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RESEARCH ARTICLE

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What a difference a CRP makes. A prospective observational study on how point-of-care C-reactive protein testing influences antibiotic prescription for respiratory tract infections in Swedish primary health care

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ABSTRACT

Objective: To explore how C-reactive protein (CRP) tests serve to support physicians in decisions concerning antibiotic prescription to patients with respiratory tract infections (RTI). *Design.* Prospective observational study. *Setting*: Primary health care centres in western Sweden. *Subjects.* Physicians in primary health care. Patients with acute RTI. *Main outcome measures*: Physician willingness to measure CRP, their ability to estimate CRP, and changes in decision-making concerning antibiotic treatment based on error estimate and the physician's opinion of whether CRP measurement was crucial. *Results*: Data from 340 consultations were gathered. CRP testing was found to be crucial in 130 cases. In 86% of visits decisions regarding antibiotic prescription were unchanged. Physicians considering CRP crucial and physicians making an error estimate of CRP altered their decisions concerning antibiotic prescription after CRP testing more often than those who considered CRP unnecessary, and those making a more accurate estimate. Physicians changed their decision on antibiotic prescription in 49 cases. In the majority of these 49 cases physicians underestimated CRP levels, and the majority of changes were from "no" to "yes" as to whether to prescribe antibiotics. *Conclusion*: CRP is an important factor in the decision on whether to prescribe antibiotics for RTIs. Error estimates of CRP and willingness to measure CRP are important factors leading to physicians changing decisions on antibiotic treatment.

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C-reactive protein; respiratory tract infections; primary health care; antibacterial agents; drug prescriptions; general practice; point-of-care systems, Sweden

KEY POINTS

- There is a generally low antibiotic prescription rate and a high frequency of C-reactive protein (CRP) testing for respiratory tract infections (RTIs) in Sweden.
- CRP testing was considered essential to further management in 38% of cases.
- In 86% of visits decisions concerning antibiotic prescription were unchanged.
- The strongest predictors for revised decisions on antibiotic treatment were error estimates of CRP and the physician's opinion that CRP measurement was crucial.

Introduction

Respiratory tract infections (RTI) are frequent causes of primary health care consultations in the Western world [1]. As an aid in determining infection severity, physicians sometimes use C-reactive protein (CRP) point-of-care tests (POCT). CRP is considered one of the most sensitive acute-phase reactants and increases rapidly in human blood in the case of inflammation [2,3]. Studies have shown that the CRP level is a strong independent predictor of antibiotic prescription for RTIs [4]. According to a Swedish study 16% of the population seek primary health care yearly for RTIs, and between 34% and 63% of these are treated with antibiotics [5]. POCTs for CRP are widely used in general practice in Scandinavia and Switzerland [6]. In Swedish primary health care CRP is measured in up to 50% of all consultations for RTIs [7,8].

However, the value of CRP testing in RTI patients has been widely debated [9,10]. Studies have shown that CRP cannot be used to differentiate between bacterial and viral lower RTIs in children [10,11], or to determine the microbial agent causing acute bronchitis in adults [12]. CRP is considered overused according to Scandinavian studies of RTIs in a non-selected and relatively healthy patient cohort attending primary care [8,13–15]. Even a slight increase in CRP (>25 mg/L) results in general practitioners (GPs) prescribing

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antibiotics despite belief in a viral aetiology [9]. On the other hand, more frequent use of CRP in primary health care may lead to lower prescription rates of antibiotics but better patient compliance with prescribed antibiotics [16–21].

There is some scientific evidence that a high CRP level indicates a severe RTI, such as pneumonia, and that the GP can use the CRP test if unsure of infection severity [22–24].

Despite previous studies, knowledge of how CRP aids the physician in primary health care in decisions to prescribe antibiotics to RTI patients is limited. Moreover, knowledge is lacking on how decision-making in antibiotic prescription is related to the physician's approach to CRP measurement, CRP levels as a reflection of RTI severity, and educational status.

The objectives of this study were to explore the role of CRP in supporting decisions on antibiotic prescription for upper and lower RTIs, and evaluate differences between specialists and non-specialists in primary health care concerning willingness to measure CRP, evaluate the estimated CRP, and the actual CRP's influence, respectively, on antibiotic prescription.

