Improving diagnostic accuracy of bacterial pharyngitis by near patient measurement of C-reactive protein (CRP)

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SUMMARY

Background. *Sore throat or pharyngitis is an extremely prevalent condition in primary care. There is a diagnostic dilemma in differentiating bacterial and non-bacterial infections for adequate use of antibiotics. Standard diagnostic procedures take too long for an immediate decision.*

Aim. *To evaluate, if near patient C-reactive protein measurement in the general practice surgery improves diagnostic accuracy.*

Method. *One hundred and seventy-nine consecutive patients with sore throat, from 15 general practitioners (GPs) in southern Germany (phase 1) and 161 consecutive patients from 14 GPs (phase 2), were examined physically and a throat-swab was taken and white blood-cell count (WBC) and CRP-measurement were performed. In phase 1, CRP was measured centrally to assess the method's diagnostic value and the adequate threshold. In the second phase, near patient CRP was measured and CRP values were used to make a diagnosis.*

Results. *Using relative operating characteristics (ROC) analysis, the diagnostic value of CRP measurement was much better than WBC count (area under curve = 0.85 versus 0.68). All diagnostic parameters improved when using the near patient CRP measurement. Sensitivity went up from 0.61 (95% confidence interval = 0.45–0.75) to 0.78 (0.61–0.90), specificity went up from 0.73 (0.65–0.81) to 0.82 (0.73–0.88). Positive and negative predictive value improved significantly as well. Diagnostic accuracy went up from 70.1% to 81.0%. Out of 1000 theoretical patients with sore throat, 109 more will be treated correctly when using CRP measurement as a diagnostic tool.*

Conclusions. *Use of near patient CRP measurement can improve diagnostic accuracy in the differentiation of bacterial and non-bacterial pharyngitis in primary care, and potentially results in a more adequate use of antibiotics.*

Keywords: sore throat; pharyngitis; antibiotics; near patient testing; C-reactive protein measurement.

Introduction

SORE throat, or pharyngitis, is an extremely prevalent condition in primary health care. Up to 5% of patients of a European or North American general practitioner (GP) present with sore throat. There is substantial variation in the prevalence according to season, geographical region, age, and weather conditions. There are peaks in the cold and wet seasons and in younger age groups, but there is a significant morbidity in other age groups[1-11] as well.

The diagnostic dilemma of primary care is to identify pharyngitis caused by bacteria, especially group A ß-haemolytic streptococci (GABS). According to guidelines of medical scientific associations, infections with bacteria known to cause pharyngitis should be treated by antibiotic regimens because of the risk of subsequent rheumatic fever, glomerulonephritis, or toxic shock syndrome. These sequalae are rare: acute rheumatic fever occurs with an estimated incidence of 10^{-5}–10^{-4} per year, glomerulonephritis with an incidence of 10^{-6}–10^{-5} per year, and toxic shock even less frequent.[10,11] Nevertheless, primary care physicians should strive to prevent these life-threatening diseases by treating the preceding disease.

Treating pharyngitis that is caused by other than bacterial agents with antibiotics is useless, hazardous, and expensive, and supports the development of resistant bacterial strains.

Unfortunately, the diagnostic and therapeutic decision in primary health care usually has to be made without any delay. The diagnostic standard in identifying bacterial pharyngitis is the microbiological culture of a throat swab,[7,10] but the test result is only available 48 to 72 hours after the patient's presentation.

In recent years, a number of new diagnostic techniques have been developed to make the differential diagnosis of sore throat more accurate. One of the newer techniques is the quantitative measurement of C-reactive protein by immunometric measurement with a commercially available immunometric-spectrometric system.[12] The system has been evaluated in a number of inpatient settings.[13] Only a few attempts have been made to evaluate the diagnostic tool in primary care. Results of these studies are conflicting.[14-17] No controlled studies have been undertaken to evaluate the diagnostic value of quantitative CRP measurement for the differential diagnosis of pharyngitis in primary care. We therefore conducted a prospective, controlled diagnostic study to assess the diagnostic accuracy, in order to differentiate between bacterial and non-bacterial pharyngitis in general practice, with or without near patient measurement of CRP levels.

Method

We conducted a sequential evaluation study to assess diagnostic parameters of CRP measurement in the differentiation of bacterial and non-bacterial pharyngitis in general practice in southern Germany. In phase 1 we assessed the diagnostic parameters of GPs' purely clinical diagnoses. Sensitivity, specificity, predictive value, and ROC analysis of CRP measurement were calculated separately and independently. In phase 2, CRP measurement was performed at the GPs' offices and CRP level was available immediately for diagnostic decision. Main outcome variables were the diagnostic parameters with and without near patient CRP measurement.

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Consecutive patients aged 16 years or over, presenting with sore throat, were enrolled in the study. After patients' agreement to participate, they were evaluated by the GP by routine physical examination, a throat swab was taken and a blood sample was drawn for WBC count, and measurement of CRP with a commercially available immuno-spectrometric test system was carried out.[12] Throat swab culture and WBC counts from the GPs' offices were processed and analysed in university laboratories. Throat swabs growing bacteria known to cause pharyngitis (group A- and C-ß-haemolytic streptococci and haemophilus influenzae) have been assumed positive for bacterial pharyngitis; all other findings were classified non-bacterial. Findings from physical examination and clinical diagnosis were documented, and data were collected and processed centrally at the University department.

In the first phase of the study, patients were evaluated purely clinically and treated according to the GP's clinical diagnosis with antibiotics or symptomatic therapy respectively. The diagnosis was made and documented prior to the knowledge of the result of the throat swab, WBC count, and CRP level. Diagnostic parameters of clinical diagnosis and CRP measurement were calculated using standard procedures;[18] CRP-threshold value and test quality were assessed by ROC analysis.[19]

In the second phase of the study, physical examination was identical and CRP values were measured in the GP's office and results were available immediately. Throat swab and WBC count were handled identically.

