C-reactive protein testing in patients with acute rhinosinusitis leads to a reduction in antibiotic use

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Objective. To evaluate the effect of C-reactive protein (CRP) testing on the antibiotic prescribing in patients with acute rhinosinusitis.

Methods. Audit-based study carried out in primary care centres in Spain. GPs registered episodes of rhinosinusitis during 3-week period before and after an intervention. Two types of intervention were considered: full intervention group (FIG) consisting in individual feedback based on results from the first registry, courses in rational antibiotic prescribing, guidelines, patient information leaflets, workshops on rapid tests and use of the CRP test. GPs in the partial intervention group (PIG) underwent all the above intervention except for the workshop and they did not have access to CRP. Multilevel logistic regression analysis was performed considering the prescription of antibiotics as the dependent variable.

Results. Two hundred and ten physicians were assigned to FIG and 71 to PIG. In 2009, 59 new physicians were included as a control group. Two hundred and sixty-seven GPs visited contacts with rhinosinusitis (78.5%) registering a total of 836 cases. In the group of GPs with access to CRP rapid test, 207 patients with rhinosinusitis (75.3%) were tested and antibiotics were prescribed in 156 patients (56.7%). Antibiotics were prescribed in 87 patients (82.9%) in the group of GPs exposed to PIG and in 52 patients (86.7%) in the control group (P < 0.001). Antibiotic prescription was significantly reduced after the intervention among physicians assigned to FIG, with an odds ratio of antibiotic prescribing of 0.12 (95% confidence interval: 0.01–0.32).

Conclusion. Physicians with access to CRP tests significantly reduced antibiotic prescription in patients with rhinosinusitis.

Keywords. Antibiotics, audit, C-reaction protein, general practice, rational use of antibiotics, rhinosinusitis.

Introduction

Acute rhinosinusitis is a frequent problem in general practice and it accounts for 3%–5% of all respiratory tract infections in primary care.1 An increasing amount of evidence confirms that, in most cases, antibiotics are of little or no benefit for routine treatment of complicated acute rhinosinusitis. Moreover, despite the fact that bacteria are present in 60% of acute rhinosinusitis, most cases resolve spontaneously.2,3 The effectiveness of antibiotic therapy in this infection is modest since 15 patients with acute rhinosinusitis-like complaints have to be given antibiotics before an additional patient is cured.4 Symptoms of bacterial
rhinosinusitis overlap with viral rhinosinusitis, and it is difficult to distinguish between the two conditions based only on a clinical examination. Uncertain diagnosis results in a significant overuse of antibiotics, which is considered to be one of the most important reasons for the development of bacterial resistance to antibiotics. In fact, it has been reported that antibiotics are prescribed roughly to 80% of patients consulting for acute sinusitis.

The gold standard to assess the aetiology of acute rhinosinusitis is sinus puncture followed by aspiration and bacterial culture. However, this invasive procedure is of limited practical value and is seldom used in primary care. Other tests, such as simple radiography, ultrasonography, computed tomography and magnetic resonance imaging, which are of diagnostic value, are not available in general practice. A raised C-reactive protein (CRP) level, an acute-phase protein produced in response to circulating cytokines from inflammatory foci, is an indicator of bacterial infection and the CRP rapid test has been shown to be useful for the diagnosis of bacterial sinusitis in general practice. The aim of this study was to evaluate the effect of CRP testing on the use of antibiotics in patients with acute rhinosinusitis.

Subjects and methods

Study design
This study constitutes a part of the Happy Audit project, a study financed by the European Commission. GPs from six countries participated in this study (Denmark, Sweden, Lithuania, Russia, Spain and Argentina). However, Spain was the only country in which two levels of interventions were undertaken. Detailed information about the study method and the intervention can be found in the study protocol, published elsewhere. Briefly, a non-randomized controlled before–after study was carried out in Spain, with the participation of three groups of GPs: (i) GPs who were allocated to the full intervention group (FIG) were offered feedback based on their individual results from the first registry, courses and guidelines on rational diagnostics and treatment of respiratory tract infections, patient information leaflets and workshops focussing on CRP testing in practice. (ii) A partial intervention group (PIG) of GPs were exposed to the same intervention as the FIG except for the workshop on diagnostic methods and they were not offered access to CRP testing. The first registry of the two groups of professionals was made prior to the intervention in January and February 2008 and a second registry was made after the intervention in January and February 2009. (iii) A control group of physicians was not exposed to any type of intervention before the registration of patients. The data were registered according to the ‘Audit Project Odense’ (APO) method described by Munck et al. The APO method for prospective self-registration uses a simple registration chart to record selected issues of medical care. In the present study, the GP recorded the age and gender for each contact, the duration of the symptoms, the different signs and symptoms, the suspected focus of infection, the tests ordered and the treatment given. If the GP used a CRP rapid test, the result was recorded in the template. Approval was obtained from the Ethical Committee of the ‘Fundacio Jordi Gol i Gurina’ (registration number: 44154).

