Towards a better diagnosis of throat infections (with group A β-haemolytic streptococcus) in general practice

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SUMMARY

Background. *Sore throat is a common complaint in general practice. However, management strategies are not very clear. A better diagnostic procedure is needed to prevent the overuse of antibiotics.*

Aim. *To assess the diagnostic value of a rapid streptococcal antigen detection test in addition to four clinical features in patients with sore throat, using throat culture and antibody titres as reference tests.*

Method. *Four clinical features [fever (history) ≥ 38.0°C, lack of cough, tonsillar exudate, and anterior cervical lymphadenopathy] were registered in 558 patients aged 4 to 60 years presenting with sore throat of no more than 14 days' duration. A rapid diagnostic test was performed, as well as a throat culture and antibody titres [fourfold increase in anti-streptolysin-O (ASO) and/or anti-deoxyribonuclease B (anti-DNAase B)] in patients aged 11 years and older.*

Results. *Throat cultures were positive for group A β-haemolytic streptococcus (GABHS) in 33% of the patients. Rapid tests were positive in 24%. Compared with the throat culture, the sensitivity of the rapid test was 65%, the specificity 96%, the positive predictive value 88%, and the negative predictive value 85%. However, for patients with three or four clinical features, the sensitivity of the rapid test was considerably higher at 75%. Children (≤ 14 years) had a slightly raised specificity and raised positive predictive value and prevalence. With the antibody titres as a reference, the rapid test performed as well as the throat culture with regard to its predictive value.*

Conclusion. *For the management of patients with sore throat in general practice, a rapid test may have an additional value, especially in patients with a high chance of having GABHS infection. However, as the sensitivity of the test studied is low, tests with a higher sensitivity are needed.*

Keywords: diagnosis; sore throat.

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Introduction

SORE throat is one of the 10 most frequently presenting complaints in general practice.[1] The most pathogenic bacterial micro-organism involved in acute pharyngotonsillitis is group A β-haemolytic streptococcus (GABHS) because of its accidental suppurative or non-suppurative sequelae.[2,3] In recent years, continued vigilance has been advised.[4,5] Antibiotics may reduce the risk of complications; however, the incidence of these complications is low, and the preventive effect is limited. At the same time, a major concern is the overuse of antibiotics, which has led to an increased number of multiple resistant strains.[6,7]

Because of these serious complications and the need to encourage limited antibiotic usage, it would be useful to have a simple but accurate parameter to differentiate between GABHS and other infectious agents. In general practice, the following diagnostic methods are available: judgement based on clinical features [e.g. fever, anterior cervical lymphadenopathy, (tonsillar) exudate, and lack of cough[8,9]] and performance of a throat culture or a rapid diagnostic antigen test. Throat culture is still the most frequently used diagnostic test. However, the interpretation of the throat culture is not unequivocal because false-negative cultures may occur,[10-12] and false-positive cultures may occur in the case of streptococcal carriers.[13] Antibody titres can be used to differentiate between carriers and truly infected persons all with a positive throat culture.[14] Several rapid group A streptococcal antigen detection tests have been developed.[15-18] The accuracy of antigen tests has been assessed in several studies using a throat culture as a reference test.

The aim of this study in general practice was to assess the diagnostic value of a rapid streptococcal antigen detection test in addition to four clinical features in patients with sore throat, with throat culture and serological titres being used as reference tests.

Method

Patients were recruited by 53 general practitioners (GPs) during the years 1990–92. Inclusion criteria were sore throat for <15 days and in those aged 4 to 60 years. In addition to age and sex, four clinical features were recorded: fever (history) ≥ 38.0°C, lack of cough, tonsillar exudate, and anterior cervical lymphadenopathy. Subsequent treatment with penicillin V was also registered.

Bacteriological assessments

Two throat samples were taken from tonsils or tonsillary fossae and the posterior pharyngeal wall with cotton swabs: one for culturing and one to perform a rapid test using liposomal technology (Directigen 1,2,3 Strep A; Becton Dickinson).[19] The physicians involved had been trained in order to improve the reliability of the throat swabs. Throat cultures were transported by mail to the Utrecht Laboratory for Primary Care Services in modified Stuart medium. Within 48 hours of collection, the cultures were inoculated with 7% sheep blood agar (Oxoid) and incubated overnight at 37°C under aerobic and anaerobic conditions. Only colonies with heavy growth on the first isolation were taken into account and reanalysed after 48 hours. Isolated haemolytic streptococci

were typed using a latex agglutination test (Streptex, Murex). For strains that could not be identified, other methods were used.[20]