Material and methods

Study design

This prospective observational study of RTI treatment was conducted within primary health care in south-western Sweden. Specialists in family medicine with 18–21 months of clinical internship and a minimum of five years of clinical practice (GPs), as well as non-specialists (non-specialist GPs) in training (interns, residents) and physicians with a medical degree but prior to licensing from five primary health care centres (PHCC), representative of Swedish primary care, participated (Table 1). All patients, children, and adults who visited the PHCC due to symptoms of acute RTI were asked to participate. Patients were included consecutively from 17 November 2011 to 31 October 2012, including only the first visit during the study period. Patients with acute otitis media were excluded because diagnostics do not usually include blood tests. Patients with chronic inflammatory disease such as an inflammatory bowel disease or a diagnosis of a rheumatic disease, with a high probability of elevated CRP levels, were also excluded.

Table 1. Number of patient visits to physicians in primary health care ($n = 340$).

Physician's educational status	*n* (%)
Specialist in family medicine (GP)	194 (57)
Non-specialist GP:	146 (43)
GP trainee/resident, family medicine	67 (20)
Physician with medical licence	40 (12)
Physician in clinical internship	28 (8.2)
Graduated/non-licensed MD[1]	3 (0.9)
Other	5 (1.5)
Unknown	3 (0.9)

[1]Physicians with medical school examination but without licence.

The Regional Ethical Review Board in Gothenburg approved the study. Written informed consent was obtained from physicians and patients.

Data collection

The physician's sex and educational status were registered on a case report form (CRF). The medical history and examination were conducted by the physician at enrolment. The physician then specified in the CRF if CRP testing would be crucial for further management, and whether antibiotic therapy was indicated. Furthermore, the physician was requested to estimate the CRP level (mg/L) and enter it on the CRF. For every case included in the study the CRP level (mg/L) was then measured from venous or capillary blood using a POCT device ranging from <5 to >160 mg/L and registered in the CRF by an assistant. The physician noted the CRP level before the end of the visit, providing the possibility to consider this in the management of the RTI patient. Figure 1 shows the consultation process. Data for actual antibiotic prescription were collected from the medical record.

Analysis

The physicians' educational status and patient management are presented along with numbers and percentages of the total number of visits. CRP levels (mg/L) are presented by the mean, standard deviation, and range (min–max).

For analysis of the agreement between CRP estimates and measured values, a Bland–Altman plot was created with 95% upper and lower limits of agreement as ± 2 SD from mean. To evaluate the presence of proportional bias, linear regression was used with difference between estimated and measured CRP as dependent variable and mean difference as independent variable.

Consultations were categorized into two groups: those involving a general practitioner specialist (GP group) and those involving a non-specialist (non-specialist GP group, including residents in family medicine). One could have categorized consultations differently, for example, as carried out by GPs, GP trainees, by "others", or by the physician's sex or age. However, we found this categorization most useful in order to reflect medical skills and experience. Consultations were also categorized into two groups based on the physician's opinion of whether CRP was necessary for further management or not. Moreover, consultations were categorized into two groups based on whether physicians changed their decision concerning antibiotic prescription after the CRP measurement.

For analyses of differences within groups, a paired t-test was used. For analyses between visits in the GP group and the non-specialist GP group and patient management, a chi-square test was used for categorical data, and Student's t-test for continuous data.

Logistic regression was used to analyse the association between the categories antibiotics needed (1) or not (0) as dependent variables, and estimated CRP (mg/L) as the independent variable. Moreover logistic regression was used to analyse the relation between the categories "changed decision" (1) or not (0) as dependent variable and the physician's sex, GP group (1)/non-specialist GP group (0), difference between estimated and measured CRP in absolute values (error estimate), and if CRP was considered crucial to further management (1) or not (0) as independent variables. Prior to the multiple logistic regression, the variables were evaluated for assumptions of multivariate analysis. The correlation matrix for the independent variables was checked.

The p-value was <0.05. SPSS™, Windows versions 20.0, 21.0 and 22.0, was used (IBM Corp, Armonk, NY, USA).

