

Performance Characteristics and Utilization of Rapid Antigen Test, DNA Probe, and Culture for Detection of Group A Streptococci in an Acute Care Clinic

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Group A streptococcus (GAS) antigen testing has become a routine point-of-care (POC) test in acute care settings. Concern about performance parameters (PP) of these tests as well as inappropriate antibiotic use has resulted in various recommendations regarding diagnosis of GAS. There were two objectives in this study. The first was to evaluate the rapid GAS antigen test presently in use (Thermo BioStar, Boulder, Colo.) and the GAS Direct probe test (Gen-Probe, San Diego, Calif.) compared to culture. The second was to define the optimal use of these technologies in a large acute care pediatric clinic. A total of 520 consecutive pediatric patients presenting with symptoms of pharyngitis at any of three Lahey Clinic acute care facilities were evaluated. Pharyngeal specimens were collected using a double-swab collection device (Copan, Corona, Calif.). One swab was used for the antigen test, the second was used for the probe test, and the pledget was placed in the collection device for culture on 5% sheep blood agar, incubated for 48 h anaerobically, and subsequently placed in Todd-Hewitt broth. After discrepant analysis, sensitivity, specificity, and positive and negative predictive values were as follows: 94.8, 100, 100, and 96.9% for the probe test and 86.1, 97.1, 93.7, and 93.4% for the antigen test, respectively. Sensitivity using an enhanced culture technique was 99.4% (163 of 164). False-positive (FP) antigen results were often seen from patients previously diagnosed and/or treated for GAS. No FP results were seen with the probe test. Colony counts for the false-negative (FN) antigen tests were higher than those for the FN probe tests. Compared to culture and DNA probe, the rapid antigen test (RAT) offered a result at the time of the patient's visit, with acceptable PP when prevalence of disease is high. Follow-up testing with the RAT of GAS patients who previously tested as positive should be avoided due to increased FP results. The probe test was comparable to culture in performance. Results indicate the probe test can be used as the primary test or as a backup to negative antigen tests. The probe test offers the advantage over culture of same-day reporting of a final result but, in contrast to a POC test, necessitates follow-up communication to the patient. Preliminary data show the specificity of the probe test to be greater than that of the RAT for patients previously diagnosed with GAS.

In 1998, the National Center for Health Statistics reported 12.2 million patient visits for cases of pharyngitis. Of these visits, 2.4 million were due to group A streptococcal (GAS) sore throat, the most common form of acute pharyngitis for which antibiotic therapy is indicated (3, 20). While other bacterial infectious agents such as members of streptococcal groups C and G and *Arcanobacterium haemolyticum* can occur, they are more typically sought in specific clinical settings (23). As a result, the use of rapid antigen tests (RATs) for the diagnosis of GAS pharyngitis has become common in many office and clinic settings. Given good performance parameters, a point-of-care (POC) test whose results are directed to the physician before the patient leaves the healthcare setting has many benefits. Positive results allow appropriate and directed therapy, are satisfying to the patient, and eliminate phone calls about follow-up results (8, 15). A standard practice for a patient with a negative POC RAT result remains undefined. The lack of a standard is reflected in the conflicting recommendations from the American Academy of Pediatrics and the Amer-

ican Thoracic Society on RAT-negative patients who present with acute pharyngitis (1, 4). Published articles support many options in the diagnosis of GAS, including the use of the RAT alone, follow-up with culture on all RAT-negative patients, and the use of culture as a single-test option (2, 6, 8, 15, 16, 25). There are advantages, disadvantages, and variable results for both RAT and culture methodologies, depending on the type of test used, the personnel performing the test, and the history of the patient. The DNA probe test adds yet another option to consider in the algorithm for use in GAS diagnosis, because the test offers benefits not available with other technologies.

The present study was conducted to address two issues. The first was to evaluate the GAS Direct probe test (Gen-Probe, Inc.) compared to the optical immunoassay (OIA) RAT (Thermo BioStar) and to culture with a 5% sheep blood agar plate (BAP) incubated anaerobically for 48 hours and subsequently inoculated into Todd-Hewitt enrichment broth (THB). The second was to define the optimal use of the various technologies for GAS diagnosis in a large pediatric acute care clinic.

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MATERIALS AND METHODS

Study population. A total of 520 patients were enrolled in the study. Consecutive patients attending the pediatric outpatient clinics at three sites (one on-site

TABLE 1. Comparison of GAS test methods^a

Parameter ^b	GAS Direct probe test		OIA RAT		Culture	
	No. of specimens (total no.)	%	No. of specimens (total no.)	%	No. of specimens (total no.)	%
Sensitivity	164 (173)	94.8	149 (173)	86.1	172 (173)	99.4
Specificity	347 (347)	100	337 (347)	97.1	347 (347)	100
PPV	164 (164)	100	149 (159)	93.7	172 (172)	100
NPV	347 (358)	96.9 ^c	337 (361)	93.4 ^d	347 (348)	99.7

^a A total of 520 specimens were evaluated.

