# Better diagnosis and treatment of throat infections caused by group A β-haemolytic streptococci

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**ABSTRACT**

This study aims to assess the diagnostic value of a rapid streptococcal antigen test in addition to four clinical features in patients with sore throat, using throat culture and antibody titre as reference tests, and to evaluate the efficacy of the current antibiotics used in the treatment of throat infections caused by group A β-haemolytic streptococcus (GABHS). Four clinical features (fever [history of] ≥38°C, lack of cough, tonsillar exudate, and anterior cervical lymphadenopathy) are recorded in 355 patients aged four years to ≥15 years. A rapid antigen diagnostic test (RADT) is performed, as well as a throat culture. Antistreptolysin O (ASO) titre is performed in patients ≥11 years. GABHS from patients are tested for susceptibility to different antibiotics. Throat cultures were positive for GABHS in 19% patients. Rapid tests were positive in 24%. Compared with throat culture, the rapid test gave a sensitivity of 91%, specificity of 91%, positive predictive value of 73% and a negative predictive value of 98%. For patients with three or four clinical features, however, the sensitivity was considerably higher at 97%. Using the ASO test as a reference, no association was found between RADT and culture results. Zithromax showed the highest prescription rate (25.5%) and produced a high cure rate (91%) in patients with GABHS pharyngitis.

KEY WORDS: Antigens, bacterial.
Diagnosis.
Pharyngitis.
Streptococcus pyogenes.
Tonsillitis.

## Introduction

Streptococcal pharyngitis (pharyngotonsillitis) is an acute infection of the oropharynx and/or nasopharynx. The main pathogenic bacterial microorganism involved in acute pharyngotonsillitis is group A β-haemolytic streptococcus (GABHS),[1,2] and in recent years continued vigilance has been advised[3,4] as GABHS pharyngitis is reported to account for 10–30% of sore throats.

Its public health importance arises from the fact that it is a precursor of two serious non-suppurative sequelae: acute rheumatic fever and post-streptococcal glomerulonephritis.[5] Although antibiotics may reduce the risk of complications, the preventive effect is limited. At the same time, a major concern is the overuse of inappropriate antimicrobial therapy, which has led to an increase in multiresistant strains.[6,7]

As a result of these serious complications and the need to encourage limited antibiotic usage, laboratories should be strong advocates for appropriate testing and judicial use of antimicrobial agents for diagnosis and management of pharyngitis. Diagnostic methods in general practice include judgement based on clinical criteria (e.g., fever, anterior cervical lymphadenopathy, tonsillar exudate, and lack of cough)[8,9] and performance of throat culture or a rapid diagnostic antigen test.

Throat culture remains the standard method for detecting the presence of GABHS. However, several variables affect the accuracy of throat culture results and both false-negative and false-positive results may be obtained.[10–12] Another limitation to conventional throat culture is the one- to two-day delay in obtaining culture results, which means that some patients are treated needlessly, while others may not be treated at all if they are lost to follow-up.[13] However, antibody titres can be used to differentiate carriers from those with true infection.[14]

Several rapid group A streptococcal antigen tests have been developed,[15,16] and the accuracy of such tests has been assessed in several studies using throat culture as a reference test.

The aim of the present study in general practice is to assess the diagnostic value of a rapid streptococcal antigen detection test (in addition to some clinical features in patients with sore throat) against throat culture and a serological test, and to evaluate the efficacy of the current antibiotics used in the treatment of throat infections caused by GABHS.

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## Materials and methods

A total of 355 patients with symptoms of pharyngotonsillitis were recruited from two types of health facility (public hospitals and private clinics) in Makkah, Saudi Arabia. In addition to age and gender, four clinical features (fever [history of] ≥38°C, lack of cough, tonsillar exudate, and anterior cervical lymphadenopathy) were recorded by the ENT clinicians. Previous and subsequent treatments were also recorded.

**Table 1.** Diagnostic value of rapid antigen detection test in patients with 0–2 or 3–4 clinical features*: comparison with throat culture.

| | 0–2 features ($n$=178) | | 3–4 features ($n$=177) | |
|---|---|---|---|---|
| | GABHS + | GABHS – | GABHS + | GABHS – |
| Rapid test + | 25 | 13 | 36 | 10 |
| Rapid test – | 5 | 135 | 1 | 130 |
| Total | 30 | 148 | 37 | 140 |
| | 0–2 | 3–4 | All | Difference |
| Sensitivity | 83% | 97% | 91% | 14% |
| Specificity | 91% | 93% | 91% | 2% |
| PPV | 68% | 77% | 73% | 9% |
| NPV | 96% | 99% | 98% | 3% |

*Fever (history of), anterior cervical lymphadenopathy, tonsillar exudates, and lack of cough.

