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Early diagnosis of streptococcal pharyngotonsillitis: assessment by latex particle agglutination test

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Abstract

Objectives: Acute pharyngitis is one of the most common diseases in pediatric practice, and the most common bacterial etiology is group A beta-hemolytic streptococcus (GABHS). Correct diagnosis and treatment are primarily of importance to the prevention of non-suppurative sequelae. Rapid tests for detecting the antigen of group A streptococcus are a useful tool for the diagnosis of streptococcal pharyngotonsillitis, due to the speed of results, accuracy and low cost; however, in our country they are little used and have been little studied. The objective of this study was to evaluate the accuracy of a GABHS rapid antigen detection test kit, in comparison with oropharynx swab culture.

Methods: Children aged 1 to 18 years with clinical diagnoses of acute pharyngitis were chosen at public emergency and private clinical services in Belo Horizonte, Minas Gerais, Brazil, with children being excluded if they had taken antibiotics within 30 days of their consultation. The final sample consisted of 229 patients, each of whom had two oropharynx swabs taken, one for rapid GABHS testing and the other to be sent for culture.

Results: We observed sensitivity of 90.7%, specificity of 89.1%, a positive predictive value of 72.1%, a negative predictive value of 96.9% and a positive likelihood ratio of 9.0 for the rapid test used here, compared with culture.

Conclusions: The rapid test studied exhibited a good correlation with culture and is, therefore, of great use in clinical practice for detection of GABHS.

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Introduction

Acute pharyngitis (AP) is one of the most common diseases in pediatric practice.[1] Although the majority of APs of viral origin, group A β-hemolytic streptococcus (GABHS) is the most common bacterial etiology (15-30% of AP).[1-3] Therefore, early diagnosis of this infection, followed by appropriate antimicrobial treatment, is extremely relevant to the prevention of rheumatic fever (RF) and suppurative complications (peritonsillar abscess, cervical lymphadenitis and mastoiditis), to the improvement of signs and symptoms, to reducing of GABHS transmission and in order to minimize the adverse effects of inappropriate antibiotics use,[1,4,5] including the emergence of resistance to antibiotics.[2]

In developing countries, RF is one of the principal causes of acquired heart disease among school-aged and adolescent children and young adults.[6,7] In Brazil, according to a World Health Organization epidemiological model, there is an estimated annual frequency of 6 million streptococcal AP, 0.3% of which, under non-epidemic conditions, result in episodes

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of acute RF, which equates to an incidence of 15,000 to 18,000 new cases annually. Around one third, i.e. 6000, of these cases progress to chronic rheumatic heart disease. The majority of mitral valve interventions carried out in our country are the result of rheumatic heart disease.[8] In Belo Horizonte, Minas Gerais, Brazil, a study carried out at a school belonging to the public education system demonstrated a prevalence of rheumatic disease of 3.6 in every 1,000 students aged 10-20 years.[9]

A large proportion of the signs and symptoms of pharyngitis due to GABHS are the same as those of non-streptococcal pharyngitis, which makes it difficult to make etiologic diagnosis on the basis of clinical signs and symptoms alone.[1,4] Many attempts have been made to develop reliable clinical criteria by means of scores and flow diagrams,[1,3,10-13] but, unfortunately, few have managed to achieve a level of accuracy comparable to that of confirmatory laboratory tests.[12]

The current recommendations of the American Academy of Pediatrics (AAP), the Centers for Disease Control and Prevention (CDC), the American Heart Association (AHA) and the Infectious Diseases Society of America (IDSA) are that, when there is a clinical suspicion of AP due to GABHS, diagnosis should be confirmed by laboratory tests employing either cultures of peritonsillar exsudate swabs or rapid antigen detection tests (RADT) of the same swabs.

The high specificity (≥ 95%) of RADT, observed by several authors, means that treatment can be initiated if the result is positive. However, a negative result from a test the sensitivity of which varies between 80 and 90% does not exclude a diagnosis of AP due to GABHS and should be confirmed by culture, which, if positive, demands immediate treatment.[1,2,14,15] According to the AAP and the IDSA, this last recommendation can be ignored if the specific RADT being used has a sensitivity that is proven to be comparable to culture.

Culture of pharyngotonsillar secretions is the conventional method and the gold standard for diagnosis of AP due to GABHS, but it has practical limitations. The wait for results (18-48 hours) causes a delay in treatment or use of antibiotics too early, causes anxiety among patients and family members and prolongs symptomatology and the period during which streptococcus dissemination occurs in cases of AP due to GABHS.

Rapid antigen detection tests have been widely studied and validated at many different centers for the diagnosis of streptococcal AP.[1,14,16-18] These tests offer results in up to 30 minutes and exhibit good concordance with culture results, making them a reliable resource that is easily accessed, is cheaper than culture and is a great aid in the correct diagnosis of AP and to judicious use of antimicrobials.

