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An intervention with access to C-reactive protein rapid test reduces antibiotic overprescribing in acute exacerbations of chronic bronchitis and COPD

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Abstract

Background. In acute exacerbation of chronic obstructive pulmonary disease (AECOPD) antibiotic overprescribing leads to antimicrobial resistance and underprescribing may cause poor patient outcomes.

Objective. This study aimed to evaluate changes in over- and underprescribing of antibiotics after two interventions to optimize antibiotic prescribing in AECOPD in Spain.

Methods. In 2008 and 2009, general practitioners (GPs) registered patients in a 3-week period before and after interventions. Two types of intervention were conducted: GPs in the full-intervention group (FIG) were exposed to a multifaceted intervention and given access to C-reactive protein (CRP) rapid test; partial-intervention group (PIG) was only exposed to the multifaceted intervention. Overprescribing was defined as antibiotic given to type III* exacerbation (≤ one Anthonisen Criteria); underprescribing was defined as no antibiotic given to type I exacerbation (three Anthonisen Criteria). A multivariate logistic regression model was used, considering antibiotic prescribing as the dependent variable.

Results. A total of 210 GPs and 70 GPs were assigned to FIG and PIG, respectively, and 952 AECOPD patients were eligible for main analysis. After adjusting for clustering at GP level and for patient age and sex, we found that GPs in FIG significantly reduced antibiotic overprescribing; odds ratio (OR) = 0.35 (95% CI: 0.18–0.68, $P = 0.003$) and underprescribing was not significantly increased; OR = 0.25 (95% CI: 0.06 to 1.0, $P = 0.075$). No statistically significant changes were found in the PIG.

Conclusion. Antibiotic overprescribing was only reduced when CRP test was available. Simultaneously, underprescribing was not significantly increased, but this could be due to sample size limitations.

Key words: Antibacterial agents, C-reactive protein, chronic obstructive pulmonary disease, drug therapy, drug prescription, general practice, respiratory tract infections, therapeutic use.

Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a common cause of consultation in primary care (1). Up to 90% of consulting AECOPD patients are prescribed an antibiotic (2). Excessive use of antibiotics is correlated with higher prevalence of antimicrobial resistance (3). Compared to other European countries, Spain has historically had both high rates of antibiotic consumption and antimicrobial resistance (3).

Antibiotic treatment in AECOPD is controversial for two main reasons. First, bacterial infections are only one of several causes of AECOPD (4) and current diagnostic tests cannot reliably distinguish between the different aetiologies (5). Second, the definite evidence to support the use of antibiotics in AECOPD outpatients with non-severe underlying chronic obstructive pulmonary disease (COPD) is lacking (6).

International guidelines (7,8) recommend the use of antibiotics in AECOPD based on the Anthonisen Criteria (AC), which comprise the following three clinical items: increased dyspnoea, increased sputum volume and increased sputum purulence (9). These recommendations include exacerbations of non-severe COPD. In order to improve assessment of AECOPD, C-reactive protein (CRP) is a promising biomarker because it is feasible and easily accessible in primary care (10). CRP has been shown to perform better in predicting pneumonia than any clinical symptoms (11), but its clinical role for antibiotic guidance in AECOPD remains to be determined (6).

AECOPD is a potential serious event leading to long-term decline in lung function, reduced health-related quality of life and increased mortality (12). Therefore, it is important in AECOPD to evaluate the appropriateness of changes in antibiotic prescribing patterns as underprescribing may lead to poor patient outcomes (10) and overprescribing leads to antimicrobial resistance (3).

The aim of this study was to investigate changes in over- and underprescribing after two multifaceted interventions to optimise antibiotic prescribing in AECOPD in primary care in Spain. The interventions only differed in the training and access to a CRP rapid test. CRP testing was not established in primary care offices in Spain before interventions.

