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Journal club

Can we use a biomarker to guide antibiotic treatment in severe COPD exacerbations?

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Commentary on:

Prins HJ, *et al.* CRP-guided antibiotic treatment in acute exacerbations of COPD in hospital admissions. *Eur Respir J* 2019; 53: 1802014.

Context

The decision to treat acute exacerbation of chronic obstructive pulmonary disease (AECOPD) with antibiotics is often controversial. In previous trials, evidence still favoured the use of antibiotics in critically ill patients admitted to intensive care units for very severe COPD exacerbations [1], and inconclusive for inpatients with severe exacerbations [2, 3] and outpatients with mild to moderately severe exacerbations [4]. According to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria, the presence of purulent sputum is mandatory to initiate patients antibiotics in AECOPD [5]. However, this recommendation is unreliable and subjective as the presence of purulent sputum is not pathognomonic of a bacterial cause of exacerbation. Clinicians are often tempted to prescribe antibiotics when patients present with worsening symptoms of AECOPD, which may not necessarily be triggered by bacterial or viral infections. Overprescription of antibiotics in AECOPD poses the risk of antimicrobial resistance, increased cost for patients and health systems, and safety issues.

Earlier, it was reported that a 30% reduction in antibiotic prescription would lead to a reduction in antimicrobial resistance [6]. The challenge has been how to identify patients who are most likely to benefit from antibiotics while minimising unnecessary use of antibiotics. C-reactive protein (CRP), B-type natriuretic peptide and procalcitonin (PCT) are useful biomarkers that have been investigated for this purpose. For instance, an antibiotic-sparing effect has been reported when the decision to use antibiotics was guided by PCT [7]. Serum CRP better predicted bacterial infection in the lower respiratory tract and was associated with the presence of potential bacterial pathogens in sputum, while PCT was not [8]. CRP testing is cheaper and more readily available in outpatient and inpatient departments of hospitals in many countries [9, 10]. Other authors also suggested that CRP might be used as a marker of significant bacterial infection when deciding whether to start antibiotic treatment. This widely used point-of-care reference has been recommended to guide the use of antibiotics in outpatients who have any two of the three criteria for diagnosing AECOPD [11]. However, these recommendations were not based on robust evidence and did not factor in nonambulatory patients with AECOPD. Given the lack of evidence on the effectiveness of biomarkers in guiding antibiotic prescription and limiting their unnecessary use, how can the use of CRP guide clinicians in deciding whether to initiate antibiotic therapy among patients hospitalised for AECOPD? The findings of the CATCH study by

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C-reactive protein (at values ≥50 mg/L) is a useful and cheap biomarker for making antibiotic decisions in patients hospitalised for an acute exacerbation of COPD with no additional risk of adverse effect or treatment failure #AECOPD http://bit.ly/342p0Nj

Prins *et al*. [12] have helped in addressing this question to a large extent.

Methods

The study was a randomised controlled trial involving 220 patients (119 in the GOLD-guided group *versus* 101 in the CRP-guided group) hospitalised using GOLD criteria for AECOPD across hospitals in the Netherlands between 2011 and 2015 [12]. Patients recruited into the study included individuals older than 40 years and hospitalised for AECOPD as defined by the GOLD criteria. Patients with malignancy, pulmonary embolism, pre-treatment prednisolone >210 mg·day^{-1}, asthma, pneumonia, bronchiectasis or any other infections requiring antibiotics were excluded from the study. Patients were randomised into two groups (the CRP group and the GOLD group). In the CRP group, patients were subject to measurement of CRP on admission and treated with amoxicillin/clavulanic acid 625 mg, three times a day for 7 days when their CRP at entry was ≥50 mg·L^{-1}. Antibiotics were withdrawn in patients with a CRP <50 mg·L^{-1}. 24 h after admission, the CRP value was re-assessed and antibiotics commenced in patients with elevated CRP over 50 mg·L^{-1}. The decision to initiate antibiotic therapy (amoxicillin/clavulanic acid, 625 mg, three times daily for 7 days) in the GOLD group was based on the patient reporting purulent sputum in combination with increased respiratory distress and/or increased sputum volume. The primary outcome measured was the proportion of patients with antibiotic treatment within the first 24 h after hospitalisation and the secondary outcomes were 30-day treatment failure (defined as persistence or worsening of symptoms or death), time to next exacerbation, length of hospital stay, subjective improvement in disease-specific symptoms, and quality of life as measured by the Lower Respiratory Tract Infection Visual Analogue Scale and Clinical COPD Questionnaire on admission and after 1 month respectively.

