

ORIGINAL RESEARCH

Point of care testing for group A streptococci in patients presenting with pharyngitis will improve appropriate antibiotic prescription

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Abstract

Objective: History, clinical examination and throat culture may be inadequate to rule in or out the presence of group A streptococci (GAS) infection in patients with sore throat in a remote location. We correlated the diagnostic accuracy for guiding antibiotic prescription of clinical decision and physiological scoring systems to a rapid diagnostic point of care (POC) test result in paediatric patients presenting with sore throat.

Methods: Prospective diagnostic accuracy study conducted between 30 June 2014 and 27 February 2015 in a remote Australian ED using a convenience sample. Among paediatric patients presenting with sore throat, the Centor criteria and clinical decision were documented. Simultaneously, patients without sore throat or respiratory tract infection were tested to determine the number of carriers. A throat swab on all patients was tested using a POC test (Alere TestPack +Plus Strep A with on board control),

considered as reference standard to detect GAS infection.

Results: A total of 101 patients with sore throat were tested with 26 (25.7%) positive for GAS. One hundred and forty-seven patients without sore throat were tested with one positive POC test result (specificity 99%; 95% CI 96–100). Positive predictive value for clinician decision-making for a positive GAS swab (bacterial infection) was 29% (95% CI 17–43), negative predictive value 78% (95% CI 63–88). Area under ROC for the Centor score was 0.70 (95% CI 0.58–0.81).

Conclusion: Clinician judgement and Centor score are inadequate tools for clinical decision-making for children presenting with sore throat. Adjunctive POC testing provides sufficient accuracy to guide antibiotic prescription on first presentation.

Key words: accuracy of antibiotic prescribing, Centor score, clinical reasoning, group A streptococci, pharyngitis, point of care testing.

Key findings

- Clinician judgement and Centor score are inadequate tools for decision-making.
- A POC test provides sufficient accuracy to guide antibiotic prescription.
- One out of four patients presenting with sore throat had a GAS infection.

Introduction

Invasive group A streptococci (GAS) infections include a wide range of conditions with different clinical presentations; patients may present in clusters and show different manifestations.¹ The global burden of GAS disease predominantly relates to two complications: acute rheumatic fever (ARF) and chronic rheumatic heart disease (CRHD). Estimates range from approximately 2 400 000² to 12 000 000³ cases of CRHD worldwide. Observations in the Northern Territory, Australia, showed an annual incidence of approximately 0.4% for ARF and 2% for CRHD, 32% of these in the age group of 35–44 years.⁴ The Indigenous population of the adjacent northwest of Queensland represents one of the highest incidences of ARF and related complications in the world with an annual incidence of up to 492/100 000 in children aged 4–15 years,⁵ correlating with a high proportion of residents living in remote communities and with

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Accepted 14 January 2016

low socioeconomic standard. It is consistent with findings from the Northern Territory.⁶ There is little evidence on the costs related to this disease burden. World Health Organisation (WHO) statements suggest that ARF and CRHD cause an additional socioeconomic burden especially in low-income countries.⁷ ARF and CRHD costs in the USA in 2002 were estimated to be approximately US\$1.9 billion,⁸ and in New Zealand, annual costs for admissions due to ARF and CRHD are as high as the hospitalisation costs for pneumococcal disease and *Haemophilus influenzae*-related otitis media combined.⁹

The prevalence of GAS among patients presenting with a sore throat ranges from close to 0% to 40%.^{10–12} While there is increasing suspicion and some evidence that ARF may also be related to chronic skin sores (pyoderma),^{4,13} the Australian guidelines⁴ focus primarily on respiratory tract infections as a cause of ARF and suggest primary prevention by ‘...treating GAS infection effectively to prevent the development of ARF in individuals’, also recommending secondary prevention with monthly benzylpenicillin injections.⁴ This has been expensive and not always effective, even if patients were compliant.¹⁴ Treating every patient presenting with a sore throat with antibiotics has been suggested for Indigenous communities in central and northern Australia, Maori and Pacific Islander people,¹⁵ but prescribing antibiotics for every sore throat is discouraged, citing risks of emerging antibiotic resistance.^{4,7}

