Point-of-care tests for group A streptococcus

Horizon Scan Report 0041

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Clinical Questions:

In primary care, what is the comparative accuracy of rapid point-of-care tests for group A streptococcal pharyngitis compared to conventional throat culture in patients with sore throat?

In patients presenting to primary care with sore throat, what is the diagnostic value and impact of performing a rapid point-of-care Streptococcal A test together with clinical scoring, compared with scoring alone?

Background, Current Practice and Advantages over Existing Technology:

Background:

Although generally self-limiting, a recent study estimated that up to 60% of patients presenting with sore throat in UK primary care are prescribed antibiotics [1], despite the fact that most cases of sore throat are caused by viruses [2] and the best evidence indicating only modest symptomatic benefit and reduction of suppurative and non-suppurative complications in cases of a bacterial aetiology [3].

Group A β-haemolytic streptococcus (GABH) is the most common causative pathogen of bacterial pharyngitis, with estimates of 15-30% of sore throats in children and 10% in adults [4]. GABH is a Gram-positive coccus which is an obligate commensal/pathogenic colonist of humans. A meta-analysis of 18 studies including 9662 patients reported an estimate of asymptomatic commensal GABH carriage amongst healthy children of 12% (95% CI: 9-14%) [5], highlighting the difficulty in distinguishing an active infection from asymptomatic carriage in routine clinical practice.

Although GABH pharyngitis is self-limiting in most cases, a considerable level of anxiety remains related to suppurative and non-suppurative sequelae that were historically common but now mostly rare in developed world contexts. Suppurative complications of infection include common and typically mild conditions such as acute sinusitis and otitis media [4], and rarer but more serious conditions such as peri-tonsillar abscess (quinsy), cervical lymphadenitis and mastoiditis [6]. Non-suppurative complications include acute rheumatic fever (ARF) with its chronic sequela rheumatic heart disease (RHD), scarlet fever, post-streptococcal glomerulonephritis, toxic shock syndrome, and potentially, paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) [7]. The prevention of complications is frequently cited as a justification for diagnostic testing and treatment. Antibiotic treatment has been shown to be effective in reducing complications of sore throat, for example a reduction of the occurrence of acute rheumatic fever

compared with placebo control groups estimated by systematic review (RR 0.27; 95% CI 0.12 to 0.60) [3]. However the authors of this review highlighted that most of the trials concerning acute rheumatic fever were conducted in the 1950s when incidence was far higher than at present and that currently in high income countries the number needed to treat to benefit is likely to be high, whereas in lower income countries with higher incidence, the numbers needed to treat to benefit will be correspondingly smaller.

Current Practice and Advantages over Existing Technology:

Diagnosis of GABH pharyngitis in UK primary care is typically performed by clinical examination, with the application of the Centor criteria [8] currently recommended in NICE and SIGN guidance [9, 10]. The Centor criteria are summarised in Appendix 2. Although application of the Centor criteria is recommended to select patients for whom antibiotics should be prescribed, a recent review of clinical guidelines and survey of UK GPs suggested that only 19% of respondents applied the criteria in patients presenting with sore throat [11]. Other scoring systems have been developed, for example the McIsaac Score [12] or FeverPAIN [13] (see Appendix 2), the latter having greater diagnostic accuracy than the Centor criteria. Neither NICE [4] nor SIGN [10] currently recommend the routine use of throat culture or rapid point-of-care tests to confirm a diagnosis of GABH infection, citing poor sensitivity of point-of-care tests.

Contrasting guidance is provided in the Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis, issued by the Infectious Diseases Society of America [14]. This guideline advocates throat swabbing and testing by rapid point-of-care test and/or culture where GABH pharyngitis is suspected, with follow-up culture for children in whom the rapid point-of-care test was negative. The guidance also suggests that there is no indication for testing of children of <3 years of age, due to GABH pharyngitis being uncommon in this group with an associated lower risk of acute rheumatic fever.

