Health Service Research

C-reactive protein point-of-care testing and associated antibiotic prescribing

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Abstract

Background. In clinical trials, the potential of point-of-care (POC) C-reactive protein (CRP) tests was demonstrated in decreasing antibiotic prescribing in adults with acute cough in general practice, but effects of implementation are unknown.

Objective. To determine the overall effect of POC CRP testing on antibiotic prescribing rate in general practice.

Methods. In an observational study, GPs were instructed to use POC CRP in adults with acute cough following current guidelines. After routine history taking and physical examination, they reported whether they intended to prescribe antibiotics (‘pre-test decision’). They reported their revised decision after receiving the POC CRP test result (‘post-test decision’). Primary outcome was the percentage of patients in whom the GP changed his or her decision to prescribe antibiotics. Secondary outcome was the difference between ‘pre-test’ and ‘post-test’ antibiotic prescribing % at group level.

Results. A total of 40 GPs enrolled 939 patients, 78% of whom were tested for CRP. GPs changed their decision after POC CRP testing in 200 patients (27%). Antibiotic prescribing before and after CRP testing did not differ (‘pre-test’ 31%, ‘post-test’ 28%; 95% confidence interval of difference −7 to 1). In 41% of the tested patients, the indication for testing was in accordance with the guidelines.

Conclusion. POC CRP influenced GPs to change their decision about antibiotic prescribing in patients with acute cough. POC CRP testing does not reduce overall antibiotic prescribing by GPs who already have a low antibiotic prescribing rate.

Key words. Community-acquired pneumonia, C-reactive protein, general practice, guideline adherence, lower respiratory tract infection, point-of-care testing.

Introduction

Acute cough is one of the main reasons for patients to consult their GP worldwide (1–3). In patients presenting with acute cough or other symptoms of lower respiratory tract infections (LRTIs), bronchitis is to be differentiated from community-acquired pneumonia (CAP), since bronchitis is usually self-limiting while CAP requires treatment with antibiotics. To support the detection of CAP, C-reactive protein (CRP) is increasingly used in the diagnostic work-up in general practice. In patients in whom diagnostic uncertainty remains after clinical examination, CRP level has added diagnostic value to detect CAP (4–6). Several randomized controlled trials (RCTs) and reviews have shown that CRP point-of-care (POC) testing, i.e. testing during GP consultation, can reduce antibiotic prescribing (7–13) and is cost-effective (14–16). Based on this evidence, guidelines advise POC...
CRP testing for patients who present with acute cough suspected of CAP (3,17).

In RCTs, however, GPs are explicitly instructed on which patients should be tested and how CRP results should be interpreted. The actual impact of CRP implementation in routine GP practice, where POC CRP tests are used at the discretion of the GP without monitoring and strict protocols on use and interpretation, might differ from the trial situation. It is not known yet whether POC CRP test results affect the GPs decision to prescribe antibiotics or not in daily practice.

The present study aims to determine the effect of POC CRP testing on antibiotic prescribing when implemented in general practice, where guidelines are already available. Firstly, we determined the overall effect of POC CRP on antibiotic prescribing rate among participants, and secondly we assessed how often the POC CRP test results did alter the GPs decision on antibiotic prescribing for individual patients. Finally, we assessed guideline adherence for (the indication of) POC CRP testing and antibiotic prescribing.

**Methods**

**Design**

A prospective observational study.

**Setting**

The study was carried out in nine general practices in the Netherlands, four in the residential area of Rotterdam and five in a new residential area near Utrecht, with in total ~60,000 patients registered. The patient population is representative for the Dutch population (1,18). Four of the practices involved in this study were academic research centres (‘academic practices’) and five were not routinely involved in research (‘non-academic practices’).

