Biomarkers in stable and acute exacerbations of COPD

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CHAPTER 2

CRP-guided Antibiotic Treatment in acute exacerbations of COPD admitted to Hospital

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Abstract

Introduction: the role of antibiotics in acute exacerbations of COPD (AECOPD) is controversial, a biomarker identifying patients who benefit from antibiotics is mandatory. We performed a RCT in patients with AECOPD comparing CRP-guided antibiotic treatment to patient reported symptoms according to GOLD strategy in order to show a reduction of antibiotic prescription

Methods: patients hospitalized with AECOPD were randomized to receive antibiotics based according the GOLD strategy or according to the CRP (≥50 mg/L) strategy.

Results: 101 patients were randomized to the CRP-group and 119 to GOLD-group. Fewer patients in the CRP-group were treated with antibiotics 31.7% versus 46.2% in the GOLD-group (p=0.028) (adjusted OR, 0.178 95%CI 0.077-0.411, p= 0.029). Thirty-day treatment failure rate was equal (CRP-group 44.5% vs GOLD-group 45.5%; (p=0.881) (adjusted OR 1.146 95%CI 0.649-1.187 p=0.630) as was time to next exacerbation (CRP-group 32 days, versus GOLD-group 28 days (p=0.713) (adjusted HR0.878 (95%CI 0.649-1.187 p=0.398). Length of stay was similar in both groups (CRP-group 7 days versus GOLD-group 6 days (p=0.167). On day 30 no difference in symptoms score, quality of life or serious adverse events was detected.

Conclusion: CRP as a biomarker to guide antibiotic treatment in severe AECOPD leads to a significant reduction of antibiotic treatment. In the present study no differences between both groups in adverse events were found. Further research is needed for the generalizability of these finding

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are associated with substantial morbidity and mortality.[1] On average a patient with COPD suffers from 1.5 exacerbations a year.[2] Viruses and bacterial infections are the most important triggers in AECOPD.[3] Coinfection of viruses and bacteria has been detected in 25% of exacerbations.[4] Molecular techniques including polymerase chain reaction can detect viral infections more accurately as trigger of AECOPD.[2] Yet, still in about a third of severe exacerbations a specific infectious agent cannot be identified.[5]

Treatment of AECOPD usually consists of corticosteroids and bronchodilators. The current GOLD strategy advises to add or withhold antibiotic treatment based upon patient reported sputum purulence.[6] This strategy assumes that both sputum purulence is a good marker of bacterial infection and that the patients' assessment of sputum colour is reliable. However, both assumptions are controversial. We have shown before that sputum colour reported by patients is not a reliable marker of bacterial presence or bacterial load in AECOPD.[7;8] As a consequence, the widespread implementation of the GOLD strategy, that dictates use of patient reported sputum purulence, may result in overuse of antibiotics in AECOPD. It is evident that unnecessary prescription of antibiotics for respiratory illness leads to higher medical costs, side effects and emerging resistance to antibiotics.[9] This is underlined by the fact that the frequency of antibiotic resistance in bacteria among different countries is proportional to their relative rate of antibiotic use.[9] Reduction of resistance (up to 30%) can be achieved by implementing recommendations that discourage antibiotic treatment.[10] Therefore, a better identification of patients with AECOPD who actually benefit from antibiotics is mandatory. A biomarker like serum C-Reactive Protein (CRP) may help in selecting these patients. CRP is an acute phase protein and a sensitive biomarker for systemic inflammation and tissue damage.[11] Although CRP is not disease specific, it can aid to clinical decision making to guide antimicrobial use. This was reported by a study in patients with lower respiratory tract infections.[12] CRP levels are significantly higher during AECOPD compared to baseline levels, especially if a bacterial origin is likely.[13] A previous study has shown that patients with an AECOPD admitted to hospital with a CRP (≥50 mg/L) showed a trend to benefit more from antibiotics than patients with low CRP values.[14] We therefore hypothesized that CRP-guided antibiotic therapy may lead to a reduction of antibiotic therapy within 24 hours after admission compared to patient reported sputum purulence strategy (as formulated in the GOLD strategy) in patients with AECOPD admitted to hospital without increasing the rate of treatment failures or adverse events within 30 days.

Material and Methods

Study design and oversight

The CRP-guided Antibiotic Treatment in COPD exacerbations admitted to the Hospital study (CATCH) was an investigator initiated multicentre randomized controlled open intervention clinical trial performed in two hospitals in the Netherlands from July 2011 - February 2015 (clinicaltrials.gov NCT01232140). Consecutive patients with AECOPD who needed hospitalization according to GOLD strategy were screened and enrolled at the emergency department or medical wards within 24-hours after presentation.[6] Inclusion and exclusion criteria can be found in the supplementary data. All patients provided written informed consent.