Results

A total of 1600 patients qualified for the study, out of whom 220 patients were randomised and the others were excluded. The mean age was 70 years. About half were men and the mean forced expiratory volume in 1 s/forced vital capacity was 40%. For the primary outcome, in the CRP group, 31.7% received antibiotics within the first 24 h compared with 46% in the GOLD group, and this was statistically significant. There was absolute reduction of 14.5% in antibiotic usage in the CRP group compared with the GOLD group. The two groups (CRP and GOLD groups) were similar with respect to treatment failure on day 30, length of hospital stay, time to the next exacerbation, adverse reaction, quality of life and perceived improvement in disease-specific symptoms [12].

Commentary

The current study reported a significantly lower antibiotic use in the CRP-guided group than the GOLD group (31.7% *versus* 46.2%) among patients hospitalised for AECOPD [12]. This is equivalent to an absolute reduction of 14.5% in the use of antibiotics. The results are similar to findings among outpatients with AECOPD attending primary care centres across England and Wales [13]. For the initial consultation and during the first 4 weeks of consultation, the England study reported lower usage of antibiotics in the CRP-group compared to the GOLD group (57% *versus* 77.4%) and there was no significant difference in the secondary outcomes measured (quality of life) between the groups [13]. The lower value of antibiotic use in the current study compared to the study from England and Wales is not surprising [12, 13]. First, in the current study, the CRP cut-off point was higher (50 mg·L^{-1} *versus* 40 mg·L^{-1}) and CRP was independently used to determine antibiotic eligibility among AECOPD patients, unlike in the England study, where physicians were instructed to base antibiotic prescription in the CRP group on a comprehensive clinical evaluation of risks and benefits, and not solely on CRP [13]. Consequently, antibiotic use was unexpectedly higher among these outpatients compared with hospitalised patients in the Netherlands study. In addition, in the current study, the proportion of participants with purulent sputum in the GOLD group (46.2%) was less than in the CRP group (61.4%, p=0.025), implying that some more patients with purulent sputum in the CRP group might possibly be spared antibiotics if they did not meet the CRP cut-off point. This supports previous finding that 50% of patients with AECOPD would have normal CRP despite purulent sputum [14]. The CATCH trial findings suggest that antibiotics could be spared through a CRP-guided approach in patients hospitalised for AECOPD. It did not mention which patient population would benefit from antibiotic therapy with respect to secondary treatment outcome or which antibiotics were best for hospitalised patients with AECOPD.

Implication for practice

The current study provides evidence for using CRP as the basis for antibiotic treatment recommendations but the patient populations that would benefit and improve from such treatment are not mentioned. It does, however, tell us that CRP-guided antibiotic treatment of hospitalised patients with AECOPD is a safe way to minimise antibiotic use with no additional risk of adverse events, decreased quality of life, worsening symptoms, re-exacerbation or

prolonged hospital stay. The absolute difference of 14.5% reduction in antibiotic use would mean that approximately 1–2 out of 10 hospitalised AECOPD patients was/were spared antibiotic therapy within the first 24 h of admission. In countries where CRP testing is available as rapid test with quick turnaround, physicians should explore using this strategy. The strategy can also be explored in a broader sense since CRP is also elevated in other suspected lower respiratory tract infections without COPD.

The lack of power of the study limits subanalysis of participant groups for secondary outcomes. For instance, it would have been interesting to determine how various measured outcomes differ by various patient populations (pre-treated with antibiotics, pre-treated with steroids, requiring assisted ventilation, GOLD classes, *etc.*), which were all included in the study. There is, therefore, a need for a more powered trial to address this question. In addition, the study only presented evidence from the use of one antibiotic (amoxicillin/clavulanic acid) within a very low-resistance population in the Netherlands. Susceptibility of strains of bacteria is not static, and varies across time periods and across settings. This limits generalisation of the findings, particularly in resource-poor countries with widespread antibiotic resistance, for instance, to fluoroquinolones. There is therefore the need for head-to-head antibiotic comparison trials (*e.g.* amoxicillin/clavulanic acid *versus* fluoroquinolones) to address this. It is important that the proposed trials harmonise measurement of treatment outcomes and tools with that of the current study to allow for objective comparison across future studies.

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Conflict of interest

V.A. Adepoju has nothing to disclose.

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