^b PPV, positive predictive value; NPV, negative predictive value.

^c FN probe test specimens had plate colony counts of <10 (3 specimens), 10 to 25 (5), and 25 and 50 (1).

^d FN OIA specimens had plate colony counts of <10 (6 specimens), 10 to 25 (8), 25 to 50 (8), and >50 (2).

and two off-site from the laboratory facilities) and presenting with symptoms of pharyngitis between March and June 2000 were included. Approximately 10% of specimens were from off-site clinics. Physicians collected a pharyngeal specimen, using a double-swab collection-transport device with 2.0 ml of liquid Amies medium in a sponge-like pledget (Copan). Specifically, the CQ138 dacron swab was used. The Copan rayon swab is not approved for probe tests and in fact gives nonreproducible results (K. C. Chapin, in-house data). Specimens were hand carried to the laboratory for the on-site or transported via courier for the off-site clinics. Specimens were delivered throughout the day to the laboratory. All specimens were received on the day of collection.

RAT. The Thermo BioStar OIA was the RAT used. The test is an immunoassay read by direct optical interpretation and was performed according to the manufacturer's instructions (OIA package insert, Thermo BioStar). The assay has been described in multiple publications (9, 15; P. P. Bourbeau, Editorial, *J. Clin. Microbiol.* 18:76–79). One swab was removed from the collection-transport device and used for the RAT. The test was performed in the STAT laboratory in the Chemistry Department of the Lahey Clinic Medical Center, following the usual protocol. Two technologists, blinded to each other's results, subjectively interpreted all test cassettes. Results were available to the physician via the laboratory information system (LIS) upon completion of the test. The second swab was transported to the microbiology laboratory for culture and DNA probe testing.

GAS probe test. The GAS Direct probe test (Gen-Probe) was performed using the second swab of the two-swab collection device. The probe test was performed according to the manufacturer's instructions (group A Strep Direct package insert). The test is a DNA chemiluminescence probe assay targeted at GAS rRNA in the specimen. DNA-rRNA hybrids are detected by release of the chemiluminescent signal upon hybrid cleavage in the Luminometer instrument. An objective result is provided based on results for positive and negative controls. Specimens were held at room temperature, and specimens were assayed at one of two time periods. The GAS Direct test was performed once at 2 p.m. and again in the evening, after all offsite specimens had been received. At the present time, DNA probe test results are available in the LIS when the assay is completed. Chart copies for both the RAT and probe test results were printed at midnight of the testing day and were available the next morning.

Culture. An enhanced culture technique was used to identify GAS. The pledget of the collection device was removed with sterile tweezers and was used to inoculate a 5% sheep BAP by tapping on the blood plate, which was subsequently placed into THB. The use of the pledget for culture has been described previously (11; Bourbeau, Editorial). The plate was incubated anaerobically at 37°C for 48 h. Colonies that were presumptive beta-hemolytic streptococci were grouped using latex agglutination reagent (PathoDX Strep grouping kit; Remel, Lenexa, Kans.). Specimens were quantitated as rare (<10 colonies), few (10 to 25 colonies), moderate in number (25 to 50 colonies), and many (>50 colonies). The broth was examined in cases in which the BAP was negative after 24 h and was subcultured to another BAP. Colonies consistent for beta-hemolytic streptococci were grouped as stated above (11, 12).

Reference standard. A true-positive result was based on the likelihood of infected patient status, as determined by positive culture for GAS and/or two or more positive independent assays. For example, if both the RAT and probe test results were positive, the patient was considered to represent a true-positive case of GAS and the culture result was considered a false negative (FN). If the culture and DNA probe test results were positive, the patient was considered a true-positive case and the RAT result was considered a FN.

Chart review. Chart review of the 10 patients with results discrepant between the rapid antigen test and culture, as well as of the 1 patient with culture-negative

but GAS antigen- and probe-positive results, was performed. Specifically, a previous history or diagnosis or antibiotic treatment for GAS in the previous month was noted. Colony counts from specimens with FN RATs and probe tests were tallied.

