Carrier rates of group A streptococci in the Australian wet tropics and their impact on the clinical usefulness of throat swabs

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Background and objective
Rapid point-of-care tests (POCT) are likely to assist with the detection of group A streptococci (GAS), but their usefulness is determined by the presence of carriers of GAS. This is insufficiently explored in the wet tropics.

Methods
This study included 77 patients attending primary care in the wet tropics complaining of a sore throat, and 49 healthy controls. Carrier rates of GAS and the positive and negative etiological predictive values (P-EPV and N-EPV, respectively) of a POCT were calculated.

Results
The carrier rates were 8.3% among healthy children and 2.7% for adults. The P-EPV for children was 71% (95% confidence interval [CI]: 0.0–100%) and for adults it was 85% (95% CI: 0.0–100%). The corresponding N-EPV was 99% (95% CI: 95–100%) for children and 99% (95% CI: 98–100%) for adults.

Discussion
N-EPV, ruling out GAS, was sufficiently high with narrow CIs to allow for defining a stopping rule to avoid unnecessary antibiotic prescribing.

AN ACUTE SORE THROAT is a common reason for visiting a primary healthcare provider.[1–3] Commonly, this is caused by viruses or group A beta-haemolytic streptococcus (GAS), but other potentially pathogenic bacteria might also be involved.[4] Existing guidelines for the management of patients with a sore throat focus on GAS.[5,6]

Judicious use of antibiotics balanced with antibiotic stewardship has become an important part of modern medicine. The use of antibiotics varies across the world and only a few countries use more antibiotics per person than Australia.[7] The appropriate use of antibiotics might prevent rheumatic fever caused by GAS.[4] Although it might be perceived that the relative high incidence of rheumatic fever in Australia explains its high use of antibiotics, there are few populations at risk for rheumatic fever in Australia and not enough to explain the country-wide high prescribing of antibiotics.

Clinical judgement misses 42% of true GAS sore throat infections and at the same time results in treating mainly viral sore throats.[8] The Australian Therapeutic guidelines[9] recommend following clinical criteria similar to the Centor criteria, but their sensitivity is only 49%,[10] missing roughly 50% of all sore throats caused by GAS. A study in Mt Isa, Australia, showed that applying the Centor criteria missed 74% of true GAS infections resulting in the treatment of mainly viral infections with antibiotics.[8] Hence, it seems likely that in Australia we currently prescribe antibiotics mainly for viral infections, leaving many GAS infections untreated, potentially contributing to an unnecessary high incidence of rheumatic fever in high-risk settings. A strategy incorporating the use of throat swabs in selected patients appears to be warranted.[11]

Throat swabs sent to a microbiological laboratory for analysing the presence of GAS are hampered by the very long delay in obtaining results.[12] However, modern point-of-care tests (POCT), delivering a result in minutes, are more useful.[8,13,14] We have been able to show that the use of a modern high-quality POCT, using antigen detection technology at a cost of $5 per test for GAS, significantly increases the diagnostic accuracy, leaving hardly any GAS infection untreated and at the same time significantly reducing the proportion of unnecessary antibiotic prescribing.[8,15] Traditional tests, commonly used outside Australia, are now gradually being replaced by rapid POCTs using lamp technology, a kind of polymerase chain reaction (PCR) technique, that has a higher sensitivity and specificity than conventional culture techniques.[16] These modern tests kits are more expensive than the simpler rapid antigen detection tests and,

in contrast to the rapid antigen detection tests, also require the purchase or leasing of a device.

The usefulness of modern POCT to detect the presence of GAS depends on the carrier rates of the pathogen among individuals ill from something else, such as a virus.[17] It has been shown that a negative test is always, in any setting, useful to rule out the tested potential pathogen as causing the symptoms.[13] However, the usefulness of a positive test to rule in that the potential pathogen actually explains the current symptoms depends upon the carrier rate of the potential pathogen.[8,13,17,18] Hence, knowing the carrier rate is important when evaluating the clinical usefulness of POCT aimed to detect the presence of GAS.

There are studies establishing the carrier rate of GAS in a temperate climate[19] and in the dry tropics, such as Mt Isa[8] and the Northern Territory.[20] The carrier rate of GAS in the dry tropics seems to be low.[8] One study from the central division of Fiji, belonging to the wet tropics, established the carrier rate of GAS among children to be 6%.[21] No publications so far have evaluated the carrier rate of GAS in the Australian wet tropics. Hence, the carrier rate of GAS in the Australian wet tropics remains to be established. The clinical usefulness of these new POCT is uncertain before this carrier rate is established. This problem is particularly relevant to Far North Queensland. Hence, the aim of this study was to establish the carrier rates of GAS in an Australian wet tropic setting and calculate its impact on the usefulness of these POCTs.