While there are a large number of studies worldwide and several studies in the Northern Territories about the epidemiology of GAS pharyngitis, no study has been published that focuses on primary prevention and the treatment decision for patients with pharyngitis in remote northwest Queensland, a region with a high number of Aboriginal patients at risk for ARF and CRHD.^{4,5}

Clinical decision aides (Centor, Breese, McIssaac, Wald and Attia scores,¹⁶ WHO scoring system) have been suggested to rule in or out patients for antibiotic treatment of suspected GAS pharyngitis but have

not proven to be reliable enough to guide antibiotic prescription.^{3,11,16,17} Throat culture has been recommended for treatment decisions.¹¹ In an ED in a remote community, it is difficult to organise re-presentation or follow up of results including treatment modifications because many patients are travelling up to several hundreds of kilometres on gravel roads to be seen in the ED.

Among the patients presenting with a sore throat, we aimed to compare the performance of the Centor criteria and actual clinical decision-making to evaluate their correlation with the presence of group A streptococci.

Objective

The study compares the accuracy of methods for decision-making to guide antibiotic prescription on patients presenting to a base hospital ED in the most remote location in Queensland with a sore throat. Clinical decision for antibiotic prescription and Centor criteria were compared with a cheap and easy to use GAS antigen test kit.

Methods

Setting

The Mount Isa Hospital ED serves 50 000–60 000 residents, travellers and fly-in-fly-out workers in an area of 308 800 km². It is a Queensland Health Clinical Services Capability Framework Level 4 Department (Base Hospital Specialist Service) seeing 29 500–40 000 annual presentations. Of the presentations, 20–25% are paediatric patients; 40% are Indigenous patients.

Design

A single centre prospective diagnostic accuracy study was conducted at the Mount Isa Hospital ED in Queensland, Australia, using a convenience sample of patients presenting between 30 June 2014 and 27 February 2015 with and without sore throat. Data were prospectively collected, the treating clinician blinded for the swab results.

Participants

Children aged 3–15 years presenting with a sore throat were enrolled. Exclusion criteria were representation for a sore throat and already taking antibiotics. Simultaneously, children with no sore throat, presenting for other reasons than a respiratory tract infection and not taking antibiotics, were enrolled as a control group.

Measurements/Protocol

Symptoms and signs were prospectively registered on a standardised score sheet for each participant. For patients presenting with a sore throat, the clinician's impression of the cause (bacterial/viral/unsure), the treatment (whether antibiotics prescribed or not) and the four Centor criteria – tonsillar exudates, swollen tender anterior cervical node, lack of a cough and history of fever¹⁷ – were documented. In the Mount Isa Hospital ED, every patient is reviewed by a Senior Medical Officer (FACEM, FACRRM or FRACGP); thus, the study reflects the senior clinician's impression.

Presence of GAS was investigated using the Alere™ TestPack +Plus Strep A (Alere, Waltham, MA, USA) with on board control (OBC). The accuracy of several rapid antigen tests has been deemed sufficient for diagnosis and management of GAS infections,^{18,19} including the Alere™ TestPack +Plus Strep A with OBC that has been proven to perform with enough accuracy^{20,21} to be comparable with a throat culture.¹² It was therefore used as the reference standard for this evaluation. After obtaining the carer's informed consent, a throat swab was obtained with a Dacron swab (Alere). This swab was stored at 6°C until the test was performed. The study team processed the swabs within 72 h. Clinicians were blinded to the result of the swab.