Randomization and Intervention

Eligible patients were randomly assigned to receive either biomarker-directed (CRP-group) antibiotic therapy or GOLD strategy directed (GOLD-group) antibiotic therapy.[6] Randomization was performed with block sizes of fifty. Treatment allocation was concealed with a pre-specified computer-generated randomisation list by an independent statistician. Patients were randomly assigned to one of two groups by sealed, opaque envelops. Envelopes were numbered with consecutive unique study numbers. After obtaining informed consent the physician in charge opened the envelope and acted according to the randomization result. Subjects assigned to CRP-group were treated days if CRP on admission was ≥50 mg/L. In patients with CRP <50 mg/L, no antibiotic was prescribed. Within 24 hours CRP levels were re-evaluated. If CRP level rose ≥50 mg/L patients were also treated with amoxicillin/clavulanic acid. Subjects in the GOLD-group were also treated with amoxicillin/clavulanic acid for 7 days if they reported increased sputum purulence in combination with increased dyspnoea and/or increased sputum volume, or if this was observed by the attending physician in the first 24 hours after admission in order to minimize protocol violations. If patients were not able to expectorate sputum and remained to do so for the first 24 hour after admission, they were considered to be non-purulent. Medical staff treating subjects allocated to GOLD guided treatment were blinded for the CRP results in the first 24 hours. If allergy to penicillin was reported another antibiotic was prescribed. In with amoxicillin/clavulanic acid 625 mg 3 times a day for 7 addition, all patients were treated with corticosteroids (oral prednisolone 60 mg for three days, followed by 30 mg for 7 days) and bronchodilators. Supplemental oxygen and physiotherapy were added at the discretion of the attending physician.

Procedures

After informed consent was obtained, baseline blood samples were drawn and baseline variables were collected. Patients were treated according to their randomization results and discharged from the hospital as deemed appropriate by the attending physician.

Patients were monitored during 1 year with scheduled visits at 1 and 6 months. Additional telephone interviews were performed at 3 and 12 months. When patients were unable to attend a scheduled visit, they were contacted by telephone. Patients were instructed to contact the investigator(s) responsible for the study immediately if there was any change in their health status. During each visit, patients were asked to report any respiratory event that required antibiotic therapy, systemic corticosteroids and/or hospitalization elsewhere, in order to capture all exacerbations and other adverse events. Serum CRP was measured by nephelometry on a Beckman Synchron DxC 800 analyser (CRP latex Reagent, Beckman Coulter Inc; Fullerton, CA) on the day of admission. Because serum CRP levels peak at about 36 h after onset of infection, this test was repeated on the second day of the admission. The highest value was used to determine whether or not a patient should be treated with antibiotics.

The Lower Respiratory Tract Infection Visual Analogue Score (LRTI-VAS) is a condition-specific questionnaire that has been used to assess the severity of symptoms in COPD.[14] The score has been shown to be a reliable tool for symptom measurement in bronchiectasis and is currently being validated for COPD.[15] A detailed description can be found in the supplementary data. Subjective improvement in quality of life was recorded using the Clinical COPD Questionnaire (CCQ).[16;17] A detailed description can be found in the supplementary data.

Endpoints

The primary endpoint was antibiotic treatment started during the first 24 hours after admission. Secondary endpoints were 30-day treatment failure rate, length of hospital stay, time to next exacerbation, difference in symptoms score, quality of life after 30 days and safety profile. Treatment failure was defined as absence of resolution of symptoms and signs, worsening of symptoms and signs, occurrence of new symptoms and signs associated with the primary or with a new infection, or death of any cause after randomization in the study.[18] Time to next exacerbation was defined as the interval between hospital discharge and the end of the study or time to additional course of antibiotics and/or corticosteroids for worsening of symptoms and signs. Subjective improvement in symptoms and quality of life was recorded using the Lower Respiratory Tract Infection Visual Analogue Scale (LRTI-VAS) and Clinical COPD Questionnaire (CCQ) at admission and after 1 month.

We also assessed 1-year treatment failure rate, the number of exacerbations after 1 year and 1 year mortality rate.

Safety

A planned safety analysis performed by the Data Safety Monitoring Board after enrolment of 100 patients showed no significant differences with regard to benefit or to adverse effects and therefore the study was continued.

Statistical analysis

The primary outcome measure was a reduction in antimicrobial prescriptions in the experimental arm compared to the control group. Based on previous data it was estimated that 20% reduction in antibiotic use (60% in the GOLD-group versus 40% in the CRP-group) would be clinically relevant.[14;19] In order to detect this difference with a power of 0.8 and α of 0.05, and a 15% drop-out a total of 220 patients was needed. Continuity correction was used as the primary outcome was based upon a percentage. The primary analysis was performed based on intention-to-treatment (ITT) principle. The secondary analysis of per-protocol treatment (PPT) included participants who met the criteria of the ITT population, received the allocated treatment, and had no other protocol violation. IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.) and R version 3.4.1 for Windows was used for data management and statistical analysis. Data are presented as median (IQR) unless stated otherwise. Continuous data were analysed with the Student's t test or Mann–Whitney U test, when appropriate. Categorical characteristics were compared by using the χ^2 test. Multivariable logistic regression was used to calculate odds ratio (OR) and adjust for confounders. Multivariable Cox regression was used to calculate Hazard ratio (HR). Kaplan-Meier's log-rank test was used to compare differences in 30-day treatment failure. In case of skewed distributions, continuous variables were logarithmically transformed for further analyses. For the construction of the confidence intervals we used the bootstrap method based on 1000 bootstraps. Overall statistical significance was set at a 2-tailed P value <0.05.

Results

A total of 1650 patients with COPD were screened for inclusion; 220 (13.3%) were eligible and were randomized (figure 1). One hundred and one patients were assigned to the CRP-group and 119 to the GOLD-group; the data of these patients were used for ITT analysis. For the per-protocol treatment (PPT) 12 patients were excluded (figure 1).

