Editorial

Doxycycline for outpatient-treated acute exacerbations of COPD: does it offers any additional value?

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Despite its accepted role, a number of controversies persist regarding the use of antibiotics for exacerbations of chronic obstructive pulmonary disease (COPD). The adequate selection of patients, the identification of biomarkers for treatment response, the adequacy to disease and exacerbation severities or the short-term impact on the exacerbation outcome in different settings remain some of the aspects under current debate (1,2). One specific topic that warrants investigation is the potential long-term impact of antibiotic prescription during exacerbations, specifically on the prevention of subsequent exacerbations. The question about whether a specific treatment during the exacerbation can have an impact on the long term preventing future acute episodes is intriguing. Beyond the potential rationale behind, the topic results to be not easy to face, since a number of factors associated with subsequent exacerbations or with re-admissions after an index event are well-known (3).

Recently, van Velzen *et al.* (4) have published a clinical trial to investigate if the antibiotic doxycycline added to the oral corticosteroid prednisolone prolongs time to next exacerbation in patients with COPD receiving treatment for an exacerbation in the outpatient setting. By using a randomized double-blind placebo-controlled design, the authors recruited a cohort of patients with COPD from different outpatient clinics in the Netherlands who were followed-up for 2 years. During the follow-up, whenever an exacerbation appeared, the case was randomly assigned to a 7-day course of oral doxycycline 100 mg daily (200 mg on the first day) or placebo. Additionally, patients in both groups received a 10-day course of 30 mg oral prednisolone daily. The hypothesis to be tested was that doxycycline therapy would be able to reduce the time to the next exacerbation as the primary endpoint.

During the study, the authors were able to randomize 305 patients out of 887 patients in the cohort, that experimented 561 exacerbations. The results of the study clearly failed to show a significant difference in the primary outcome. In this trial doxycycline added to the oral corticosteroids (OCS) prednisolone did not prolong time to next exacerbation compared with prednisolone alone. This finding was consistent across all subgroups tested. Additionally, the authors did not observe significant effects of doxycycline on any of the secondary outcomes, including treatment non-response at day 21 and 84, mortality, quality of life, and lung function decline. Total antibiotic use over the 2 years of follow-up, however, was twice as high in patients randomly allocated to doxycycline as in those randomly allocated to placebo.

Although antibiotics have proven to be of benefit in patients hospitalized, their impact in the community for non-severe exacerbations is under debate. Findings from a systematic review (5) showed that antibiotics for acute exacerbations of COPD reduced treatment non-response and mortality in patients admitted to hospital, but not in outpatients receiving treatment for mild-to-moderate

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exacerbation. Interestingly, van Velzen *et al.* (4) declare in the discussion section of the paper that if the results from this study was added to those from this Cochrane review, short-term treatment nonresponse would significantly be lower in the doxycycline group than in the placebo group, with a risk ratio of 0.77 (95% condifence interval: 0.63–0.94; P=0.01) (4). Therefore, this new trial adds evidence to the debate behind. In the light of the data provided, some comments can be of interest to discuss.

First, although the primary endpoint was the time for the next exacerbation, the short-term efficacy of doxycycline was not thoroughly evaluated. Previous clinical trials have reported that the use of antibiotics for exacerbations in the community have yielded positive results. A recent analysis showed that the use of antibiotics for COPD exacerbations in the community resulted in cost savings and an improvement in all outcomes analyzed including general practitioner visits, hospitalizations, community respiratory team referrals, infections and subsequent antibiotics prescriptions that were lower for the antibiotics group (6). Notably, the economic analysis in this paper suggested that the use of antibiotics for COPD exacerbations is a cost-effective alternative to not prescribing antibiotics for patients who present to their general practitioner, and remains cost-effective when longer time horizons of 3 and 12 months are considered (6). Therefore, concluding that antibiotic use is not supported in van Velzen *et al.* study because their results fail to find an association with re-exacerbation is probably going too far. Of note, we already have treatments to prevent exacerbation. Some of these are bronchodilators, corticosteroid-containing regimens, phosphodiesterase 4 inhibitors, anti-infectives, mucoregulators, and non-pharmacological approaches including smoking cessation, rehabilitation, and lung volume reduction (7). The question arises whether we should select the exacerbation therapies based on the short-term efficacy of the exacerbation and select other treatments to prevent future exacerbations. In this regard, it has been strengthened that a close post-exacerbation visit should be scheduled to re-evaluate the case, confirm the diagnosis and assess long-term treatments (8-10).