Method

Setting

This study was conducted in primary care clinics in Spain as part of the Health alliance for prudent prescribing, yield and use of antimicrobial drugs in the treatment of respiratory tract infections (RTIs) (HAPPY AUDIT) project financed by the EU (13). The original objective was to demonstrate whether the Audit Project Odense (APO) method comprising a multifaceted intervention and a self-registration method could optimise diagnostic procedures and antibiotic treatment of RTIs in primary care (13).

Registration

Registration took place during 3-week periods in the winter months of both 2008 (first registration) and 2009 (second registration), covering a total of 15 working days in both registrations. Patients were registered using a prospective self-registration method based on a registration chart completed by the general practitioner (GP) after each consultation. Only first-time contacts for the current disease were registered. The registration chart included the following patient variables: age, sex, symptoms and signs, primary diagnosis, CRP value, antibiotic treatment, patient demand for antibiotics and hospital admittance.

GPs and intervention type

Three groups of GPs were included: A full-intervention group (FIG) was formed by GPs from eight autonomous communities in Spain. This intervention consisted of follow-up meetings with individual feedback on results from the first registration, discussion of clinical guidelines, training courses on appropriate use of antibiotics for RTIs, patient brochures and posters for waiting rooms, workshops on the use of CRP rapid test and subsequent access to the test in the offices for the second registration. The CRP workshops took place approximately two months before the second registration in 2009. GPs were advised to use CRP test only in cases of doubt, and not as a stand-alone test, withholding antibiotic therapy for CRP values <20 mg/l and prescribing an antibiotic for values >100 mg/l. A partial-intervention group (PIG) comprising GPs from Catalonia, including all of the above interventions except for the workshops on CRP rapid test and subsequent access to the test. CRP analysis was carried out using the NycoCard CRP® apparatus (Axis-Sheild, Norway). A CRP test result was available within three minutes after obtaining a drop of blood by finger prick. A comparison group was formed in 2009 and comprised GPs from two other autonomous communities. The comparison group had no exposure to any type of intervention.

In the scope of this *post hoc* study, GPs in the PIG and the FIG were only included if they participated in both registrations.

Study population

The study population comprised patients with a GP's diagnosis of acute exacerbation of COPD or chronic bronchitis fulfilling the inclusion criteria and having no exclusion criteria. The study profile is presented in Figure 1. Please note that, for simplicity in this article, the study population is only referred to as having AECOPD.

The exacerbation types originally defined by Anthonisen *et al.* (9) were grouped by presumed antibiotic appropriateness based upon international guidelines (7,8) and the HAPPY AUDIT guideline. International guidelines have different antibiotic guidance for COPD patients with two AC depending on the combination of criteria. However, they agree on antibiotic recommendations for COPD patients with three AC and that no antibiotics should be given in patients with only one AC. The HAPPY AUDIT guideline only advised antibiotics to patients fulfilling three AC. Consequently, type I exacerbations was defined by appropriate indications for antibiotic prescription including patients with three AC. Type II exacerbation was defined by unknown antibiotic recommendation including patients with two AC. Type III* exacerbation was defined as inappropriate indications for antibiotic prescribing including patients with one or none AC.

Endpoint

Underprescribing was defined as no antibiotic given to a patient with type I exacerbation and overprescribing was defined as antibiotic given to a patient with type III* exacerbation.

Statistical analysis

Baseline patient characteristics in each of the five groups of GPs are presented as proportions for categorical data and means for continuous normally distributed variables. Results are presented with 95%

