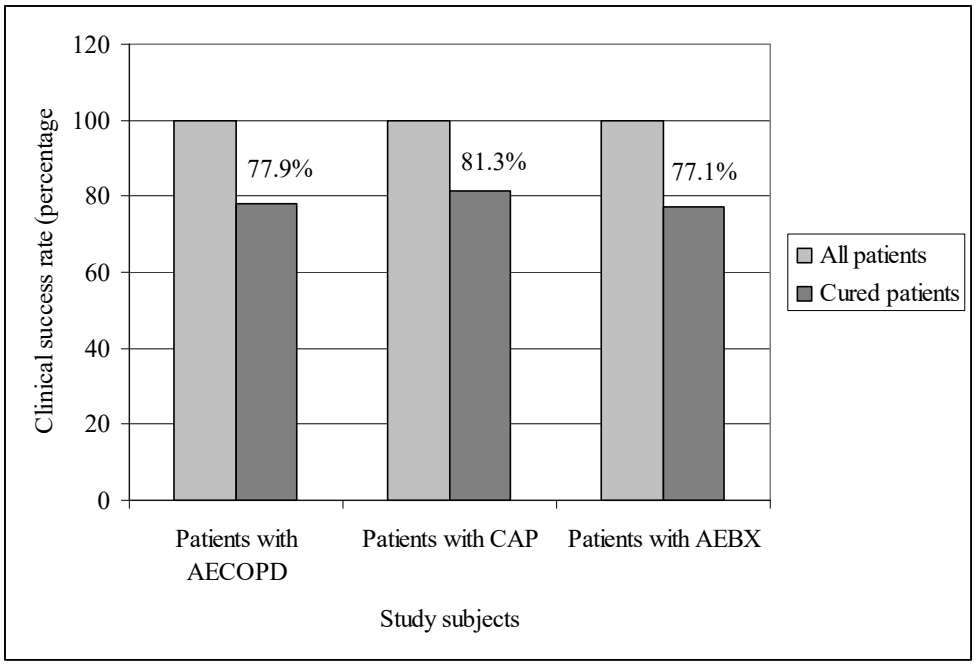

Fig. 1. Clinical success rate of cefpodoxime in patients with LRTI

Mean time to complete resolution of clinical symptoms and signs or their return to the baseline severity varied from 6.5 ± 0.3 days in patients with AECOPD, 7.8 ± 0.5 days in patients with CAP to 10.7 ± 1.2 days in patients with AEBX (Figure 2).

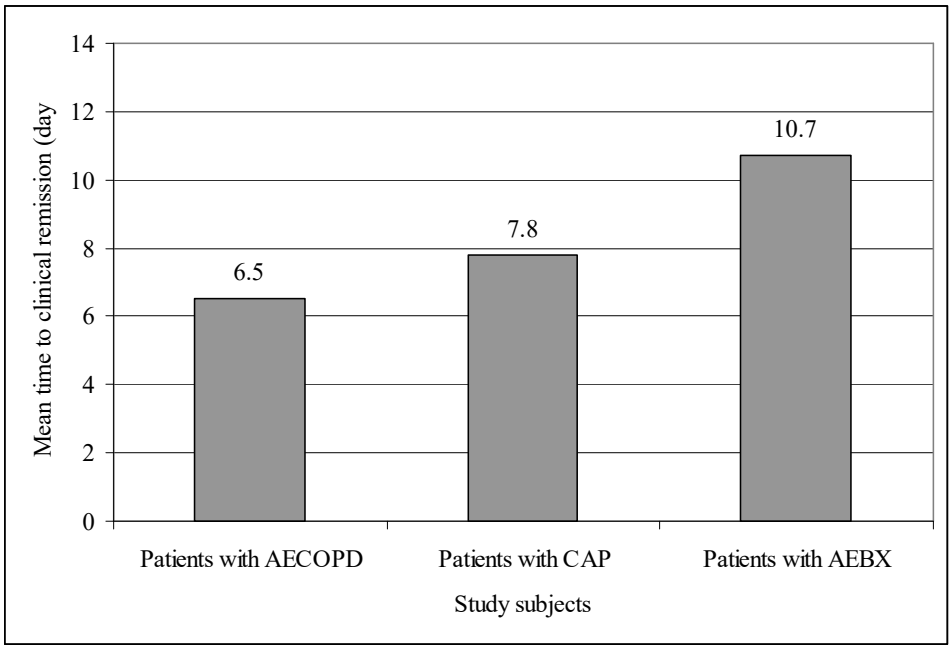

Fig. 2. Mean time to clinical remission (days)

Incidence of side effects during the treatment with cefpodoxime varied from 10.2% (6/59) in patients with AECOPD, 12.5% (4/32) to 8.6% (3/35) in patients with AEBX (Figure 3). Registered side effects (nausea, diarrhea, and dizziness) were mild and self-limited and did not require premature discontinuation of the treatment.