Second, the antibiotic tested was doxycycline. Randomized, placebo-controlled trials of the effects of antibiotics on exacerbations in patients with well-defined COPD are scarce. Of the two main published trials (11,12), only one (12) considered time to next exacerbation as a secondary outcome using amoxicillin and clavulanate. In this trial, time for the next exacerbation was significantly longer in the active group (233 days) than in the placebo group (160 days). Although in the Netherlands doxycycline is a first-choice antibiotic for COPD exacerbation treatment since resistance of common pathogens causing COPD exacerbations is rare and the posology is convenient, it is possible to speculate that different antibiotics may yield different long-term effect on COPD exacerbations.

There are some factors that may explain the different outcome of these two clinical trials (4,12). Both the type and the severity of the exacerbations should be considered (13). Recent advances into the understanding of the clinical presentation of COPD in stable disease and during exacerbations have shown that there is variability in the inflammatory response underneath with potential implications for management. Since the seminal study by Bafadhel *et al.* (14), different authors have consistently evaluated different exacerbations types according to different criteria (15-18). Some authors have proposed a simpler scheme with neutrophilic and eosinophilic exacerbations as the main exacerbation types that would need different therapeutic scheme (19). According to this hypothesis, COPD patients with neutrophilic exacerbations would experience worse clinical outcomes than eosinophilic exacerbations, in which the peripheral blood eosinophil count may be a useful predictor of clinical progress of this exacerbation. Therefore, the type of exacerbation is extremely relevant to analyze short-term clinical outcomes and long-term influence on subsequent exacerbation.

Accordingly, one key element to consider would be to identify exacerbations caused by a bacterial infection, since this would strongly advice about the use of antibiotics (13). Unfortunately, at present, we do not have a rapid on-site tool that is able to correctly identify those exacerbations caused by a bacterial infection and the classical Anthonisen criteria (11) are still accepted for daily practice. Although the results in the study by van Velzen *et al.* (4) did not find different results in those patient with and without purulent sputum, whether this implies that the response is the same in bacterial and non-bacterial infections or that sputum purulence is simply a bad marker of bacterial infection needs further scrutiny. Of note, previous analysis has shown that in fact the latter might be the case (20).

Fortunately, some biomarkers are under investigation for the selection of antibiotics with promising results. One of the most promising is procalcitonin. Serum procalcitonin concentrations are increased and return quickly to normal in response to antibiotic treatment in patients with acute respiratory tract infections (21). Further, in these patients,

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procalcitonin-guided antibiotic treatment reduces antibiotic exposure and antibiotic side-effects with similar clinical efficacy (22-27). However, procalcitonin concentrations do not distinguish between bacterial, viral, and non-infectious causes of COPD exacerbations (28,29). Although, in patients with COPD exacerbations admitted to an intensive-care unit, procalcitonin seemed to be a better marker than C-reactive protein to predict the presence of airway infection (30).

Similarly, the severity of subsequent exacerbations may also be worth discussing. Although van Velzen *et al.* (4) do not provide evidence on the severity of subsequent exacerbation as compared to the index one after antibiotic therapy, it is possible that although the number or the delay may be similar between the two arms, the severity of the subsequent exacerbations for those patients receiving Doxycycline might be different. Of note, to have an objective assessment on the severity of the exacerbations, proper validated tools to assess exacerbation severity should be used. At the moment, there are quite a few number of scores that allow us to stratify exacerbation severity at the emergency room (31-34). Regrettably, there are no scores available for the evaluation of exacerbation severity that has been validated in the community, which remains being a challenge for clinicians.

Finally, comorbidities need to be placed in the equation to complete the picture. The relationship between different comorbidities and the presence of an exacerbation is outstanding, not only for being a recognized risk factors for exacerbations, but also due to the un-specificity of exacerbation symptoms that might be hiding different conditions different from an exacerbation itself. Most concomitant chronic diseases share with COPD clinical manifestations like fatigue and dyspnea. For this reason, in patients with comorbidities, the exacerbation of respiratory symptoms may be particularly difficult to investigate, as it may be caused by exacerbation of COPD or a comorbidity without necessarily involving the respiratory system (35). In fact, it has been acknowledged that not every increase in symptoms reflects an exacerbation (36,37). Although not exclusive, this is especially relevant for cardiovascular conditions. Accordingly, several initiatives and algorithms have been proposed to consider comorbidities in the management of exacerbations (38) and should always be considered and ruled out in exacerbation-related trials.

In summary, although antibiotic treatment continues to be one of the pillars of the pharmacological treatment of the exacerbation of COPD, at the present time, there are still several controversial aspects in relation to the best selection of candidate patients, the short-term efficacy and its long-term impact on the future progression of the disease. In the future, upcoming studies should elucidate on these relevant issues, so that we are able to provide the best treatment for each patient and clinical context.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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