

Rapid Antigen Detection Testing In Diagnosing Group A β -Hemolytic Streptococcal Pharyngitis

Sue A. Joslyn, PhD, Gregory L. Hoekstra, DO, and John E. Sutherland, MD

Background: The purpose of this study was to determine the accuracy of diagnosing group A β -hemolytic streptococci (GABHS) with rapid antigen testing compared with throat culture methods commonly used.

Methods: Two separate studies were conducted. Initially, 182 patients with acute pharyngitis had both throat culture (sheep blood agar or Strep Select Agar) and rapid antigen detection screening tests (Directigen₁₋₂₋₃ Group A Strep) performed. For the second study, a rapid antigen detection test (Directigen₁₋₂₋₃ Group A Strep) was obtained from 614 patients. All subjects who screened negative ($n=469$) received a throat culture. All subjects who screened positive ($n=145$) were treated with antibiotics, and 31 of these patients received a throat culture. Statistical analyses included calculating sensitivity, specificity, positive and negative predictive values, and prevalence.

Results: For the initial 182 patients, the prevalence of GABHS was 12 percent. Sensitivity was 95.45 percent, specificity was 96.25 percent, positive predictive value was 77.78 percent, and negative predictive value was 99.35 percent. In the second group of subjects, four false-negatives were present (negative predictive value = 99.18 percent).

Conclusions: Results of these pilot studies indicate that an extremely low percentage (<1 percent) of subjects with GABHS escaped detection with our rapid screening test methods. These results conflict with results from previous investigations, which have reported relatively low specificity and sensitivity of rapid antigen detection tests when compared with throat cultures. Results from this study support treatment protocols based on a rapid screening test as a single diagnostic test. (J Am Board Fam Pract 1995; 8:177-82.)

In the United States acute pharyngitis is the third leading reason for physician office visits, accounting for nearly 27 million office visits annually.¹ Approximately 5 to 15 percent of acute pharyngitis cases are caused by group A β -hemolytic streptococcus (GABHS).^{2,3} Until recently GABHS infections and their sequelae have not been considered a major public health problem, even though as many as 4 percent of untreated or ineffectively treated cases could lead to acute rheumatic fever.⁴ During the 1980s published reports indicated an increase in numbers of cases of acute rheumatic fever in several areas of the United States⁵⁻⁷ associated with several specific streptococcal surface M proteins.^{4,5} Severe GABHS infections have been reported recently in the press from around the world.

The best strategy to detect and treat all cases of GABHS remains controversial. Some clinicians prescribe an antibiotic for every patient who has signs and symptoms of acute pharyngitis. This method results in unnecessarily treating an estimated 85 to 95 percent of patients,^{2,3} which could result in adverse reactions, allergic reactions, and increased resistance to antibiotics. This method also adds \$10 to \$60 in costs for antibiotics to the patient's office visit. Other clinicians obtain throat cultures from all patients with acute pharyngitis, which is relatively expensive (\$17 to \$35) and time consuming (24 to 48 hours for results).

Many clinicians consider clinical characteristics, such as fever, tender cervical adenopathy, oral petechiae and exudate, and the absence of common cold symptoms, before recommending treatment or throat culture. Signs and symptoms of GABHS are nonspecific, however, and have a highly variable natural course and outcome. Overall accuracy of clinical assessment alone is about 50 percent.⁸⁻¹¹

Compounding the problem of making treatment decisions are the many patients who expect immediate antibiotic therapy to reduce symptoms

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From the School of Health, Physical Education, and Leisure Services, University of Northern Iowa, Cedar Falls, IA (SAJ), and the Waterloo Family Practice Program and the Department of Family Practice, The University of Iowa College of Medicine, Waterloo (GLH, JES). Address reprint requests to Sue A. Joslyn, PhD, Community Health Education, University of Northern Iowa, Cedar Falls, IA 50614-0241.

of acute pharyngitis. Physicians might feel compelled to satisfy the patients' desire for antibiotics.

Rapid antigen screening methods have been developed that are quick (10 minutes versus 24 to 48 hours for culture) and relatively less expensive (approximately \$10). The reported sensitivity of screening tests, however, ranges from 50 to 100 percent when compared with conventional culture methods¹²⁻²⁰ and 31 to 50 percent when compared with two-plate culture methods.²¹ If these reports are correct, many patients with GABHS would go untreated if a rapid screening test were the only basis for treatment. Most frequently, rapid screening tests are used in conjunction with throat cultures, where all negative screening tests are cultured. This diagnostic option will add a considerable expense to the majority of patients' charges.