CRP analysis was carried out using the NycoCard CRP® apparatus (Axis-Shield, Norway). A CRP test result was available within 3 minutes after obtaining a drop of blood by finger prick. Physicians assigned to FIG were offered a training session on how to perform CRP analysis before the second registration period. The GPs were also informed about the evidence regarding its use in respiratory tract infections in general practice and the evidence-based use of CRP testing given by the study team. In this workshop, the study team emphasized that the test result should always be interpreted in combination with patient history recording and clinical examination. A CRP test result >40 mg/l was interpreted as a support for the decision to prescribe antibiotics, while a CRP test result <10 mg/l supported the decision on no antibiotic prescribing.

Statistical analysis
The data were analysed with the Stata v.11 statistical program, performing univariate descriptive statistics. A multilevel logistic regression model was estimated with two levels: (i) level patients with acute sinusitis and (ii) level physicians. Antibiotic prescription was considered as a dependent variable. The variables of interest were the use of the CRP and the five clusters of physicians (control group, FIG before and after the intervention and the PIG group before and after the intervention). The model was adjusted for the following covariables: age and gender, symptoms and signs presented, patient demand for antibiotics and the result of radiographic examinations of sinuses. Statistical significance was considered with a P value <0.05.

Results

Contacts with rhinosinusitis
A total of 332 GPs were invited to voluntarily participate in the study in 2008, with 235 being assigned to the FIG and 97 to the PIG. Of these two groups, a total of 309 (93.1%) physicians registered patients in the first audit in January–February 2008 and 281 (84.6%) professionals carried out the intervention in 2008 and made the second registry in January–February 2009. Of the 340 GPs who completed the study, 267
registered at least one episode of rhinosinusitis (78.5%). Figure 1 shows the general scheme of the study. The mean number of patients registered with sinusitis was 1.8, ranging from 1 to 20 different patients per physician. Fever was present in 33.4% of patients with rhinosinusitis. The average number of days with symptoms before first consultation was 7.4 days, being greater among patients attended by physicians assigned to FIG after the intervention (8.4 days, \( P < 0.05 \)). Among the physicians assigned to FIG in the second year, a CRP rapid test was carried out in 75.3% of the cases. The percentage of GPs considering acute rhinosinusitis as a viral infection was higher in the group of doctors assigned to FIG in the second year, with almost 40% of the cases. As shown in Table 1, antibiotics were prescribed in <60% of the patients with sinusitis attended by physicians assigned to FIG after the intervention. Nevertheless, the reduction of antibiotics was only marginal after the intervention among GPs assigned to FIG.

**Antibiotic prescribing and CRP results**

A total of 275 patients with rhinosinusitis were registered by the GPs assigned to FIG after the intervention. The rate of antibiotic prescription for patients with rhinosinusitis in the group of GPs who used rapid CRP testing was 46.7% compared with 82.9% in the group of GPs who did not use this test (\( P < 0.001 \)) (Fig. 2). Among the GPs using the CRP rapid test, antibiotics were only prescribed in 10.2% of the cases when test result was <10 mg/l, which was the case of 51.8% of the contacts with rhinosinusitis. However, when the value was >10 mg/l, GPs were more prone to give antibiotics, with these drugs being administered in 92.5% of these cases (Fig. 2).

