

Exacerbation of Chronic Obstructive Pulmonary Disease: A Role of Antibiotics?

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ABSTRACT

In order to discuss a role of antibiotics, a 73-year old patient was presented, having an exacerbation of Chronic Obstructive Pulmonary Disease (COPD) and to whom amoxicillin/clavulanate antibiotic was prescribed. Literature search has indicated that antibiotics are recommended for COPD patients in two cases. Firstly, they are recommended in the patients having an acute exacerbation with increased dyspnoea, sputum volume, and sputum purulence. Common options usually include amoxicillin, amoxicillin/clavulanate, azithromycin, and doxycycline. Secondly, it is also recommended for preventive purposes in patients with severe COPD having frequent exacerbations. But, still remain uncertainty on the antibiotic used in outpatients, having mild or moderate COPD.

Key words: COPD, exacerbation, antibiotics, preventive use of antibiotics

Introduction

A chronic obstructive pulmonary disease (COPD) is common conditions seen in family medicine (FM) characterized by shortness of breath, cough, and sputum production. A prevalence in adult populations is around 5%, therefore average family doctor (FD) could expect to have around 50 to 100 patients in his/her practices¹. In 2012, it ranked as the third-leading cause of death¹. As in many other chronic diseases, several problems are challenging the patients and the doctors too. The very often multiple drug therapy, lasting along the whole life-span is sometimes difficult for the patients to adhere and adjust to. But, one of the most challenging is the smoking, important for ethyology and prognosis of the disease. In spite of research results, everyday experience with patients is not promising about smoking cessations². Another, also challenging moment in dealing with COPD patients, is the frequent exacerbations, usually needing antibiotic treatment³. Does the patients need to be treated with antibiotics in every exacerbation and how to choose the antibiotics is very challenging, especially for FDs working in a low technological environment. Therefore, the aim of this case report is to present a patient case in the light of evidence-based of antibiotic use.

Case Report

My well-known, 73-year old patient, asked me for home visit because of increased shortness of breath,

raised temperature (37.7 °C), extensive caught and purulent sputum. Six years ago, a COPD was diagnosed, mainly related to smoking of two boxes of cigarettes for more than 30 years. At that time, a FEV1 was at the level of 71%, and a FEV1/FVC of 67%. There were no symptoms and signs of a cor pulmonale. He started therapy with teofilinum, tiotropium and salbutamol if he felt dyspnoea. He decreased the number of cigarettes, but never stopped smoking. He also refused a flu vaccination. Because of the deterioration of hepatic enzymes and because of the frequent respiratory infections, his therapy was several times changed, presently taking long acting β agonist (LABA, Serevent) or long acting anti-muscarinic (LAMA, Spiriva) bronchodilators and inhaled corticosteroid, fluticasone.

Physical examination, performed at home visit, indicated more frequent breathing then usually (around 24/min), bronchial sound all over the chest, wheezing and prolonged expiration. Puls-oxymeter indicated oxygen saturation at the level of 93%.

A similar situation is usually happening to him several times a year, once he had to be hospitalized because of pneumonia. Having experience of such situations and taking into the account his resistance to hospitalization, amoxicillin with clavulonic acid was prescribed, as well as salbutamol and oral corticosteroids. It was also recommended to continue with LABA and LAMA, but to stop

fluticasone inhalation. After two hours, he has made phone call telling that he felt better, shortness of breath and cough is also going better. During the next several days, he completely recovered and continues with his regular therapy.

Discussion and Conclusion

It is not only this patient who make doctors to think on the role of antibiotics in the treatment of COPD exacerbations, because it can accelerate lung function decline, decrease quality of life, and, when severe, increase mortality⁴. Infections cause an estimated 50 to 70% of COPD exacerbations, therefore the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend using antibiotics to treat exacerbations in patients with moderate or severe COPD who have increased dyspnoea, sputum volume, and sputum purulence⁵. Furthermore, the costs of exacerbation are usually higher in patients not treated with antibiotic, mainly because of hospital care; 9.6% of the costs for drugs and 72.9% for hospital care⁶.