**Study population**

From February 2012 to February 2013, 40 participating GPs enrolled all patients aged 18 years and over consecutively, presenting in routine general practice with acute cough (<24 days). GPs provided care as usual, i.e. decided on diagnostic work-up (including possible POC CRP testing) and management according to their routine practice. GPs did not receive formal additional training on indications and interpretations of POC CRP test results for study purposes, yet the research team did notify GPs of the existing professional guideline ‘Acute Cough’ from the Dutch College of GPs (2011), in which indications for CRP testing are described (17). The Act on Medical Research involving human subjects did not apply to this study and therefore an official approval of this study by the Medical Ethics Research Council of the University Medical Center Utrecht was not required.

**Measurements**

GPs reported characteristics, and their diagnostic and therapeutic management of all patients included on case registration forms (CRFs): age, relevant comorbidities, fever reported by patients, auscultation abnormalities (defined by crackles or reduced vesicular breathing), tachypnoea (>24 breaths/minute), tachycardia (pulse >100/minute), hypotension (blood pressure < 90/60 mmHg) and mental state of confusion and drowsiness. Relevant comorbidity was defined as heart failure, diabetes mellitus, chronic obstructive pulmonary disease, asthma, impaired immunity, malignancy, severe neurologic illness, renal failure, congenital heart disease or congenital lung disease. On the CRF, GPs registered before ordering a POC test (or not) whether they intended primarily to prescribe antibiotics (‘pre-test’ decision). The POC CRP test was performed by the practice assistant. CRP level measurement was carried out using Alere Afinion® AS100 POC CRP test devices (19) in accordance with the manufacturer’s instructions. After disclosure of the POC CRP test result, GPs registered whether they actually prescribed antibiotics (‘post-test’ decision). Within 28 days follow-up, the GPs reported for all included patients whether or not the patient presented for re-consultation, whether or not they had prescribed antibiotics during re-consultation and whether or not they had referred the patient to a pulmonologist because of suspected CAP.

**Indications for point-of-care C-reactive protein testing**

Risk groups for CAP and indications for POC CRP testing were defined according to the guideline ‘Acute cough’ from the Dutch College of GPs (17). This is the main (consensus) guideline in Dutch general practice. It focuses on two steps in the diagnostic process. Firstly, patients who present with acute cough are classified into three risk categories based on signs and symptoms: (a) low, (b) intermediate and (c) high risk of complicated LRTI (for complete definition of these subgroups, see Fig. 1). Secondly, recommendations are given for each risk group category on whether to test POC CRP and to prescribe antibiotics. For patients with acute cough in category (a), the guideline recommends to refrain from both POC CRP testing and antibiotics. For category (c), the guideline recommends not to test, but to prescribe antibiotics or refer to secondary care instantly. For category (b), the group with largest diagnostic uncertainty, the guideline recommends to perform a POC CRP test. If POC CRP results are <20 mg/l, the advice is to refrain from antibiotics, if POC CRP results are between 20 and 100 mg/l, GPs must base prescribing antibiotics or not merely on their clinical assessment, and for results >100 mg/l, it is recommended to start antibiotic treatment.

**Outcomes**

The primary outcome was at patient level: the change in decisions of the GPs on antibiotic prescribing in individual patients ‘pre-test’ compared to ‘post-test’. Secondary outcome was the difference between ‘pre-test’ and ‘post-test’ antibiotic prescribing rate. Thirdly, we assessed guideline adherence for requesting POC CRP tests and guideline adherence for prescribing antibiotics. Fourthly, we summarized follow-up data as absolute numbers (counts) for all intermediate-risk [category (b)] patients.

**Data analysis**

Clinical characteristics, POC CRP test results, guideline adherence for POC CRP, guideline adherence for antibiotic prescribing and follow-up data were analyzed using descriptive statistics. Percentages were computed to summarize categorical variables. Mean and standard deviations (SDs) were used for continuous variables. To test whether there was a difference between ‘pre-test’ and ‘post-test’ antibiotic prescribing rate, the McNemar test was used. Post hoc subgroup analysis of possible differences in antibiotic prescribing rate (on group level) between GPs in academic practices and GPs from non-academic practices was performed. Guideline adherence for POC CRP testing was assessed as follows: If GPs requested a POC CRP test in intermediate-risk [category (b)] patients, this was considered as adherent testing. POC CRP testing in low/high-risk [category (a) and (c)] patients was considered as non-adherent. We also assessed the guideline adherence for antibiotic prescribing. For
all low-risk [category (a)] patients, a prescription was not according to the guideline and for all high-risk [category (c)] patients a prescription was guideline adherent. For the intermediate-risk [category (b)] patients, a prescription was guideline adherent when POC CRP results >100 mg/l.