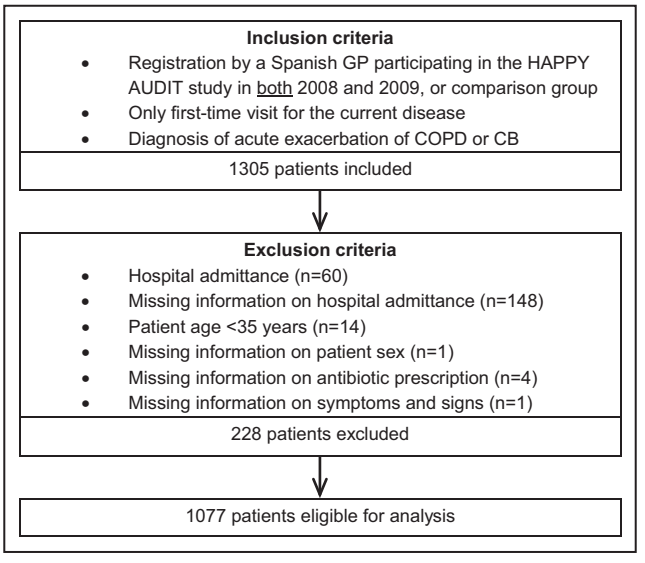

Figure 1. Study profile, inclusion- and exclusion criteria. CB, chronic bronchitis, *n*, number of patients.

confidence interval (CI) adjusted for dependence between observations at GP level.

Fisher's exact test was used to compare crude estimates of prescription habits between the comparison group of 2009 and the pre-intervention groups of 2008.

A logistic regression model was constructed in order to examine antibiotic prescribing changes in post-intervention groups versus their respective pre-intervention group. The dependent variable was antibiotic prescription. The model was multivariably adjusted for patient covariables: age and sex. Results are presented as odds ratio (OR) with 95% CI. These analyses were also subdivided according to exacerbation types. Correlation between observations due to multiple patients per GP was adjusted for using generalized estimating equations (GEE; SAS PROC GENMOD).

The nominal statistical significance level was P <0.05. SAS (version 9.3) was used in analyses.

Results

Descriptive data

A total of 332 GPs were invited to participate in the study in 2008, with 235 being assigned to the FIG and 97 to the PIG. Of these two groups, 280 (84.3%) GPs undertook the intervention and completed registrations in both 2008 and 2009, with 210 in the FIG and 70 in the PIG. The reasons for GP nonparticipation and dropout were: not wishing to participate (FIG: 11/235, PIG: 10/97), not completing registrations (PIG: 3/97) and not completing intervention (FIG: 14/235, PIG: 14/97). Fifty-nine GPs were assigned to the control group and 58 completed registrations in 2009

In a considerable proportion of cases (234/618), a GP did not register a patient with AECOPD in either one of the registration periods. In the cases where a GP registered patients with AECOPD in a registration period, the median number was three registrations (IQR 2–6, range 1–16). Baseline patient characteristics are presented in Table 1.

Main outcome: changes in antibiotic prescribing rates

As shown in Table 2, antibiotic prescribing rates after intervention increased in the PIG (PIG 2008: 79.4% versus PIG 2009: 82.5%) and reduced in the FIG (FIG 2008: 86.5% versus FIG 2009: 74.5%). After adjusting for clustering at GP level and for patient age and sex, we found that GPs exposed to the full intervention with access to CRP testing (FIG) significantly reduced antibiotic prescribing; OR = 0.46 (95% CI: 0.31–0.68, P < 0.001). In the group of GPs exposed to the partial intervention without access to CRP testing (PIG), there were no significant changes in antibiotic prescribing after the intervention (Table 3). Among GPs exposed to full intervention, we found the same trend of antibiotic reduction for all subgroups of patients with AECOPD. However, only in patients with type III* exacerbations the effect was significant; OR = 0.35 (95% CI: 0.18–0.68, P = 0.003). Among GPs exposed to the partial intervention, there was no clear trend in changes of antibiotic prescribing.

CRP test

The CRP rapid test was only used by GPs in the post-intervention FIG and was measured in 29.4% of AECOPD patients in this group. For patients being underprescribed, a CRP test was determined in six out of eight cases with four patients having a CRP value of ≤8 mg/l and two patients having CRP values of 10 and 21 mg/l, respectively. For patients being overprescribed, a CRP test was performed in 16 out of 37 cases (excluding one patient with invalid CRP value) with a median CRP value of 39 mg/l (IQR: 17.3–60.3 mg/l, range ≤8 to 187 mg/l).