RESULTS

A total of 520 patient samples were evaluated. Of those patients, 172 were considered infected for GAS, based on positive culture results, and 1 additional patient was considered positive, based on positive rapid antigen GAS and positive probe results. The total of 173 infected GAS patients represented a disease prevalence of 33% during the study period from all clinic sites evaluated. Results for performance of the rapid antigen test and the probe test compared to culture are shown in Table 1. Colony counts for the culture-positive-antigen-negative tests and culture-positive-probe-negative specimens are footnoted at the bottom of Table 1. Based on infected patient status as described above, sensitivity, specificity, and positive and negative predictive value results for the Thermo BioStar RAT were 86.1, 97.1, 93.7, and 93.4% and 94.8, 100, 100, and 96.9% for the GAS Direct probe test, respectively. Culture was 99.4% sensitive. The THB did not identify additional positive specimens compared to those identified by the primary BAP culture at 48 h. False-positive (FP) results with the RAT were seen in 10 patients. Of those FP results, five were from patients previously treated for GAS and evaluated because of symptoms of pharyngitis. No FP results were noted with the probe test, including those for tests of patients who were previously treated and reviewed. FN results were seen with all methods, 24 with the Thermo BioStar OIA, 9 with the GAS probe test, and 1 with culture. Colony counts for the FN RAT and probe test results were distributed throughout the colony count range evaluated. The FN antigen test specimens exhibited higher colony counts (Table 1) than those of the probe test result. The 9 specimens FN by probe testing were also FN by the RAT. Cross-reactivity was not seen with either the RAT or the probe test in the 2 patients with group C streptococcus.

DISCUSSION

The results seen in this study are similar to those previously published for both the Thermo BioStar RAT and the GAS Direct probe assay (5, 8, 9, 10, 11, 15, 17; Bourbeau, Editorial; W. M. Dunne, Jr., J. C. Mohla, and J. M. Campos, *Abstr. 93rd Gen. Meet. Am. Soc. Microbiol.* 1993, abstr. C-340, p. 506,

1993). However, no peer-reviewed paper has been published presenting a side-by-side comparison of these two methods from the same patient sample. One abstract describing this type of comparison corroborates the results seen here (S. Wood, H. Takahashi, and J. Fusco, *Abstr. 39th Intersci. Conf. Antimicrob. Agents Chemother.*, abstr. 1567, p. 224, 1999).

Interestingly, the Thermo BioStar RAT performed nearly identically to that used in a study performed 3 years earlier at this institution, when the test was introduced to the market (87.1% sensitive, 97.4% specific) (15). Subsequent review of 1,500 RATs at this institution since the study period ended showed the sensitivity of the OIA to be consistent at 87%. Other studies have documented the sensitivity of the OIA to be quite high, ranging between 91.5 and 99% (8, 9, 11, 15). Other studies contradict these favorable results, with sensitivities from 77 to 81% reported (2, 5, 8).

Many variables affect specificity or the occurrence of FP results with RATs. Related specifically to the OIA, studies have shown specificities from a low of 89% (8, 18) to a high of 96 to 98.4% (5, 8, 9, 11). Cross-reactivity with other beta-hemolytic streptococci has not been reported. However, subjective and/or difficult interpretation of the OIA membrane has been noted and has led to an unidentified number of false results and site-dependent variable interpretations (4; K. C. Chapin and M. A. Flintoff, *Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother.*, abstr. D-122, p. 134, 2002). Such difficulties were not an issue in this study. In addition, it should be noted that RATs have also been shown to correctly identify patients that had unusual GAS isolates not identified by culture (19, 22).

FP results of RATs for patients returning with continued pharyngitis or recently recurrent pharyngitis are unrecognized and underreported. The manufacturer does not recommend the use of the OIA RAT for patients previously treated for GAS or reinfected with GAS or to determine chronic carriers of GAS. This is because the test detects both viable and non-viable antigen, which may result in possible FP results. Typically, a 4-week delay after GAS diagnosis by RAT and/or treatment is recommended as a guideline before reusing a RAT (OIA package insert, Thermo BioStar). As demonstrated in other studies (11, 18), this study showed a number of FP RATs. All of these FP RATs had both negative probe test and culture results, and many were from patients previously diagnosed with GAS and treated with penicillin. The shedding of GAS antigen postdiagnosis and -treatment is well documented, and as such, it should be clear to physicians that all RATs exhibit this trait and would not be appropriate for patients with suspected GAS treatment failure or subsequent reinfection.

Performance of any RAT is most satisfying while the patient is still within the healthcare setting and so can be treated immediately upon a positive result. Critically, relative acceptable sensitivity and specificity with a RAT allows for a great proportion of patients to be treated appropriately (24). However, the time per test, when performed adequately, requires a dedicated technical person in a high-volume setting and one experienced in interpreting the membrane technology. Individual cassettes are costly. These unfavorable features have been noted to be of importance when considering the appropriateness of the test for a given practice setting (8). Most importantly, the prevalence of disease in this study was very high

(33%), and the predictive value of the RAT was 93.7%. For a prevalence of 10%, the predictive value of this test would be only about 75%. Physicians using only RATs for diagnosis of GAS should be aware of this critical limitation.

