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MINIREVIEW

Group A Streptococcus Testing in Pediatrics: the Move to Point-of-Care Molecular Testing

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ABSTRACT Each year, there are an estimated 11 million visits to ambulatory care centers for pharyngitis in children between the ages of 3 and 18 years. While there are many causes of pediatric pharyngitis, group A streptococcal pharyngitis represents 15 to 30% of infections and is the only cause for which treatment is recommended. Unfortunately, clinical suspicion is insufficient for the accurate diagnosis of group A streptococcal pharyngitis, and laboratory testing for confirmation of *Streptococcus pyogenes* infection is required to prevent complications of infection. Traditionally, throat swabs are inoculated onto agar plates for isolation of the large-zone beta-hemolytic streptococcus. However, traditional culture methods present a potential delay in treatment due to turnaround times of 18 to 48 h. In order to improve turnaround times and enhance antimicrobial stewardship, multiple point-of-care assays have been developed. This review describes current point-of-care testing for group A streptococcal pharyngitis, including rapid antigen detection tests and more recent molecular methods. Additional attention is given to the diagnostic considerations when choosing a method for group A streptococcal point-of-care testing, implementation of molecular group A streptococcal testing, and the institutional cost of immunoassays compared to those of newer molecular methods.

KEYWORDS *Streptococcus pyogenes*, group A *Streptococcus*, pediatrics, point-of-care testing

Each year, there are an estimated 11 million visits to ambulatory care centers for pharyngitis in children between the ages of 3 and 18 years (1). Approximately 15 to 30% of those children will be diagnosed with group A streptococcal (GAS) pharyngitis (1–3). While there are many causes of pharyngitis, including multiple viral etiologies, GAS is the only cause for which treatment is recommended (4). Therefore, an accurate diagnosis is critical for GAS pharyngitis.

GAS infection most frequently occurs in children between the ages of 5 and 15 years and primarily in the cooler months of winter and early spring (4). Patients typically present with a sudden-onset sore throat, pain upon swallowing, and fever. Additional symptoms may include malaise, headache, nausea, vomiting, and abdominal pain (4). Physical examination will reveal tonsillopharyngeal erythema, and exudate may be present on the posterior pharynx and tonsillar pillars. Enlarged anterior cervical lymph nodes are frequently present early in the course of infection (3, 4). Without treatment, symptoms may last 8 to 10 days, and patients are infectious for up to 1 week following the acute presentation (3).

Unfortunately, physical examination findings and clinical suspicion are insufficient for the accurate diagnosis of GAS pharyngitis. Symptoms of GAS infection overlap the symptoms of other infectious causes of pharyngitis. As early as the 1950s, routine pharyngeal culture of suspected GAS infection was suggested due to a sensitivity of 70% for clinical diagnosis alone (5). Multiple clinical criteria have since been developed for aiding in the diagnoses of GAS pharyngitis, such as the Centor criteria with or

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TABLE 1 Methods for CLIA-waived group A *Streptococcus* testing

Laboratory test	% sensitivity	% specificity	Method	Turnaround time (min)	CLIA complexity	Secondary confirmation recommended upon negative results
Latex agglutination	53–92[a]	85–96[b]	Visual agglutination[c]	<10	Waived	Yes
Lateral flow immunoassay	85–87[d]	92–96[d]	Visual identification of antigen capture[c]	<10	Waived	Yes
Optical immunoassay	71–95[e]	69–96[e]	Optical density change with antigen capture[c]	<8	Waived	Yes
Roche cobas strep A assay	95.0[f]	94.2[f]	PCR amplification	<15	Waived	No
Abbott strep A and strep A2 assays	98.5[f]	93.4[f]	Isothermal DNA amplification	2–6	Waived	No
Xpert Xpress strep A assay	99.4[f]	94.1[f]	RT-PCR amplification[g]	18–24	Waived/moderate	No