Statistical analysis

Continuous variables were summarised using mean (standard deviation), while discrete variables were summarised using counts (proportion). The Student's *t*-test was used to calculate significance of difference between means, and the χ^2 test was used to calculate

significance of difference between proportions, except where value in a cell was less than 5, when the Fisher's exact test was used. Using the POC test results as the reference standard, clinical decision-making and Centor criteria were evaluated for specificity, sensitivity, predictive values and likelihood ratios to detect GAS infection and reported with 95% confidence intervals (CIs). The clinicians' impression (GAS infection or viral infection) and prescription of antibiotics were documented. Predictive accuracy of accumulative effect of these variables within the Centor score was assessed by measuring the area under a receiver operating characteristic (ROC) curve. All analyses were conducted using STATA v 11.0 (StataCorp, College Station, TX, USA). A *P*-value of <0.05 was considered to be statistically significant.

For the purpose of sample size calculation, we assumed a true positive rate of samples tested using the POC to be 99% and a minimum clinically important true positive rate of clinical decision-making to be 90%. Using 95% CI (two-sided alpha of 0.05) and power of 80%, the sample size estimated was 100 patients presenting with a sore throat.

The study was approved by the Townsville Hospital and Health Service Human Research and Ethics Committee (HREC/13/QTHS/260).

Results

There were 250 children aged 3–15 years screened, and 248 throat swabs collected. Two parents refused the collection of swabs. Among these 147 children presented without a sore throat (79 [54%] male, mean age of 8.3 (3.5) years, 71 (48%) Indigenous). Out of these, one POC test result was positive. Hence, the specificity of the POC to rule out true infection caused by GAS can be estimated to 99% (95% CI 96–100).

There were 101 patients included that presented with a sore throat (43 [43%] were male, mean age 7.9 years, 49 [49%] Indigenous; 52 were prescribed antibiotics). There were no differences in demographics between patients prescribed antibiotics and those that were not. Antibiotic

prescription was more common in the presence of tonsillar exudate and tender anterior cervical lymph nodes (Table 1). Twenty-six (26%) patients tested positive for GAS; 11 of these were not prescribed antibiotics. Except for one of these cases, this was consistent with the clinician's impression that the pharyngitis/sore throat was not of bacterial origin.

The positive predictive value for clinician decision-making for a positive GAS swab (bacterial infection) was 29% (95% CI 17–43), with a negative predictive value of 78% (95% CI 63–88). Specificity of clinical decision-making was 51% (95% CI 39–62), sensitivity was 58% (95% CI 37–77), a positive likelihood ratio of 1.17 (95% CI 0.78–1.75) and a negative likelihood ratio of 0.83 (95% CI 0.51–1.38). Performance of the Centor score to detect GAS infection showed

an area under ROC of 0.70 (95% CI 0.58–0.81) (Fig. 1).

Sensitivity, specificity, positive and negative likelihood ratios of different cut-point values for the Centor score are shown in Table 2. The association between Centor score and the number of patients with GAS positive is listed in Table 3. The positive predictive value for a Centor score of 1 point or more and positive GAS swab was 50% (95% CI 31–69), with a negative predictive value of 84% (95% CI 70–91).

Discussion

Patients presenting to the Mount Isa Hospital ED with a sore throat showed a high prevalence of GAS infection (26%), resulting in a high positive predictive value of the POC test. While there have been high GAS prevalence found in the USA (20–30%)¹² and

TABLE 1. Demographics and clinical characteristics of patients presenting with a sore throat

	No antibiotics prescribed (<i>n</i> = 49)	Antibiotics prescribed (<i>n</i> = 52)	<i>P</i>
Age (years)	7.6 (3.2)	8.5 (4.3)	0.22
Male sex	20 (41%)	23 (44%)	0.73
Race			0.95
Caucasian	23 (47%)	23 (44%)	
Indigenous	23 (47%)	26 (50%)	
Other	3 (6.2%)	3 (5.8%)	
Tonsillar exudate	2 (4.1%)	15 (29%)	<0.01
Tender anterior cervical lymph nodes	12 (25%)	24 (46%)	0.02
Absence of cough	8 (16%)	13 (25%)	0.28
Fever	17 (35%)	21 (40%)	0.55
Clinical diagnosis			<0.01
Uncertain	1 (2.0%)	7 (14%)	
Strep throat	1 (2.0%)	22 (42%)	
Other bacterial	0	4 (7.7%)	
Viral	47 (96%)	19 (37%)	
Centor criteria score			0.05
0	22 (45%)	12 (23%)	
1	18 (37%)	21 (40%)	
2	7 (14%)	8 (15%)	
3	1 (2.0%)	8 (15%)	
4	1 (2.0%)	3 (5.8%)	