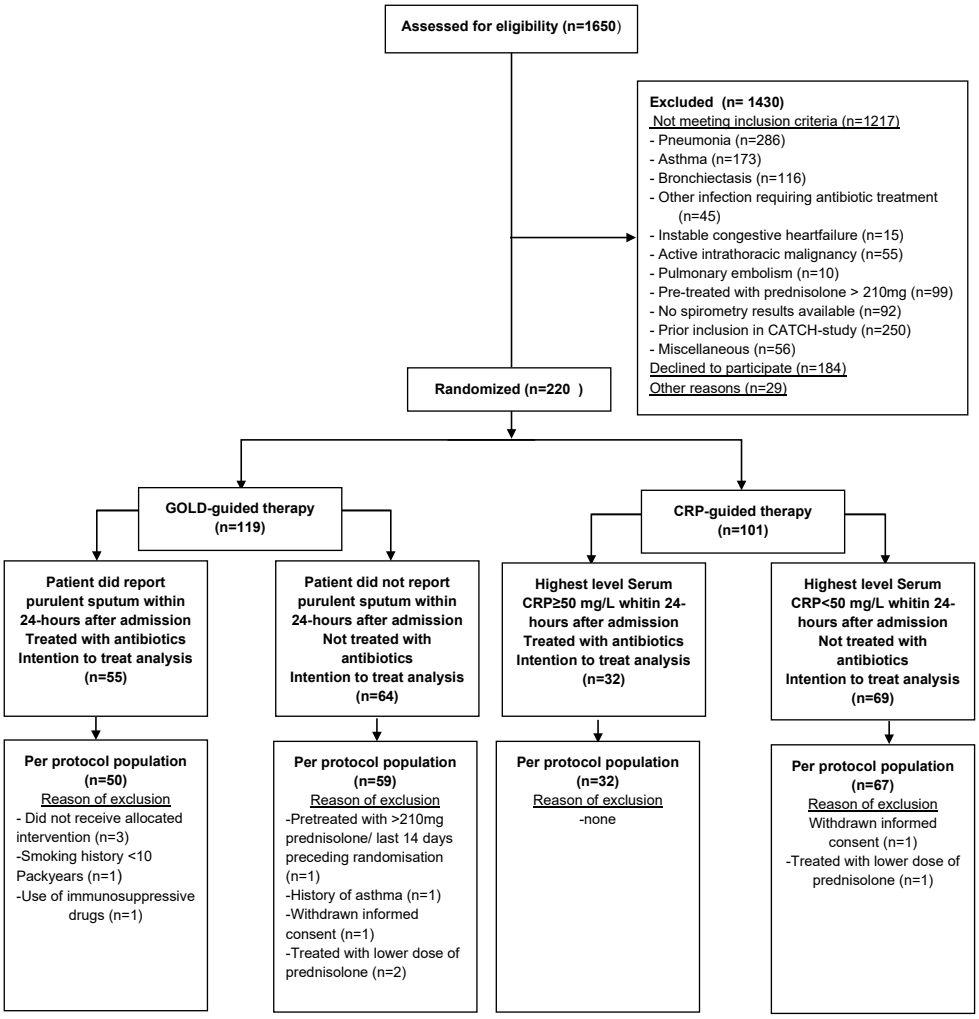


Figure 1: CONSORT flow diagram describing the screening and randomisation of participants. GOLD: Global Initiative for Chronic Obstructive Lung Disease; CRP: C-reactive protein.

The baseline characteristics of both groups in the ITT analysis are summarized in table 1 and were well balanced except for gender and sputum purulence. Also, the patient characteristics of the PPT groups were comparable (table1 supplementary data).

Table 1 Baseline characteristics

	GOLD-group (n=119)	CRP-group (n=101)
Age (SD) years	70.8 (11.8)	68.4 (12.0)
Gender male No. (%)[a]	67(56.3)	41(40.6)
Current Smoking No. (%)	35(29.4)	38 (37.6)
Pack years (SD) years	45.1(34.2)	40.5 (23.0)
BMI (SD) kg/m²	25.1(5.7)	25.0 (5.3)
FEV1 (SD) L[b]	1.21(0.54)	1.14 (0.44)
FEV1 (SD) % predicted	46(17)	45 (16)
FVC (SD) L[b]	2.9(1.04)	2.6 (0.9)
FVC (SD) % predicted[b]	85 (22)	84 (21)
FEV1/FVC ratio (IQR) %[b]	40(31-49)	37(31-52)
Number of exacerbations in the last year No. (IQR)	1 (1-2)	2 (1-2)
Type of exacerbation[c]		
Type 1 No. (%)	48 (40.3)	50 (49.5)
Type 2a purulence present No. (%)	7 (5.9)	12 (11.9)
Type 2b purulence not present No. (%)	25 (21.0)	14 (13.9)
Type 3 No. (%)	39 (32.8)	25 (24.8)
Sputum purulence present No. (%)[a]	55 (46.2)	62 (61.4)
Positive sputum culture at admission No. (%)	43 (36.1)	38 (37.6)
Co-morbidities		
Ischaemic heart disease No. (%)	19 (16.0)	15 (14.9)
Heart failure No. (%)	18 (15.1)	16 (15.8)
Cerebrovascular disease No. (%)	12 (10.1)	10 (9.9)
Diabetes mellitus No. (%)	11 (9.2)	10 (9.9)
Pre-treatment[d]		
Inhaled corticosteroids No. (%)	100 (84.0)	80 (79.2)
Pre-treatment with systemic corticosteroids No. (%)	58 (48.7)	52 (51.5)
Pre-treatment with antibiotics No. (%)	38 (31.9)	41 (40.6)
Short-acting beta adrenoceptor agonist No. (%)	68(57.1)	57(56.4)
Short-acting muscarinic antagonist No. (%)	29(24.4)	23(24.2)
Long-acting beta adrenoceptor agonist No. (%)	93(78.2)	71(70.3)
Long-acting muscarinic antagonist No. (%)	68(57.1)	61(60.4)
Vital parameters at admission		
Respiratory rate (IQR) per minute	20(16-24)	20 (18-24)
Temperature (IQR) °C	37.1(36.6-37.7)	37.1 (36.7-37.5)
Laboratory results at admission		
WBC (SD) 109/L	11.0(3.9)	10.7 (4.3)
Blood eosinophil count (IQR) 109/L	0.0 (0.0-0.2)	0.0 (0.0-0.1)
CRP (IQR) mg/L[e]	27(6.7-98)	19(5.6-75)
CRP≥50mg/L No. (%)[e]	49(41.2)	32(31.7)
Assisted ventilation		
None No. (%)	110(92.4)	93(92.1)
Non-invasive ventilation No. (%)	8(6.7)	7(6.7)
Invasive ventilation No. (%)	1(0.8)	1(1.08)