Both the AAP and the IDSA recommend that each center that employs RADT for diagnosis of AP should validate them and compared their sensitivity and specificity with results from culture.[1,14]

Brazilian data on RADT remain scarce.[19-21] This study aims to evaluate the sensitivity, specificity, positive predictive value, negative predictive value and positive likelihood ratio (LR) of an RADT compared with culture in a sample of patients in the pediatric age group seen at primary care services.

Methods

This is a cross-sectional study, undertaken in Belo Horizonte, Minas Gerais, Brazil, during the period from January 1997 to January 2001. Pediatric patients aged 1 to 18 years were selected at public emergency and private clinical services, with a clinical presentation of acute pharyngitis. Use of benzathine penicillin within the previous 30 days and/or other antimicrobial drugs within the previous 15 days were exclusion criteria. The present study was approved by the Ethics Committee at the Universidade Federal de Minas Gerais.

After consent had been obtained, each child was interviewed, in the presence of a parent, by a first examiner who filled out a specific protocol and took two swabs simultaneously from the tonsils and posterior pharyngeal region. A second examiner (double-blind test), performed latex particle agglutination testing (Patho Dx®, DPC, Los Angeles, United States) on one of the swabs, according to the manufacturer's instructions. The second swab was used to seed an agar and 5% lamb's blood plate within 20 minutes, which was then incubated for 18 to 24 hours in microaerophilic conditions at 37 ºC. The plate was subsequently interpreted based on colony morphology and hemolysis pattern by a microbiologist who was unaware of the result of the latex test. Suspect colonies were confirmed as beta-haemolytic streptococcus by means of latex agglutination testing (Pastorex®, Sanofi Pasteur, France).

The patients included had presented with signs of pharyngotonsillitis, among others, complaining of sore throat and/or hyperemic tonsils or oropharynx, observed during the clinical examination performed at the time of enrollment on the study.

Streptococcal AP due to GABHS (case): patients with clinical diagnosis of AP and a culture positive for GABHS.

Negative (control): patients with clinical diagnosis of AP and a culture negative for GABHS.

The sample size was calculated, using Epi-Info version 6.0, at 126 patients in order to achieve a sensitivity of 91%, and at 138 patients in order to achieve a specificity of 90%, taking the culture as gold standard and with an alpha error of 5%, with amplitude of variation of 15% of the 95% confidence interval.

Frequency distributions were employed to assess the population's characteristics in terms of sex, age, number of inhabitants in family home and parents' education.

Table 1 - General characteristics of the study population (n = 229)

Variable	n	%	95%CI
Male sex	99	43.2	36.8-49.9
Female sex	130	56.8	50.1-63.2
Age (months)*			
17- 49	17	7.5	4.5-11.9
50-120	170	74.9	68.6-80.3
121-219	40	17.6	13.0-23.3
Education/years' schooling†			
0-8	141	63.5	56.8-69.8
9-11	24	10.8	7.2-15.8
> 12	57	25.7	20.2-32.0
Number of people‡			
2-4	98	44.3	37.7-51.2
5-9	120	54.3	47.5-61.0
> 10	3	1.4	0.3-4.2

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy, with their respective 95% confidence intervals, and the positive LR of the RADT were all calculated in relation to culture.

The protocol, database and statistical analysis were all produced electronically using Epi-Info, versions 6.0 and 2002.

Results

Initially, 238 patients were included; eight of these were excluded due to doubtful latex results and/or contaminated culture. The sample analyzed comprised 229 children.

The characteristics of the study population are given in Table 1.

There was a predominance of females (56.8%) and of patients aged from 4 to 10 years (74.9%). We observed that parents had a low educational level, with a predominance of those who had had 0 to 8 years' schooling (63.5%).

The most common clinical findings were fever (88%), swollen tonsils (73.8%), pain when swallowing (73.4%) and prostration (73.4%). The frequency distribution of clinical signs and symptoms across the study group can be observed in Table 2.

The data in Table 3 demonstrate that the age group with most positive latex results was the over-fives (n = 64; 30.1%). There was no difference in the proportion of positive cultures between patients younger than 5 years (n = 4; 23.5%) and those older than 5 years (n = 50, 23.6%).

Table 4 illustrates the comparison of the RADT results with those of the oropharynx swab culture.

The figures observed for the test were: sensitivity (S) of 90.7% (95%CI 85.1-96.4); specificity (SP) of 89.1% (95%CI 83.0-95.2); positive predictive value (PPV) of 72.1% (95%CI 63.3-80.9); negative predictive value (NPV) of 96.9% (95%CI 93.5-100.3) and a positive LR of 9. All calculations were performed to a confidence interval of 95%.

Discussion

The sensitivity of RADT for detecting GABHS (90.7%) found in this study is comparable with the results of previous publications (80-90%).[1,3,10,19,20,22,23] Possible explanations for the presence of the false negatives observed in this study include the culture incubation time, which was 24 hours (increasing the incubation period to 48 hours increases positivity and, therefore, the sensitivity of the test[1,22]), and the possibility of low numbers of colonies with this test, which was not assessed in our analysis.