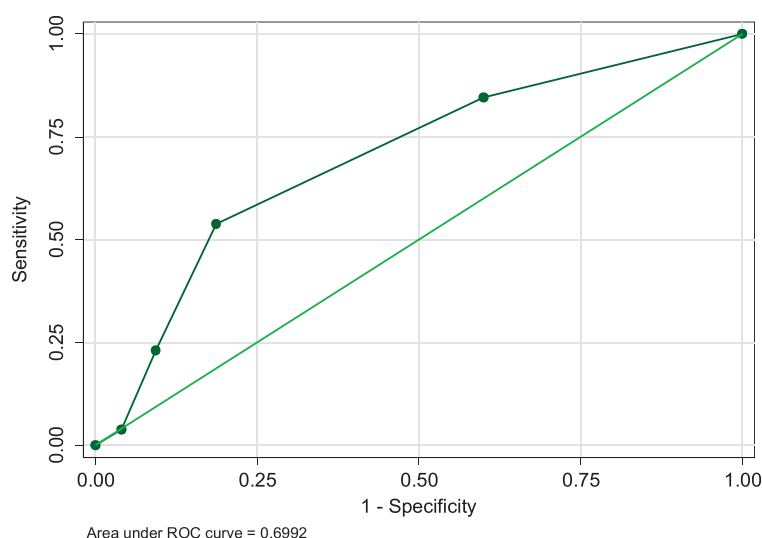


Figure 1. Receiver operating characteristic curve (1 – specificity) for Centor score to predict group A streptococci positive swab. The four Centor criteria are: tonsillar exudates, tender swollen anterior cervical nodes, lack of a cough and history of a fever (one point for each positive criterion).

Europe (30–40%),²² studies in the northern parts of the Northern Territory show a very low prevalence of GAS infection (0.1%).¹⁰ This alerts to the fact that the prevalence documented in studies in other areas of Australia may not apply to northwest Queensland.¹⁰

The positive predictive value of the clinicians' decision to prescribe antibiotics was low, with prescription of antibiotics being appropriate in less than one out of three patients. Importantly, in about one out of three patients, no antibiotics were prescribed despite the presence of a GAS pharyngitis (positive GAS POC test). The Centor criteria showed a similar result in detecting GAS infections. This finding is consistent with the results of the study defining the Centor variables in

1981;¹⁷ the area under ROC is also comparable with the one reported for the Attia score.²³

The incidence of GAS colonisation of the pharynx of asymptomatic patients in literature is controversial and ranges from less than 2% to 11% per year.^{13,24} The positive rate of GAS swabs in the control group was low (<1%) much lower than found in the Northern Territory (3.7%).¹⁰ Therefore, it is unlikely that they have confounded the results, implying that the test has some value for ruling in patients with positive GAS swab for antibiotic treatment in a setting similar to Mount Isa with high prevalence of GAS pharyngitis and low prevalence of asymptomatic carriers. However, in settings with lower prevalence and higher carrier rates, the positive

TABLE 3. Centor score and throat swab result

Centor score	Swab negative	Swab positive	Total
0	30	4	34
1	31	8	39
2	7	8	15
3	4	5	9
4	3	1	4

predictive value of the POC test will be too low to rule in patients for antibiotic treatment.