All data are represented as mean (SD) unless specified otherwise.
Definition of abbreviations: BMI: body mass index (kg/m2), FEV1: forced expiratory volume 1 second, FVC: Forced Vital Capacity, WBC: white blood cell count, CRP: C-reactive protein SD: standard deviation, IQR: inter quartile range.
[a]: p-value <0.05, [b]: Last recorded post bronchodilator value in a stable state before admission, [c]: according to Anthonissen [19], [d]: in the two weeks prior to randomisation [e]: Highest level recorded in the first 24-hours

Primary endpoint

In the ITT population antibiotics were prescribed in 32 patients (31.7%) of the CRP-group and 55 patients (46.2%) of the GOLD-group (p=0.028) (table 2). By using the CRP strategy, an absolute antibiotic reduction of 14.5 % was achieved which was a 31.4% reduction compared to the GOLD guided antibiotic strategy. This remained significant after correction for statistically significant confounders including sputum purulence, gender and FVC (L) (adjusted OR, 0.178 95%CI 0.077-0.411, p= 0.029). In the per protocol treatment a comparable result was found (table 2 supplementary data). Forty patients who were initially not treated with antibiotics were prescribed antibiotics due to treatment failure during admission. Twenty-one patients (30.4%) in the CRP group compared to 19 patients (29.7%) in the GOLD group (p=0.925).

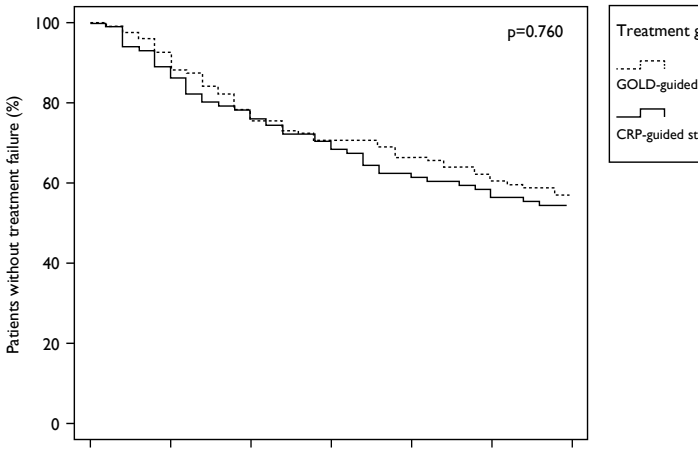
Table 2 Primary and secondary endpoints

	GOLD-group (n=119)	CRP-group (n=101)	Difference	95% bootstrap CI	p-value
Primary endpoint					
Patients treated with antibiotics No. (%)	55 (46.2)	32 (31.7)	-14.5	-1.9;-26.9	0.028
Secondary endpoints					
30-day treatment failure rate No. (%)	53 (44.5)	46 (45.5)	1.0	-14.7;11.7	0.881
Time to next exacerbation days (IQR)	28 (3-209)	32 (0-327)	4	-57.9;19.1	0.713
Length of stay days (IQR)	6 (4-8)	7 (4-9)	1.0	-0.1;2.7	0.167
CCQ score change on day 30 (IQR)	-1.00 (-1.95;-0.20)	-0.90 (-1.40;-0.1)	-0.1	-0.54; 0.16	0.336
LRTI-VAS score change on day 30 (IQR)	-8.5 (-14.0;-3.0)	-7.5 (-15.0;-2.0)	1.0	-2.3;2.9	0.723

All data are represented as median (IQR) unless specified otherwise. Differences are represented as percentages or differences in medians.
Definition of abbreviations: CCQ: Clinical COPD Questionnaire, LRTI-VAS: Lower Respiratory Tract Infection Visual Analogue Scale

Treatment failure rate

Treatment failure on day 30 was similar between the groups; 46 patients (45.5%) in the CRP-group versus 53 patients (44.5%) in the GOLD-group (p=0.881) (figure 2).



No. at risk							
GOLD-guided strategy group	119	105	90	84	79	72	66
CRP-guided strategy group	101	87	77	69	62	57	55
No of exacerbations							
GOLD-guided strategy group	0	14	29	35	40	47	53
CRP-guided strategy group	0	14	24	32	39	44	46

Figure 2: Kaplan-Meier Curve for treatment failure over 30 days. GOLD: Global Initiative for Chronic Obstructive Lung Disease; CRP: C-reactive protein.