[a]See references 12 to 14.
[b]See references 13 and 14.
[c]Optical readers are available for interpretation for various vendors.
[d]See references 14 and 15.
[e]See reference 14.
[f]Manufacturers' reported sensitivity and specificity data.
[g]RT-PCR, real-time PCR.

without the McIssac modification and the Breese score (3). The Centor criteria, validated on adults, scores patients on four clinical features: tonsillar exudate, swollen and tender anterior cervical lymph nodes, fever, and lack of cough (6). Using these criteria alone, only 53% of patients with GAS infection were accurately identified (7, 8). McIsaac et al., using modifications to the Centor criteria that include criteria for age, increased the sensitivity of clinical diagnosis of GAS infection in children only to 68% (7). Across all groups, the Breese score, as defined in the original publication, had a 79% accuracy across all groups, positive and negative. When comparing scores of >30, the rate of correct diagnosis of patients positive for GAS infection was 77.6% (9). In practice, the Breese score has fallen out of favor secondary to the need of a white blood cell count for interpretation.

CURRENT DIAGNOSTIC RECOMMENDATIONS

The Infectious Diseases Society of America (IDSA) released updated recommendations for the diagnosis and management of GAS pharyngitis in 2012 (4). Due to the low sensitivity of clinical diagnosis, clinicians are encouraged to test children over 3 years old for GAS using either a rapid antigen detection test (RADT) or standard throat swab culture. Due to the variability in sensitivities of current RADTs (Table 1), negative results should be backed up with bacterial culture in pediatric patients. The use of routine back-up culture is not required for positive RADT results due to high specificities. Testing should be reserved for patients who do not exhibit signs of viral infection such as cough, rhinorrhea, hoarseness, or oral ulcers.

Accurate diagnosis is needed for GAS pharyngitis for multiple reasons. Most importantly, treatment of GAS pharyngitis prevents serious complications like acute rheumatic fever or glomerulonephritis, in addition to suppurative complications like peritonsillar abscess, cervical lymphadenitis, and mastoiditis. Additionally, treatment decreases the severity and duration of symptoms while also decreasing transmission from person to person. Improved diagnosis of GAS pharyngitis improves antibiotic stewardship and decreases the exposure of antibiotics to patients who do not require therapeutic intervention (4). Current treatment recommendations are a 10-day course of penicillin or amoxicillin for patients who are not allergic to these antibiotics. For penicillin-allergic patients, a first-generation cephalosporin, clindamycin, or clarithromycin can be prescribed for 10 days or azithromycin for 5 days (4).

DIAGNOSTICS FOR GROUP A STREPTOCOCCUS

Culture. Bacterial culture is considered the gold standard for the diagnosis of GAS due to high sensitivity and specificity. To isolate GAS (*Streptococcus pyogenes*), throat swab samples are cultured on sheep blood agar plates and incubated for 18 to 24 h at 37°C. An additional 24 h of incubation at room temperature may be beneficial for the

identification of additional positive cultures. The use of selective media and anaerobic conditions may also increase detection rates (10). Overall, the turnaround times (TAT) are 18 to 24 h for positive cultures and 24 to 48 h for negative cultures, depending on the method utilized. Sensitivities for culture have been reported to be as high as 95%, but most of those studies occur in clinical reference laboratories with highly standardized processes. In real-world studies, sensitivities for culture have been shown to range from 72 to 87% (11).

RADTs. The clinical need for rapid diagnostics developed secondary to the long TAT of standard culture methods and led to the development of rapid antigen detection tests (RADTs). The RADTs were designed to be used either within the clinical microbiology laboratory or as point-of-care tests (POCTs) allowing clinically actionable information to be obtained in the physician office, so that antibiotics could be administered without delaying care.

