DEM Journal Club

Article Appraisal

Article: **CRP testing to guide antibiotic prescribing for COPD exacerbations**

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Background and Study Objective(s):

Patients with chronic obstructive pulmonary disease (COPD) can acutely decompensate for a multitude of reasons. Although 80% of these exacerbations are infectious, many of these won't benefit from antibiotics, as up to 50% of these are viral infections (1). Overuse of antibiotics for respiratory infections is associated with bacterial resistance, and most of these prescriptions come from the primary care setting (2). An exacerbation is defined as an acute worsening of symptoms requiring additional therapy (3). This typically involves the presence of one or more Anthonisen Criteria, which includes increased dyspnea, sputum volume or sputum purulence (4). When indicated, antibiotics can shorten recovery time, length of hospitalization, and reduce the risk of treatment failure (3). Current recommendations suggest that antibiotics be given in patients requiring mechanical ventilation, or in more stable patients when all three Anthonisen criteria are present, or when two are present, one of which must be an increase in sputum purulence (3,4). Because these measures are subjective, finding an objective measure to guide treatment decisions would be ideal.

C-reactive protein (CRP) is a non-specific acute phase reactant that is found to be elevated in most patients with local or systemic infection, inflammation or tissue damage (5). CRP as a laboratory marker has been shown to be a helpful objective measure to predict the need for antibiotics in mild-moderate COPD patients, especially if >40 ug/L with a NNT 7 for improvement at 9-11 days (6). It is not known whether its use would affect prescribing practice in the primary care setting. This study aims to answer this question, using point of care (POC) CRP testing on patients who present with an acute exacerbation of COPD.

Study Design:

This study is a multicenter, open-label, randomized, controlled trial involving patients with a diagnosis of COPD in their primary care clinical record who presented within 24 days of symptom onset to a clinician at one of 86 general

medical practices in England or Wales from 2015-2017. Eligible patients were 40 years of age or older and were included if they had the presence of least one Anthonisen criteria. Patients were excluded if they had a severe exacerbation, or a history of exacerbations requiring ICU admission, if they had an active inflammatory condition (that may affect CRP results) or if they were already taking antibiotics or required them for a concurrent infection. Patients were randomly assigned in a 1:1 ratio to receive usual care alone (usual care group) or usual care guided by CRP POC testing (CRP guided group).

Physicians were asked to perform a POC CRP test as part of their initial assessment of patients who belonged to the CRP-guided group, while patients in the usual care group did not undergo CRP testing. This open-label design prevented blinding of patients, who had to provide the POC blood sample. Physicians were also not blinded as they were asked to interpret the CRP value for the CRP-guided group iin the context of a provided guidance stating patients with a CRP level lower than 20 mg/L, or between 20 to 40 mg/L without sputum purulence were not likely to benefit from antibiotics, and patients who had a CRP above 40 mg/L were likely to be of benefit from antibiotics.

Two primary outcomes were used in order to determine if a reduction in the use of antibiotics was accompanied by any negative effects on patient well-being. The first primary outcome was patient-reported antibiotic use for an acute exacerbation of COPD within 4 weeks after randomization. The second primary outcome was COPD-related health status, as measured by the Clinical COPD Questionnaire (CCQ), 2 weeks after randomization. This scale ranges from 0 (very good) to 6 (extremely poor) with a clinically significant change defined as 0.4. Multiple secondary outcomes were measured, including the use of any antibiotics or other COPD medications within 4 weeks, adverse effects of antibiotics, health care utilization, health utility (measured by EQ-5D-5L Questionnaire) and quality of life (measured by CRQ-SAS Questionnaire) and can be referenced in the Supplementary Material.

The main analysis of clinical effectiveness was performed in a modified intention to treat analysis. The study achieved its number of patients, powered to detect an estimated 15% reduction in the use of antibiotics, and a change in CCQ score of 0.3 with 90% power, and 20% loss to follow-up. Patients in each group were similar with respect to demographics, each had moderate (GOLD 2) COPD at baseline, and presented with a CCQ score 3.2 during their exacerbation. 12% of patients in the CRP-guided group grew pseudomonas in their sputum, while only 3% did in the Usual Care group. There was great followup, with about 97% of patient had outcomes reported up to 4 weeks, and medical records were monitored for 6 months. The primary analysis of antibiotic use involved a two-level logistic-regression model with an adjustment for the number of Anthonisen criteria present before randomization. The analysis of the total score on the CCQ involved a two-level analysis of covariance. Non-inferiority was set at an upper limit of the confidence interval of 0.3, arbitrarily chosen to be better than the cited clinically significant difference of 0.4.

Results:

563 patients had data on the primary outcomes, showing a significant 20.4% absolute reduction in initial antibiotic use from 77.4 to 57% (OR 0.31, 1-tailed 95% CI 0.20-0.47) NNT 5 in the CRP-guided group. They failed to show non-inferiority with a non-clinically significant reduction in CCQ score in the CRP-guided group of -0.19 (2-tailed 90% CI -0.33 to -0.07).

There was no significant difference in any secondary outcome, even without adjusting results for multiple testing. There were two deaths in the usual care group (pneumonia and respiratory failure) which, were stated to be unrelated to the initial COPD exacerbation.

Validity of Results:

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Generalizability of Results:

This study focussed on patient centered subjective outcomes and antimicrobial stewardship, which is important in the primary care setting where many COPD patients are seen, and many antibiotic prescriptions are given for respiratory infections. These outcomes are likely not the ones we would like to focus on in the Emergency Department, where mortality, return visits and length of hospital stay may be more important. This is because the population who presents to the Emergency Department are likely sicker, presenting because they are not stable enough to wait 1-24 days to present to their primary care physician. Additionally, POC CRP testing is not available in most Emergency Departments, and it is unclear how the levels of these POC machines correlate with those of our laboratory tests.

Interestingly, this study included patients who had one or more Anthonisen criteria present in their exacerbation of COPD. The choice to include patients who have only one of three criteria means that a subset of patients in the study probably would not require antibiotics in the first place, and it is arguable that adding POC CRP testing to help make this decision is unnecessary.

The Bottom Line:

Although this study shows that POC CRP testing clearly reduces antibiotic use in mild-moderate outpatient COPD exacerbations with a NNT 5, the undetectable difference in adverse clinical outcomes likely reflected the lack of acuity and illness severity of these patients, most of whom were unlikely to benefit from antibiotics in the first place. These results can not be applied to more severe exacerbation, which are likely more representative of those patients seen in the Emergency Department.

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