Similar results were found after adjusting for confounders (OR 1.146 95%CI 0.649-1.187 p=0.630). Day 10 treatment failure rates showed no difference between the two groups; CRP-group 24 patients (23.8%) had treatment failure versus 29 patients (24.4%) in the GOLD-group (p=0.916). During 1 year of follow up 78 patients (77.2%) had treatment failure compared to 102 patients (85.7%) in the GOLD-group (p=0.104 e-figure 1).

Time to next exacerbation

Time to next exacerbation in the CRP-group was 32 days (IQR 0-327) versus 28 days (IQR 3-209) in the GOLD group (p=0.713) (figure 3A). No difference was found in HR after adjusting for confounders. The adjusted HR of time to next exacerbation in the CRP guided group was calculated to be 0.878 (95%CI 0.649-1.187 p=0.398) compared to the GOLD-group. The number of exacerbations in the year after randomization was similar in both groups; CRP-group 1 exacerbation (IQR 0-3) versus 2 exacerbations (IQR 1-4) in the GOLD-group (p=0.109) (figure 3B).

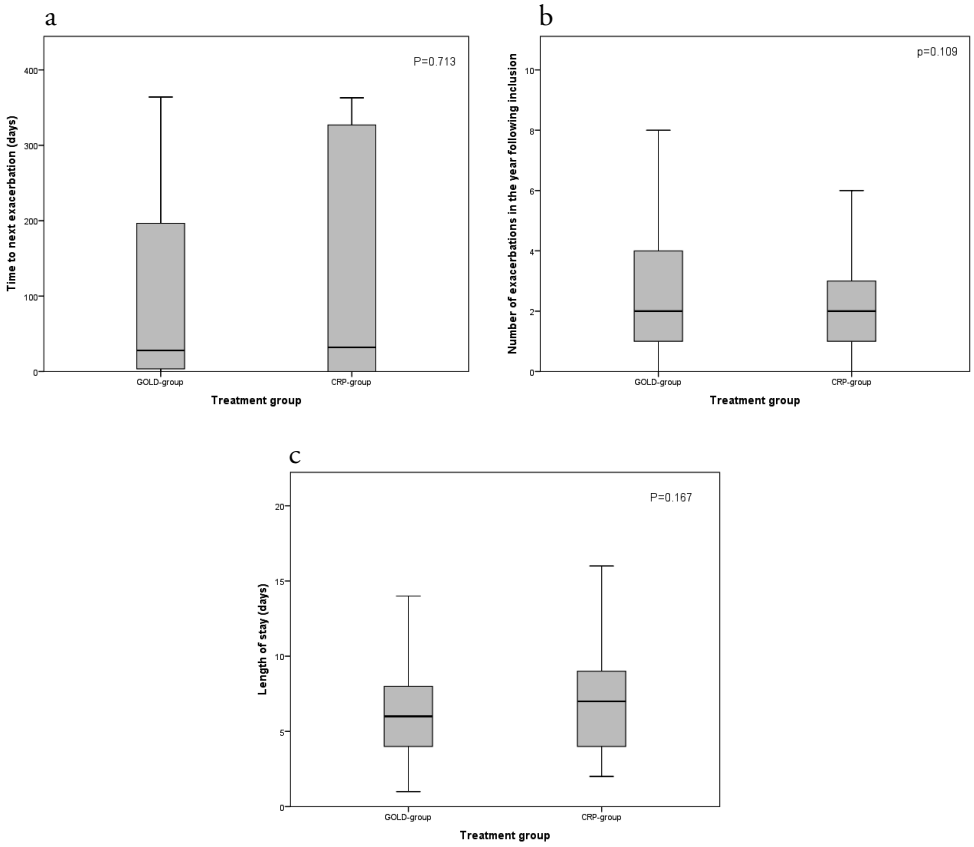


Figure 3: Comparison of treatment groups for a) time to next exacerbation, b) number of exacerbations in the year following inclusion and c) hospital length of stay. GOLD: Global Initiative for Chronic obstructive Lung Disease; CRP: C-reactive protein.

Length of hospital stay

Median length of hospital stay (LOS) in the CRP-group was 7 days (IQR 4-9) versus 6 days (IQR 4-8) in the GOLD-group (p=0.167) (figure 3C). The variable length of hospital stay was logarithmically transformed to accomplish a normally distributed variable. Linear regression analysis showed mean difference between the treatment groups of 0.14. The resultant ratio of geometric means after back transformation was 1.15 (95%CI: 0.98-1.34). After correction for gender, purulence and FVC in multivariable analyses this ratio changed to 1.12 (95%CI: 0.95-1.31)

Symptoms and Quality of Life scores

Baseline CCQ was equal in both groups, median 3.80(IQR 3.10-4.20) in the CRP-group compared to 3.55(IQR 3.00-4.05) in the GOLD-group. LRTI-VAS score was median 23 (IQR 21-28) in the CRP-group compared to 24 (IQR 18-27) in the GOLD-group (p=0.186).

The median change in total CCQ score on day 30 was -1.00(IQR -1.95--0.20) in the GOLD-group versus -0.90(IQR -1.40--0.10) in the CRP-group (p=0.289). The median change in LRTI-VAS was -8.5(IQR -14.0--3.0) in the GOLD-group versus -7.5(IQR -15.0--2.0) in the CRP-group (p=0.723). Additional scores CCQ and LRTI-VAS are noted in table 3 and 4 in the supplementary data.