Methods

A throat swab was prospectively collected from patients attending primary care with a main complaint of a sore throat, as well as from healthy controls. This information was used to establish carrier rates of GAS and the positive and negative predictive value of presence or absence of GAS.

Patients were recruited as part of a larger study,[15] approved on 5 March 2018 by the Townsville Hospital and Health Service Human Research Ethics Committee (Registration no. HREC/17/QTHS/246). Healthy controls were recruited over the same time interval and from the same geographical area as patients after approval (7 February 2018) from the James Cook University Human Research Ethics Committee (Registration no. H7283).

Inclusion criteria

Patients attending the Hinchinbrook Health Care Clinic in Ingham, Queensland (one of the wettest places in Australia), with a main complaint of an acute sore throat were labelled as 'cases'. Patients presenting for other reasons to the same healthcare clinic were labelled 'healthy controls' if they fulfilled the following criteria: no history of any infection in the preceding 30 days; no history of antibiotic use in the preceding 30 days; no history of taking medication known to influence the immune system in the preceding 30 days, such as immunosuppressive medication and systemic corticosteroids apart from topical steroids; no known chromosomal aberration, such as Down syndrome; and no known illness that might influence the immune system, such as malignancies or diabetes.

All participants were provided with written and verbal information and given the opportunity to ask questions. All participants (or carers, on behalf of children) signed a consent form approved by the relevant human research ethics committee.

Data collection

A simple one sheet, one-page registration tool was used to collect the following de-identified patient information: age, gender, inclusion criteria stated above, outcome of a test for the presence of GAS and, for patients also, clinical signs allowing calculation of their Centor score.

Testing for the presence of GAS

A throat swab was taken and analysed as soon as possible at the general practice clinic using the Abbott IDNow device. This diagnostic test used loop-mediated DNA amplification. This can be considered as 'isothermal PCR' with similar test characteristics as PCR but without the possibility for quantification. This test has a 99% sensitivity and 99% specificity to detect GAS compared with conventional PCR.[16] This test was approved by the Australian Therapeutic Goods Administration (TGA) for use in patients with a sore throat. The clinic received education from Abbott to run the test. The test was easy to manage and the training was done via video conferencing. All staff received structured training via video link on how to collect samples and use the test; they had to demonstrate competence. This session took approximately one hour. The throat swab was obtained by a trained nurse and processed by the same nurse.

Outcome measures and statistical analysis

The outcome measures were as follows: the proportion of cases and controls harbouring GAS; the probability that finding a GAS was related to the patient's symptoms (positive predictive value of the test); and that a negative test indicating absence of GAS ruled out a link between GAS and the symptoms (the negative predictive value of the test). All patients aged 3–16 years were defined as children; patients aged >16 years were defined as adults.

We used a specific statistical technique, the etiological predictive value (EPV), which allows adjustment of predictive values for the impact of carriers of GAS being ill from something else while harbouring GAS, so-called carriers.[17,18,22–24] The positive EPV (P-EPV) estimates the probability for a link between the presence of GAS and the symptom of a sore throat. The EPV is presented as a percentage ranging from 0% to 100%. If the POCT indicates the presence of GAS equally often in patients as in controls, the point estimate of the P-EPV will be 0% with a 95% confidence interval (CI) from 0.0% to an upper limit determined by the sample size. The point estimate of P-EPV will gradually approach 100% when the difference in the prevalence of GAS between patients and controls increases. Similarly, the negative EPV (N-EPV) expresses the probability that the patient's symptoms are not related to GAS when the POCT is negative. The EPV requires input of the sensitivity of the test to detect GAS. Although this test has a 99% sensitivity, we assumed a more conservative 95% sensitivity when calculating the EPV.

The EPV is a clinically useful estimate that is easy to use for clinicians less experienced in statistics. The EPV has already been used by other researchers as a measure of determining the probability for disease when the carrier rates for the causative agent for that disease need to be considered.[13,25,26]

Results

Between April 2018 and February 2019, 77 cases (56 adult, 21 children; Table 1) were recruited to the study. During the same time, we recruited 49 healthy controls (37 adults, 12 children; Table 1). Among adult cases, there were 23 men and 33 women; among child cases, seven were male and 14 were female. For healthy controls, there were 14 male and 23 female adults and seven male and five female children.