A review of international guidelines for the management of acute pharyngitis in adults and children [15] identified two opposite approaches, with some countries advocating no routine diagnostic testing (the UK, the Netherlands and Belgium), versus others that do (North America, Finland and France). The review suggests that the major issue related to GABH infection is rheumatic fever, which although rare in developed countries is considered to pose sufficient risk to justify testing and treatment by advocates. The advantages of rapid point-of-care tests over conventional culture is rapid rule-in/out of GABH presence (approximately 10 minutes) versus an overnight delay or longer with culture. The rationale of those who do not advocate testing is based around the low incidence of rheumatic fever in developed countries and the costs and harms associated with routine testing and treatment with antibiotics [15].

Details of Technology:

The table in Appendix 1 provides an overview of 20 group A streptococcus tests identified.

The majority of currently available devices detect the presence of GABH antigen in aqueous extracts prepared from throat swabs with proprietary extraction buffers. The time taken for tests to yield results ranges from 5 minutes (majority of tests) to ≤ 7 minutes (Orion Diagnostics, QuikRead go® Strep A), although this does not usually include the time required to take and process the sample

prior to application to the device. In comparison, conventional throat swab and subsequent culture on blood agar in a laboratory normally takes from 24 – 48 hours [16]. The majority of the tests listed in Appendix 1 are small disposable lateral flow devices which could be carried in a physician's case during home visits or used in the surgery with no additional equipment requirement, save for the associated sample preparation materials (also portable). The exceptions (Quidel Sofia Strep A Fluorescent Immunoassay (FIA); Becton Dickinson BD Veritor System™ - rapid detection of GAS; Orion Diagnostics QuikRead go® Strep A) are accompanied by a hand-held or table-top reading device and may thus be more practically deployed in a surgery.

All of the point-of-care devices identify the GABH surface antigen (with the exception of the molecular test detailed below), however the specific target epitopes are not typically specified by manufacturers. The majority of devices utilise an immunochromatographic assay which yields a colorimetric change in the results pane of the device in the presence of the antigen, which can be read directly or using a small machine. In the case of the Quidel Sofia Strep A Fluorescent Immunoassay (FIA), fluorescently conjugated antibodies bind and fluoresce in the presence of the GABH antigen. Fluorescence is read and interpreted by the Sofia bench-top unit.

A number of molecular based tests are currently available, which employ isothermal or conventional PCR amplification of pathogen specific sequence. Although highly sensitive and specific, molecular tests generally have a much greater time to result than rapid antigen detection tests (approx. 60 mins) and do not readily fit into the current model of UK primary care provision. Hence, the only molecular test considered here is the Alere™ i Strep A test which yields results in 8 minutes or less and is conducted using a small desktop unit, the Alere™ i platform.

Patient Group and Use:

- Rapid point-of-care GABH tests are typically marketed for ruling in or out the presence of GABH in throat swabs taken from patients who present with sore throats to ambulatory care.

Importance:

Sore throat is a common cause of attendance in UK primary care, with an estimated 60 visits per 1000 patients per year [4]. However evidence obtained within the UK healthcare system suggests that rapid point-of-care tests for GABH have no significant benefit over and above the use of a clinical prediction rule in terms of complications or prescription of antibiotics [13].

The importance of rapid point-of-care tests for GABH is context-dependent, with perhaps a greater need in developing world healthcare where serious complications of GABH infection remain common [17] and where pathology laboratory services may be limited. Although rare in developed regions, acute rheumatic fever and rheumatic heart disease remain the cause of a significant burden in terms of morbidity and mortality in developing countries and in particular demographic groups within developed countries (i.e. some indigenous and migrant populations) [18-20]. The link between acute rheumatic fever and economic status is further illustrated by the disparate prevalence of the condition between the relatively affluent and the poor within the same geographical region (e.g. South Africa) [17].

Rapid point-of-care tests do not currently provide any information concerning the virulence of the infecting strain [21]. Certain strains of GABH have been clearly associated with historical outbreaks of acute rheumatic fever [21]. There would be greater utility if rapid point-of-care tests can be developed which have the capacity to discriminate between virulent and avirulent strains, particularly given that GABH can be present asymptomatically [5] resulting in false positive test results [22].