Discussion

Main findings

Our study demonstrates that the intervention programme plus access to CRP testing reduced antibiotic overprescribing in type III* exacerbations. The implementation of the intervention programme, on its own, had no significant effects on antibiotic prescribing rates in AECOPD.

The impact of the full-intervention on underprescribing was statistically non-significant, but a trend towards an increase in underprescribing should be noted (OR = 0.25, 95% CI: 0.06–1.0, P = 0.075). Although underprescribing was a relatively rare event, the confidence interval was wide in the direction of fewer antibiotics being prescribed in type I exacerbation.

Table 1. Baseline characteristics of AECOPD patients subdivided by groups of general practitioners

Patient characteristics	2008		2009		
	PIG	FIG	Comparison group	PIG	FIG
Male sex (%)	64.4 (56.7–71.4)	64.6 (58.4–70.3)	64.0 (54.4–72.6)	70.6 (60.9–78.8)	65.6 (58.9–71.7)
Age, years (mean)	70.5 (68.2–72.9)	69.8 (68.5–71.0)	69.3 (67.2–71.3)	71.8 (69.0–74.5)	70.1 (68.7–71.5)
Fever, >38.5°C (%)	23.1 (15.5–33.1)	27.3 (22.3–33.1)	32.8 (22.5–45.0)	26.2 (17.9–36.6)	29.4 (23.6–36.1)
Increased dyspnea (%)	66.9 (58.5–74.3)	62.0 (56.1–67.5)	63.2 (53.0–72.4)	64.3 (51.7–75.2)	67.4 (59.1–74.7)
Increased sputum volume (%)	78.8 (70.8–85.0)	78.1 (73.2–82.4)	67.2 (55.9–76.8)	83.3 (73.4–90.1)	81.2 (75.2–86.0)
Increased sputum purulence (%)	52.5 (40.6–64.1)	56.3 (49.7–62.6)	58.4 (46.8–69.2)	54.0 (44.2–63.4)	51.8 (43.1–60.4)

Data are presented as percentage (%) or mean with 95% confidence intervals adjusted for clustering at the general practitioner level.

Table 2. Antibiotic prescribing for patients with acute exacerbation of COPD subdivided into the groups of general practitioners

Exacerbation type	2008		2009		
	PIG	FIG	Comparison group	PIG	FIG
Type I	51/52 (98.1)	114/116 (98.3)	37/38 (97.4)	32/34 (94.1)	83/91 (91.2)
Type II	51/62 (82.3)	134/151 (88.7)	42/46 (91.3)	54/62 (87.1)	89/107 (83.2)
Type III*	25/46 (54.3)	84/117 (71.8)	26/41 (63.4)	18/30 (60.0)	38/84 (45.2)
Total	127/160 (79.4)	332/384 (86.5)	105/125 (84.0)	104/126 (82.5)	210/282 (74.5)

Data are presented as *n*/*N* (%). *n*, number of patients with antibiotic prescription; *N*, total number of patients.

Table 3. Odds ratio for changes in antibiotic prescribing in AE-COPD patients after intervention

Intervention group	Odds ratio (95% CI)	*P* value
Partial-intervention group		
Total		
Antibiotics? Yes	1.29 (0.67–2.48)	0.454
No	1	
Type I	0.29 (0.02–4.43)	0.420
Type II	1.48 (0.47–4.67)	0.510
Type III*	1.33 (0.40–4.46)	0.651
Full-intervention group		
Total	0.46 (0.31–0.68)	<0.001
Type I	0.25 (0.06–1.0)	0.075
Type II	0.57 (0.27–1.18)	0.147
Type III*	0.35 (0.18–0.68)	0.003

Post-intervention group compared with its respective pre-intervention group.