The observed specificity of 89.1% was lower than the average in the literature, where figures are above 95%. We could speculate that there might be a high prevalence of healthy carriers of GABHS, the prevalence of whom is unknown in our country, since the test does not allow differentiation between colonized and infected patients, and that this increased the number of false positives. Another possible explanation is that different test kits were used in different studies.

Hjortdahl et al. used the same RADT kit used here and observed a specificity of 91%, but they attributed the divergence from other study results not to the kit itself, but to the low level of precision of results caused by the introduction of a new laboratory diagnostic test; the subjectivity of RADT readings (a reaction that is weakly positive may be interpreted as positive); problems inherent to the "gold standard" employed, since oropharynx swab cultures can produce around 10% false-negatives; and to the occurrence of other streptococci with hemolysis patterns and antigens A, C, F or G.[24,25]

Table 2 - Clinical characteristics of the patients studied (n = 229)

Sign and/or symptom	n	%
Headaches		
Present	144	62.8
Absent	83	36.2
Not known	2	1.0
Coryza		
Present	78	34.1
Absent	148	64.6
Not known	3	1.3
Fever		
Present	201	88.0
Absent	26	11.0
Not known	2	1.0
Cervical lymphadenopathy		
Present	120	52.0
Absent	102	45.0
Not known	7	3.0
Pain swallowing		
Present	166	72.4
Absent	61	26.6
Not known	2	1.0
Hyperemic palate		
Present	40	17.5
Absent	185	80.8
Not known	4	1.7
Swollen tonsils		
Present	169	73.8
Absent	57	24.9
Not known	3	1.3
Hyperemic tonsils		
Present	188	82.1
Absent	32	13.9
Not known	9	4.0
Prostration		
Present	166	72.4
Absent	61	26.6
Not known	2	1.0
Hyporexia		
Present	162	70.7
Absent	63	27.5
Not known	4	1.8

* Two patients missing information;
† Parents' education; seven missing information;
‡ Number of inhabitants at home; eight patients missing information.

Berezin et al. observed sensitivity and specificity of 78 and 90%, respectively,[19] whereas Santos et al. found 96.7 and 94.4%.[20] In this last study, the elevated specificity was the result of the exclusion of patients with signs and symptoms of viral infection, which was not performed in our study. The present analysis included patients (with nonspecific complaints) with uncertain clinical status of GABHS infection with the intention of assessing a sample that was representative of the reality faced by the majority of professionals working at emergency services and in primary care. Earlier studies

Table 3 - Positive latex particle agglutination tests and cultures by age

	Latex n (%)	Culture n (%)	Total n (%)
< 5 years	4 (23.5)	4 (23.5)	17 (100)*
> 5 years	64 (30.1)	50 (23.6)	212 (100)†

* Total number of patients studied aged under 5 years;
† Total number of patients studied aged over 5 years.

have shown that prior selection of patients to be investigated with RADT with presentation strongly suggestive of AP of streptococcal etiology (sudden onset of fever, sore throat, without conjunctivitis, coryza, coughing, hoarseness or diarrhea) increases the pre-test prevalence and, consequently, the sensitivity and specificity of the test.[23,26,27]

In a study carried out by Araújo Filho et al. with the adult population (18 to 69 years), the values observed for the sensitivity and specificity of the latex test were 93.9 and 68.7%, respectively. In that case, the specificity was lower than found in this article.

The LR is a statistical analysis that assesses the quality of a diagnostic test and helps with the selection of an appropriate diagnostic test.[28] It offers advantages over determination of sensitivity and specificity because it alters less in response to the prevalence of a given disease. In a review of the literature, just one study was identified which had calculated the LR of an RADT, coming up with a value of 17.[20] Our study found a positive LR of 9, which means that it is nine times more likely to observe a positive latex result in a patient who has a positive culture than in a patient with a negative culture.

The figures for sensitivity, specificity, NPV, PPV and positive LR observed here for the RADT used allow us to consider it a clinically useful method. In cases where the RADT result is negative, the current recommendations of the AAP, CDC, AHA and IDSA should be followed and an oropharynx swab culture be taken with the objective of maximizing conclusive etiologic diagnoses.

Table 4 - Comparison between oropharynx swab culture and latex particle agglutination test for detecting GABHS*

Latex	Culture					
	Positive		Negative		Total	
Positive	49	90.7%	19	10.9%	68	29.7%
Negative	5	9.3%	156	89.1%	161	70.3%
Total	54	100%	175	100%	229	100%

negative predictive value = 96.9 (95%CI 93.5-100.3); positive likelihood ratio = 9.0; positive predictive value = 72.1% (95%CI 63.3-80.9); sensitivity = 90.7% (95%CI 85.1-96.4); specificity = 89.1% (95%CI 83.0-95.2);
* Group A beta-hemolytic streptococcus.

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