Safety

In one year of follow-up serious adverse events occurred in 48 patients (40.3%) in the GOLD-group (64 events) compared to 42 patients (41.6%) in the CRP-group (53 events) one year after inclusion (p=0.851). During the same period 41 patients had 49 adverse events, events were evenly distributed among both groups. Adverse reactions related to the study medication occurred in 5 patients (4.2%) in the GOLD-group compared to 1 patient (2%) in the CRP-group (p=0.145).
All-cause mortality after one year was equal in both groups. Twenty patients (16.8%) died in the GOLD-group compared to 9 patients (8.9%) in the CRP-group (p=0.082). Thirty-day mortality in the GOLD-group was 5 patients (4.2%) compared to 1 patient (1.0%) in the CRP-group (p=0.145). Five patients died of AECOPD and one patient died of inoperable colon carcinoma.

Discussion

CRP-guided antibiotic therapy for patients hospitalized with AECOPD was associated with a 14.5% decrease of antibiotic use at admission compared with GOLD-guided antibiotic therapy. The CRP-guided strategy was not associated with an increase of adverse events or 30-day treatment failure rates. Finally, similar outcomes between groups were observed with regards to exacerbation recovery (difference in QoL and respiratory symptoms) and time to next exacerbation.

The current GOLD strategy advocates the use of antibiotics during exacerbations in patients with increased sputum purulence.[6] Reported or witnessed sputum purulence as a criterion to guide antimicrobial prescription, has several shortcomings. Regardless of sputum discoloration or purulence, studies have shown that antibiotics can improve short term outcomes.[20] A recent guideline by the ERS/ATS conditionally recommends the use of antibiotics in patients with AECOPD.[21] Yet this guideline only provides a treatment advice for ambulant patients and did not take into account a recent randomized controlled clinical trial not showing effect of antibiotics in ambulant patients.[22] The improvements ascribed to antibiotics are therefore marginal and antibiotics may be associated with increased morbidity.[20] Adverse effects of antibiotic treatment are gastrointestinal complications as diarrhea, allergic reactions and an increase in bacterial

resistance.[23;24] The results of the current study are in line with the findings of a previous study from our group which showed a trend towards more benefit in patients with a CRP ≥50 mg/L.[14] Similar results were found in another study using a cutoff point of 40 mg/L in which patients with a moderate AECOPD who were treated with antibiotics or placebo.[25]

Another biomarker used in AECOPD is Procalcitonin (PCT). A recent meta-analysis showed that PCT guided antibiotic treatment is associated with a 35.5% reduction of antibiotic use without an increase in LOS or adverse events.[26] This larger reduction may be explained by the observation that 80.1% of the patients in the control groups of the included studies were treated with antibiotics. In the current study only 46.2% of the patients in the control group were treated with antibiotics and only 31.7% of the patients in the intervention group were treated with antibiotics which is lower compared to PCT-guided strategy. There are some advantages of using CRP as a biomarker. First, serum CRP may better reflect bacterial infection in the lower airways. We have shown earlier that CRP is related to the presence of potential bacterial pathogens in sputum, whereas PCT is not.[27] Secondly, CRP is cheap and available in hospitals all over the world, whereas PCT is more costly and mainly used in research settings. As a consequence, implementation of CRP-guided antibiotic treatment might very well be cost-effective as it requires no changes in laboratory infrastructure.

Our data suggest that CRP guided antibiotic therapy is able to reduce antimicrobial pressure, while maintaining the patient safety. Although the effect size of reduced antibiotic consumption was less than the 20% we anticipated, a significant reduction of 14.5% was nonetheless found in the CRP-guided treatment strategy compared to the GOLD-guided treatment strategy. Perhaps the effect size was less than expected, because the proportion of participants with sputum purulence in the GOLD-group (46.2%) was less than in the CRP-group (61.4%; p=0.025). This was further emphasized by two other studies showing a sputum purulence of 53% and 59% respectively.[25;28]Thirty-day treatment failure rates were comparable in both groups and comparable to earlier research.[14] Time to next exacerbation was equal in both groups. In our study time to next exacerbation was considerably shorter compared to other studies. This reduction may be explained by a different definition of time to next exacerbation as well as the fact that both these studies were performed in GP practices.[22;25] In the present study LOS was the same in both groups, but shorter than was found in another study. This can be explained by a different study design as patients in our study were treated with oral corticosteroids instead of standardized intravenous corticosteroids for 6 days.[14] Of course these secondary endpoints should be interpreted with caution as the study was not powered on these outcomes. However, in the present study no important differences between the two groups were detected.

The strengths of our study are the real-life design of the study including patients with all GOLD classes, patients who were pre-treated with antibiotics and/or systemic corticosteroids as well as treatment naïve patients and finally patients needing assisted ventilation were not excluded from participation. The second strength of this study is the fact that all patients were treated uniformly with corticosteroids and bronchodilators. The third strength of the study was the fact that medical staff treating subjects allocated to GOLD guided treatment were blinded for the CRP results in the first 24 hours, thereby reducing the risk of starting antibiotics based upon CRP levels instead of patient reported sputum colour. One potential limitation to this study is the fact that patients, hospital staff and investigator were not blinded for the results of randomization allowing for a risk of performance bias. A second possible limitation is the low bacterial resistance in the country in which the study was performed. This might limit the generalisability. A third limitation is the imbalance at baseline regarding sputum purulence and gender, this might have influenced our results although after correction for confounders results remained statistically significant. The fourth limitation is that the results regarding patients requiring assisted ventilation must be interpreted with caution, as the groups were too small to draw a firm conclusion.