Strengths and limitations

A great strength of the study was the large number of GPs included and the fact that only few GPs abandoned the study. In addition, CRP testing was not established in primary care offices in Spain before intervention (14), allowing the effect of the audit to be estimated separately from the availability of CRP testing.

One limitation of this study is the fact that GPs participated on a voluntary basis and their prescribing habits may not reflect the average use of antibiotics in primary care in Spain. GPs participating in audits may be more interested in research and quality development than other GPs (15). In addition, the study observers have probably influenced each other, because the majority of enrolled GPs worked in group practices with other study participants. Participation in the intervention on rational antibiotic use may have influenced the GPs to prescribe more rationally in the first registration. Data were reported by the GPs themselves and were not doubled-checked with the actual prescriptions. However, the reliability of the APO method is high and findings correlate with actual prescriptions (16).

Although this was not a clinical trial, we allowed comparison of prescribing rates in order to determine the quality of the change after the interventions. Importantly, the before–after study design suffers from a time factor limitation and the intervention may have occurred dependently on other changes that affect antibiotic prescribing. However, no statistically significant differences in crude estimates of antibiotic prescribing were found between each of the pre-intervention groups of 2008 and the control group of 2009, thereby indicating that the time factor may not have influenced the results. These results also indicate that there were no major differences among the GPs. In addition, no important differences on antibiotic prescribing are found across the different communities in Spain (17). However, no descriptive data were available on the GPs and the GP groups were from different parts of Spain. The lacking information on GP comparability is a major limitation. Although patient demand for antibiotics is a known predictor of antibiotic prescribing (2), the results are unadjusted for this effect, as part of the intervention was to educate consulting patients on the importance of rational use of antibiotics.

We consider our results to have sufficient power. The smallest decrease in antibiotic prescription that can be detected for PIG with 80% power in the present data, assumig an intraclass correlation of 0.2 between patients of the same GP, is from the observed 80% in 2008 to 68% in 2009. This is a similar decrease as for FIG. Hence the analysis for PIG is powered to investigate the hypothesis that the decreases for PIG and FIG are similar. Note that antibiotic prescribing actually increases for PIG so the absence of effect cannot be ascribed to lack of power.

A major limitation of this study is the inclusion of patients without a spirometric diagnosis of COPD. Consequently, patients with exacerbation of chronic bronchitis were also included. This limitation mimics a previously described clinical problem in primary care in Spain, where COPD often is erroneously diagnosed by clinical symptoms without spirometrical confirmation (18). In this study, some patients with three cardinal symptoms might not fulfill the requirement for an antibiotic prescription. On the other hand, international guidelines recommend the use of AC for antibiotic guidance in AECOPD regardless of underlying COPD severity (7,8).

Our study did not address type II exacerbations. We are aware that some guidelines recommend an antibiotic prescription to patients with type II exacerbations, mainly when sputum purulence is present (8). However, the HAPPY AUDIT guideline only addressed outpatients and did not recommend antibiotics to type II exacerbations. We focused on patients with type I and type III* exacerbations, because in these subtypes there are clear guideline recommendations for the use of antibiotics (7,8).

Another limitation is that important variables were not taken into account which may have influenced the antibiotic prescribing rate, including forced expiratory volume in 1 s, smoking status, comorbidities, use of oral corticosteroids and history on previous exacerbations. Another problem is the everlasting concern about the evolution of patients not treated with antibiotics. Patient referrals were considered in the study, but only for the first-time visit. Reducing the rate of antibiotic prescribing is fair, but only if an increase in referrals and complications are not associated. Therefore, the lack of clinical evaluation after diagnosis of an exacerbation is an important limitation. The study only focused on initial consultation and was not designed to assess patient outcomes.

