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Etiologic predictive value of a rapid immunoassay for the detection of group A Streptococcus antigen from throat swabs in patients presenting with a sore throat

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SUMMARY

Background: Clinical reasoning utilizing certain symptoms and scores has not proven to be a reliable decision-making tool to determine whether or not to suspect a group A Streptococcus (GAS) infection in the patient presenting with a sore throat. Culture as the so-called 'gold standard' is impracticable because it takes 1 to 2 days (and even longer in remote locations) for a result, and thus treatment decisions will be made without the result available. Rapid diagnostic antigen tests have demonstrated sufficient sensitivities and specificities in detecting GAS antigens to identify GAS throat infections.
Methods: Throat swab samples were collected from patients attending the Mount Isa Hospital emergency department for a sore throat; these samples were compared to swab samples collected from healthy controls who did not have a sore throat. Both groups were aged 3–15 years. All swab samples were analyzed with a point-of-care test (Alere Test Pack +Plus with OBC Strep A). The etiologic predictive value (EPV) of the throat swab was calculated.
Results: The 95% confidence interval for positive EPV was 88–100% and for negative EPV was 97–99%, depending on assumptions made.
Conclusion: This study demonstrates that the point-of-care test Alere Test Pack +Plus Strep A has a high positive predictive value and is able to rule in GAS infection as long as the proportion of carriers is low. Also the negative predictive value for ruling out GAS as the etiologic agent is very high irrespective of the carrier rate. Hence, this test is always useful to rule out GAS infection.

1. Introduction

With an incidence of 3–13 cases per 100 patient-years, Group A Streptococcus (GAS) pharyngitis is a common presentation, not only in primary health care but also in emergency departments.[1] Amongst all patients presenting with a sore throat, the incidence of GAS infection reported in the literature ranges from almost 0% to 40%.[2,3] Both the incidence of acute presentations and the severity may vary over time, and infections may occur in clusters.[4]

GAS pharyngitis is a main cause of acute rheumatic fever (ARF) and rheumatic heart disease.[5] Whilst the absolute global burden of GAS disease is not exactly known, estimated annual numbers of rheumatic heart disease cases worldwide of approximately 2 400 000[6] to 12 000 000[7] have been reported. North Queensland, Australia, has one of the highest incidences of ARF and rheumatic heart disease in the world, especially within the indigenous

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communities, with reported incidences of 54–492 cases per 100 000 population.[5,8] This is due to a high percentage of residents in this region living in remote communities, often in varying degrees of poverty and crowding, and is consistent with findings in the Northern Territory, Australia.[9]

Whilst there is increasing suspicion and some evidence that ARF may also be related to chronic skin sores (pyoderma),[5] patients having a sore throat remain the main focus.

Identifying the individual patient presenting with a sore throat as having a GAS infection is more challenging than it seems on first sight, not even taking into account whether all positive GAS results actually represent an acute bacterial infection.[10] Utilizing clinical decision rules based solely on symptoms and signs, such as the Centor criteria and World Health Organization criteria, does not appear to be reliable enough to clarify whether the infective agent is GAS or not, and thus whether to treat with antibiotics or not.[10,11] The resulting problems are an untreated GAS infection that may lead to ARF, and more often, the unnecessary prescription of antibiotics leading to side effects as well as the potential of bacteria developing antibiotic resistance.

Throat culture has been recommended as an aide for treatment decisions.[1,12] However, it has been shown that the 1–2 days of delay until the result is available results in the decision being made without considering the outcome of the culture.[13,14] Furthermore, in the setting in which a large number of patients travel several hundred kilometers to see a doctor and where there is limited phone reception, it is difficult to organize re-presentation or follow-up of the results including treatment modifications.

An excellent solution for this dilemma would be a bedside rapid antigen detection test (RADT) for GAS that provides a positive or negative result within 5–10 min, thus directly influencing the treatment decision. Such RADTs have been evaluated previously using throat culture as the gold standard and initially showed insufficient sensitivity and specificity.[12,15] Later studies have provided evidence that the sensitivity of GAS RADT is equal or superior to culture, and specificity close to 100%.[16,17,18]

The aim of this study was to evaluate the ability of a RADT to rule in or out a true link between the symptom of a sore throat and the test outcome while considering the potential of GAS carriers.