For both practical and financial reasons, blood specimens were drawn at the initial visit from only a selection of patients aged 11 years and older. For patients with three or four clinical features, a non-selective sample was analysed serologically. For patients with fewer than three clinical features a selective sample of sera was analysed; most of the patients in this sample were put forward by GPs who were experienced in administering throat swabs. Furthermore, selection was aimed at analysing relatively more GABHS-positive patients. At a scheduled follow-up visit after 14 days, convalescent blood specimens were drawn. All sera were stored at –70°C and were analysed by the Department of Clinical Microbiology of Rotterdam University at the end of the study. Anti-streptolysin (ASO) and anti-deoxyribonuclease B (anti-DNAase B) antibodies were determined. ASO titres were estimated according to Rantz and Randall.[21] DNAase B was prepared according to the method of Marker and Gray,[22] and anti-DNAase B titres were measured as described by Klein and colleagues.[23] A significant antibody response was defined as a rise in titre of two dilution increments (= fourfold) or more between the acute and convalescent sera of either ASO or anti-DNAase B, or both.[12,24]

Data analysis

The data were analysed using the SPSS X and SPSS-PC programs,[25] and the EGRET statistical package.[26] Results are presented as numbers, percentages, and 95% confidence intervals.[27] The diagnostic value of the tests is expressed as sensitivity, specificity, and predictive value of a positive and a negative test result,[28] and as positive and negative likelihood ratios.

For comparison of the results of the rapid test and the throat culture, the influence of the number of clinical features (three or four and fewer than three respectively) and the influence of age category (4 to 14 years and ≥15 years) was assessed by stratified analysis.

The diagnostic value of the rapid antigen test was assessed in comparison with the throat culture and with the antibody titres. The result of the throat culture was compared with the antibody titres. The influence of the duration of sore throat before enrolment and of the antimicrobial treatment on the antibody titres was assessed by calculating the odds ratio (OR).

Results

Of 558 patients included, 183 cultures showed GABHS (Table 1). For patients with three or four clinical features, the relation between the rapid test and throat culture is shown in a Venn diagram (Figure 1). The sensitivity of the rapid test was 75% compared with 48% in patients with fewer than three features (Table 2). Both sensitivity and specificity of the rapid test were slightly higher in children (≤14 years; Table 3).

In older patients with three or four clinical features, the prior probability of GABHS was 43% (87/202; Table 3). A total of 75 of these 202 patients had a positive rapid test, increasing the posterior probability of GABHS to 84% (63/75). In patients with a negative rapid test result, the probability decreased to 19% (24/127).

In older patients with fewer than three features, the prior probability of GABHS was 18% (50/277) (Table 3). With a positive rapid test result, the posterior probability of GABHS increased to 85% (22/26), but a positive test result was seen in only 9% (26/277). With a negative rapid test result, the posterior probability decreased to 11% (28/251).

Paired blood samples were analysed in 139 patients aged 11 years and older (Table 1). The mean number of clinical features and the percentage of GABHS-positive patients were higher in the sample than in the whole group. The antibody titres were not influenced by the duration of sore throat before enrolment (OR = 1.1; 95% CI = 0.9–1.5) or by the use of penicillin (OR = 0.9; 95% CI = 0.3–2.2).

Thirty-eight per cent of the GABHS-positive and 8% of the GABHS-negative patients showed a fourfold or higher increase in titre (Table 4). We further established (data not shown) that nearly half (31/65) of the GABHS-positive and 42% (31/74) of the GABHS-negative patients appeared to have a second titre above a cut-off point, chosen as ASO ≥400 IU ml^{-1} and/or anti-DNAase B≥320 IU ml^{-1}, without fulfilling the fourfold criterion.

Discussion

The rapid test appeared to have a high specificity, a valuable characteristic for general practice use. However, the low sensitivity still limits its value. The test studied appeared to be more suitable in patients with a higher probability of GABHS. If, as in our study, patients with three or four clinical features (harbouring GABHS in 47%) are tested with a rapid test, 40% of these patients are positive. Thus, for the remaining 60% with a negative test result, a reduction in treatment is possible. However, a minority of this group had a positive throat culture and could have benefited from treatment.

In several studies, the same rapid test has been investigated. Two studies in a hospital setting reported sensitivities of about 65%.[29,30] Two other studies in general practice reported sensitivities of 73%[31] and 95%.[32] Proper training, experience, and quality control are said to lead to greater accuracy of the screening tests. In our study, the reliability of the throat swabs was increased by training the GPs and by reanalysing all beta-haemolytic microorganisms.