Clinical decision making for treatment of acute pharyngitis should be based on several factors: (1) cost of diagnosis (culture or rapid screening), (2) time to diagnosis and treatment, (3) high sensitivity of the test to avoid missing patients with disease, and (4) high specificity of the test to avoid treating patients unnecessarily. The need arises for testing methods that address these concerns. We conducted a pilot study of GABHS rapid antigen testing to determine whether clinically accurate results (high sensitivity and specificity) could be obtained quickly and inexpensively with rapid antigen testing.

Methods

Adult and pediatric patients complaining of symptoms of acute pharyngitis at a community-based family practice residency program office during spring through fall 1993 were included in this study. Two separate pilot studies were conducted on this patient population. For the first study 182 consecutive patients had both throat culture and rapid screening tests performed. Throat swabs were obtained by 1 of 3 laboratory technicians by simultaneously rubbing two sterile rayon-tipped swabs (Sterile Rayon-Tipped Applicator, Abco, Milwaukee, WI) over the posterior pharynx and both tonsils (or tonsillar fossae). One swab from each pair was immediately streaked onto a blood agar plate (Strep Select Agar or sheep blood agar, Bioclinical Systems, Annapolis Junction, MD). A bacitracin disk (Taxos A disc, Becton Dickinson Microbiology Systems, Cock-

eysville, MD) was placed on the primary inoculum and allowed to incubate at 37°C. The plates were examined at 24 and 48 hours for presence of GABHS. This culture method is easily replicated and currently the standard culture method used in primary care offices. Although more sensitive culture methods are available, they are more expensive and more complicated than this method and are not necessarily practical in primary care settings.^{14-17,19,22-24}

The second swab from each patient was used to perform rapid GABHS antigen testing using Directigen₁₋₂₋₃ Group A Strep (Becton Dickinson Microbiology Systems, Cockeysville, MD) according to the manufacturer's directions. Three drops of the specimen extract were passed through a membrane impregnated with antibodies specific for group A streptococcus antigen. Antibody liposome complexes containing a pink dye were then passed through the membrane. The liposomes immediately bound any trapped group A streptococcus antigen that was present. A test was considered positive if a complete triangle could be discerned on the membrane. Faint triangles were considered positive. A pink control dot (only) was present on the membrane for a negative GABHS screen.

For the second pilot study, a rapid screening test was obtained from 614 patients, using the Directigen₁₋₂₋₃ Group A Strep test, as described above. For the 469 patients with negative screening results, a throat culture was obtained using methods described above. If screening results were positive (n=145), patients were treated with antibiotics; 31 of these patients were selected for throat culture as a convenience sample to check for proportion of false-positive screening tests.

The rationale for the second pilot study was as an analysis of available data. Because the specificity of the first study was very high, we discontinued culturing all patients but thought the subsequent data revealed important results. The number of false-positive screening tests were of much less concern than false-negative screening tests.

Statistical analyses included calculating sensitivity, specificity, positive and negative predictive values, and prevalence for the initial 182 patients. Descriptive results are presented for the subsequent 500 patients (this excludes patients who tested positive with the rapid screening and who did not receive a follow-up throat culture). Sensi-

tivity, specificity, positive predictive value, and negative predictive value for the screening test used in these pilot studies are based on results of the culture method described above. Although we recognize the limitations of this method, it remains a practical and commonly used culture method.

Results

Average age for this group of patients was 19.88 years (standard deviation 16.74 years). Fifty-one percent were aged 18 years or younger. Approximately 62 percent of the patients were female. For the first pilot study, 182 consecutive patients received both a rapid screening test and a throat culture. Results of this patient sample are categorized in Table 1. The prevalence of GABHS was 12 percent in this population (data were collected during low-prevalence seasons). Sensitivity was 95.45 percent, indicating that of all patients with GABHS, more than 95 percent were found. Specificity was 96.25 percent, which signifies that of all patients without GABHS, 96 percent were accurately categorized as such. Predictive value for a positive test was 77.78 percent, indicating that of all patients who screened positive, almost 78 percent actually had GABHS. Predictive value for a negative test was 99.35 percent, which meant that of all patients who screened negative, only 0.65 percent of cases with GABHS were missed by the screening test (one false-negative).

Results from the second group of patients are presented in Table 2. All patients with a negative screening test, along with a convenience sample of those with a positive screening test, received a throat culture. Only four false-negatives were present in this sample (negative predictive value=99.18 percent).

Table 1. Results from 182 Patients Receiving GABHS Rapid Screening Test and Throat Culture.