2. Materials and methods

Two groups of participants were recruited consecutively. The first comprised healthy controls. These were children aged 3–15 years presenting consecutively at the Mount Isa Hospital emergency department (ED) in northwest Queensland, Australia, for reasons other than infection, thus ensuring that a positive GAS RADT result in this group would represent asymptomatic carriage. The second group comprised patients with a sore throat. These were children aged 3–15 years presenting consecutively at the Mount Isa Hospital ED in northwest Queensland, Australia, for a sore throat. None of these children had previously had rheumatic fever.

Once consent was obtained, a throat swab was collected from each child. This was done using the Dacron swab provided with the test kit. The swab was sealed in a specimen bag, together with a data collection sheet and a signed consent form, put in an envelope, and stored in a refrigerator at approximately 6 °C outside the clinical area.

The study team processed the swabs within 72 h using the Alere Test Pack +Plus with OBC Strep A kit (Alere, Waltham, MA, USA). This test kit has shown a 95%[19] to 97%[17] sensitivity (the manufacturer quotes a 97% sensitivity) and a specificity of 95%[17] to 100%[19] to detect GAS. In this study the outcomes were compared with the assumption that the sensitivity of the point-of-care test was 95% and with the assumption that the sensitivity was 97%. The treating clinician was blinded to the point-of-care test result.

The intention was to collect up to 200 samples in each group, with an interim analysis after approximately 50% of samples had been obtained.

2.1. Statistical analysis

The etiologic predictive value (EPV) is a statistical method developed to link symptoms and signs to test findings, hence linking potential etiologic agents such as a bacterium, while taking carriers into consideration.[20] To calculate the EPV, it is necessary to have the proportion of positive tests among patients, the proportion of positive tests among a healthy control population, and the sensitivity of the test to find what it is designed to look for. This enables the positive and negative predictive values, including 95% confidence intervals, to be calculated in a situation where a gold standard for comparison is not present or is questionable and the population prevalence of GAS is previously unknown.[20] The influence of different assumptions for theta (the assumed ratio between the proportion of carriers of GAS among healthy individuals and those with a sore throat caused by a virus) was also explored.[21]

Ethics approval was granted by the Townsville Hospital and Health Service, Human Research and Ethics Committee (HREC/13/QTHS/260).

3. Results

From June 30, 2014 to February 27, 2015, 248 throat swabs were collected and examined within 72 h. Two parents refused the collection of swabs for the purpose of this study. Out of the 101 patients presenting with a sore throat, 26 (26%) tested positive for GAS. Only one (0.7%) of the 147 control patients had a positive test result. Statistical analysis showed both the positive and negative EPV to be high (Table 1). The confidence intervals in this interim analysis were deemed to be narrow enough and hence further data collection was cancelled.

4. Discussion

The main finding of this study was that both the positive and negative EPV indicated that this RADT can be used to both rule in and rule out a link between symptoms and GAS for the study population. However, this conclusion may not be valid in other circumstances where the prevalence of carriers or the proportion of patients having GAS is different. The incidence of GAS colonization of the pharynx in asymptomatic patients reported in the literature is controversial and ranges from less than 2% to 11%.[22] Some authors refer to GAS carriers as sources for recurrent infections and deem the rate of asymptomatic carriers to be as high

Table 1
Etiologic predictive value (EPV) of the tests[a]

Estimated sensitivity to find GAS	Estimation of theta[b]	Positive EPV	Negative EPV
0.97	1.0	98 (88–100)%	99 (98–99)%
0.95	1.0	98 (88–100)%	98 (97–99)%
0.97	1.1	98 (88–100)%	99 (98–99)%
0.95	1.1	98 (88–100)%	98 (97–99)%

GAS, group A Streptococcus.

[a] The EPV of tests states the probability that the test finding is linked to symptoms/signs while considering symptomatic carriers ill from another agent (such as a virus).

[b] Theta is the estimated prevalence of GAS among symptomatic patients ill from something other than GAS, usually a virus; 1.0 means the prevalence is the same as among the healthy individuals and 1.1 means a 10% higher prevalence than in asymptomatic healthy individuals.