**Table 2.** Diagnostic value of rapid antigen detection test in patients aged 4–14 years and those ≥15 years: comparison with throat culture.

| | Aged 4–14 ($n$=107) | | | | Aged ≥15 ($n$=248) | | | |
|---|---|---|---|---|---|---|---|---|
| | GABHS + | | GABHS – | | GABHS + | | GABHS – | |
| | 0–2 | 3–4 | 0–2 | 3–4 | 0–2 | 3–4 | 0–2 | 3–4 |
| Rapid + | 5 | 17 | 7 | 4 | 18 | 19 | 6 | 8 |
| Rapid – | 2 | 3 | 28 | 41 | 3 | 0 | 109 | 85 |
| Total | 7 | 20 | 35 | 45 | 21 | 19 | 115 | 93 |
| | Aged 4–14 | | | | Aged ≥15 | | | |
| Sensitivity | 81% | | | | 93% | | | |
| Specificity | 86% | | | | 93% | | | |
| PPV | 67% | | | | 73% | | | |
| NPV | 93% | | | | 98% | | | |

Two throat swabs were taken from tonsils or the tonsillar fossa and the posterior pharyngeal wall with cotton swabs and were sent in Amies transport medium to the medical microbiology laboratory at the Faculty of Medicine and Medical Sciences, Umm Al-Qura University.

One throat swab was subjected immediately to the rapid antigen detection test (RADT; Detector Strep A Direct Kit), while the second swab was plated on horse blood agar plates with a bacitracin susceptibility disc and incubated overnight at 37°C under aerobic and anaerobic conditions. Only colonies with heavy growth on the first isolation were re-analysed after 48 h. Suspected colonies of β-haemolytic streptococci were confirmed as GABHS using latex agglutination (Atlas Medical, Cambridge).

Blood was obtained from a selection of patients and the sera stored at –20°C prior to analysis using the antistreptolysin O (ASO) test (Bio Kit, Barcelona, Spain) at the end of the study.

*Data analyses*

Data were analysed using SPSS software. Results are presented as numbers and percentages, and the diagnostic value expressed as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

For comparison of the rapid test and throat culture, the influence of the number of clinical features and the influence of age was assessed by stratified analysis. Means and proportion were compared by the $\chi^2$ test for RADT and throat culture, and the influence of ASO titre and that of previous antibiotic treatment.

**Table 3.** Comparison of rapid antigen detection test and throat culture with ASO test.

| | ASO test | | |
|---|---|---|---|
| | Positive | Negative | Total |
| Rapid test + | 12 (32%) | 28 (21%) | 40 |
| Rapid test – | 25 (68%) | 105 (79%) | 130 |
| Total | 37 | 133 | 170 |
| Throat culture + | 8 (22%) | 25 (19%) | 33 |
| Throat culture – | 29 (78%) | 108 (81%) | 137 |
| Total | 37 | 133 | 170 |

$\chi^2$ =2.1 for result of ASO and RADT ($P$>0.05).

$\chi^2$ =1.5 for result of ASO and culture ($P$>0.05).

## Results

Of the 355 patients studied, 151 (43%) showed evidence of GABHS pharyngotonsillitis. The RADT was positive in 84 patients (24%) and throat culture was positive in 67 patients (19%). The relationship between the rapid test and throat culture is shown in Table 1.

A breakdown of the diagnostic value of the RADT against throat culture is shown in Table 2. In older patients with three or four clinical features, the probability of GABHS was 17% (19/112; Table 2). A total of 27 of these 112 patients had a positive RADT, increasing the probability of GABHS to 70% (19/27). In patients with a negative RADT, probability was zero. In older patients with fewer than three diagnostic features, probability of GABHS was 15% (21/136; Table 2). With a positive RADT, the probability of GABHS increased to 75% (18/24), but a positive test result was seen in only 18% (24/136) of cases. With a negative RADT, probability of GABHS decreased to 3% (3/112).

A blood sample was analysed in 177 patients (Table 3), and 32% of those with a positive RADT and 68% of those with a negative RADT were ASO-positive. For throat culture, 22% of positives and 78% of negatives were ASO-positive.

Tables 4 and 5 show antibiotic prescription rates and the efficacy of antibiotics in treating patients with GABHS, respectively.

## Discussion

Streptococcal pharyngotonsillitis has been a matter of medical concern, due to its potential for causing serious problems such as rheumatic fever and suppurative

complications. The prevalence of acute pharyngotonsillitis caused by GABHS is 28–40% worldwide; however, the figure varies from region to region.[17]

Pharyngotonsillitis due to GABHS is common among five- to 15-year-old children.[8] However, the present study reveals that the majority of patients with GABHS pharyngitis were in the older age group. This incidence can be attributed to the crowding, close contact and health service location, but the population studied also had an impact, as it did not include material from paediatric clinics.