The probe assay exhibited performance parameters comparable to those of culture and was easy to perform as a batch test in the laboratory during both first and second shifts. Sensitivity reported in this comparison for the GAS Direct probe test is similar to that of other studies, for which reported sensitivities were between 86 and 98% compared to those of culture (11, 17; Dunne et al., *Abstr. 93rd Gen. Meet. Am. Soc. Microbiol.*, 1993; Wood et al., 39th ICAAC). Reported specificity has always been high (98 to 100%), and this level of specificity was seen in this evaluation as well (11, 17; Dunne et al., *Abstr. 93rd Gen. Meet. Am. Soc. Microbiol.*, 1993; Wood et al., 39th ICAAC). Despite the high prevalence of GAS in this pediatric population, other studies with the probe test have shown comparable performance in low-prevalence-of-disease populations and for adults with pharyngitis as an incidental and not a primary complaint (17). There were no FP probe test results, either in those patients returning with repeat symptoms who had previously been treated or in those cross-reacting with other beta-hemolytic streptococci. We found no reported studies of evaluations of the life of the rRNA target for GAS after treatment. However, studies evaluating mycobacteria show that the rRNA target may be an adequate hallmark of acute infection (7, 14). Testing with the probe after treatment failures or reinfection may be an option equal in usefulness to culture for these patients, since the target disappears quickly after treatment (7, 14). Additional studies are necessary to confirm the use of the probe after treatment or GAS and to assess the length of time that the rRNA is present. The probe test did miss some positive cultures over the range of colony counts. The lower colony counts (<10 and 10 to 25) were also missed by the OIA in these patients. Specificity of the probe was higher than that of the OIA RAT in this direct comparison. The 100% specificity level also assures a high positive predictive value, regardless of the prevalence of disease.

Results from the probe test indicate that it can be used as the single primary test or as a backup test for less-sensitive methods and that it offers benefits not provided by other technologies. As a backup test to less-sensitive subjective methods, the probe test offers the ability to report an objective result. In contrast to adequate culture, which takes at least 24 to 48 h from the time of specimen receipt in the laboratory, the probe test can be reported on the same day as specimen collection. The use of culture is warranted to detect group C and G streptococci for patients who persist with pharyngitis after GAS testing results have been found to be negative or in specific epidemiological settings (23). The downside of the probe as a primary test is that it is not a POC test and necessitates follow-up with patients for relaying results.

The DNA Direct probe test as an alternative to culture was chosen for use after discussions between the departments of Pediatrics and Laboratory Medicine. Excellent performance parameters, a <24-h turnaround time to a final result, a greater number of patients receiving directed and appropriate antibiotic therapy, and less cost in labor allowed for an easy consensus for the use of the probe test over culture. Costs for each of the tests in our particular setting were fairly equivalent.

Specific costs related to the institution would need to be evaluated for each practice setting.

The suggestion of using a RAT alone without a backup test method and using culture for all RAT negative test results exhibits the two extreme sides of the diagnosis and testing issue. Clinicians and laboratorians should be aware of exuberant arguments for both sides of this issue, since the clinical and diagnostic settings are not always equal when it comes to resources, testing options, clinical judgment, and test performance. In addition, inappropriate antibiotic treatment for FP results is becoming an issue of equal importance to those of FNs and the risk of rheumatic fever or subsequent suppurative and nonsuppurative sequelae (15, 16, 23). In this study, 73% of the results would have required follow-up testing because of a negative RAT result. Clearly, a RAT result that is reliable and that a physician can act on before the patient leaves the office can be tremendously beneficial. However, patients with presumed treatment failure or reinfection and a negative RAT result for a very ill-appearing child warrant a follow-up test, given an OIA RAT sensitivity of 86% and questionable specificity in these settings.

Clinician judgment of an individual patient's case is key when using the testing algorithm for GAS. Physicians should be aware of the POC performance parameters of the particular test used in their setting and other available options. In conjunction with the laboratory, physicians can assess the best plan for the resources available and needs of the clinical setting. In our acute care setting, the current algorithm is the use of a double swab as the standard throat specimen collection. Physicians have a choice for GAS test diagnosis. While the POC RAT remains the primary test, physicians can choose the RAT only, the DNA probe test only, or the RAT with a follow-up DNA probe test for RAT-negative patients. Further evaluation of Direct GAS probe test, RAT, and culture results from patients with presumed treatment failure and/or reinfection is necessary to address RNA persistence.

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