Results

All physicians asked to participate accepted ($n = 42$). Patient enrolment including 340 visits is shown in Figure 2. Each physician could contribute more than once; however, no registration was made on how many patients were seen by a specific physician. In the GP group slightly more than half the visits were to a male physician (52%, $n = 100$), and in the non-specialist GP group the figures were 69% ($n = 100$) for females and 30% ($n = 43$) for male physicians, respectively. In three cases the consultation was to a physician of unknown sex. More than half the visits (194/340) were to a specialist in family medicine, a GP (see Table I). Mean estimated CRP was 25 mg/L (SD 21; range 8–150) and mean measured CRP level was 25 mg/L (SD 30; range 5–160). The Bland–Altman plot shows a slightly asymmetric distribution around the mean with some outliers and wide limits of agreement (± 60 mg/L) ($p < 0.001$) (Figure 3).

In 21% (70/340) of visits the physician was willing to prescribe antibiotics before CRP testing. The higher the estimate of CRP the more willing the physician was to prescribe antibiotics (OR 1.06; CI 1.04–1.07). The estimates of CRP levels were statistically significantly higher in the non-specialist GP group (29 mg/L; SD 26) than in

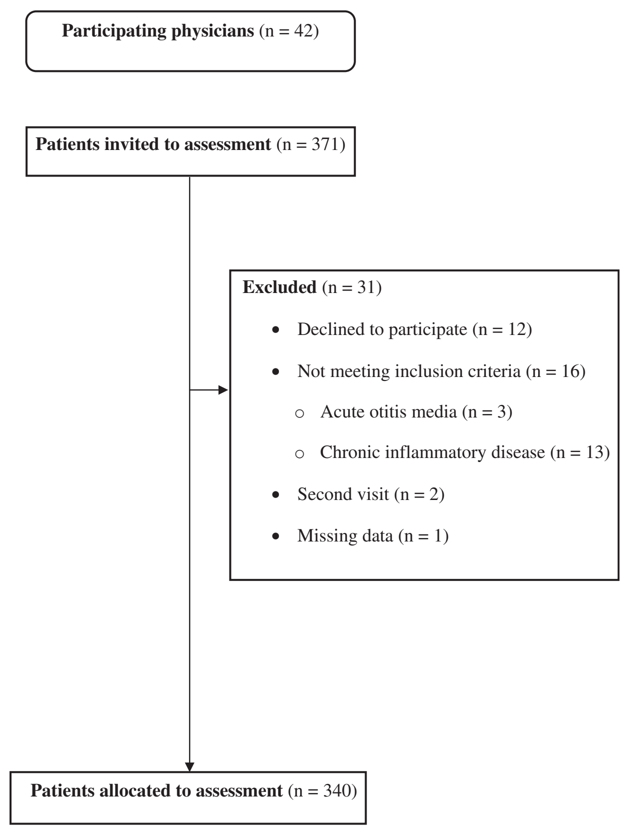

Figure 2. Participant flow.

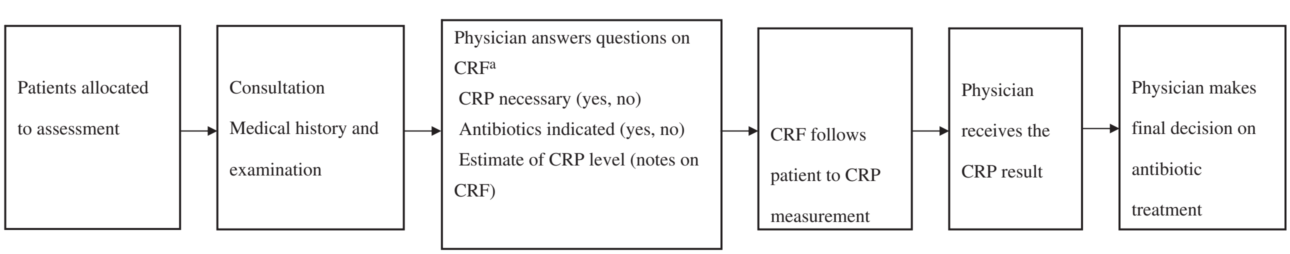

Figure 1. Consultation process and decision-making in chronological order.
[a]Case report form.