The primary objective of the present study was to find a reliable method to reduce overtreatment with antibiotics in AECOPD. Clearly antimicrobial pressure promotes antibiotic resistance.[9] Antibiotic resistance in bacteria among different countries is proportional to their relative rate of antibiotic use.[9] Reduction of resistance up to 30% can be achieved by implementing specific recommendations that discourage antibiotic treatment.[10] In a recent study the appropriate use of antibiotics in the management of hospitalized patients with AECOPD in 13 European countries was studied.[29] Overall in 86% of admissions antibiotics were prescribed but only 61.4% cases met the GOLD criteria justifying antibiotic prescription. This misuse of antibiotics also depends on the assumption that we fully rely on the reported "purulence" of sputum by the patient which is probably a highly unreliable parameter.[8] Beliefs, expectations and incentives are important drivers of antibiotic overuse among physicians. A fundamental change in behaviour among physicians is urgently needed to curb the daunting emergence and spread of antimicrobial resistance. For this purpose, biomarkers may be helpful to guide antibiotic treatment in AECOPD.

In conclusion, the present study shows that using serum CRP (cut-off value 50mg/L) to direct antibiotic treatment can lead to a significant reduction of antibiotic use in patients with severe AECOPD. Implementation of this strategy could contribute to the battle against emerging bacterial resistance. However, a prerequisite for implementation of this strategy is safety. Although we observed no negative effects of the CRP-guided strategy on treatment failure, length of stay and adverse events, this study was underpowered for the assessment of these endpoints. Future studies are required to resolve this issue.

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Chapter 2 supplementary data

Inclusion and Exclusion criteria.

The inclusion and exclusion criteria that were used for the CRP-guided Antibiotic Treatment in COPD exacerbations admitted to the Hospital study (CATCH) study were:

Inclusion criteria

- Age 40 years and older. No upper age limit will be employed.
- Written informed consent obtained.
- AECOPD according to the GOLD guideline. An exacerbation of COPD is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.
- Criteria for hospital admission according to the GOLD.
  - marked increase in symptoms (i.e. resting dyspnoea)
  - severe underlying COPD
  - onset of new physical signs (cyanosis, oedema)
  - failure to respond to initial medical management
  - significant co morbidities
  - frequent exacerbations
  - newly occurring arrhythmias
  - diagnostic uncertainty
- Former of current smoker with a minimum smoking history of 10 pack years.
- Patients have to be capable of ingesting oral medication.
- Patients have to be mentally capable of participating in the study (able to complete questionnaires and perform lung function tests).
- Life expectancy ≥ 30 days.

Exclusion criteria

- Pregnant or lactating women, or women of childbearing age not using an acceptable method of contraception.
- Pre-treatment with corticosteroids (cumulative dose >210 mg) for the present exacerbation.
- Strong clinical suspicion of pneumonia
- Progression or new radiographic abnormalities on the chest X-ray.
- Cystic fibrosis.
- Tuberculosis.
- Immunodeficiency disorders such as AIDS, humoral immune defect, ciliary dysfunction etc., and the use of immunosuppressive drugs (>30 mg prednisolone/day maintenance dose or equivalent for more than 4 weeks).

- Recent or unresolved lung malignancy.
- Other disease likely to require antibiotic therapy, such as recurrent sinusitis or urinary tract infection.
- Significant gastrointestinal or other conditions that may affect study drug absorption.
- Instable congestive heart failure or recent stroke.
- Newly diagnosed pulmonary embolism

Questionnaire description

LRTI-VAS description:

The Lower Respiratory Tract Infection Visual Analogue Scale(LRTI-VAS) consists of a set of 4 horizontal lines with 2 anchor points, one at each extreme, each line representing a different symptom - dyspnoea, fatigue, cough and sputum colour. Each symptom is scored from 1 to 10, the patients being unaware of the numbers. Higher scores indicate more severe symptoms. Separate scores were calculated for each symptom, with a total score consisting of all symptom scores added.

CCQ description:

The Clinical COPD Questionnaire is a health-related quality of life questionnaire that has been widely used in both COPD and asthma research and includes 10 items across three domains: symptoms, activity and impact. Higher scores indicate more severe symptoms. It has been validated extensively and can accurately monitor the course of recovery of outpatients as well as that of inpatients with AECOPD