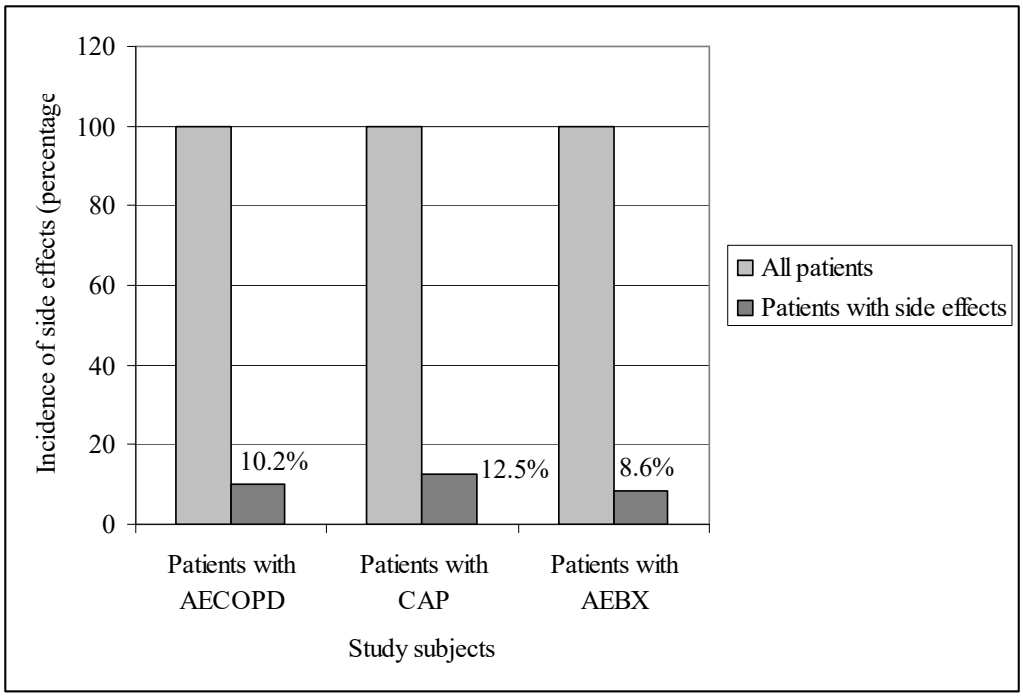

Fig. 3. Incidence of side effects during the treatment with cefpodoxime

Discussion

Acute LRTIs are a leading cause of sickness both in children and adults worldwide. Furthermore, according to the Global Burden of Disease 2015 study (GBD 2015), chronic obstructive pulmonary disease (COPD) and lower respiratory tract infections (LRTIs) represent the third and fourth most common causes of death, respectively, after ischemic heart disease and cerebrovascular disease. While the burden had decreased in children younger than 5 years of age, it had increased in many regions for individuals older than 70 years[27]. Unfortunately, acute LRTIs are not uniformly defined and this may hamper a true appreciation of their epidemiological importance. As it is mentioned above, LRTI is a broad terminology which includes different diseases including acute bronchitis, influenza, pneumonia, and acute exacerbation of chronic lung diseases such as COPD or bronchiectasis. LRTIs are largely preventable causes of death, as vaccines are available against both influenza and pneumococcal respiratory infections. Furthermore, while antiviral therapy is available for the treatment of influenza infections, the mainstay of treatment for CAP, bacterial AECOPD and AEBX, is the use of antibiotics.

In the present study we assessed efficacy and tolerability of cefpodoxime, a third generation cephalosporine with a broad spectrum of activity, in the treatment of LRTIs of bacterial origin. Study population included patients with AECOPD, CAP and AEBX who

met criteria for treatment in an outpatient setting. Males were dominant in the group of patients with AECOPD, while in the groups with CAP and AEBX the number of males and females did not differ significantly. In addition, the mean age in the group of patients with CAP was significantly lower than the mean age of patients in the groups with AECOPD and AEBX. The mean BMI value indicating overweight was similar in all groups. Similarly to the results of our previous studies, we found a large proportion of current smokers and passive in the three groups[28].