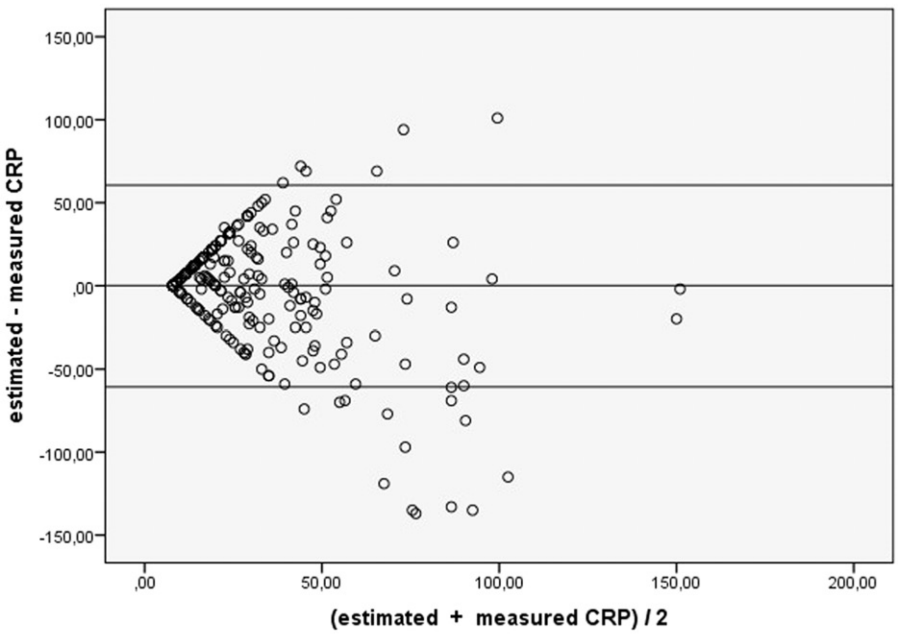

Figure 3. Bland–Altman limits of agreement plot for CRP estimates and measured values.

Table 2. Differences in C-reactive protein (CRP) estimations between visits to family medicine specialists (GP group) and physicians with other educational status (non-specialist GP group) in primary health care.

	Visits to GP group ($n = 194$)	Visits to non-specialist GP group ($n = 146$)	p-values[1]
CRP crucial for treatment, yes, *n* (%)[2]	65 (34)	65 (45)	**0.038**
Physician's estimate of CRP (mg/L)[3]	24 (19)	29 (26)	**0.039**
Differences between estimated and measured CRP (mg/L)[3]	−1.4 (29)	2.1 (33)	0.30

Notes:
[1]Student's t-test for comparison of quantitative data and chi-square test for qualitative data.
[2]2.6% ($n = 9$) did not check the ''yes'' or ''no'' box on the case report form, four in the GP group, five in the non-specialist GP group.
[3]Mean values (standard deviation).

the GP group (24 mg/L; SD 19) $p = 0.039$. No differences between the estimated CRP and measured CRP levels were seen within the GP group ($p = 0.50$) and the non-specialist GP group ($p = 0.45$), respectively. This non-significant result remains in a between group analysis (Table 2).

In 38% of visits (130/340) the physician found CRP testing to be crucial to further management. The non-specialist GP group found it significantly more important to measure CRP ($p = 0.038$) (see Table 2). In the non-specialist GP group, physicians who found CRP essential for further management changed their decision to prescribe antibiotics to a statistically significantly higher degree than those who found CRP to be unnecessary ($p = 0.011$). This result was similar for the total number of visits including both GP and non-specialist GP groups ($p = 0.0018$), but was not seen in the GP group alone (Table 3).

In 70 visits physicians found antibiotic treatment necessary prior to CRP testing and in 28% of visits (96/340) antibiotics were prescribed.

