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# C-reactive protein point of care testing: the answer to antibiotic prescribing in ambulatory patients with exacerbations of chronic obstructive pulmonary disease?

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## 1. Introduction

Antimicrobial resistance is a growing problem threatening human health. Inappropriate antibiotic use is the main driver of the growing development and spread of antimicrobial resistance, but may also cause adverse effects, negatively affect the microbiome of patients, and importantly, distracts from potentially more effective interventions. Moreover, infections with antibiotic-resistant bacteria are associated with an increased risk of complications and mortality. For example, in vulnerable patients with chronic obstructive pulmonary disease (COPD), exposure to antibiotics has been linked to a predisposition to airway colonization by multidrug-resistant bacteria, which may subsequently cause pneumonia [1]. The World Health Organization has acknowledged the optimization of the use of antibiotics as one of the five pillars to control antimicrobial resistance [2].

As many as two-thirds of all cases of ambulatory exacerbations of COPD (ECOPD) may be due to noninfectious or viral infections as bacterial pathogens cannot be detected in most exacerbations. Even in the hospital setting, noninfectious factors may account for approximately one fifth of ECOPD [3]. However, more than 80% of these patients in affluent countries receive antibacterial prescriptions [4]. There is therefore reason to believe that many of these prescriptions could be avoided, in particular in primary care [5].

## 2. Anthonisen criteria for prescription of antibiotics in ECOPD

The dilemma is to identify which patients are most likely to benefit from antibiotics while avoiding unnecessary antibiotic use. The landmark study, published by Anthonisen et al. in 1987, found a significant benefit from antibiotics for patients with the presence of three criteria (i.e. increased dyspnea, increased volume and purulence of sputum), and to a lesser extent for those with two criteria [6]. The European Respiratory Society/American Thoracic Society guidelines on management of COPD exacerbations suggest the administration of antibiotics for ambulatory ECOPD [7]. The evidence supporting this recommendation comes from the evaluation of studies that shows

a reduction of the risk of failure and increased time between exacerbations with antibiotics, particularly when the episodes present with purulent sputum and taking into account the severity of COPD.

Therefore, decisions regarding antibiotic use in an individual patient with ECOPD should be based on the pretest probability for bacterial infection, which is usually based on clinical examination and severity of the underlying disease. However, clinicians working in the outpatient setting may not actually see either the sputum specimens or the lung function tests and, thus, may not be able to adequately address the type of exacerbation and the severity of the baseline disease.

## 3. Role of biomarkers in exacerbations of COPD

Due to the limitations and lack of specificity of the clinical manifestations of ECOPD there has been an intense research on biomarkers to help in clinical decisions. Since ECOPD are associated with increased local and systemic inflammation, there has been an interest in finding systemic biomarkers, which can predict etiology, disease severity and/or outcome [3]. Various biomarkers have been studied, but the majority have failed to predict clinical outcomes. In contrast, Hurst et al. found that C-reactive protein (CRP) was increased in ECOPD and was the best biomarker to differentiate an exacerbation from a stable condition [8]. Regarding prognosis of ECOPD, a recent meta-analysis, including 10 studies, confirmed that COPD patients with higher baseline CRP levels have a higher risk of early mortality, with a hazard ratio of 1.17 (95% CI, 1.06–1.28) [9]. Serum CRP levels at baseline also predict in-hospital mortality in very severe COPD patients [10].

Regarding etiology there is increasing interest in the role of blood eosinophil counts (BEC) as a marker of inflammatory exacerbations [11]. Several studies have shown that patients with higher BEC are more likely to have no bacteria or lower bacterial counts during exacerbations and stable state compared with patients with low BEC [12]. Therefore, COPD patients with this eosinophilic profile, also known as mixed COPD-asthma phenotype (ACO) are less likely to require antibiotics during ECOPD, particularly if exacerbations do not present with purulent sputum.

Several randomized trials have found use of procalcitonin to result in a significant reduction of antibiotic usage with a similar resolution of clinical symptoms in patients with respiratory infections, including ECOPD [13]. However, some studies suggest that CRP can be more reliable to identify bacterial infection in the case of ECOPD and procalcitonin cannot be considered as a rapid test since obtaining the result takes longer than the average duration of outpatient consultations and, therefore, it is not useful in clinical practice in primary care [14].