A change from 'pre-test: yes' to 'post-test: no' was considered guideline adherent for POC CRP results of <20 mg/l. Alternatively, a change from 'pre-test: no' to 'post-test: yes' was deemed adherent for POC CRP results >100 mg/l. For intermediate-risk [category (b)] patients with POC CRP levels of 20–100 mg/l, all changes were considered non-adherent, since for these cases the guideline recommends to rely predominantly on clinical findings; for the purpose of this study, the 'pre-test' antibiotic prescribing decision ('yes' or 'no') was considered to reflect the GPs interpretation of clinical findings. Five patients had missing CRP values and were left out of the analyses. Statistical packages SPSS for Windows 20.0.0 (SPSS, Inc., Chicago, IL) were used.

Results

A total of 939 patients were included (mean age 47 [SD 15] years, 38% male). For 735 (78%) patients, the GPs requested a POC CRP test. Demographics, symptoms, signs and comorbidity are presented in Table 1.

Antibiotic prescribing

On individual patient level, POC CRP test results prompted changes in antibiotic prescribing decisions in 200 (27%) of all POC CRP-tested patients. In 114 (16% of total, 57% of changes) of the tested patients, the decision on antibiotic prescribing changed from ‘pre-test: yes’ to ‘post-test: no’ and in 86 (12% of total, 43% of changes) vice versa (Fig. 2). GPs intended to prescribe antibiotics in 290 (31%) patients, after performing the POC CRP test, they actually prescribed antibiotics to 262 (28%) patients [difference −3%, 95% confidence interval (CI): −7 to 1] (P = 0.06; Fig. 3). Post hoc subgroup analysis of the antibiotic prescribing rate showed that in academic practices, the ‘pre-test’ antibiotic prescribing rate was 25% and the ‘post-test’ antibiotic prescribing rate 28% (difference: 3%, 95% CI: −3 to 8) (P = 0.19). For non-academic practices, the prescribing rate was 38% ‘pre-test’ and 27% ‘post-test’ (difference: −11%, 95% CI: −17 to 4) (P < 0.001).

Guideline adherence

According to the professional guideline, 335 (46%) of the POC CRP-tested patients had low risk (a), 97 (13%) high risk (c) and 303 (41%) intermediate risk (b) of complicated LRTI. For the definition of these subgroups, see Figure 1. The intermediate group is the only group for which the guideline recommends testing, hence 303 (41%) of indications were in accordance with the guideline. As for guideline adherence on antibiotic prescribing, for low-risk [category (a)] patients, post-test no prescribing was guideline adherent for 264 of 335 (79%). In the high-risk group [category (c)], guideline adherence was the case in 44 of 97 patients (46%). Details on CRP levels and antibiotic prescribing in patients with an intermediate risk (b) are shown in Figure 3. For 93 (31%) of the 303 intermediate-risk patients, the POC CRP result prompted the GP to change their decision on antibiotic prescribing. The change in decision on antibiotic prescribing was in line with recommendations of the guideline in 56 out of these 93 (60%) patients (online Supplementary Figure S1).

Follow-up

A total of 144 patients with intermediate risk (b) presented for re-consultation, 48 received a (second) prescription of antibiotics at re-consultation and 5 were referred to the pulmonologist because of suspected CAP (online Supplementary Figure S1).

Discussion

Summary of results

POC CRP testing in nine general practices in the Netherlands resulted in a change in the decision to prescribe antibiotics in 27% of tested patients. It did not reduce antibiotic prescribing for patients presenting with acute cough. About 41% of POC CRP tests were indicated according to present guidelines. In the group of patients who were indicated for CRP testing according to the guidelines, 40% of changes in decisions on antibiotic prescribing after testing was not according to guideline recommendations.

