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Bacterial superinfection in upper respiratory tract infections estimated by increases in CRP values: A diagnostic follow-up in primary care

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Abstract

Objective. The aim of this study was to estimate the rate of bacterial superinfection in patients with URTI by using on-site determination of C-reactive protein (CRP). **Design.** A prospective cohort study. **Setting.** A total of 30 primary care practices. **Subjects.** Patients with URTI. **Intervention.** The CRP value was determined at the first consultation and at a follow-up within 3–5 days. CRP values of 30 units (mg) or higher were considered to be an indication of bacterial involvement. **Main outcome measures.** CRP values during follow-up and duration of illness. **Results.** Among the 506 patients included, 73.1% exhibited a CRP value below the defined limit at their first visit and were considered to suffer from URTI of viral origin. The rate of subsequent bacterial superinfection was 8.1%. Compared with patients suffering from URTI of bacterial or viral origin the duration of illness in patients with bacterial superinfection was significantly longer. **Conclusion.** During follow-up of patients with URTI, the prevalence of bacterial superinfection detected by using a near patient CRP determination is surprisingly low. This result should help to reduce the prescription rate of antibiotics in primary care.

Key Words: Bacterial superinfection, CRP, family practice, primary care, upper respiratory tract infection

Infections of the upper respiratory tract (URTI) are among the most frequent reasons for encounter in general practice [1–4]. The fear of prolonged sickness or of serious complications is known to result in an overuse of antibiotics although in the majority of cases the causal agent is of viral origin [1,4,5]. The course of URTI of viral origin might be complicated by bacterial superinfection within the first days after onset of illness [1]. Such patients benefit from specific treatment with antibiotics [5,6].

However, precise detection of bacterial superinfection is difficult and its frequency is unknown; gold standards [5,7,8] are not suitable for the primary care setting. In general, to differentiate between infections of viral or bacterial origin in clinical practice mainly erythrocyte sedimentation rate (ESR) and the determination of C-reactive protein (CRP) values have been used, since they

Although the majority of infections of the upper respiratory tract (URTI) are caused by viruses, their course might be complicated by bacterial superinfection, the frequency of which is unknown.

- The rate of bacterial superinfection in patients with URTI of viral origin is 8.1% as assessed by near patient CRP determination.
- The duration of illness in these patients is significantly longer.

increase in infections of bacterial origin [9]. Therefore, the aim of this study was to observe the frequency of bacterial superinfection in patients with URTIs using on-site CRP determination at

the onset of illness and for follow up within the primary care setting [7,10–12].

Material and methods

This prospective cohort study was conducted from November 2002 until March 2003 in the offices of 30 participating general practitioners (GPs). Each of the supporting GPs included up to 20 consecutive patients within the study period meeting the following inclusion criteria: an age over 4 years, elevated body temperature of more than 37.5°C, and at least one characteristic symptom of an URTI (sore throat, sinus pain, cough, stuffy nose) [5,9,13].

Patients in whom pneumonia or another underlying disease associated with an elevated CRP value (e.g. pyelonephritis, rheumatoid arthritis, etc.) was known or suspected and persons already treated with antibiotics for a different reason were excluded [9]. Written informed consent was obtained from all patients or their parents; the study was approved by the ethics committee of the Medical University of Vienna.

Study protocol and examinations

At the first consultation name, age, and a list of symptoms including the date of onset and the present health status was documented. Further, 25 µl capillary blood were taken from the patients and used to determine the CRP (CRP1) value as described [14] using the whole blood NycoCard® CRP Single Test of Axis Shield [10,11,15] and a portable colour densitometer (Nyocard Reader) to quantify the intensity of the membrane colour.

According to the test instructions and a number of earlier studies values of 30 units (mg/l) or higher were considered to be an indication of possible bacterial involvement, while values below 30 units were considered as a sign of probable viral infection [7,9,12,16]. Patients with a CRP1 value higher than 30 units were supposed to receive conservative treatment [6,17] such as antiphlogistics, antipyretics, inhalations, and other advice and were assigned to appropriate antibiotic prescription at their physician's option. Patients with a CRP1 value below 30 units were treated symptomatically only. All patients were asked to return to the office within 3–5 days after the first consultation for a recheck of their symptoms and for a second determination of CRP (CRP2). Only if the value had increased above 30 units bacterial superinfection was assumed and prescription of an antibiotic was recommended. In addition, all patients were asked to return or to call the office for notification of the first day of full recovery, which was taken as the end of the illness. In

those cases where a sick leave certificate had been issued, the duration of absence from work was documented.