The RADT used in the study showed a high specificity, a valuable characteristic for general practice use, but a low, variable sensitivity limits its value. The test studied appeared to be more suitable for patients with a higher probability of GABHS. The sensitivity of the RADT was 97% for patients with three or four clinical criteria and 83% for those with two or fewer criteria. This compares well with the results of the study by Di-Matteo *et al*,[18] although other studies have produced different sensitivity results.[16,19]

The so-called spectrum bias (spectrum effect) referred to by some investigators[20] has often been found in relation to the severity of disease.[18,21] The results of the present study demonstrate that spectrum bias may occur when RADT is used to diagnosis GABHS pharyngotonsillitis in children. The sensitivity of RADT was lowest (71%) for children with up to two criteria and highest (85%) for those with three or four criteria. Other studies have found similar spectrum bias when RADT is used to diagnose GABHS pharyngitis in children.[19,22]

One contributing factor could be the quantity of bacteria in the pharynx, with higher numbers in patients with more severe clinical manifestations. This might increase the probability of positive test results for patients with severe symptoms and high bacterial loads.

The present study does not report quantitative data on cultures; however, the information on the commercial test used does provide data on the sensitivity of the test, which increases as the number of colonies present in the culture increases. The specificity was high and agreed with that reported in other studies, which ranges between 81% and 96%.[19,23,24]

In countries where rapid detection tests are used routinely, a controversy exists about whether or not confirmatory culture is necessary when the results are negative. However, recent new guidelines suggest that confirmation of a negative RADT for GABHS in adults is only necessary if the sensitivity is <80%.[25,26] However, backup culture is generally recommended.[25]

Serology is the gold standard for diagnosing streptococcal infection in patients with suspected acute rheumatic fever, but it has limited application in pharyngitis.[27] No statistically significant association between ASO titre and RADT and culture ($P>0.05$) was seen in the present study; however, a limitation was that only patients aged 11 years and over were used. Furthermore, only one blood sample was taken from a selection of the patients studied and thus antibody rise could not be detected.

Inappropriate antibiotic treatment for GABHS pharyngitis is becoming a major issue, and an important goal for all clinicians should be to reduce unnecessary antibiotic prescriptions.[28] The present study showed that azithromycin was prescribed most often (25.5%). Although a 10-day course of penicillin V is effective in GABHS pharyngitis, the regimen has a number of drawbacks that limit prescription rates in many countries.[29,30]

**Table 4.** Prescription rates of antibiotics received by the patients.

| | Number | Percentage |
|---|---|---|
| Zithromax | 84 | 25.5 |
| Tabiclor | 80 | 24.3 |
| Claritt | 70 | 21.3 |
| Augmentin | 31 | 9.4 |
| Keflex | 26 | 7.9 |
| Zinnat | 14 | 4.3 |
| Others (including penicillin) | 24 | 7.3 |
| Total | 329 | 100 |

**Table 5.** Efficacy of antibiotics in the cure rates of patients with positive GABHS.

| | Level of improvement (%) | | | | |
|---|---|---|---|---|---|
| | Obvious | Mild | No improvement | Unknown* | Total |
| Zithromax | 19 (90.5) | 2 (9.5 | 0 | 0 | 21 |
| Tabiclo | 12 (54.5) | 5 (23) | 1 (4.5) | 4 (18) | 22 |
| Claritt | 12 (50) | 9 (37.5) | 1 (4.2) | 2 (8.3) | 24 |
| Augmentin | 3 (60) | 1 (20) | 0 | 1 (20) | 5 |
| Keflex | 3 (30) | 7 (70) | 0 | 0 | 10 |
| Others | 3 (100) | 0 | 0 | 0 | 3 |

*Patients not available for follow-up.

Several antibiotic compounds with shorter dosing regimens give similar or better results for GABHS eradication.[31,32] Azithromycin showed a high cure rate (91%) in the present study, which confirmed the results of other studies that showed >90% clinical efficacy.[33–35]

In conclusion, for the management of GABHS pharyngitis in general practice, a rapid test provides results faster; so rapid identification and prompt treatment of patients with streptococcal pharyngitis can reduce the risk of the spread of GABHS and the acute morbidity associated with the illness.[4] It can be treated effectively with non-penicillin V antibiotics with shorter regimens and simple once-a-day dosing.[30] The new macrolides, including azithromycin, are considered suitable for the empirical treatment of bacterial pathogens including GABHS that are a common cause of respiratory tract infection.[36] The results of the present study notwithstanding, further study is needed to develop a test with higher sensitivity that would make culture unnecessary in all cases of GABHS pharyngitis. □

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