Interpretation of findings in relation to previously published work

Our colleagues in the HAPPY AUDIT study group (2) demonstrated that GPs who already have access to CRP rapid testing prescribe fewer antibiotics in AECOPD outpatients than those who do not. However, the result mainly reflects the use of CRP testing in Scandinavian countries, where CRP testing has been used in more than a decade. Our result in the FIG reflects a change in prescribing behaviour, when GPs are given access to a CRP test.

Compared to other European countries, Spain has high rates of outpatient antibiotic prescribing (3). After the introduction of CRP testing in the FIG, total antibiotic prescribing rate was 74.5%, and overprescribing was still common (45.2%). In comparison, the total antibiotic prescribing rate in AECOPD was 48.9%, when prescribed by Danish GPs participating in the HAPPY AUDIT study before intervention (2), indicating that further improvement may have been possible in the FIG.

In our study, the CRP rapid test was introduced to distinguish pneumonia from self-limiting acute lower RTIs. Our study did not specify any usefulness of CRP testing in AECOPD. This explains why a CRP test was only performed in 29.4% of the patients in FIG 2009. By the time this study was started there were no studies about the benefit of CRP to predict evolution of outpatients with AECOPD. However, a CRP cut-off value of 40 mg/l was recently found to predict clinical success with a sensitivity and specificity of 0.655 and 0.876, respectively (10). Application of the CRP cut-off-value could hypothetically have enhanced the reduction in overprescribing in the FIG of 2009, as a considerable proportion (8/16) of the overprescribed patients with CRP test results had a value ≤40 mg/l. Yet the goal was not to eliminate our definition of overprescribing, as AECOPD patients with only one AC may benefit from antibiotic treatment, in particular those with sputum purulence (19). However, the number of patients with sputum purulence as the only AC was relatively small (31/1077), and only one was not prescribed an antibiotic.

To our knowledge, no studies have adequately evaluated the effect of reducing antibiotic prescribing in AECOPD on outpatient outcome. Observational data suggest an association between reductions in antibiotic prescription for lower RTIs in general practice and an increase in community-acquired pneumonia mortality (20). Cals *et al.* (21) did not observe any differences on clinical recovery, reconsultations or patient satisfaction among patients with lower RTIs treated by doctors with access to a CRP test versus controls, despite the fact that fewer antibiotics were prescribed in the CRP group. This study had no analyses for AECOPD.

Antibiotic treatment seems to be clinically important for AECOPD outpatients with appropriate indications (9,10). Llor *et al.* (10) found that outpatients with exacerbation in mild-moderate COPD and three AC assigned to antibiotic treatment had a significantly higher clinical success and lower clinical failure than similar patients assigned to placebo. No significant difference was found between the antibiotic and placebo group in patients with only one AC. The study also investigated long-term outcomes, but this analysis was not subdivided by AC. Among all outpatients with clinical cure at the end of therapy, significantly fewer exacerbations were observed the following year in patients initially assigned to antibiotic treatment compared with those assigned to placebo. These results emphasises that underprescribing may have clinically unwanted effects on both short- and long-term patient outcome.

Implications for future research, policy and practice

A randomized clinical trial with the use of symptom diaries analysing the duration and severity of symptoms is definitely necessary. This future study should include shorter outcomes such as number of visits to health care departments in the first month. This is the only way of preventing biases and will enable us to answer if we can safely reduce antibiotic overprescribing for AECOPD.

Conclusion

To the best of our knowledge, this is the first study to demonstrate that GPs who are given access to CRP testing reduce antibiotic overprescribing in type III* exacerbations of COPD. Simultaneously, underprescribing did not significantly increase, but should be interpreted as inconclusive since the result of antibiotic prescribing change in type I exacerbation pointed in the direction of a reduction and patient outcomes were not assessed. This study was a *post hoc* analysis and had several limitations. Future well-designed randomized clinical trials are needed to answer if we can safely reduce overprescribing of antibiotics in AECOPD.

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Declaration

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