Analyses of the data

Based on the CRP determinations three groups of patients were defined: group 1 consists of patients with CRP1 values above the limit who were considered to have an infection of bacterial origin; patients in group 2 exhibited CRP values below the limit throughout the whole study period ("viral origin"); patients in group 3 had a low CRP1 value which increased within 3 to 5 days to CRP2 values above the limit (suspected "bacterial superinfection").

Descriptive values (frequencies or mean values, respectively, and 95% confidence intervals, CI) are given and Pearson correlation coefficients (ρ) were calculated. An analysis of variance was calculated in order to compare the mean values of the variable "duration of illness" of the three groups. The logarithm of the dependent variable was calculated in order to get a symmetrical distribution. Tukey's test for multiple comparisons was calculated.

A stepwise linear regression analysis was performed to analyse the influence on the duration of illness of: CRP, age, sex, cough, sore throat, sinus pain, rhinitis, fever, auscultatory findings, and antibiotic prescription. The probability to enter or remain in the model was set at 0.05, p-values and parameter estimates (p.e.) and R^2 are reported. All analyses were carried out using SAS 8.02 (SAS Institute Inc., Cary, NC, USA) [18].

Results

A total of 506 patients (261 female and 223 male) were recruited. Their mean age was 34.79 years (4–83 years, CI for the mean: 33.2–36.4); the majority of patients (88.15%) were ill for more than 3 days.

Figure 1 illustrates all participants and the different subgroups. Of 506 participants the following 90 patients were excluded from further analyses: 37 patients from group 2 (10%; CI 7.1–13.5) who received an antibiotic prescription despite their low CRP1 value and 36 patients (10.8%, CI 7.7–14.7) in which the CRP2 value could not be determined, as well as 7 patients from group 1 who did not receive antibiotic treatment despite their high CRP1 value and 10 patients who did not show up for the CRP2 determination.

As can be seen in Table I, about a quarter of the patients included showed a CRP1 value of 30 units or higher. Among remaining patients with a low CRP1 value (see Figure 1) 8.1% had an increase in their CRP2 value above the limit (Table I). No

Figure 1. Entire study population (first and second visit corresponding to CRP determinations). Hatched squares =: excluded patients.

gender difference for the distribution of CRP values could be found.

The mean CRP values in the three study groups and their course throughout the study period were clearly different (Table II) and patients in group 3 showed the longest mean duration of illness (9.46 days). Analysis of variance resulted in a significant difference for the mean duration of illness between the three groups ($p=0.0002$).

Tukey's test for multiple comparisons further shows a significant difference in the duration of illness for group 3 compared with group 1 ($p=0.01$) as well as with group 2 ($p=0.0002$). No significant difference can be found between patients in group 1 and those in group 2 ($p=0.12$). By comparing patients in group 3 with those in group 2 a statistically significant difference can be found for their CRP1 values ($p<0.0001$).

A high association between the two determinations of the CRP value could be found; Pearson's correlation coefficient is 0.35 ($p<0.0001$; $n=456$). Both CRP values correlate significantly with the duration of illness (CRP1: $\rho=0.11$, $p=0.02$,

$n=459$; CRP2: $\rho=0.29$; $p<0.0001$, $n=429$).

Correlations between the length of illness and the age of the participant ($\rho=0.21$, $p<0.0001$) as well as between the age and the CRP2 value ($\rho=0.12$, $p=0.01$) could also be identified. A stepwise regression analysis showed that the age ($p<0.0001$; $p.e.=0.005$), the logarithm of CRP1 values ($p=0.001$; $p.e.=0.05$) and the presence of cough ($p=0.01$; $p.e.=0.14$) all have a significantly positive influence on the duration of illness ($R^2=0.08$).

Discussion

To our knowledge this is the first study to assess the rate of bacterial superinfection in patients with URTIs within the primary care setting.

Among the patients included, 73.1% exhibited a CRP1 value below the limit at their first visit. Although specific identification of the causal agent in the different secretions – considered to be the gold standard in the secondary care setting – was not performed, it can be assumed that CRP values below 30 units in patients with URTIs are caused by viral infections [11].