The specificity we found was high and in agreement with other studies, which have reported specificities of between 81% and 100%.[29,33-37] Recently, tests using optical immunoassay have been developed and are thought to have higher sensitivity and a sufficiently high specificity and predictive value.[38]

The majority of GABHS-positive patients did not show a significant antibody rise, resulting in a carrier rate (62%) similar to other studies.[11,34,39] Nevertheless, this carrier rate estimate may be too high, as the period elapsed between the first and second sample has been reported to play a role,[11,24,40] and the second blood sample after 14 days in our study may have been taken too

Table 1. Characteristics of all patients included in the study (*n* = 558) and of patients in the 'serological sample' (*n* = 139).

	n = 558	*n* = 139
Mean age (SD)	27.2 (12.6)	29.0 (11.4)
Mean duration of complaints in days (SD)	3.8 (2.9)	3.9 (3.0)
Presence of three or four clinical features (%)	247 (44)	78 (56)
Presence of GABHS in throat culture (%)	183 (33)	65 (47)
Positive rapid test (%)	135 (24)	47 (34)

Table 2. Diagnostic value of rapid antigen detection test in patients with none to two, and three or four clinical features:* comparison with throat culture.

Number of clinical features		0–2 (n = 311)		3–4 (n = 247)	
Culture		GABHS+	GABHS–	GABHS+	GABHS–
Rapid test	+	32	4	87	12
	–	35	240	29	119
Total		67	244	116	131

	0–2	3–4	All	Difference	95% CI of difference
Sensitivity	48	75	65	27	13–42
Specificity	98	91	96	7.5	2–13
Predictive value +	89	88	88	NC	
Predictive value –	87	80	85	7	–1 to 14
Prevalence	22	47	33	25	18–33

*Fever (history), anterior cervical lymphadenopathy, (tonsillar) exudate, and lack of cough. NC = not calculated.

Table 3. Diagnostic value of rapid antigen detection test in patients aged 4–14 years and 15 years and older: comparison with throat culture.

Age category (years)		4–14 (n = 79)				15 and older (n = 479)			
Culture		GABHS+		GABHS–		GABHS+		GABHS–	
		0–2	3–4	0–2	3–4	0–2	3–4	0–2	3–4
Rapid test	+	10	24	0	0	22	63	4	12
	–	7	5	17	16	28	24	223	103
Total		17	29	17	16	50	87	227	115

	4–14 years	15 years and older	95 % CI of difference
Sensitivity	74	62	–3 to 27
Specificity	100	95	2–27
Predictive value +	100	84	9–23
Predictive value –	73	86	0.5–26
Prevalence	58	29	18–41

Table 4. Comparison of rapid antigen detection test and throat culture with presence (+) or absence (–) of two dilution increments or higher increase of ASO and/or anti-DNAase B antibodies (n = 139); likelihood ratios (LRs) of a positive and negative result of rapid test and throat culture compared with antibodies.

		Antibody titres +	Antibody titres –	Total
Rapid test	+	19	28	47
	–	12	80	92
Total		31	108	139
Throat culture	+	25	40	65
	–	6	68	74
Total		31	108	139

	Rapid test	95% CI	Throat culture	95% CI
Sensitivity	61	42–78	81	63–93
Specificity	74	66–82	63	54–72
Predictive value +	40	26–56	39	27–51
Predictive value –	87	78–93	92	83–97

	LR+	LR–
Rapid test	2.35	0.53
Throat culture	2.19	0.30

early. A large group of patients showed a titre at or above the cut-off point, with little or no rise or even a fall afterwards. Whether this is a sign of current infection or of a previous GABHS infection has been the subject of discussion for years.[11,24] The false-negative culture rate (negative culture combined with significantly increased titre) was in accordance with the 10% false-negative rate usually mentioned. One author reported a false-negative culture rate of 45%.[11] When taking into account patients with a second titre above the cut-off point, we found a false-negative rate of 42%.

In our study, almost half of the patients with negative rapid test results and a positive culture showed a significant antibody rise. The negative predictive value of the rapid test was high when using the antibody titres as a reference test. The positive predictive value of the test was low and similar to the throat culture. A comparison of a rapid test with antibody titres was reported in only two other studies.[16,31] De Meyere[31] could not demonstrate a correlation between the ASO titre and the same rapid test we studied. A limitation in our study is that only patients aged 11 years and over were used. Furthermore, a non-random selection with a high proportion of GABHS was investigated because they are the most important in daily practice. Larger studies are still needed for the comparison of rapid test and antibody titres.

The best way to reach a reduction in the number of unnecessary prescriptions would be to enhance the pretest probability of streptococcal pharyngitis by taking into account the clinical picture of patients.[8,10,41] In a previous study,[9] four clinical features appeared to be useful for selecting patients with a higher probability of GABHS. In addition to these features, the rapid test has a sufficiently positive predictive value and a sufficient percentage of positive test results.

In conclusion, for the management of sore throat in general practice, a rapid test may have an additional value. The advantage of the use of a rapid test may be that, in the case of a negative test, the physician feels safer when telling a patient during a consultation that an antimicrobial drug is not needed.[42] Further study is needed to develop a test with higher sensitivity that would make culturing superfluous in all cases.

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