Previous Research:

Accuracy compared to existing technology

Two systematic reviews with meta-analyses published in 2014 [23, 24] assessed the accuracy of rapid point-of-care tests for GABH. In both reviews bacterial culture from throat swabs was defined as the reference standard, analysing data from 48 [23] and 59 studies [24], respectively. This report will concentrate on assays which employ lateral flow immunoassays and immunochromatographic technologies, together with a single molecular test which can be completed within a similar timeframe (see previous justification in Details of Technology). The review of Lean et al. covered accuracy studies on the Alere Acceava® Strep A Dipstick, Quidel QuickVue+ Strep A Test, Quidel QuickVue In-Line Strep A Test, OSOM® Strep A Test, and the DectraPharm Streptatest. The review of Stewart et al. covered studies on the Alere Acceava® Strep A Dipstick, Quidel QuickVue+ Strep A Test, Quidel QuickVue In-Line Strep A Test, Quidel Quickview Dipstick Strep A Test, OSOM® Strep A Test, and the DectraPharm Streptatest 1.

Summarised accuracy data extracted from the two reviews are detailed in Table 1. The two reviews yielded similar accuracy values for paediatric populations and a mixed population with moderate sensitivity and high specificity; however the second review claimed a higher sensitivity estimate for adult strata, albeit with some overlap of the confidence intervals for the paediatric population.

Table 1. Summary diagnostic accuracy data obtained from two systematic reviews with meta analyses

Review	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)	Population Constituents
[23]	84% (80 to 88%)	96% (94 to 97%)	Mixed
	85% (80 to 89%)	97% (95 to 98%)	Paediatric
[24]	91% (87 to 94%)	93% (92 to 95%)	Adult
	86% (85 to 87%)	96% (95 to 96%)	Paediatric

A study of 892 children subsequent to the systematic reviews assessed the accuracy of the Quidel QuickVue Strep A Cassette test in children (0 – 17 years), with conventional culture on blood agar as reference standard [16]. Sensitivity and specificity of the point-of-care test were 59.5% and 97.2% respectively. Stratification of children by age demonstrated that accuracy was similar in children aged 0-6 years versus older children.

A single multicentre prospective trial has assessed the Alere™ i Strep A molecular test [25]. The trial recruited subjects of all ages across healthcare outlets in the US who presented with sore throat and symptoms of pharyngitis. The study compared the Alere™ i Strep A test against conventional culture

on blood agar as the reference standard, with reported sensitivity and specificity of the index test of 96.0% and 94.6% respectively.

Evidence presented in the aforementioned systematic reviews and subsequent studies suggest that in general lateral flow immunoassay and immunochromatographic rapid point-of-care tests for GABH appear to be more useful for rule in rather than rule out due to high specificity but poorer sensitivity, and that this is particularly so in the paediatric population. Therefore point-of-care tests might be used to reinforce the decision to prescribe treatment, but may not sway a doctor's decision away from prescription should a test be negative. In contrast, the Alere i Strep A test has achieved a high level of sensitivity and specificity in the single study reported [25] and may thus provide a superior alternative to the other devices reviewed here, allowing this test to be used confidently for both rule-in and out by physicians. Conclusions regarding the Alere i Strep A test come with the caveat that the approximately 8 minute run time of the test would not readily fit into the current model of primary care appointments in the UK, thus limiting its utility.

Impact compared to existing technology

A prospective observational study conducted in Spain on 196 adult patients in general medicine outpatient clinics who presented with suspected streptococcal pharyngitis examined the interaction between point-of-care GABH test use and antibiotic adherence. The study recruited patients into the study who fulfilled three or four of the Centor criteria, prior to and following the introduction of a rapid point-of-care test. Physicians were advised not to prescribe antibiotics with negative tests, however they had freedom to decide whether to test at all and whether or not to prescribe antibiotics (it was not possible to ascertain from the study whether the non-test group were all recruited prior to the introduction of the point-of-care test, or whether some were recruited post introduction where the physician decided against use). The results suggested that patient adherence to prescribed antibiotic regimes was significantly higher (p < 0.01) in the group which received the point-of-care test (n = 80; 80.1% and 88.1% adherence for thrice-daily and twice daily dosing regimens respectively) than those assessed on clinical criteria alone (n = 116; 70.8% and 76.5% adherence for thrice-daily and twice daily regimens respectively) [26].