The needs for antibiotic use in COPD exacerbation were found in the review studies too. WITHDRAWN review shows that in COPD exacerbations with increased cough and sputum purulence, antibiotics, regardless of choice, reduce the risk of short-term mortality by 77%, decrease the risk of treatment failure by 53% and the risk of sputum purulence by 44%; with a small increase in the risk of diarrhea. But, they pointed that the results should be interpreted with caution due to the differences in patient selection, antibiotic choice, small number of included trials and lack of control for interventions that influence outcome, such as use of systemic corticosteroids and ventilator support. Nevertheless, this review supports antibiotics for patients with COPD exacerbations with increased cough and sputum purulence who are moderately or severely ill⁷. In recent, Cochrane Database Systematic Review done in 2012, the sixteen trials with 2068 participants were included; outpatients considering to have a mild to moderate exacerbation, and inpatients to have a severe exacerbation and intensive care unit (ICU) patients to have a very severe exacerbation. The author's conclusion should be formulated in a way that antibiotics for COPD exacerbations showed large and consistent beneficial effects across outcomes of patients admitted to an ICU. However, for outpatients and inpatients the results were inconsistent. The risk for treatment failure was significantly reduced in both inpatients and outpatients when all trials (1957 to 2012) were included but not when the analysis for outpatients was restricted to currently used antibiotics. Also, antibiotics had no statistically significant effect on mortality and length of hospital stay in inpatients and almost no data on patient-reported outcomes exist. These inconsistent effects call for research into clinical signs and biomarkers that help identify patients who benefit from antibiotics and patients who experience no effect, and in whom downsides of antibiotics (side effects, costs and multi-resistance) could be avoided⁸.

According to other studies as well as to the GOLD guidelines, the choice of antibiotic is usually based on doctors' experience and the local situation^{5,9,10}. Common options usually include amoxicillin, amoxicillin/clavulanate, azithromycin, and doxycycline^{4,11}. In spite of this, antibiotics' choice is still under debate. A study done by Llor and colleagues, provide the evidence that treatment of ambulatory exacerbations of mild-to-moderate COPD with amoxicillin/clavulanate is more effective and significantly prolongs the time to the next exacerbation compared with placebo⁴. Blasi and colleagues concluded that both prulifloxacin and levofloxacin showed efficacy rates higher than 90% in the treatment of severe COPD patients with exacerbations of chronic bronchitis, with no statistically significant differences between the two antibiotics¹². The similar situation is with levofloxacin versus cefuroxime¹³. Looking at those studies, one can make a conclusion that if the broad range of antibiotics is appropriate to use, the choice should be based on side-effects, easy administration, availability, but also the antibiotics' costs and the availability of public or patients resources¹⁴.

Another question related to the described patients' case is also about the preventive use of antibiotics. Does he need to take some antibiotics regularly? Again, Cochrane Database Systematic Review from 2013, based on seven RCTs, involving 3170 patients brought some lights. They concluded that the continuous prophylactic use of antibiotics results in a clinically significant benefit in reducing exacerbations in COPD patients. They pointed out, that all trials of continuous antibiotics used macrolides hence the noted benefit applies only to the use of continuous macrolide antibiotics. The impact of pulsed antibiotics remains uncertain and requires further research. The trials in this review included patients who were frequent exacerbates and needed treatment with antibiotics or systemic steroids, or who were on supplemental oxygen. There were also older individuals with a mean age of 66 years. The authors pointed out, that results of these trials apply only to the group of patients who were studied in these trials and may not be generalizable to other groups. Because of concerns about antibiotic resistance and specific adverse effects, consideration of prophylactic antibiotic use should be mindful of the balance between benefits to individual patients and the potential harms to society created by antibiotic overuse¹⁵. Similar results come from the study of Han and colleagues. They have found out that daily azithromycin decreases acute exacerbations of chronic obstructive pulmonary disease (AECOPD), but long-term side effects are unknown¹⁶. In UK, the most commonly used long-term antibiotics were oxytetracycline, doxycycline, and penicillin. Azithromycin, erythromycin, and clarithromycin were less frequently used. There was little evidence of the use of rotating courses of antibiotics. It is also found that men, people aged 50–79 years, non-smokers, and patients with poorer lung function were more likely to receive long-term antibiotic treatment. But, rel-