Screening Test	Culture	
	Positive	Negative
Positive	21	6
Negative	1	154

Sensitivity: 95.45%; specificity: 96.25%; positive predictive value: 77.78%; negative predictive value: 99.35%.

Table 2. Results from 500 Patients; Cultures on All Patients with Negative Screening Results and a Sample of Those with Positive Screening Results.

Screening Test	Culture	
	Positive	Negative
Positive	25	6
Negative	4	465

Predictive value negative: 99.18%.

Discussion

The purpose of this study was to determine whether clinically useful and accurate results could be obtained from a rapid, inexpensive screening test for GABHS in a primary care setting. Results of these pilot studies indicate that an extremely low percentage (<1 percent) of subjects with GABHS escaped detection with our rapid screening test methods.

Our study was conducted during a period of relatively low prevalence, which would make case detection more difficult. Thus, although estimates reported in this paper for sensitivity, specificity, positive predictive value, and negative predictive value were quite high, they would be conservative estimates of actual values. These results conflict with results from previous investigations, which report relatively low specificity and sensitivity of rapid antigen detection tests^{17,20,21,25-29} when compared with throat cultures. We believe these statistical differences could be a result of differences in laboratory techniques. Our laboratory technicians strictly adhered to standard techniques for throat swabs, screening tests, and culturing. If laboratory technicians did not believe subjectively they obtained a good throat swab, they would attempt repeated firm swabbing of tonsils and posterior pharynx until they were confident of a good swab. Greater accuracy of rapid screening tests might be realized with proper training, experience, and quality control.

When a large number of subjects are needed for a study of acute pharyngitis and GABHS, they are often recruited from emergency department or urgent-care settings.²⁸⁻³¹ Results and recommendations from those studies might not be generalizable to primary care office settings. Reports of studies conducted in settings similar to ours show their results to have a range of sensitivity from 45 to 93 percent and specificity from 75 to 98 percent,³¹⁻³⁴

indicating that the differences in results are due to factors other than differences in clinical settings.

Current recommendations for accuracy of GABHS diagnostic tests are less than 2 percent false-negatives and less than 10 percent false-positives.³⁵ Fewer false-negatives are acceptable, because failure to treat a patient with GABHS is considered worse than unnecessarily treating a patient who does not have GABHS. These recommendations for acceptable number of errors would yield a sensitivity of ≥ 94 percent, a specificity of ≥ 89 percent, a positive predictive value of ≥ 73 percent, and a negative predictive value of ≥ 98 percent. Results from our study are well within these guidelines and therefore support treatment protocols based on a rapid screening test as a single diagnostic test. This single test would eliminate the need for expensive and time-consuming throat cultures. In our practice the following treatment protocols have been proposed: if the laboratory technician obtains a subjectively "good" swab, and the screening test is negative, no treatment will be given. Conversely, if the rapid screening test is positive or if specific clinical signs indicate presence of GABHS, antibiotic treatment will be initiated appropriately. There will remain a very small number of patients with GABHS who have nonspecific signs and symptoms and who test negative and do not receive treatment. This problem also occurs with the commonly used throat culture methods described above, which are not 100 percent sensitive or specific.

One benefit of using a rapid screening test for diagnosis of GABHS is the ability to begin palliative measures immediately when the test is positive. Although patients infected with GABHS want a reduction in signs and symptoms as soon as possible, some researchers and clinicians prefer delaying antibiotic treatment so the patient can generate antibodies against the organism. In one study that compared immediate with delayed (48 hours) treatment, researchers found statistically significant differences in relapses (7 percent versus 2 percent, respectively), early recurrences (16 percent versus 5 percent, respectively), and late recurrences (13 percent versus 3 percent, respectively).³⁶ Previous investigators have reported no sequelae of GABHS when a patient is treated within 9 days of onset of sore throat.³⁷ Results of these studies might generate more controversy in selection of treatment regimens.

As a result of this study, we propose that further testing be done in primary care practice settings on a larger number of patients using the techniques described above. Further study would include using the throat culture method most convenient to primary care practices for reproducibility and generalizability of the results of this investigation in other primary care settings. We also recommend a study of the accuracy of GABHS rapid antigen detection testing using more sensitive and specific culture methods as the standard. Anaerobically incubated selective streptococcal agar (5 percent sheep blood agar containing crystal violet, colistin, and trimethoprim-sulfamethoxazole) is more sensitive and specific in detecting cases of GABHS^{21,38-41} and could reduce the number of false-positives found with rapid screening tests that might, in fact, be cases of GABHS.

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