Retrospective evaluation of the implementation of a rapid GABH point-of-care test in primary care in an undefined population in Austria suggested that the introduction of the diagnostic test had a small but significant influence, reducing the relative total antibiotic prescription frequency from 17.1 to 16.4% [27].

A systematic review and meta-analysis of clinical prediction rules, their variables, and their efficacy in the diagnosis of streptococcal pharyngitis of studies in 10523 children between 1975 and 2010 concluded that some of the clinical prediction rules examined had similar performance in rule-out of GABH pharyngitis as some rapid point-of-care tests, but were insufficiently effective to rule-in (low specificity) GABH infection [28]. The authors concluded that only the Joachim score (see Appendix 2 for details of the score) was both sufficiently accurate and suitably validated to be used to rule out GABH in children (LR- 0.3 (95% CI 0.2 to 0.5)), although they expressed concerns related to the utility of the score given the large number of variables (9) to be considered by the physician. Given the capacity of clinical prediction rules to rule out GABH pharyngitis, the authors speculated that the most optimal strategy may be for clinical prediction rules to guide the use of rapid point-of-care tests for GABH in children, so as to confirm GABH presence in those where clinical prediction rule

scores do not rule out infection. The study also concluded that clinical prediction rules could be used by those clinicians who do not utilise point-of-care tests, in order to rule out GABH infection and reduce antibiotic prescription [28].

More recently, a randomised controlled trial conducted in UK primary care with 631 participants aged ≥3 years [13, 29] examined whether a simple clinical prediction rule (FeverPAIN – see Appendix 2) in isolation versus in combination with the targeted use of a rapid point-of-care test for GABH, and empirical delayed prescription of antibiotics, had an impact on antibiotic use and outcomes in patients presenting with acute sore throat in primary care [13, 29]. The results of the trial suggested that both the clinical prediction rule and the clinical prediction rule + GABH point-of-care test combination had the capacity to moderately improve symptom control (improvement of scored symptom severity in days 2 – 4) and reduce antibiotic use when compared with the delayed antibiotic prescription group (29% and 27% lower antibiotic use for the clinical prediction rule and the clinical prediction rule + GABH point-of-care test groups respectively). A qualitative survey of a small cohort of patients (n=9) which utilised semi-structured face-to-face and telephone interviews indicated that the use of rapid point-of-care tests for GABH was well received [29]. Patients reported that they were reassured by the test, felt that availability of point-of-care tests would not influence their decision to see their GPs for sore throat, and patients voiced a preference not to receive antibiotics unless required, which they felt was supported by the use of point-of-care tests.

Health Economics:

Health economics analysis of the aforementioned HTA report [29] concluded that within the context of the NHS, of the three groups assessed (delayed prescription of antibiotics, clinical prediction rule guided use of GABH point-of-care test, and clinical prediction rule alone), the latter was the most likely to be cost effective both in terms of cost per point change in symptom score and cost per Quality of Life Year gained.

An earlier exercise compared six strategies to diagnose and manage acute pharyngitis in a Spanish paediatric population using a decision tree model and taking a payer's perspective. The strategies included treat all, clinical scoring using modified Centor criteria, rapid point-of-care testing, conventional culture, rapid test and conventional culture, and Centor-guided use of rapid point-of-care testing. The test accuracy and probability data fitting parameters of the model came from a literature search but the data sources were not reported clearly [30]. Effectiveness of intervention was calculated as the proportion of subjects cured without complications of the disease or treatment (penicillin). This study concluded that the CPR guided by rapid point-of-care testing was the most cost effective scenario.

A cost effectiveness assessment calculated from the societal perspective and expressed in terms of cost per acute rheumatic fever case prevented annually in 5 – 17 year old children was conducted on US Census data [31]. The study considered the following interventions; treat all, treat none, rapid point-of-care test with intention to treat, conventional culture with intention to treat, and rapid point-of-care test confirmed by conventional culture with intention to treat. The study concluded that the rapid point-of-care test in isolation was the most cost-effective intervention to prevent acute rheumatic fever; however this study did not consider clinical prediction rules.