![Diagram](https://academic.oup.com/fampra/article-abstract/29/6/653/453858)

**Figure 1** General scheme of the study

**Table 1** Characteristics and antibiotic therapy prescribed depending on the group

<table>
<thead>
<tr>
<th></th>
<th>CG</th>
<th>PIG pre</th>
<th>PIG post</th>
<th>FIG pre</th>
<th>FIG post</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>60</td>
<td>111</td>
<td>105</td>
<td>285</td>
<td>275</td>
<td>836</td>
</tr>
<tr>
<td>Men (%)</td>
<td>18 (30.0)</td>
<td>48 (43.2)</td>
<td>30 (28.6)</td>
<td>103 (36.1)</td>
<td>94 (34.2)</td>
<td>293 (35.0)</td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>38.8 (12.6)</td>
<td>39.9 (15.3)</td>
<td>38.0 (16.9)</td>
<td>38.5 (15.0)</td>
<td>41.9 (16.3)</td>
<td>39.8 (15.6)</td>
</tr>
<tr>
<td>Duration of symptoms, days (SD)</td>
<td>6.5 (4.7)</td>
<td>6.2 (6.0)</td>
<td>5.6 (4.6)</td>
<td>7.9 (9.8)</td>
<td>8.4 (6.1)</td>
<td>7.4 (7.4)</td>
</tr>
<tr>
<td>Fever</td>
<td>26 (43.3)</td>
<td>38 (34.2)</td>
<td>31 (29.5)</td>
<td>89 (31.2)</td>
<td>95 (34.5)</td>
<td>279 (33.4)</td>
</tr>
<tr>
<td>Cough</td>
<td>49 (81.7)</td>
<td>66 (59.5)</td>
<td>68 (64.8)</td>
<td>230 (80.7)</td>
<td>222 (80.7)</td>
<td>635 (76.0)</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>16 (26.7)</td>
<td>19 (17.1)</td>
<td>16 (15.2)</td>
<td>64 (22.5)</td>
<td>50 (18.2)</td>
<td>165 (19.7)</td>
</tr>
<tr>
<td>Purulent rhinorrhea</td>
<td>18 (30.0)</td>
<td>16 (14.4)</td>
<td>15 (14.3)</td>
<td>60 (21.1)</td>
<td>45 (16.4)</td>
<td>154 (18.4)</td>
</tr>
<tr>
<td>CRP rapid test</td>
<td>0 (–)</td>
<td>0 (–)</td>
<td>0 (–)</td>
<td>1 (0.4)</td>
<td>4 (1.4)</td>
<td>5 (1.5)</td>
</tr>
<tr>
<td>Sinusal radiography</td>
<td>0 (–)</td>
<td>3 (2.7)</td>
<td>2 (1.9)</td>
<td>4 (1.4)</td>
<td>4 (1.5)</td>
<td>13 (1.6)</td>
</tr>
<tr>
<td>Bacterial aetiology suspected</td>
<td>47 (78.3)</td>
<td>96 (86.5)</td>
<td>79 (75.2)</td>
<td>236 (82.8)</td>
<td>145 (52.7)</td>
<td>603 (72.1)</td>
</tr>
<tr>
<td>Antibiotics prescribed</td>
<td>52 (86.7)</td>
<td>97 (87.4)</td>
<td>87 (82.9)</td>
<td>252 (88.4)</td>
<td>156 (56.7)</td>
<td>644 (77.0)</td>
</tr>
</tbody>
</table>

CG, control group; post, post-intervention; pre, pre-intervention.
Predictors of antibiotic prescribing in acute rhinosinusitis

A two-level multilevel logistic regression model was estimated including as first-level patients with acute rhinosinusitis (n = 836) and as second-level physicians (n = 267). In this analysis (Table 2), the use of the CRP was a significant protective factor for antibiotic prescription. Thus, with CRP results <10 mg/l, the odds ratio (OR) of antibiotic prescription was 0.008 compared with the no use of this test [95% confidence interval (CI): 0–0.015]. After adjusting for the remaining variables, no statistically significant differences were found in antibiotic prescription between the two pre-intervention and the control groups. In contrast, the post-intervention ORs were lower than those of the control and pre-intervention groups, but it was only significant among physicians assigned to FIG. In comparison with the control group, the OR for antibiotic prescription was 0.115 (95% CI: 0.008–0.321). The sign most associated with antibiotic prescription was the presence of purulent rhinorrhea followed by fever. Curiously, male gender was also significantly associated with the prescription of antibiotics.

Discussion

Main findings

An important reason for performing the CRP rapid test is to avoid the prescription of antibiotics in patients with non-bacterial acute rhinosinusitis. We found that the percentage of antibiotics prescribed for acute sinusitis was nearly halved among GPs who used the CRP rapid test compared with those who did not use this test.