Strengths and limitations

Several limitations need to be addressed. Firstly, the antibiotic prescribing rate in our study was relatively low compared to international data from previous studies (9–13), which limits the potential
Table 1. Baseline characteristics of all included patients, all point-of-care C-reactive protein-tested patients and all non-tested patients, presenting in routine general practice with acute (<24 days) cough, between February 2012 and 2013

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All included patients, n = 939</th>
<th>Point-of-care C-reactive protein-tested patients, n = 735</th>
<th>Non-tested patients, n = 204</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>47 (15)</td>
<td>47 (15)</td>
<td>48 (15)</td>
</tr>
<tr>
<td>Male gender</td>
<td>356 (38)</td>
<td>274 (37)</td>
<td>82 (40)</td>
</tr>
<tr>
<td>CRP, mean in mg/l (SD)</td>
<td>24 (33)</td>
<td>24 (33)</td>
<td>--</td>
</tr>
<tr>
<td>&lt;20 mg/l</td>
<td>514 (55)</td>
<td>514 (70)</td>
<td>--</td>
</tr>
<tr>
<td>20–100 mg/l</td>
<td>190 (20)</td>
<td>190 (26)</td>
<td>--</td>
</tr>
<tr>
<td>&gt;100 mg/l</td>
<td>31 (3)</td>
<td>31 (4)</td>
<td>--</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breathlessness (reported)</td>
<td>379 (40)</td>
<td>321 (44)</td>
<td>85 (28)</td>
</tr>
<tr>
<td>Allergic to antibiotics</td>
<td>50 (5)</td>
<td>43 (6)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Fever (reported) 7 days or more</td>
<td>38 (4)</td>
<td>31 (4)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>326 (35)</td>
<td>264 (36)</td>
<td>62 (30)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>16 (2)</td>
<td>12 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>72 (8)</td>
<td>49 (7)</td>
<td>23 (11)</td>
</tr>
<tr>
<td>COPD</td>
<td>74 (8)</td>
<td>39 (8)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Asthma</td>
<td>122 (13)</td>
<td>107 (15)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>17 (2)</td>
<td>16 (2)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>21 (2)</td>
<td>18 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Neurology</td>
<td>14 (2)</td>
<td>11 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>8 (1)</td>
<td>7 (1)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Congenital</td>
<td>4 (0.5)</td>
<td>2 (0.3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal auscultation</td>
<td>156 (17)</td>
<td>129 (18)</td>
<td>27 (13)</td>
</tr>
<tr>
<td>(crackles or diminished vesicular breathing)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia (pulse &gt; 100 bpm)</td>
<td>82 (9)</td>
<td>62 (8)</td>
<td>20 (10)</td>
</tr>
<tr>
<td>Tachypnoea (respiratory rate &gt; 24/minute)</td>
<td>59 (6)</td>
<td>43 (6)</td>
<td>16 (8)</td>
</tr>
<tr>
<td>Hypotension (SBP &lt; 90 and DBP &lt; 60 mmHg)</td>
<td>3 (0.3)</td>
<td>3 (0.4)</td>
<td>–</td>
</tr>
<tr>
<td>Confusional mental state</td>
<td>1 (0.1)</td>
<td>–</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Sedation</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