Guidelines and Recommendations

The NICE clinical knowledge summary (CKS) for sore throat (accessed 2015) [4] does not recommend the use of rapid point-of-care tests for suspected GABH pharyngitis. The CKS cites poor sensitivity and limited impact on prescribing decisions as justification. The CKS does suggest that testing may be useful in high-risk groups in order to guide treatment decisions if initial treatment fails to work, however the guideline recommends swabs and culture rather than rapid point-of-care tests. SIGN clinical guidance on acute sore throat issued in 2010 draws similar conclusions and suggests that there is insufficient evidence to warrant a recommendation for the use of rapid point-of-care tests for suspected GAS infection [10].

Research Questions:

1. Given the moderate sensitivity of currently available point-of-care tests, can more sensitive tests be developed to better rule out GABH infection?
2. Can rapid point-of-care tests which discriminate between avirulent and virulent strains of GABH be developed?
3. Would the identification of virulent strains of GABH by rapid point-of-care test have any impact on morbidity and mortality from serious sequelae where virulent strains are prevalent, and what impact could this have on the prescription of antibiotics?
4. Could markers of antibiotic resistance be incorporated into new rapid point-of-care tests?

Suggested next steps:

1. Additional impact studies when new tests become available which have improved sensitivity and thus rule-out potential.
2. Studies to explore the feasibility of developing enhanced rapid point-of-care tests for GABH which yield information pertaining to strain virulence (i.e Capacity to identify rheumatogenic strains of GABH), or tests which can distinguish between GABH carriage and acute infection.
3. Assessment of the potential impact of enhanced tests on prescription of antibiotics and the burden of disease in resource rich and poor contexts.

Expected outcomes:

Current rapid point-of-care tests for GABH appear to add little over and above well formulated clinical prediction rules in terms of prescription of antibiotics, or achieving symptomatic relief in patients presenting with acute sore throat in the developed world.

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This report was prepared by the Primary Care Diagnostic Horizon Scanning Centre Oxford
Authors: Philip J. Turner, Carl Heneghan, Christopher P. Price, Yaling Yang, Ann Van den Bruel, Annette Plüddemann
Contact details: Dr. Annette Plüddemann; Email: dec@phc.ox.ac.uk

