DEM Journal Club

Article Appraisal

Article: CRP-guided antibiotic treatment in acute exacerbations of COPD in hospital admissions

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Background and Study Objective(s):

Acute exacerbations are common in patients with chronic obstructive pulmonary disease (COPD) and often become recurrent with disease progression. According to a recent 2018 Cochrane systematic review, the utility of antibiotics in treating acute exacerbations of COPD remains controversial, with no strong evidence in support of use in inpatients not admitted to ICU. Widespread overprescribing of antibiotics may lead to increased antibiotic resistance, medication side effects, and increasing health care costs. This trial aimed to determine if measurement of the biomarker C-reactive protein (CRP) could assist care providers in reducing unnecessary antibiotic use in patients presenting with acute exacerbations of COPD who were being admitted to hospital.

Study Design:

This study was a randomised controlled trial performed in two hospitals in the Netherlands between 2011 and 2015. The investigators enrolled consecutive patients who presented with acute exacerbations of COPD and required hospital admission based on 2018 Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, specifically outlined in the study's supplementary data. Patients were randomized in blocks of fifty to either the intervention group, which used a CRP-guided antibiotic prescribing strategy with a recommended cutoff of ≥50 mg/L for prescribing antibiotics, or the control group, which used a GOLD-based antibiotic prescription strategy based on patient-reported or physician-observed Anthonisen criteria. Patients who received antibiotics in either arm received amoxicillin/clavulanic acid 625mg TID for 7 days. All patients in the study received bronchodilators as well as oral prednisolone at a dose of 60 mg for 3 days and 30 mg for 7 days. Supplemental oxygen and physiotherapy were left to the discretion of the treating physician. The study's primary endpoint was the proportion of patients in whom antibiotic treatment started within the first 24 hours of admission, while secondary endpoints included 30-day treatment failure, hospital length of stay, time to next exacerbation, and patient quality of life and symptoms, and adverse events.

Results:

Within the first 24 hours of admission, 32 patients (31.7%) in the CRP-strategy group received antibiotics compared to 55 patients (46.2%) in the GOLD-strategy group. This represents an absolute reduction in antibiotic use of 14.5% with wide 95% confidence intervals (CIs) ranging from -1.9% to -26.9%. During the remainder of the hospital stay, another 21 patients (30.4%) in the CRP group and 19 patients (29.7%) in the GOLD group were given antibiotics due to treatment failure. There were neither statistically significant nor precise differences with regards to secondary outcomes of 30-day treatment failure, time to next exacerbation (32 days in the CRP group compared to 28 days in the GOLD group), hospital LOS, symptoms and quality of life scores at 1 month, and adverse events.

Validity of Results:

Despite being a randomized trial with appropriate intention to treat analysis, this study contained several problems raising questions about its internal validity. The lack of blinding of patients, physicians, and investigators presented an opportunity for performance bias during clinical interactions, which could have impacted the study results, given that the Anthonisen criteria used in the GOLD group are based on subjective self-reporting. From the beginning of the article there appeared to be investigator bias towards the use of CRP as the authors expressed that use of a biomarker to guide antibiotic prescription is “mandatory.” Use of supplementary oxygen and non-pharmacological supports such as physiotherapy was also left to the subjective discretion of unblinded treating physicians, and the study failed to ensure equal rates of use in each group, introducing room for potential confounding. Other potential sources of confounding include differences in gender proportions and incidence of sputum purulence, both of which were higher in the GOLD group than CRP group. Other Table 1 disparities between groups included average CRP and proportion of patients with CRP ≥50 mg/L, both of which were higher in the GOLD group. These differences in Table 1 characteristics suggest the GOLD group contained sicker patients, introducing the risk of a Type II error in the study’s (underpowered) finding of no differences in secondary outcomes.

Generalizability of Results:

The greatest difficulty with generalizing this study’s findings to our local practice lies in its temporally limited primary outcome of 24 hours. It is consequently difficult to conclude whether changes in local Emergency department prescribing patterns of antibiotics would have any meaningful effect on overall use of antibiotics during our patients’ hospital stays. The consensus shared at our Journal Club was that often admitting consultants will start our patients with acute exacerbations on antibiotics if we did not already initiate them, rendering any short term changes in our practice inconsequential.

Furthermore, this study was conducted in the Netherlands, which has demographic and cultural differences with our population in Canada. An example of this can be seen in the lower baseline rates of cardiovascular comorbidities among this study’s COPD patients. The study authors also acknowledge that rates of bacterial resistance are lower in the Netherlands, which may limit the generalizability of secondary outcome findings such as rates of treatment failure or time to next exacerbation. In addition, the chosen antibiotic dosing was unusual, at 625 mg TID compared with our local higher dose of 875 mg TID. Moreover, the study was not adequately powered to detect differences in secondary outcomes, the absence of which would be important to confirm to ensure patient safety before radically changing clinical practice.

The Bottom Line:

The efficacy of antibiotics in treating acute exacerbations of COPD in inpatients not admitted to ICU remains controversial. The utility of a biomarker such as CRP in distinguishing patients who may or may not benefit remains undecided. This study explores an interesting hypothesis. But, due to several problems with internal validity and the results’ generalizability, its findings and conclusions are neither directly applicable nor necessarily helpful to our practice. Rather than using CRP as a surrogate means to reduce unnecessary antibiotic use, it would seem better for us to revisit our prescribing patterns based on the evidence, or lack thereof, behind using antibiotics in COPD exacerbations.