#### 4. Use of C-reactive protein results in a reduction of unnecessary antibiotics

Point-of-care tests are being promoted by government organizations and by clinical guidelines to better target antibiotic prescribing and help contain antimicrobial resistance. CRP is an acute-phase protein that can be measured within three minutes at the point of care and has shown to safely reduce antibiotic prescribing for more common infections, mainly in lower respiratory tract infections. Interestingly, a 2015 survey showed that countries that employed a rapid test of CRP in primary care in Europe were also the 12 lowest prescribers of antibacterials [15]. Based on 10 randomized clinical trials, performing CRP rapid testing resulted in a significant reduction of antibiotic prescriptions given at the index consultation, with a pooled effect estimate risk ratio of 0.81 (95% CI, 0.71–0.92). However, when the use of CRP is accompanied by evidence-based clinical guidance on interpretation, even a greater reduction of unnecessary antibiotic prescribing is achieved [16].

Regarding the use of the CRP rapid testing in ECOPD, a recent randomized clinical trial performed in the UK, compared CRP guidance or usual care in a total of 653 outpatients with COPD. For those in the CRP group, doctors were advised to withhold antibiotics with CRP concentrations below 20 mg/l, and consider them as slightly beneficial between 20 and 40 mg/l if purulent sputum is present and beneficial with CRP levels >40 mg/l. The CRP-guided strategy resulted in a 20% absolute reduction in patient-reported antibiotic consumption over 4 weeks (57% vs. 77%) [17]. Despite the reduction in antibiotics, health care utilization outcomes or measures of patient well-being at 6 months did not differ meaningfully between the trial groups. In addition, CRP rapid testing was broadly acceptable to patients and doctors. In this study, there may have been potential for further safe reductions in antibiotic use, since one-third of the participants with low CRP concentrations were still inappropriately prescribed antibiotic therapy.

#### 5. Redefining the Anthonisen criteria for antibiotic prescribing in COPD exacerbations

The landmark Anthonisen's trial has been the basis of recommendations for antibiotic treatment of ECOPD during the last 30 years [7,18]; however, patients were recruited from hospitals and they had severe to very severe COPD with a mean forced expiratory volume in the first second (FEV1) of only 33% predicted [6]. In order to verify the validity of the Anthonisen's criteria in a population of patients with ECOPD more

representative of those attended in primary care, a placebo-controlled randomized trial on mild to moderate ambulatory COPD patients (mean FEV1 of 65% predicted) was conducted. The results showed a significant effect of antibiotics, but only purulence of sputum and high CRP were independent predictors of the need for antibiotics, with the best CRP cut off for predicting the need for antibiotics being 40 mg/L [19].

The analysis of the placebo group of this study showed that the purulence of sputum and a CRP>40 mg/L were associated with an increased risk of failure without antibiotics (odds ratios 6.1 and 13.4, respectively). But more interestingly, the predictive value of the classical Anthonisen criteria for the need of antibiotic showed an area under the curve (AUC) of 0.708, but with the addition of CRP levels the AUC increased significantly to 0.842 [20]. These results indicate that two of the classical Anthonisen criteria, namely increase in dyspnea and in sputum volume, have no role in predicting the need for an antibiotic, and only the increase in purulence and a high CRP level are reliable as indicators for the need of antibiotic therapy in ambulatory ECOPD. The demonstration of low BEC may add even more precision to determine the need for antibiotics in this clinical situation.

#### 6. Implications for clinical practice

Outpatients with ECOPD should not be treated with antibiotics as standard therapy, since there is now compelling evidence that CRP testing, with the associated guidance for clinicians on how to interpret the results, is able to safely reduce unnecessary antibiotic use in these patients. However, in the context of a low risk situation and a low pretest probability for bacterial infection, such as in patients with COPD and a known eosinophilic or ACO phenotype and no sputum or clear sputum, CRP rapid testing may not be necessary.

In patients with an uncertain etiology, mainly when color of sputum cannot be assessed, CRP rapid testing should be recommended, as a low CRP level can aid in ruling out bacterial infection. In case of intermediate CRP levels, the presence of purulent sputum and the evidence of low BECs in clinical records favor antibiotic prescription. These recommendations will help health-care professionals to make responsible prescribing decisions, which will not only help people manage their condition but also reduce the risk of antimicrobial resistance.

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