In 14% of total visits ($n = 49$) physicians changed their decision to prescribe or not prescribe antibiotics after gaining knowledge of the actual CRP level. In all, 71% (35/49) of those who changed their decision prescribed antibiotics although they had answered ''no'' prior to CRP testing (mean measured CRP 56 mg/L (SD 48; range 8–160), which means that in 10% of the visits (35/340) the physician changed from ''no'' to ''yes'' for prescribing antibiotics, and the majority of these (21/35) had underestimated the CRP. In 14/340 visits (4.1%) the change went in the opposite direction from ''yes'' to ''no'', and a majority of these (11/14) had overestimated the CRP (mean measured CRP 16 mg/L; SD 13; range 8–48). For the 49 decision changes on antibiotics, CRP levels were underestimated significantly more often

Table 3. Physician behaviour in light of their opinion on antibiotic prescription issues prior to C-reactive protein (CRP) testing, after viewing the actual CRP level.[1]

	Antibiotics retracted [*n* (%)]	Decision unchanged [*n* (%)]	Antibiotics prescribed [*n* (%)]	*p* Values[2]
Visits to GP group ($n = 190$)				0.22
CRP crucial for treatment	2 (3.1)	53 (82)	10 (15)	
CRP unnecessary for treatment	2 (1.6)	113 (90)	10 (8.0)	
Visits to non-specialist GP group ($n = 141$)				**0.011**
CRP crucial for treatment	9 (14)	48 (74)	8 (12)	
CRP unnecessary for treatment	1 (1.3)	68 (90)	7 (9.2)	
Total visits ($n = 331$)[3]				**0.0018**
CRP crucial for treatment	11 (8.5)	101 (78)	18 (14)	
CRP unnecessary for treatment	3 (1.5)	181 (90)	17 (8.5)	

[1]"Antibiotics retracted" and "Antibiotics prescribed" means change in approach to prescribing antibiotics.
[2]Chi-square test.
[3]2.6% ($n = 9$) did not check the "yes" or "no" box on the case report form, four in the GP group, five in the non-specialist GP group.

Table 4. Logistic regression analysis showing odds ratio for physician's change in approach to prescribing antibiotics: Pre-CRP testing unwilling to prescribe antibiotics changing to prescribe antibiotics post-CRP testing and vice versa as dependent variable (1).

	Unadjusted odds ratio (CI 95%)	*p* Values	Adjusted odds ratio (CI 95%)	*p* Values
Sex (female 1)	1.5 (0.81–2.7)	0.21	–	–
Educational status (GP 1)[1]	1.5 (0.81–2.7)	0.20	–	–
Differences between estimated and measured CRP (mg/L)[2]	1.02 (1.01–1.03)	**<0.001**	1.03 (1.01–1.04)	**<0.001**
CRP crucial for treatment (yes 1)	2.6 (1.4–4.8)	**0.0025**	2.9 (1.5–5.5)	**0.0016**

[1]General practitioner specialist group (GP group) and the group that visited non-specialists (non-specialist GP group, including residents in family medicine).
[2]Difference between estimated and measured CRP in absolute values.
Statistically significant p-values are in bold ($p<0.05$).

compared with visits where the initial decision (86% (291/340)) was unchanged. Means (SD) were –14 (49), 2.4 (24), $p = 0.028$, respectively.

The strongest predictors for changing a decision on antibiotic treatment were differences between estimated and measured CRP (error estimate), regardless of whether the CRP was over- or underestimated, and the physician's opinion that CRP measurement was crucial (Table 4).

Discussion

In summary, CRP measurements were used in 44% (150/340) of the visits, i.e. at those consultations where CRP was considered essential for treatment and/or where the decision concerning antibiotics was changed (see Table 3). In visits where physicians considered CRP crucial, the decision concerning antibiotics after CRP testing was changed more often compared with visits where CRP was considered unnecessary. This was most obvious for non-specialist physicians, who relied more on the actual CRP level for their decisions. Furthermore the decision was changed more often in visits where the physician had over- or underestimated CRP. In 49 visits, where a majority of the CRPs were underestimated, physicians changed their decision concerning antibiotic prescription, and the majority of changes were from "no" to "yes". In 86% (291/340) of visits decisions concerning antibiotic prescription were unchanged.