Limitations

Our data must, however, be interpreted with caution due to a number of limitations. The GPs participated on a voluntary basis and their prescribing habits may not represent the average use of antibiotics in our country. The GPs participating were willing to register their antibiotic prescriptions and may have been more interested in quality development and research than GPs in general. Furthermore, they were willing to dedicate sufficient time to complete patient reports without remuneration. The amount of time involved to participate in this project could be considered as a relevant barrier against GP participation, given the numerous consultations and limited time frame available for each patient in primary care. However, earlier studies using the same type of data registration did not find it very time-consuming since each registration takes <1 minute. GPs in the intervention groups were requested to register cases in 2008 and 2009 and GPs in the control group were only requested to fill out the registration charts in 2009. Without any type of intervention, a difference in antibiotic prescription should not be expected between these two consecutive years. Furthermore, the rates of antibiotic prescription were steady in our country from 2007 to 2009. A potential limitation is the Hawthorne effect, which may have introduced bias because GPs in the control group may have altered their prescription habits. To reduce this risk, GPs in the control group were specifically instructed to follow their usual care. Furthermore, registration of antibiotic use may in itself influence prescribing habits. Practices using CRP measurement in the second year may a priori have had a positive attitude towards a more rational use of antibiotics. However, studies have shown that the reliability of this methodology applied in different countries is high and findings are correlated with the real prescribing in practice. In our study, we asked the GPs to register what happened during the consultation, but patients were not followed after the consultation and thus, we have no knowledge about the consequence of reducing antibiotic prescription among the patients involved.
Comparison with other studies
Diederichsen et al.\textsuperscript{19} found that the CRP rapid test had no impact on the use of antibiotics in general practice. However, this study included all patients with respiratory tract infections and the number of cases with rhinosinusitis was very low. In a study focussing on patients with symptoms of rhinosinusitis, Hansen et al.\textsuperscript{20} found that a raised CRP level or sedimentation rate in combination with a pain score was useful to identify patients, who benefited from treatment. In another study using a methodology similar to that of the present study, Bjerrum et al.\textsuperscript{21} found a significantly lower rate of antibiotic prescription among the physicians who used the CRP rapid testing (59% versus 78% observed among those who did not use the rapid test). In the best study carried out to date, Cals et al.\textsuperscript{22} observed that GPs assigned to CRP point-of-care tests prescribed significantly fewer antibiotics compared to those who did not use these tests (45.2% versus 60.3%) in a Dutch clinical trial. Interestingly, recovery was similar between the two groups.\textsuperscript{22}

In a partial intervention without point-of-care rapid testing, antibiotic prescription was not or was only marginally reduced. Similarly, the implementation of guidelines on acute rhinosinusitis produced modest changes in the management of acute maxillary sinusitis in Finland.\textsuperscript{23} Based on the results of the present study, the CRP rapid test was the factor that was found to have the greatest influence on whether a patient with acute rhinosinusitis was prescribed antibiotics. In practices using this test, the results strongly influenced the rate of antibiotic prescription. A little more than half of the patients tested had CRP levels <10 mg/l and only 10% of these received antibiotics. In contrast, >90% of patients with CRP levels >10 mg/l were treated with antibiotics. There is no tradition of delaying antibiotic prescription in our country but perhaps, it should have been offered in cases of doubt such as those with intermediate CRP results. According to a questionnaire-based survey, Høy et al.\textsuperscript{24} found that the most common diagnosis for Norwegian GPs to issue a wait-and-see prescription was acute rhinosinusitis.

This is a pragmatic study in which registration of patients was performed in a natural practice setting. Patients were not informed about the project prior to the consultations. Thus, patients were attended as if they were not participating in the study. Therefore, it is most likely that our results can be extrapolated to other areas and practices with similar settings. In summary, a CRP test result adds incremental information to the information obtained from the medical history and physical examination. In particular, a low CRP test result of <10 mg/l, which was the case in >50% of our patients, may be helpful in ruling out a bacterial aetiology of rhinosinusitis.

Implications for future research
This study indicates that implementing the CRP rapid test in general practice may lead to a reduction in antibiotic prescription in patients with rhinosinusitis. However, based on the observational design of the study, we cannot conclude that the use of CRP tests was the only reason for lower prescribing. Other factors may be involved, and the association found may not be based on a causal relationship. Further studies are needed to investigate patients’ outcomes due to the reduction in antibiotic prescribing and to analyze the cost-effectiveness of implementing CRP rapid tests for rhinosinusitis in general practice.

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Declaration
Ethical approval: Ethical Committee of the ‘Fundació Jordi Gol i Gurina’ (44154).
Conflict of interest: none.

References