(i) Latex agglutination assays. Latex agglutination was one of the first rapid antigen detection tests used in the diagnosis of group A streptococcal pharyngitis in the early 1980s (12). With TATs as short as 10 min, the test allowed rapid screening of pharyngeal swab samples for the presence of GAS carbohydrate antigen. The presence of agglutination, graded 1+ through 4+, was interpreted as a clinically significant infection with GAS in the appropriate context. Clinicians could use the result to make an in-office decision on patient care, such as the initiation of antibiotic therapy. While latex agglutination is a fast, simple, and office-friendly GAS RADT, it has multiple shortcomings for the purpose of a screening test. First and foremost, latex agglutination demonstrates a wide range of sensitivities, from 53% to 92% (12–14). In addition to the variations in sensitivities, the test also has the lowest specificity, with some studies demonstrating a specificity below 90% (13, 14). This is problematic for a physician choosing to treat children with positive results, due to the concern for false positives. Lastly, the overall endpoint of agglutination grading is subjective and highly dependent on user level of experience. This results in high interobserver variability (15).

(ii) LFIAs. Lateral flow immunoassays (LFIAs) have been available for testing for the presence of GAS carbohydrate antigen since 1984. Similar to latex agglutination, LFIAs are point-of-care tests that are run in two steps, an extraction step and a testing step. The overall endpoint of the test is easier to interpret than is the case for latex agglutination. If the antigen is present, a colored line will be present within the positive testing window. A study by Stewart et al. showed that LFIAs had the best performance among RADTs in the pediatric population, despite a high degree of heterogeneity in the various studies (16). Despite a reported sensitivity and specificity of >95% according to the manufacturer's insert, one review demonstrated an average sensitivity of 85% and a specificity of 97% (14).

(iii) OIAs. The optical immunoassay (OIA) was first developed in 1994 for use in the diagnosis of GAS pharyngitis (15). Similar to other GAS RADTs, the test procedure has an extraction and testing phase that requires the release and capture of GAS carbohydrate antigen. The test is referred to as an optical test due to the color change of a silicon wafer from a gold/yellow color to purple when GAS carbohydrate antigen is captured. Most importantly, compared to traditional cultures, the OIA had at its development >95% sensitivity and specificity, which improved, similar to those of other RADTs, with increasing prevalence and clinical indication of GAS infection (17). The OIA is a valuable assay due to its ease of interpretation. A color change signifies the presence of GAS carbohydrate antigen, which allows clinicians to know if GAS is present in a child presenting with pharyngitis. No interpretation of grade, as in latex agglutination, is required, and because the extracted antigen does not need to elute, as in LFIAs, fewer false negatives are thought to occur. The overall sensitivity and specificity of the OIA are 86% and 94%, respectively (14).

Molecular POCTs. Due to the lower sensitivities of RADTs and the need to treat patients based on diagnostic results, nucleic acid amplification tests (NAATs) have been developed for the detection of GAS. While multiple assays and instruments have been

developed, this review will focus on FDA-approved, CLIA-waived NAAT assays that can be used as POCTs in ambulatory care settings (Table 1) as reported in the FDA CLIA categorized medical device database (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/Search.cfm). All the platforms discussed below are also FDA approved for the testing of additional pathogens, including influenza A/B and respiratory syncytial virus (RSV). Additional tests may be added to the test menus in the future, broadening the utility of these instruments.

(i) Roche cobas strep A assay. The first CLIA-waived platform and assay for GAS were the cobas Liat platform and the cobas strep A assay (Roche Molecular Diagnostics, Indianapolis, IN) (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/Detail.cfm?ID=43105). Approved in 2015, the cobas Liat platform is a small benchtop analyzer that utilizes nucleic acid purification and PCR for organism detection. The cobas strep A assay can detect *Streptococcus pyogenes* in throat swabs with a limit of detection (LOD) of 5 to 20 CFU/ml. The manufacturer's claimed sensitivity is 95% (95% confidence interval [CI], 93.4 to 99.2%) and specificity is 94.2% (95% CI, 89.9% to 95.6%). Results are available in approximately 15 min (18).