Supplementary data table 1 Baseline characteristics per protocol population

	GOLD (n=109)	CRP (n=99)
age (SD) years	71.1(11.8)	68.4(12.1)
Gender male No (%)[a]	65(59.6)	41(41.1)
Current Smoking No (%)	33(30.3)	36(36.4)
Packyears (SD) years	46.9(34.4)	40.5(23.2)
BMI (SD) kg/m²	24.6(5.4)	24.9(5.2)
FEV1 (SD) L [b]	1.23(0.56)	1.14(0.44)
FEV1 (SD) % pred [b]	46(18)	45(16)
FVC (SD) L [ab]	2.91(1.05)	2.64(0.86)
FVC (SD) % pred[b]	85(22)	83(21)
FEV1/FVC ratio (IQR) % [b]	39(31-49)	38(31-52)
Number of exacerbations in the last year(IQR) No	1(1-2)	1(1-2)
Anthonissen type exacerbation.		
Type 1 No (%)	44(40.4)	48(48.5)
Type 2a purulence present No (%)	6(5.5)	12(12,1)
Type 2b purulence not present No (%)	23(21.1)	14(14.1)
Type 3 No (%)	36(33.0)	25(25.3)
Sputum purulence present No (%) [a]	50(45.9)	60(60.6)
Positive sputum culture at admittance No (%)	40(36.7)	37(37.4)
Co-morbidities		
Ischaemic heart disease No (%)	17(15.6)	15(15.2)
Heart failure No (%)	17(15.6)	16(16.2)
Cerebrovasculair disease No (%)	10(9.2)	10(10.1)
Diabetes mellitus No (%)	8(7.3)	10(10.1)
Pre-treatment		
Inhaled corticosteroids usage No (%)	90(82.6)	78(78.8)
Pretreatment with systemic corticosteroids No (%)	54(49.5)	51(51.5)
Pretreatment with antibiotics No (%)	30(27.5)	40(40.4)
Vital parameters		
Respiratory rate (IQR) per minute	20(16-24)	20(18-24)
Temperature (IQR) °C	37.0(36.6-37.6)	37.1(36.7-37.5)
Laboratory results day 1		
WBC (SD) 10x9/L	11.0(4.03)	10.7(4.3)
Blood eosinophil count (IQR) 10x9/L	0.0(0.0-0.2)	0.0(0.0-0.01)
CRP (IQR) mg/L[C]	27(6.7-104)	19(5.6-83)
CRP≥50mg/L No (%)[c]	47(43.1)	32(32.3)
Assisted ventilation		
none No (%)	100(91.7)	91(91.9)
Non-invasisve ventilation No (%)	8(7.3)	7(7.1)
Invasive ventilation No (%)	1(0.9)	1(1.0)

All data are represented as mean (SD) unless specified otherwise.
Definition of abbreviations: BMI: body mass index (kg/m2),
FEV1: forced expiratory volume 1 second, FVC: Forced Vital Capacity,
WBC: white blood cell count, CRP: C-reactive protein SD: standard deviation, IQR: inter quartile range
[a]: <0.05, [b]: Last recorded postbronchodilator value in a stable state before admission, [c]: Highest level recorded in the first 24 hours

Supplementary data table 2 Primary & secondary outcomes per protocol population

Primary outcome	GOLD (n=109)	CRP (n=99)	Difference	95% CI bootstrap interval	p-value
Patients treated with antibiotics No (%)	50(45.9)	32(32.2)	-13.7	-1.4;-26.9	0.046
Secondary outcome					
30-day treatment failure rate No (%)	46(42.2)	45(45.5)	3.3	-10.8;16.2	0.637
Time to next exacerbation (IQR) days	28(5-210)	34(0-328)	6	-54.6;22.6	0.916
Length of stay(IQR) days	6(4-8)	7(4-9)	1	-0.1;2.7	0.157
CCQ score change on day 30	-1.0(-2.0;-0.2)	-0.9(-1.40;-0.1)	0.1	-0.53;0.16	0.655
LRTI-VAS score change on day 30, (IQR)	-9(-14;-5)	-7(-15;-2)	2	-3.3;2.2	0.540

All data are represented as mean (SD) unless specified otherwise. Differences are represented as percentages or differences in medians.
Definition of abbreviations: CCQ: Clinical COPD Questionnaire, LRTI-VAS: Lower Respiratory Tract Infection Visual Analogue Scale

Supplementary data table 3 Symptom score LRTI-VAS and CCQ at admission

	GOLD (n=100)	CRP (n=90)
LRTI-VAS score t=0(IQR)	24(18-27)	23(21-28)
Dyspnea t=0(IQR)	7(6-9)	8(7-9)
Fatigue t=0(IQR)	8(5-9)	8(6-9)
Cough t=0(IQR)	5(4-7)	6(5-8)
Sputum purulence t=0(IQR)	3(1-5)	3(1-5)
Clinical COPD Questionnair total t=0(IQR)	3.55(3.00-4.05)	3.80(3.10-4.20)
CCQ symptoms t=0(IQR)	4.00(3.00-4.50)	3.75(3.25-4.5)
CCQ mental t=0(IQR)[a]	2.00(1.00-3.00)	2.50(1.50-3.50)
CCQ functional t=0(IQR)	4.00(3.25-4.75)	4.25(3.00-4.75)

Definition of abbreviations: CCQ: Clinical COPD Questionnaire, LRTI-VAS: Lower Respiratory Tract Infection Visual Analogue Scale [a]: p=<0.05

Supplementary data table 4 Symptom score change on day 30 LRTI-VAS and CCQ

	GOLD (n=80)	CRP (n=78)	p-value
LRTI-VAS score change on day 30(IQR)	-8.5(-14.0--3.0)	-7.5(-15.0--2.0)	0.831
dyspnoea change on day 30(IQR)	-2.0(-5.0-0.0)	-2.0(-5.0-0.0)	0.856
fatigue change on day 30(IQR)	-2.0(-4.0-0.0)	-1.0(-3.5-0.0)	0.104
cough change on day 30(IQR)	-3.0(-4.5-0.0)	-2.0(-5.0-0.0)	0.611
sputum purulence change on day 30(IQR)	-1.0(-3.0-0.0)	-1.0(-3.0-0.0)	0.696
Clinical COPD Questionnaire total change on day 30(IQR)	-1.00(-1.95--0.20)	-0.90(-1.40;-0.10)	0.289
CCQ symptoms change on day 30(IQR)	-1.25(-2.13-0.00)	-0.75(-1.75;-0.25)	0.289
CCQ mental change on day 30(IQR)	-0.50(-1.50-0.00)	-0.50(-1.50;-0.00)	0.728
CCQ functional change on day 30(IQR)	-1.00(-2.13--0.13)	-0.75(-1.25;-0.00)	0.192