All data were collected and analysed with SPSS® version 6.0 and WHO's Epi-Info© version 6 statistical packages using standard procedures.

The study was approved by the University's ethical affairs committee.

Results

In phase 1, 179 patients were enrolled in the study; in phase 2, 161 patients were enrolled. Demographic data are shown in Table 1.

In phase 1, 46 (25.7%) throat swab cultures were positive; in phase 2, 38 were positive (23.6%). To assess the quality of the CRP test and to identify the adequate cut-off level, the ROC of the CRP measurement were calculated using the WBC count as control (Figure 1). The areas under the curves are 0.85 for CRP value and 0.68 for WBC count respectively. According to ROC analysis, a CRP level of 35 mg/l was the most appropriate cut-off level for the differentiation between bacterial and non-bacterial pharyngitis.

Diagnostic parameters (sensitivity, specificity, positive and negative predictive value, 95% confidence intervals) were calculated for purely clinical diagnoses in phase 1 (data are shown in Table 2).

Thirty-five milligrammes per litre was suggested as the best cut-off level to identify bacterial pharyngitis in phase 2. We calculated the same parameters for diagnostic accuracy in diagnosing bacterial pharyngitis with additional support by the CRP level.

All diagnostic parameters improved in phase 2. With use of CRP values, 81% of the patients presenting with sore throat were diagnosed correctly, whereas only 70% of patients had been diagnosed correctly without use of CRP measurement.

Using the data generated by the study, we calculated a model of 1000 hypothetical patients presenting to their GP with sore throat. Without CRP measurement, 701 patients are diagnosed correctly; using near patient CRP measurement, 810 patients are diagnosed correctly (Table 3).

Discussion

Quantitative CRP measurement is an accurate method to improve diagnosis of pharyngitis in primary care. In this study, 70% of patients were diagnosed correctly by clinical diagnosis alone. Using CRP measurement with a threshold of 35 mg/l as an additional diagnostic tool, 81% of patients were diagnosed correctly.

It could be argued that the improvement might be the result of increasing awareness and competence of GPs in the clinical examination of study-patients. If an effect like this is real, it is most likely to happen in the very beginning of the study, improving clinical diagnosis of phase 1 patients as well as phase 2 patients.

A reasonable uncertainty of the study is the accuracy of throat swabs in the diagnosis of bacterial infection of the throat. In a

Table 1. Sex, age, and throat swab status of patients enrolled in phase 1 and phase 2 respectively.

	Phase 1		Phase 2	
	n	%	n	%
Total number	179	100	161	100
Sex				
Male	83	46.4	75	46.5
Female	89	49.7	81	50.3
Age				
Mean (± SD)	34.3±13.4		34.2±15.1	
Range	16–75		16–78	
Median	32.5		31	
Throat swabs				
positive for bacteria[a]	46	25.7	38	23.6

[a]Group A, C, or ß-haemolytic streptococci or haemophilus influenzae.

Table 2. Sensitivity, specificity, positive and negative predictive value and 95% CI are calculated for purely clinical diagnosis (phase 1) and combined diagnosis (clinical diagnosis with aide of CRP value: phase 2).

	Phase 1	95% CI	Phase 2	95% CI
Sensitivity	0.61	0.45–0.75	0.78	0.61–0.90
Specificity	0.73	0.65–0.81	0.82	0.73–0.88
Positive predictive value	0.44	0.32–0.57	0.57	0.42–0.70
Negative predictive value	0.84	0.76–0.90	0.92	0.85–0.96

Table 3. Hypothetical model of 1000 adult patients with sore throat diagnosed purely clinically or clinically with aide of CRP value, among 1000 hypothetical patients 247 with bacterial pharyngitis and 753 with non-bacterial pharyngitis.

	Purely clinical diagnosis	Clinical diagnosis including CRP measurement
True bacterial	151	193
	550	617
True non-bacterial		
Correct diagnosis	701	810
False bacterial[a]	203	136
	96	54
False non-bacterial[b]		
Incorrect diagnosis	299	190
Total	1000	1000

[a]Treatment with antibiotics, though not appropriate. [b]No antibiotics, though recommended.

recent study in Sweden,[20] a proportion of 2.4%–3.7% of unsymptomatic carriers of ß-haemolytic streptococci, in a healthy adult population, was found. Other authors[21] report a rate of 6%–40% of false-positive throat swabs in healthy persons. On the other hand, proportions of up to 12% false-negative test results in throat swabs for streptococci have been reported.[21,22] Nevertheless, throat swab culture is a standard procedure for the identification of bacterial pharyngitis, and there are no feasible alternatives in primary care.

In Centor's study,[23] the accuracy of throat swab cultures was approximately 90%. Earlier, a clinical scoring scheme for the diagnosis of bacterial throat infection, based on clinical findings and history only, was proposed by Dobbs.[24] The score was found to have a sensitivity of 0.71 and a specificity of 0.71. The parameters in our study seem to indicate a certain improvement as compared with Dobbs' score.

In a controlled study of various group A streptococcal immunological test systems,[25] the sensitivity of various tests ranged from 0.82 to 0.90, and the specificity from 0.89 to 0.92. In this study, selected patients in an academic medical centre were studied and no data were reported if the test systems did or did not improve the accuracy of the clinical diagnosis.

Based on our data, the measurement of CRP in a primary care setting can improve diagnostic accuracy of the infections of the throat. Thereby, the proportion of patients diagnosed correctly and treated adequately can be increased as compared with purely clinical diagnoses.

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