Studies have compared the performance of the cobas Liat strep A assay against different comparator methods. For example, Wang et al. compared the cobas Liat strep A assay and RADT in the primary care setting to results from reference culture (19). Their study demonstrated a sensitivity and specificity of 97.7% (95% CI, 93.4 to 99.2%) and 93.3% (95% CI, 89.9 to 95.6%), respectively, for the cobas Liat assay, while the RADT had a sensitivity and specificity of 84.5% (95% CI, 77.3 to 89.7%) and 95.3% (95% CI, 92.3 to 97.2%), respectively. This multicenter study demonstrated increased sensitivity and ease of use of the NAAT assay compared to the RADT, as the test was operated at five different clinical sites by 16 different medical staff members. A single-site study comparing the cobas Liat, an RADT, and bacterial culture to a laboratory-based GAS NAAT demonstrated results similar to those of the previous study for both the cobas Liat assay (sensitivity, 95.5% [95% CI, 89.7 to 98.5%]; specificity, 99.3% [95% CI, 96.2 to 99.9%]) and the RADT (sensitivity, 85.5% [95% CI, 77.5 to 91.5%]; specificity, 93.7 [95% CI, 88.5 to 97.1%]) (11). Both studies showed lower sensitivities for bacterial culture performed in clinical laboratories (72 to 87%) (11, 19).

(ii) Abbott strep A and strep A2 assays. The ID Now instrument, formerly known as the Alere i (Abbott Diagnostics, Scarborough, ME), received CLIA-waived status in 2015 (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/Detail.cfm?ID=43007). The ID Now platform uses isothermal DNA amplification for the qualitative detection of different pathogens, including GAS. The Abbott strep A assay was FDA cleared in 2015, and the updated Abbott strep A2 assay was cleared in 2018. Due to improved sensitivity over the previous version, culture confirmation for negative results is not required for the Abbott strep A2 assay. Results are available in as little as 2 min for a positive result and 6 min for a negative result. The manufacturer's claimed sensitivity and specificity versus bacterial culture are 98.5% (95% CI, 95.6 to 99.5%) and 93.4% (95% CI, 91.4 to 94.9%), respectively (20). The rates of invalid results during the prospective clinical trial were 0.4 to 0.9%. The limit of detection for this assay is 25 to 147 CFU/ml.

Berry et al. compared the Abbott strep A assay and an RADT to bacterial culture in two pediatric outpatient clinics (21). Their study demonstrated 100% (95% CI, 91.6 to 100%) sensitivity and 91.3% (95% CI, 86.1 to 95.1%) specificity for the NAAT. For the RADT, the sensitivity and specificity were 76.2% and 93.6%, respectively. A second study, also comparing the Abbott strep A assay to an RADT and bacterial culture, demonstrated a sensitivity and specificity of 98% and 100%, respectively, for the Abbott strep A assay (22). As seen with other studies, the RADT demonstrated a lower sensitivity (88.5%) and specificity (91%). There are currently no published studies evaluating the Abbott strep A2 assay.

(iii) Xpert Xpress strep A assay. The Xpert Xpress strep A assay (Cepheid, Sunnyvale, CA) received FDA clearance and CLIA waiver in 2018 (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/Detail.cfm?ID=39757). This assay utilizes PCR for the qualitative detection of GAS. Results are available in 18 to 24 min, and the limit of

detection for this assay is 9 to 18 CFU/ml. The manufacturer-reported sensitivity and specificity are 99.4% (95% CI, 96.5 to 99.9%) and 94.1% (91.6 to 95.9%), respectively (23). Unlike the two assays described above, the Xpert Xpress strep A assay can also be performed as a moderately complex assay using GeneXpert analyzers found in many clinical microbiology laboratories.