In contrast to the high rate of antibiotics prescribed for URTI [4,19–21], only approximately one-quarter of URTIs in our study appear to be of bacterial origin (see Table I). These results compare well with those of Gulich [7] who studied the diagnostic accuracy of near patient CRP measurement in patients with pharyngitis.

Similarly, an increase in the CRP value at the second determination can be considered to indicate bacterial superinfection. Assessed by CRP determination, the rate of bacterial superinfection among

Table I. Distribution of CRP1 and CRP2 values above and below the limit at the first and second consultation.

	1st visit (n=506)	2nd visit (n=297)*
CRP2 <30	370 (73.1%; CI 69.0–76.9)	273 (91.9%; CI 88.2–94.8)
CRP2 ≥30	136 (26.9%; CI 23.1–31.0)	24 (8.1%; CI 5.2–11.8)

Notes: *The distribution of CRP2 values from patients included with a CRP1 below 30 units. In 36 out of 333 patients CRP2 values were missing (see Figure 1).

Table II. Mean CRP values and duration of illness referring to the three defined groups.

Group		Variable	n	Mean	CI for the mean	
1	“Bacterial infection” CRP1 ≥ 30	CRP1	129	62.95	56.09	69.81
		CRP2	119	18.53	14.38	22.68
		duration (days)	116	7.17	6.46	7.88
2	“Viral infection” CRP1 < 30 + CRP2 < 30	CRP1	333	8.40	7.44	9.37
		CRP2	273	5.84	5.02	6.67
		duration (days)	257	6.40	5.99	6.82
3	“Superinfection” CRP1 < 30 + CRP2 ≥ 30	CRP1	333	16.69	12.83	20.56
		CRP2	24	58.50	45.27	71.73
		duration (days)	24	9.46	7.92	10.99

patients with URTI of viral origin is 8.1% (see Table I). From a previous study, the frequency for bacterial superinfection based on 41 patients can be calculated to be 4.88% [9]. However, physicians tend to prescribe antibiotics rather quickly [20–22], because in many countries there is no reliable near patient test for the causal agent routinely available [10,23] and the rate of bacterial superinfection is therefore overestimated. In addition, patients with URTI in primary care might demand antibiotic medication [17,20].

As can be seen in Table II, patients in group 2 with low CRP1 values also show low CRP2 values, while patients in group 3 showed initially higher CRP1 values than those in group 2. This might indicate the early stage of an initial bacterial infection in group 3. Supporting the fundamental difference between the two groups the duration of illness in patients in group 3 is clearly longer than that of patients in group 2 or group 1.

The strength of our study is that it has been performed in the primary care setting where the near patient CRP determination helps to improve clinical decision-making in patients with suspected bacterial superinfection. Based on the feedback of participating GPs, both patients and physicians appreciate the quick test result as a rationale for subsequent shared decisions about the treatment [10,23]. In addition, this procedure [15,24,25] is of minimal discomfort for patients when compared with intravenous blood sampling at an outpatient laboratory.

Some limitations of our study have to be acknowledged. First, a total of 90 patients of the initial 506 patients included dropped out (Figure 1). This might influence the results of our study. Second, the parameter followed (CRP) and its cut-off level used can be questioned. However, the determination of CRP is used in a variety of conditions to differentiate between bacterial and viral infections [26,27]. Further, the cut-off level chosen refers to the test instructions and to a number of earlier

studies [9,14,16,27]; in particular, those dealing with URTIs have shown that CRP values in patients with viral infections mostly remain below 30 units [9,12,16]. Despite this we might have included patients with a CRP1 value above the limit as bacterially infected, while their CRP values could have been increased due to other unrecognised reasons. Overall, this would have resulted in an overestimation of bacterial infection and superinfection, respectively. We tried to address this possibility by strict exclusion criteria based on the GP’s knowledge of the patient’s history. Third, our study has been performed within a certain time period in Central Europe during the winter season. Therefore, we cannot exclude that the relationship between viral and bacterial infections might be different during other time periods or in other regions [1,28].

In summary, our study shows that bacterial superinfections during follow-up of URTIs can be estimated easily and that their frequency is surprisingly low (8.1%); the duration of illness in these patients is significantly longer. These observations and conclusions might help to reduce unnecessary antibiotic prescriptions for URTIs [13,20,22,23,29] and to slow down the increase of antibiotic resistance [24,30].

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Conflict of interest statement

All authors declare that they have no conflicts of interest.

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