The carrier rate of GAS among healthy controls was 8.3% (95% CI: 1.5–35%) for children and 2.7% (95% CI: 0.48–14%) for adults (Table 1). Compared with the healthy controls, a higher proportion of patients was positive for the presence of GAS, with a prevalence of 24% (95% CI: 8.2–47%) for children and 16% (95% CI: 7.6–28%) for adults.

The P-EPV (probability for a true link between findings of GAS and the symptom of a sore throat) was 71% (95% CI: 0.0–100%) for children and 85% (95% CI: 0.0–100%) for adults. The corresponding N-EPV (ruling out GAS as linked to the symptom of a sore throat) was 99% (95% CI: 95–100%) for children and 99% (95% CI: 98–100%) for adults. Only testing patients with three to four Centor criteria resulted in a P-EPV of 87% (95% CI: 0.0–100%) for children and 98% (95% CI: 47–100%) for adults. The corresponding N-EPV for patients with three to four Centor criteria was 97% (95% CI: 57–100%) for children and 93% (95% CI: 0–100%) for adults.

Discussion

The carrier rates in this study were 8.3% for children and 2.7% for adults. These figures are similar to previously published data[26,27] indicating that the wet tropics in Australia do not differ dramatically from other settings. Important is that the N-EPV, ruling out an acute GAS infection, was very high (99%) with narrow CIs, making a negative POCT very reliable and clinically useful.

It is often perceived that because the POCT cannot distinguish between carriers and patients ill from GAS it renders it useless. Our study confirms that if a high-quality, appropriately used POCT shows no presence of GAS, it has a very high negative predictive value, regardless of the proportion of carriers of GAS.[13,17,18,22] The presence of carriers only influences the clinical value of a POCT positive for GAS (the positive predictive value). However, in most patients the POCT will be negative and because this result is very reliable, it can clinically be used as a stopping rule to significantly reduce inappropriate antibiotic prescribing.[13] Although the testing of all patients seems reasonable in high-risk settings, a recent study concluded that in a setting with low risk for rheumatic fever it would be enough to test as little as 10–15% of all patients attending with a sore throat, making the use of POCT feasible.[4]

Strengths and limitations

Our prevalence figures are similar to previous studies,[28,29] stating a higher prevalence in children than in adults. However, our CIs are wide, and to obtain narrow CIs for the prevalence of GAS and P-EPV would have required a larger number of participants.

Recruitment was slower than anticipated and we had to stop recruitment when our test kits expired because there was no funding to purchase more test kits. Hence, we included fewer individuals than intended. The sample size was insufficient to reliably estimate point prevalence as well as the P-EPV of a positive test (rule-in). The sample size we managed to include was sufficient to estimate the N-EPV of a negative test (rule-out) with narrow CIs. This is fortunate because most tests will have a negative outcome, making most test outcomes informative and clinically useful.

In a setting with low risk for rheumatic fever, it is recommended to only test patients with three to four Centor criteria.[4] Few patients in our study had three to four Centor criteria, so the CIs for P-EPV and N-EPV in these selected patients became very wide.

Conclusion

This study confirms that a throat swab can be used to rule in GAS as the aetiological agent in adults due to the low rate of carriers among adults. In children, a throat swab is not as useful to rule in GAS as the aetiological agent. The main conclusion is that a modern POCT showing no presence of GAS is sufficient as a stopping rule to stop incorrect antibiotic prescribing.[4,14] It is recommended that further larger studies of GAS carrier rates in the wet tropics be conducted to verify our findings; alternatively, results from several studies could be compiled in a systematic literature review with meta-analysis.

Table 1. Findings of group A streptococci

	Patients				Healthy controls	
	0–4 Centor criteria[A]		3–4 Centor criteria[A]		Positive test	Negative test
	Positive test	Negative test	Positive test	Negative test		
Children (age 3–16 years)	5	16	2	3	1	11
Adults (age >16 years)	9	47	4	3	1	36

Data show the number of patients in each group.

[A]The Centor criteria are a combination of four clinical signs in patients with an acute sore throat: a history of fever, the absence of cough, tonsillar exudates and swollen tender anterior lymph nodes. Each sign is awarded a score of 1. Hence, scores for the Centor criteria may range from 0 to 4, with scores of 0, 1, 2, 3 and 4 indicating a 2.5%, 6.5%, 15%, 32% and 56% probability, respectively, of finding group A streptococci in a throat swab.

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