Clinical identification of GAS throat infection may be challenging,²⁵ and a high number of patients may be treated inadequately, including both unnecessary antibiotic prescriptions and patients belonging to high-risk groups left untreated. Clinical decision rules have not shown appropriate predictive values to be deemed sufficient for clinical decision-making alone whether or not to treat a sore throat as a GAS infection.^{3,12,26}

Prescribing antibiotics to every patient presenting with a sore throat is not recommended because of potential side effects and the risks of increasing antibiotic resistance.^{4,7,27} Focussing on patients with severe pharyngitis alone may increase the positive predictive value of a decision-making rule, but would focus only on a small subgroup of patients,²⁷ leaving a large proportion inadequately treated and at risk of future complications. Use of an appropriate POC test appears to improve the number of appropriately treated patients presenting with a sore throat, not only in avoiding unnecessary antibiotic

TABLE 2. Performance of the Centor score at different cut-points

Cutpoint	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio
≥0	100 (95–100)	0.0 (0–13)	74 (65–82)	—	1.0 (1.0–1.0)	—
≥1	85 (65–96)	40 (29–52)	88 (73–97)	33 (22–45)	1.4 (1.1–1.8)	0.39 (0.15–0.99)
≥2	54 (33–73)	81 (71–89)	50 (31–69)	84 (73–91)	2.9 (1.6–5.2)	0.57 (0.37–0.87)
≥3	23 (9.0–44)	91 (82–96)	46 (19–75)	77 (67–86)	2.5 (0.9–6.7)	0.85 (0.68–1.1)
=4	3.9	96	25 (0.63–81)	74 (64–83)	0.96 (0.10–8.8)	1.00 (0.92–1.1)

treatment but also in appropriately treating those with a positive GAS result.

Utilising a GAS POC test is expected to reduce long-term costs by lowering the disease burden of complications of streptococcal infections, especially ARF and CRHD. Antibiotic treatment with penicillin will cost approximately AUD \$10 for every unnecessary penicillin prescription (not including costs for potential side effects). Performing a GAS POC test will cost approximately AUD\$4 per test and will be outweighed by the cost savings due to avoiding unnecessary antibiotic prescriptions in regions of low prevalence of GAS pharyngitis.

Culture has been deemed the gold standard, not only for diagnostics in clinical practice but also for rating other diagnostic methods.^{11,18} However, a throat culture is much more expensive than a POC test, and sensitivity of throat cultures is not higher than sensitivity of modern POC tests. Polymerase chain reaction (PCR) testing has shown positive results on patient samples testing positive with a rapid antigen test but negative with culture, demonstrating that sensitivity of culture is not 100%.²⁸ The later generations of rapid antigen detection tests are cheap, easy to use and have been more sensitive than culture when assessed against PCR as the standard,^{28,29} also demonstrating negative predictive values around 99%.³⁰ Therefore, a POC rapid antigen test is an ideal tool to support decision-making – not only in EDs but also in other primary care settings.

Limitations

It is a single centre design study using a small convenience sample. However, this small study demonstrates that testing and treatment decisions need to be tailored to the region. A larger, ongoing collection of samples from patients in the region presenting with sore throat is recommended, including following up those with sore throat and positive initial test to gain more information about chronic GAS colonisation and asymptomatic GAS carriers; however, it would need appropriate funding.

Longer-term follow up was not available and would have been useful

to define the clinical relevance and outcome of treatment linked to the test results, especially in regards to avoiding representations and complications. The value of a POC test in comparison with clinician decision-making or clinical decision rules may differ between populations.

Conclusion

Clinical decision-making and utilisation of clinical decision rules are inadequate to guide treatment of children presenting with sore throat.

The use of a POC test is indicated to improve the accuracy of antibiotic prescribing for children presenting with sore throat in the setting of a remote ED.

Acknowledgements

We thank Alere Australia for providing the test kits at no cost without being involved in design, conduction or interpretation of the results of the study. We also thank all staff of the Mount Isa Hospital ED, children and parents for supporting the present study.

Competing interests

None declared.

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