atively few COPD patients are currently prescribed long-term antibiotics in UK¹⁷.

Long-term or intermittent antibiotic treatment has been shown to prevent COPD exacerbations and hospitalizations. These effects may be achieved by reducing bacterial load in the airways in stable state and/or bronchial inflammation. Although systemic antibiotics are likely to remain the core treatment for patients with moderate to severe exacerbated COPD, inhaled antibiotics may represent a more optimal approach for the treatment and prevention of COPD exacerbations in the future^{17,18}. The budget impact analysis demonstrated that annual hospital savings of 950 million resulting from fewer exacerbations outweighed additional expenditure on azithromycin of 595 million, implying that the prevention of COPD exacerbations with azithromycin is a cost saving strategy in Belgium¹⁹.

Although, the aim of this study is to find out the evidence on the role of antibiotics in the exacerbation of COPD, a role of other treatment options should not be forgotten. As Aaron pointed out in his review paper, no obvious benefit has been seen in recent clinical trials of anti-tumor necrosis factor therapy, anti-leukotriene therapy, intensive chest physiotherapy, or early inpatient pulmonary rehabilitation for treatment of exacerbations. By contrast, clinical trials of prevention rather than acute treatment have shown promising results. Long acting β agonist (LABA) or long acting anti-muscarinic

(LAMA) bronchodilators and inhaled corticosteroid-LABA combinations prevent exacerbations in patients at risk, with relative risk reductions averaging 14–27% for each of these drugs relative to placebo. Triple therapy with inhaled corticosteroid-LABA plus LAMA may provide additional benefit, although study results to date are heterogeneous and more studies are needed. Pneumonia is an important complication of treatment with inhaled corticosteroid-LABA products, and the risk of pneumonia seems to be doubled in patients with COPD who use fluticasone. The addition of azithromycin to usual COPD therapy prevents exacerbations, although it may prolong the Q-T interval and increase the risk of death from cardiovascular disease in patients prone to arrhythmia. New potential drugs, including mitogen activated protein kinase inhibitors, phosphodiesterase 3 inhibitors, and monoclonal antibodies to the interleukin 1 receptor, offer additional hope for treatments that may prevent exacerbations in the future²⁰.

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EGZACERBACIJA KRONIČNE OPSTRUKTIVNE PLUĆNE BOLESTI: ULOGA ANTIBIOTIKA?

S A Ž E T A K

Prikazan je primjer 73-godišnjeg pacijenta u egzacerbaciji kronične opstruktivne plućne bolesti (COPB) kojemu je propisana antibiotska terapija s namjerom da se prodiskutira uloga antibiotika u egzacerbaciji COPB. Sukladno literaturi, primjena antibiotika je poželjna u dva slučaja. Prvo, u akutnoj egzacerbaciji, i to najčešće amoxicillin, amoksicilin/klavulonska kiselina, azitromicin, i doksiciklin. Drugi je slučaj preventivnog uzimanja, osobito u slučajevima teških oblika COPB, s čestim egzacerbacijama, najčešće makrolida. Međutim, još uvijek postoji dilema primjene antibiotika kod blagih i umjerenih oblika bolesti i u uvjetima primarne zdravstvene zaštite. Izgleda da je najoptimalniji individualan pristup pacijentu, temeljan na stanju pacijenta i iskustvu liječnika.