There are currently no published studies evaluating the performance of the Xpert Xpress strep A assay in a POC setting. Parker et al. examined the performance of this assay and compared it to the cobas Liat and Luminex Aries NAATs and one RADT in a clinical laboratory setting (24). In their study, the Xpert Xpress strep A assay had a sensitivity of 100% and a specificity of 97.4% compared to those of bacterial culture. This was identical to the results for the cobas Liat assay and similar to the results for the Luminex Aries assay. The Luminex Aries assay is only approved as a moderately complex assay and, therefore, is not performed as a POCT (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/Detail.cfm?ID=45588). A second study using the Xpert Xpress strep A test also evaluated the performance of the assay in a clinical laboratory and demonstrated similar sensitivity (100%) but much lower specificity (79.3%) compared to those of bacterial culture (25). The authors of this study attribute the possible false-positive PCR results to a combination of cross-reactivity with non-group A beta-hemolytic streptococci, the presence of residual organisms, or the presence of GAS nucleic acid after recent infection. The assay used in this study was not FDA approved at the time of testing.

Outcomes with the utilization of molecular POCTs. Although only 15 to 30% of pharyngitis is caused by GAS, antibiotics are prescribed for approximately 60% of all pharyngitis cases (1, 4). The overuse of antibiotics has been attributed to delayed TATs in waiting for culture confirmation results, with the result of antibiotics being prescribed at the time of the clinic visit or physicians not performing any diagnostic test before prescribing antibiotics (26). The CLIA-waived molecular GAS tests currently available all claim that culture confirmation is not required in most settings due to the increased sensitivities compared to those of RADTs, which can significantly reduce TATs for negative GAS tests.

Multiple studies have tried to capture possible improved outcomes with the use of these new molecular assays in a POC setting. Rao et al. determined that the use of molecular POCTs resulted in the appropriate prescribing of antibiotics in 97.1% of cases, compared to 87.5% of cases utilizing RADT plus confirmatory bacterial culture ($P = 0.0065$) (11). Regardless of the test used, this study did not show any impact on patient follow-up visits or hospitalizations (11). Berry et al. performed a retrospective chart review to determine the hypothetical impact on antibiotic prescription (21). They determined that 36% of patients who were prescribed antibiotics at the time of the clinic visit were done so inappropriately, as they were later confirmed to be negative for GAS by molecular testing. An additional 6% of patients who were not prescribed antibiotics at the time of the visit were later determined to be positive for GAS infection by molecular testing (21).

CONSIDERATIONS FOR THE SELECTION OF GAS DIAGNOSTIC TESTING

The selection of the best GAS diagnostic testing algorithm is not straightforward. Following the IDSA guidelines, one should not yet consider molecular testing, whether in the clinical laboratory or POC setting (4), although the last recommendations were published in 2012, before molecular GAS testing became readily available. In examining test performance, molecular GAS tests have higher sensitivities than RADTs and bacterial culture and have faster overall TATs when culture confirmation is required. Additionally, many RADTs rely on visual examination of agglutination, color change, or the presence or absence of a line which lends itself to increased interobserver variability and subjectivity. To reduce this subjectivity, optical readers, such as the BD Veritor system (Becton, Dickinson and Company, Sparks, MD), have been developed for the interpretation of uncertain cases.

The prevalences of GAS in symptomatic compared to asymptomatic children have

been demonstrated to be 37% and 12%, respectively (27). These asymptomatic children are believed to be carriers of GAS. This carriage state can present issues with testing, as GAS carriers with a viral cause of pharyngitis may be indistinguishable from true GAS infection from both clinical presentation and GAS diagnostic testing. Importantly, these two states, symptomatic and carriage, should have different treatment pathways. There is concern that the increased sensitivity of molecular GAS testing will increase the detection of GAS carriers. Parker et al. identified one patient as positive by two different molecular tests who was negative by bacterial culture (24). In another study, 13/15 results that were positive by molecular POC testing and negative by culture were confirmed by a second molecular method (21). Weinzierl et al. did not demonstrate discrepancies between molecular testing and negative bacterial culture (22). Finally, in one study, samples from 13 patients that were initially negative by a molecular POC assay were later confirmed to be positive after additional preanalytical steps (11). All of these samples had high PCR cycle thresholds and, therefore, represented low bacterial burdens. Chart review indicated no negative consequences for these patients with deferred treatment based on the POC test results (11). To decrease possible detection of GAS carriers, clinicians should follow IDSA guidelines (with or without clinical diagnostic algorithms, such as the Centor score) for patient selection (4). Additional studies should be undertaken to further enhance our understanding in this area.