We found a high clinical success rate, defined as a complete resolution of clinical symptoms and signs or their return to the baseline severity, in all three groups. The clinical remission rate was around 80%, being similar in patients of the three groups. In addition, the mean time for clinical remission in cured patients varied from 6.5 days in patients with AECOPD, 7.8 days in patients with CAP to 10.7 days in patients with AEBX. As it is mentioned above, cefpodoxime is active against bacteria that are considered as the most important causative factors of LRTIs, such as *Haemophilus influenzae, Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus, Klebsiella pneumoniae,* etc., so similar results were obtained in several studies on clinical efficacy of cefpodoxime in an outpatient treatment of bacterial LRTIs. The relevance of these findings increases in the light of growing resistance rate of *Streptococcus pneumoniae* and *Haemophilus influenzae* to penicillins and macrolides, which in some regions exceeds 30%[29].

We registered a high clinical success rate (81.8%) in our study on efficacy and safety of cefpodoxime in an outpatient treatment of AECOPD performed in 2014[30]. As similar results were obtained in several studies on efficacy of cefpodoxime in an outpatient treatment of bacterial AECOPD performed in the last two decades, it is considered as a first-line empiric antibiotic for outpatient treatment of patients with AECOPD who are unlikely to have infection with *Enterobacteriaciae* or *Pseudomonas aeruginosa* besides doxycycline, clarithromycin, azithromycin, amoxicillin clavulanate, and cefdinir[31-34]. According to the Johns Hopkins ABX Guide 2017, cefpodoxime is indicated as a first-line antibiotic for treatment of AECOPD caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarhalis*[35].

Current American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) guidelines indicate cefpodoxime as a first-line or second-line antibiotic for empirical treatment of CAP in an outpatient setting, i.e., combined with macrolide or doxycycline in outpatient adults with comorbidities (diabetes, chronic heart, lung, liver, or renal disease, alcoholism, asplenia, etc.) or as a monotherapy in previously healthy adults without comorbidities [22]. Cefpodoxime was not mentioned as an antibiotic of first or second choice for an outpatient treatment of CAP in the European and American guidelines created in the first decade of this century[36-38]. On the other side, in the Japanese Manual of Prescription for Antibacterial Drugs prepared at that time, cefpodoxime was indicated as a first-line drug (categorized as Class I and Class II) for ambulatory patients with CAP[13].

According to the current consensus guidelines, AEBX in an outpatient setting should be treated 14 days with antibiotic therapy guided by previous sputum microbiology[39]. Results obtained in the present study indicated a high clinical success rate in patients with AEBX. To our knowledge, in the existing literature there is no

published survey on clinical efficacy of cefpodoxime in an outpatient treatment of AEBX so there is a need of further investigations in this domain.

Incidence of adverse effects in the present study varied from 8.6% to 12.5% that is in the range of data published in the existing evidence[12,14,15]. Side effects which occurred in all patients were mild and did not require discontinuation of the treatment with cefpodoxime.

Results of the present study must be interpreted in the context of its limitations. First, the study design, since the study was neither blinded nor randomized and, therefore, can be a subject to possible selection bias. Second, a small number of the study subjects may have certain implications on data obtained and its interpretation. On the other hand, the study design may be its strength, as it is documented by other real life-studies. In addition, an investigation of clinical efficacy and safety of cefpodoxime in an outpatient treatment of a few bacterial LRTIs may also be the strength of the study.

Conclusion

In conclusion, in an observational, non-randomized, open-label study (a real-life study) aimed to assess clinical efficacy and safety of cefpodoxime in the outpatient treatment of LRTIs (AECOPD, CAP and AEBX) of bacterial origin we found a high clinical success rate and a low incidence of side effects. Our findings support the use of cefpodoxime as a first-line antibiotic in an outpatient treatment of bacterial LRTIs.

Ethical Approval

The Ethics Committee of the Institute of Occupational Health of R. North Macedonia, Skopje gave approval for performing the study and publishing the results obtained (03-0302-148 - 12.02.2020).

Competing Interests

All authors hereby have declared that no competing interests exist.

Authors Participations

JM and SS participated in the study design, writing the protocol, data collection, managing the analyses of the study, and 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. JM, SS, DM, and DB participated in data collection. All authors read and approved the final manuscript.

References

1. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. *Clin Microbiol Infect* 2011; 17 (6): E1-E59.
2. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; 26: 1138-1180.
3. Acute lower respiratory infections. In: European Lung White Book. Sheffield, UK: *European Respiratory Society*, 2020.

4. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: A systematic analysis for the global burden of disease study 2015. *Lancet* 2016; 388: 1459–1544.
5. Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: A literature review. *Thorax* 2013; 68: 1057–1065.
6. Global Initiative for Chronic Obstructive Lung Disease 2020 Report. Available at: *www. goldcopd.org/* (Accessed 12.09.2020).
7. Chalmers JD, Aliberti S, Blasi F, et al. Management of bronchiectasis in adults. *Eur Respir J* 2015; 45: 1446-1462.
8. Musher DM, Thorner AR. Community-acquired pneumonia. *N Engl J Med* 2014; 371: 1619–1628.
9. Miravittles M, Llor C, Naberan K, et al. 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.
10. Polverino E, Goeminne PC, McDonnell M, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017; 50: 1700629.
11. Cefpodoxime. Available at: *www.drugs.com* (Accessed 28.12.2020).
12. Geddes AM. Cefpodoxime in the treatment of lower respiratory tract infections. *Drugs* 1991; 42: 34-40.
13. Niki Y, Kawanishi M. Clinical efficacy of cefpodoxime proxetil against community-acqured pneumonia. *Jpn J Chemother* 2005; 53 (7): 403-411.
14. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol* 2011;64:395–400.
15. Wong T. Cephodoxime proxetil (January 1, 2017). Available at: *www.reliasmedia.com/* (Accessed 14.09.2020).
16. Minov J, Karadzinska-Bislimovska J, Petrova T, et al. Efficacy and tolerability of eight antimicrobial regimens in the outpatient treatment of exacerbations of chronic obstructive pulmonary disease. *Maced J Med Sci* 2014; 7 (3): 519-524.
17. Minov J, Stoleski S, Petrova T, et al. Moxifloxacin in the outpatient treatment of moderate exacerbations of chronic obstructive pulmonary disease. *OA Maced J Med Sci* 2018; 6 (11): 2017-2022.
18. Minov J, Stoleski S, Petrova T, et al. Efficacy and safety of levofloxacin in the outpatient treatment of exacerbations of chronic obstructive pulmonary disease: levofloxacin 750 mg vs. levofloxacin 500 mg. *Health Prim Care* 2020; 4: 1-5.
19. Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. Chichester, UK: John Wiley & Sons Ltd, 2017.
20. Acute lower respiratory infections. In: European Lung White Book. Sheffield, UK: ERS, 2020.
21. Anthonisen NR, Menfreda J, Warren CP, et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106 (2): 196-204.

22. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Acults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Disease Society of America. *Am J Respir Crit Care Med* 2019; 200 (4): e45-e67.
23. Pasteur MC, Bilton D, Hill AT, et al. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010; 65: (1): i1–i58.
24. Hill AT, Haworth CS, Aliberti S, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J* 2017; 49: 1700051.
25. WHO Report on the Global Tobacco Epidemic, 2019, Geneva: World Health Organization, 2019.
26. Calculate your Body Mass Index. Available at: *https://www.nhlbi.nih.gov* (Accessed 28.12.2020).
27. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: A systematic analysis for the global burden of disease study 2015. *Lancet* 2016; 388:1459–544.
28. Minov J. Smoking among Macedonian Workers. Saarbrücken: LAP LAMBERT Academic Publishing, 2013.
29. Antibiotic resistance in the European Union and European Economic Area (EARS-Net) 2018. Available at: *www.ecdc.europa.eu/* (Accessed 29.12.2020).
30. Ефикасност и подносливост на цефподоксимот во амбулантското лекување на егзацербациите на хроничната опструктивна белодробна болест [Efficacy and tolerability of cefpodoxime in the outpatient treatment of exacerbation of chronic obstructive pulmonary disease, in Macedonian]. *Vox Medici* 2014; 82: 304-309.
31. Aaron SD. Management and prevention of exacerbations of COPD. *BMJ* 2014; 349:g5237.
32. Wedzicha JA, Miravitlles M, Hurst JR, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline *Eur Respir J* 2017; 49(3): pii:1600791.
33. Putcha N. Medication regimens for managing COPD exacerbations. *Respir Care 2018*; 63 (6): 773-779.
34. Dobler CC, Morrow AS, Beuschel B, et al. Pharmacologic therapies in patients with exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 2020; 172 (6): 413-423.
35. Johns Hopkins ABX Guide 2017. Available at: *www.hopkinsguides.com* (Accessed 21.12.2020).
36. Bartlett JG, Dowell SF, Mandell LA et al. Practice Guidelines for the Management of Community acquired Pneumonia in Adults. Guidelines from the Infectious Disease Society of America. *CID* 2000; 31: 347-382.
37. Systemic antibiotic treatment in upper and lower respiratory tract infections: official French guidelines. Copyright by the European Society of Clinical *Microbiology and Infectious Diseases CMI* 2003; 9: 1162-1178.

38. Lim WS, Baudouin SV, George RC, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; 64 (Suppl. III): iii1-iii55.
39. Chalmers JD, Aliberti S, Blasi F. Management of bronchiectasis in adults. *Eur Respir J* 2015; 45: 1446-1462.