Appendix 1: Table of Available Devices – manufacturer quoted information

Company	Product name	Sample Type	CE marked?	FDA approved?	Time to result	Storage Temp. (Degress C)	Sensitivity	Specificity	Type	Antigen
Alere	Acceava® Strep A Dipstick	Liquid extract prepared from throat swab in extraction tube	No	CLIA waived	5 mins	2-30	97%	95%	Immunochromatographic assay - lateral flow	Strep A antigen
	Alere™ TestPack +Plus Strep A	Liquid extract prepared from throat swab in extraction tube	Yes	No	5 mins	2-30	97.60%	98.40%	Immunochromatographic assay - lateral flow	Strep A antigen
	BinaxNOW® Strep A	Liquid extract prepared from throat swab on board the device	Yes	Yes + CLIA-waived	6 mins	15-30	92%	100%	Immunochromatographic assay - lateral flow	Strep A antigen
	Alere™ i Strep A	Throat swab extracted in proprietary cartridge and buffer	No	Yes + CLIA-waived	8 mins	N/A	95.9%	94.6%	Molecular – isothermal PCR reaction	Strep A-specific molecular sequence
Quidel	Sofia Strep A Fluorescent Immunoassay (FIA)	Liquid extract prepared from throat swab in extraction tube	Yes	Yes + CLIA-waived	5 mins	15-30	90.60%	96.10%	Fluorescent lateral flow Immunoassay - requires Sofia benchtop unit to read	Strep A antigen
	QuickVue+ Strep A Test	Liquid extract prepared from throat swab in extraction tube	Yes	?	5 mins	15-30	95%	98%	Lateral flow immunoassay	Strep A antigen
	QuickVue In-Line Strep A Test	Liquid extract prepared from throat swab on board the device	Yes	CLIA waived	5 mins	15-30	92%	99%	Lateral flow immunoassay	Strep A antigen
	QuickVue Dipstick Strep A Test	Liquid extract prepared from throat swab in extraction tube	Yes	CLIA waived	5 mins	15-30	92%	98%	Lateral flow immunoassay	Strep A antigen
Becton Dickinson	BD Chek™ Group A Strep Test	Liquid extract prepared from throat swab in extraction tube	No	CLIA waived	5 mins	2-30	97%	95%	Chromatographic immunoassay	Strep A antigen
	BD Veritor System™ - rapid detection of GAS	Liquid extract prepared from throat swab in extraction tube	No	CLIA waived	5 mins	2-30	95.40%	95.70%	Chromatographic immunoassay - machine read by Veritor System	Strep A antigen
Beckman Coulter	ICON DS Strep A test kit	Liquid extract prepared from throat swab in extraction tube	No	CLIA waived	5 mins	2-30	96.20%	98.70%	Immunochromatographic assay	Strep A antigen
	ICON SC Strep A test kit	Liquid extract prepared from throat swab in extraction tube	No	CLIA waived	5 mins	2-30	96.20%	98.70%	Immunochromatographic assay	Strep A antigen
Sekisui Diagnostics	OSOM® Strep A Test	Liquid extract prepared from throat swab in extraction tube	Yes	CLIA waived	5 mins	15-30	96.00%	98.00%	Immunochromatographic assay	Strep A antigen
Orion Diagnostics	QuikRead go® Strep A	Liquid extract prepared from throat swab in extraction tube	?	?	< 7 mins	2-25	83%	97%	Immunoturbidimetric - machine read	Strep A antigen
DectraPharm	Streptatest	Liquid extract prepared from throat swab in extraction tube	Yes	No	5 mins	2-30	96.80%	94.70%	N/A	Strep A antigen
BTNK INC	Rapid ResponseTM Strep A Antigen Test Cassette	Liquid extract prepared from throat swab in extraction tube	?	?	5 mins	2-30	?	?	Lateral flow immunoassay	Strep A antigen
BTNK INC	Rapid ResponseTM Strep A Antigen Test Strip	Liquid extract prepared from throat swab in extraction tube	?	?	5 mins	2-30	?	?	Lateral flow immunoassay	Strep A antigen
Nova Century Scientific	Strep A Twist Device	Liquid extract prepared from throat swab on board the device	No	CLIA waived	5 mins	2-30	90	94	Lateral flow immunoassay	Strep A antigen
Nova Century Scientific	Strep A Test Device (Throat Swab)	Liquid extract prepared from throat swab in extraction tube	No info	No info	5 mins	2-30	94	98	Lateral flow immunoassay	Strep A antigen
Moore Medical	MooreBrand® Strep A Dipstick	Liquid extract prepared from throat swab in extraction tube	No info	CLIA waived	5 mins	RT?	97	95	N/A	Strep A antigen
Ultimed Products (Deutschland) GmbH	Strep A Cassette	Liquid extract prepared from throat swab in extraction tube	?	?	5 mins	?	?	?	Chromatographic immunoassay - lateral flow	Strep A antigen

Appendix 2. Clinical scoring systems for the prediction of infection by GABH. Higher scores indicate a higher probability of infection

Centor Criteria [8]	Points		McIsaac Score Criteria [12]	Points		FeverPAIN [13]	Points		Joachim Score [32]	Points
Tonsillar exudates	1		Temperature ≥ 38°C	1		Fever during 24 hours prior to consultation	1		Age	
Swollen tender anterior cervical nodes	1		Absence of cough	1		Purulence	1		≤35 months 36 – 59 months ≥60 months	1 2 3
History of fever	1		Tender anterior cervical nodes	1		Attend rapidly (within three days)	1		Tender cervical nodes Petechia on palate	1 1
Absence of cough	1		Swollen tonsils or exudate	1		Inflamed tonsils (severe)	1		Abdominal pain	1
			Age 3 – 14 years	1		Absence of cough/coryza	1		Sudden inset (<12 hours)	1
			Age 15 – 44 years	0					Conjunctivitis Coryza Diarrhoea	-1 -1 -1
			Age ≥ 45 years	-1						