Strengths and limitations of the study

This study was conducted in an environment reflecting clinical practice in primary health care. No differentiation of RTI or patient characteristics was presented nor was it the aim of the study to do so since the focus was on physicians' case management and not on patients or severity of infection. There might be a risk that the willingness to measure CRP is underrated due to the fact that physicians knew they later would gain knowledge of the actual CRP levels. Furthermore, measuring CRP for every RTI patient is not routine in clinical practice.

CRP does not provide the whole truth regarding an RTI and this study does not claim to assess decisions.

CRP as decision support

One can claim that CRP serves to support a decision when the physician considers it crucial for further management, and in cases when it influences physicians to change their opinions regarding antibiotic treatment. According to this approach, CRP served as a decision-making support in 44% of visits. This was most obvious for non-specialist physicians, who relied more on the actual CRP level for their decision. The results indicate that the less experienced non-specialists needed more than a clinical examination for treatment decision. Measuring and interpreting CRP levels involves, as for all blood tests, an element of learning for the less experienced, and the greater the experience the lesser the tendency toward CRP testing.

Transformed to a clinical setting CRP testing would have made a difference for treatment only in those cases where physicians found it crucial for further management to have CRP analysed, and where it also changed their decisions (9%, $n = 29$). Thus, CRP testing would not have affected treatment in terms of antibiotic prescriptions in 91% of cases. From this point of view one could claim that CRP in some cases seems to be used mainly to support an earlier decision, but, on the other hand, physicians' antibiotic prescription was influenced by CRP levels even when they had not requested the test, especially when the physician found an unexpectedly high CRP.

This study indicates that an anticipated high CRP correlates with a higher grade of antibiotic prescription, but one cannot tell if the physician's pre-test opinion of whether antibiotics are needed is influenced by the CRP estimate or vice versa. Furthermore, physicians rely on CRP for decision support, and even change their minds on antibiotic prescription, in situations when their estimate of CRP differs from measured CRP levels, and when finding CRP measurements crucial for further management.

There are national and regional guidelines based on recommendations from the Swedish Medical Products Agency (Läkemedelsverket) and the Swedish strategic programme against antibiotic resistance (STRAMA) to refrain from measuring CRP for a number of common RTIs, such as the common cold, pneumonia, tonsillitis, rhinosinusitis, and acute bronchitis. According to these recommendations, medical history and clinical examination are sufficient for the assessment of infection severity and further management including possible antibiotic prescription [25]. However, in this study physicians found CRP testing to be crucial for treatment in more than one-third of visits, a number that corresponds well with earlier studies [7,8]. According to national and regional guidelines our study indicates an overuse of CRP testing in a way that brings no additional benefit to the clinical examination. However, physicians in almost half of the visits (44%) seem to have felt comfortable using the test in the way they did. Following guidelines written by authorities such as Public Health Agencies in every situation in daily practice can possibly cause some difficulties.

This study cannot say whether patients benefited from antibiotic therapy. Perhaps the extensive use of CRP testing in general contributes to the low antibiotic prescription rate in Swedish primary care [26], but the test sometimes seems to serve as an argument for prescribing antibiotics when the physician is uncertain.

Previous studies have pointed out that CRP measurements can lower antibiotic prescription [16,19,21], while other studies have shown no impact from CRP measurements on antibiotic prescription [27,28]. In this study CRP measurements seem to have had a different influence on antibiotic prescription whereas the assumed need for antibiotics went from 21% to 28% after testing. However, this should be seen in light of a generally low prescription rate of antibiotics to outpatients in Sweden [26]. This might indicate that the lower the prescribing rate – perhaps paradoxically due to a high use of the test – the less useful the test is for reducing antibiotic prescribing.

It is possible that CRP measurements in selected cases in Swedish primary health care can aid in determining which RTI patients may benefit from antibiotics. Furthermore, there are probably a number of other motives for physicians to measure CRP than only for decisions on antibiotic prescription, such as accommodating requests from patients or patients' parents to "do something" more than just carry out an examination. These issues could be considered for further research. This study reflects on some aspects of CRP use, but the question concerning the most rational way of using CRP in RTIs remains to be further investigated.

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Ethical approval

The Regional Ethical Review Board in Gothenburg approved the study (Dnr 477-11). Written informed consent was obtained from physicians and patients.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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