If providers choose to move toward molecular POC tests for GAS as the only means of testing, it is possible to miss other causes of pharyngitis. In addition to numerous viral causes, there are multiple other bacteria that cause acute pharyngitis and may be identified using bacterial culture. These bacteria include other beta-hemolytic streptococci (groups C and G), *Arcanobacterium haemolyticum*, *Corynebacterium diphtheriae*, *Neisseria gonorrhea*, *Fusobacterium necrophorum*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* (4). Many of these bacteria require special culture conditions and would not be identified using classic GAS culture. Physicians should maintain close communication with their clinical microbiology laboratories to understand what is available for additional diagnosis of pharyngitis should the need arise.

Another consideration for testing is cost and reimbursement. The cost for molecular POC tests is significantly more than for RADTs due to increased costs of reagents and instrumentation. The cobas Liat and ID Now only allow one test at a time per instrument, while the Cepheid Xpert CLIA-waived instrument has space for up to four assays at one time. Although costs are higher for molecular testing, reimbursement rates are better than for RADTs and bacterial culture. In Georgia, the home state of the authors, the Medicare reimbursement rate for a GAS RADT is $16.53, while for a molecular GAS assay, it is $38.99. Additional return on investment for molecular testing may be from decreased costs due to appropriate antibiotic prescribing, decreased technical time performing cultures, and decreased personnel time on following up culture confirmation results.

The implementation of any POC assay should be done with appropriate training and oversight by trained personnel. However, the use of molecular technology in POC assays requires additional considerations. Most health care providers who have not had laboratory training are not as aware of issues like specimen collection and environmental contamination that must be closely monitored with molecular testing. Fortunately, all of the CLIA-waived molecular GAS assays available today have closed sample devices, which decreases the risk for amplicon contamination. Regardless, the College of American Pathologists (CAP) have now added several accreditation checklist items in the 2019 checklist to address molecular POC testing. Molecular assays must be monitored for possible false-positive results that may occur due to nucleic acid contamination (checklist item POC.08675). This can be accomplished in many different ways, including monitoring of statistics, performing environmental sampling, or a combination of both. A second checklist item (POC.08690) pertains to sample handling and limiting preanalytical risk. There must be procedures in place regarding collection, processing, and storage. This is especially important if some or all of the specimen will be sent to a clinical laboratory for further testing. The third checklist item (POC.08715)

addresses the safe handling of specimens to prevent possible exposure to emerging pathogens. Finally, the fourth new checklist item requires a summary of the testing methodology and any information required for interpretation to be included on the final report (POC.08730). All of these new checklist items parallel existing microbiology-specific CAP checklist items for molecular testing. Due to the recent introduction of these checklist items, there are limited data to show the effects of these additional regulations. One study examining the use of a molecular POCT in a clinic setting monitored for environmental contamination weekly at all study sites by swabbing the instruments and surrounding benchtops. They did not find any contamination during their study (28).

CONCLUSIONS

GAS pharyngitis in children has been estimated to cost between $224 million and $539 million annually, including both health care and non-health care costs, such as time off from work and childcare expenses (29). Additionally, approximately 24% of patients presenting with acute pharyngitis receive antibiotics unnecessarily, an issue that can potentially lead to adverse reactions, increased costs, and antimicrobial resistance (1). The IDSA recommends testing for all children who meet specific clinical criteria for GAS pharyngitis in order to receive appropriate treatment and reduce the risk of developing suppurative and nonsuppurative disease. Diagnostics for GAS are evolving and improving rapidly. Clinicians who wish to perform GAS testing in a POC setting should work closely with their clinical microbiology laboratories and POC teams to select and implement the most appropriate diagnostics for their patients. The move toward molecular POC testing presents many exciting opportunities, including improved sensitivities, but the pros and cons must be weighed carefully.

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