All characteristics are shown as absolute numbers, between brackets in % unless otherwise specified. COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Figure 2. Flow chart of individual changes in ‘pre-test’ and ‘post-test’ antibiotic prescribing decisions for point-of-care C-reactive protein-tested patients. CRP, C-reactive protein; POC, point-of-care.
of POC CRP in reducing overprescribing of antibiotics. Yet, the prescribing rate in our study is representative for that in respiratory tract infections in Dutch general practice, which decreased over recent years (20). Caution should be made when interpreting antibiotic prescribing by GPs. Although patient population is representative for the Dutch population, we included relatively many academic practices and therefore we performed a post hoc sensitivity analysis comparing practices with relatively high (38%; in our case mostly non-academic practices) and relatively low prescribing rates (26%; in this study mainly the academic practices), and we found that indeed in practices with higher prescribing rates implementation of POC CRP reduced antibiotic use ‘post-test’, the difference in the non-academic practices was −11% (95% CI: −17 to −4). Secondly, GPs completed CRFs for most acute cough patients for whom they performed POC CRP testing, yet for acute cough patients in whom they did not request POC CRP, the CRF was often forgotten. Therefore, the 78% POC CRP test rate in the study population of the present study is likely to be an overestimation. To estimate the true POC CRP test rate, we extracted anonymous registration data of all patients presenting with acute cough in four of the participating practices during 6 months of the inclusion period. A total of 1473 eligible patients were identified of whom only 342 (23%) were POC CRP tested, i.e. a much smaller proportion than in the study sample. We did not evaluate patient characteristics like preference for antibiotics which also may have influenced the GP in prescribing (or not).

Comparison with literature
Our finding that POC CRP did not reduce antibiotic prescribing differs from RCTs reporting a decrease in antibiotic use in CRP-tested LRTI patient groups (7,9–11). This difference could partly be explained by the low antibiotic prescribing rate in practices in our study. Both ‘pre-test’ and ‘post-test’ prescribing rates in our study were ~30%, which is comparable to the rate of the CRP-tested intervention groups from the previous trials which ranged from 31% to 38% (7,9–11,13). The difference in results could also be due to differences in training. As our goal was to study daily practice, we did not offer formal training to GPs when implementing POC CRP testing. This might have contributed to the lack of impact on antibiotic prescribing rates at group level.

Implications for practice
In our study, GPs did not use and interpret POC CRP tests according to the guidelines in the majority of patients. This is in contrast with previous reports showing that in general, GPs comply with professional guidelines in ~60–70% of their management decisions (21). In the remaining part of decisions, GPs will sometimes deviate from guideline recommendations, and in other cases not. The fact that GPs did not follow the guideline in most patients in our study might be explained by a number of factors: (i) the advice in the guideline is too complicated to apply, (ii) the recommendation itself is still under debate within the profession and therefore GPs may be ambivalent to comply and (iii) implementation of new evidence and advices asks for changing consultation behaviour. This takes time and (repeated) efforts. In the first case (i), the guideline committee needs to look for ways to simplify the guideline without losing quality. The second (ii), however, is more complex, as it may indicate that the decision to incorporate the CRP test in the LRTI guideline is not well founded. There is some argument for that: the guideline advice is based on previous trials on POC CRP, evaluating POC CRP testing in all patients presenting with LRTI. In the Dutch guideline, POC CRP was introduced however as ‘selective testing’ in coughing patients with an intermediate risk for CAP, accompanied by a newly developed algorithm. In the third case (iii), GPs should be better facilitated by training and support. Integrated ICT decision support systems could improve the adherence to guidelines and lead to more appropriate decisions.
Conclusion

POC CRP testing resulted in considerable changes in the decision whether or not to prescribe an antibiotic in this observational study. It did not reduce overall antibiotic prescribing, when used by GPs who already have a low antibiotic prescribing rate. Better targeting antibiotic prescribing by reducing diagnostic uncertainty and thus reducing antibiotic prescribing is an important rationale for implementing POC CRP in general practice. In addition, given the low adherence rate, apparently other factors than mentioned in the guideline prompt GPs to use POC CRP tests. Future studies should focus on other indications for POC CRP than LRTIs and a better and effective use of tests like POC CRP in daily practice.

Supplementary material

Supplementary material is available at Family Practice online.

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Declaration

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Ethical approval: The Medical Ethical Research Council of the institution reviewed the protocol of this study and deemed it as usual care not requiring ethical approval.

Conflict of interest: TJMV received a research grant from Pfizer within the last ethical approval reviewed the protocol of this study and deemed it as usual care not requiring ethical approval.

References


