Biomarkers in stable and acute exacerbations of COPD

Prins, Hendrik J

DOI:
10.33612/diss.136484081

CHAPTER 2.1

2.1

Safety of CRP-guided antimicrobial treatment in hospitalized AECOPD

HJ Prins, TS van der Werf, WG Boersma

European Respiratory Journal Oktober 2019

To the editor,

We thank Dr Miravitlles and colleagues for their interest in our work.[1] They express concern about our failure rate - 24% at 10 days, and 45% at day 30; they feel that 31% and 46% of patients treated with antimicrobials is low in this high-risk population of hospitalized patients. Although treatment failure is high in our study, it reflects the severity of our population. Indeed the proportion of patients on antimicrobials is lower than the out-patient study population in a recently published trial from the UK however our COPD population is more severe and consists of hospitalised patients.[2] Their concern is safety - have we caused harm in our patients by withholding antimicrobial treatment? First, in our study population, there was no significant difference in failure rates at days 10 and 30 between the CRP and GOLD group - which strongly argues against their point that antimicrobial treatment might have prevented harmful events; see table 1.

Table 1 Antimicrobial prescription and outcome stratified according to GOLD and CRP guidance

	Antimicrobial treatment (n=87)			No antimicrobials (n=133)		
	GOLD group (n=55)	CRP group (n=32)	p-value	GOLD group (n=64)	CRP group (n=69)	p-value
10-day treatment failure rate, No. (%)	6 (10.9)	4 (12.5)	0.822	23 (35.9)	20 (29.0)	0.392
30-day treatment failure rate, No. (%)	10 (31.3)	17 (30.9)	0.974	36 (52.2)	36 (56.3)	0.637
Time to next exacerbation, days (IQR)	34 (22;72)	55 (15;121)	0.761	19 (7;68)	17(6;53)	0.792
Length of stay, days (IQR)	6 (5-8)	6 (5-9)	0.933	7 (4-11)	6 (4-9)	0.077

Neither failure during admission, nor relapse was significantly different between both study arms. Indeed, relapses among patients with AECOPD admitted to hospital are common especially among individuals with a low FEV-1, but antimicrobial treatment especially among those that had low inflammatory markers may not necessarily prevent this.[3] Slow recovery and early relapse have also been associated with increased inflammation, e.g. reflected by persistently increased CRP, and in patients characterised by chronic bronchitis, but whether these individuals might benefit from antimicrobial treatment if their CRP is below a given threshold, has not been addressed in clinical studies.[4,5] An earlier study suggested that patients with CRP >50 mg/L benefit more from antibiotic treatment compared to patients with CRP below this threshold.[6] Second, they argue that perhaps the active study arm treated with co-amoxiclav as the primary antimicrobial agent might have been inadequate. Although antimicrobial susceptibility data have not been listed in our paper, *Pseudomonas* spp or other high-risk pathogens were covered if retrieved from sputum, and patients known with colonisation with high-

risk pathogens were provided with tailored antimicrobial regimens.
Third, we agree with Dr Miravitlles and colleagues that our study was not powered to demonstrate safety beyond all reasonable doubt for patients in whom antimicrobial treatment was withheld based on the CRP decision rule alone.[7] Besides the initial reduction of antibiotics of more than 30% (from 46.2% to 31.7%) associated with the CRP algorithm, around 30% of the patients were additionally treated with antibiotics due to treatment failure (equally distributed between the two groups). Importantly, this did not result in an increase of adverse events or length of hospital stay.
Our study provides preliminary data suggesting safety, and therefore argues in favour of a larger international multicentre trial to address this question more definitively for patients with exacerbated COPD that are hospitalized.
Antimicrobial treatment may cause serious harm – first of all, for individuals themselves. [8] Differences across geographic regions suggest that out-patient antimicrobial prescription is at least in part culturally, not scientifically triggered [9]. Indeed Spain, Cyprus and Mongolia do worse than some other locales, e.g. the Netherlands. If we fail to reduce our antimicrobial footprint, sooner or later we will lose the war on antimicrobial resistance.[10]

Reference List

1. Prins HJ, Duijkers R, van der Valk P, et al. CRP-guided antibiotic treatment in acute exacerbations of COPD in hospital admissions. Eur Respir J 2019; 53(5).
2. Butler CC, Gillespie D, White P et al. C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations. N Engl J Med 2019; 381(2):111-120.
3. Cao Z, Ong KC, Eng P et al. Frequent hospital readmissions for acute exacerbation of COPD and their associated factors. Respirology 2006; 11(2):188-195.
4. Wageck B, Cox NS, Holland AE. Recovery Following Acute Exacerbations of Chronic Obstructive Pulmonary Disease - A Review. COPD 2019; 16(1):93-103.
5. Ko FW, Chan KP, Hui DS et al. Acute exacerbation of COPD. Respirology 2016; 21(7):1152-1165.
6. Daniels JM, Schoorl M, Snijders D et al. Procalcitonin vs C-reactive protein as predictive markers of response to antibiotic therapy in acute exacerbations of COPD. Chest 2010; 138(5):1108-1115.
7. Schuetz P, Stolz D. Guiding antibiotic treatment with inflammatory biomarkers in COPD? Another brick in the wall. Eur Respir J 2019; 53(5).
8. Shehab N, Patel PR, Srinivasan A et al. Emergency department visits for antibiotic-associated adverse events. Clin Infect Dis 2008; 47(6):735-743.
9. Goossens H, Ferech M, Vander Stichele R et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005; 365(9459):579-587.
10. Limmathurotsakul D, Sandoe JAT, Barrett DC et al. 'Antibiotic footprint' as a communication tool to aid reduction of antibiotic consumption. J Antimicrob Chemother 2019; 74(8):2122-2127.