Accuracy of Rapid Strep Testing in Patients Who Have Had Recent Streptococcal Pharyngitis

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Background: **Some clinicians have questioned the accuracy of rapid diagnosis of group A streptococcal pharyngitis by commercial immunochemical antigen test kits in the setting of recent streptococcal pharyngitis, believing that the false-positive rate was increased because of presumed antigen persistence.**

Methods: **We studied 443 patients – 211 cases – who had clinical pharyngitis diagnosed as group A β-hemolytic streptococcus infection in the past 28 days and compared them with 232 control patients who had symptoms of pharyngitis but no recent diagnosis of streptococcal pharyngitis. Our aim was narrowly focused to compare the rapid strep test with the culture method we used in our clinical practice.**

Results: **We found that the rapid strep test in this setting showed no difference in specificity (0.96 vs 0.98); hence, the assertion that rapid antigen testing had higher false-positive rates in those with recent infection was not confirmed. We also found that in patients who had recent streptococcal pharyngitis, the rapid strep test appears to be more reliable (0.91 vs 0.70, $P < .001$) than in those patients who had not had recent streptococcal pharyngitis.**

Conclusions: **The findings of this study indicate that the rapid strep test is both sensitive and specific in the setting of recent group A β-hemolytic streptococcal pharyngitis, and its use might allow earlier treatment in this subgroup of patients. (J Am Board Fam Pract 2002;15:261–5.)**

Streptococcal antigen testing has been an important development in the office management of patients with pharyngitis. It has improved the appropriateness of antibiotic therapy[1] and allowed earlier laboratory, evidence-based treatment of group A β-hemolytic streptococcal pharyngitis. The main reason to treat streptococcal pharyngitis is to prevent rheumatic fever. Appropriate treatment can be started within the time it takes to get results from both rapid strep testing, which assesses the presence of streptococcal antigens, and laboratory culture. Earlier treatment is preferred by many patients and might also decrease transmission, symptom duration, and suppurative complications, such as peritonsillar abscess, retropharyngeal abscess, and cervical adenitis.[2]

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Clinical criteria alone, even with the use of various scoring systems, are not reliable enough to diagnose group A β-hemolytic streptococcal pharyngitis.[3–6] Rapid strep testing has been shown to be sensitive in the range of 70% to 95% compared with the most accurate culture methods.[7–10] At our institution during the study interval our rapid strep test methods were shown by internal quality control data to detect 71% to 83% of positive cases, so it was our policy to back up negative rapid strep tests with a follow-up culture of the same swab, read at 24 and 48 hours. We thus had both methods available. When clinical judgment dictated, clinicians were able to choose one method rather than the other.

Lack of consensus within our shared group practice about the accuracy of rapid strep testing in the setting of recent streptococcal pharyngitis caused considerable confusion to patients and nursing staff. About one half of our physicians firmly asserted that the rapid strep test was not accurate when a patient had had recent streptococcal pharyngitis. They believed that the false-positive rate was substantially higher and that a 24- to 48-hour

culture was the only test indicated in this situation. This group further believed that although antibiotics might kill the streptococcal bacteria, undegraded antigenic proteins could persist even in the absence of viable streptococcal bacteria in the pharynx. Destroying an organism's cell wall or metabolic capacity might not immediately remove the antigenic proteins from the area. Because the rapid strep test is based on the presence of antigen, not on antibody testing or culture, which tests for viable organisms, the possibility of a high false-positive rate seemed plausible to many members of our group. Other members of the group believed as strongly that the test was equally accurate in either clinical circumstance.

This difference of opinion caused logistical difficulties and increased the clinical workload, because the nurse performing the culture before the physician evaluation had to find a physician, assess that physician's belief about this clinical quandary, and assign the patient to that physician. Alternatively, the nurse could risk having to do a second throat culture, conflict with the physician, and further confusion by guessing which testing method the physicians working that particular shift would chose. As a result, patients often received conflicting and inconsistent messages about what test would be done and whether it would be accurate in their particular clinical circumstances. This confusion did not improve patient satisfaction and increased waiting time.

A search of 20 years of English MEDLINE abstracts and articles failed to find this question addressed in the medical literature. Because we are a consensus driven organization, we could not solve the problem by edict, so we chose to study this focused clinical question.

It was our aim to compare the rapid strep test with the two-step culture method we used in our clinical practice to determine whether there was a difference between these methods when assessing streptococcal pharyngitis in patients who had recently been treated for streptococcal pharyngitis and those who had not.

Although additional data collection, including serial antistreptolysin-O (ASO) testing, would have answered broader clinical questions, the focus of our study was narrowed to trying to answer only the specific question of whether the rapid strep test had a substantially higher false-positive rate in the group of patients recently treated for streptococcal pharyngitis.

Methods

We elected to perform a prospective trial of the rapid strep test, comparing those patients with complaint of sore throat who had recently had streptococcal pharyngitis (infection within the past 28 days) with patients who had a sore throat but had not had streptococcal pharyngitis diagnosed in the past 28 days. Pharyngitis was defined as the subjective complaint of sore throat, dysphagia, and described exudates, with or without constitutional symptoms of fever and malaise. Electronic access to a unified laboratory database from all our clinical sites was extremely helpful in determining the time intervals since the last diagnosis and treatment of streptococcal pharyngitis. All patients complaining of a sore throat during the study interval were invited and agreed to participate.

This study was conducted at our Urgent Care Center, which has an average annual visit rate of approximately 70,000 patients per year. Medical staffing was provided by physicians (from the departments of family medicine, community pediatrics, and community internal medicine) who spent from 10% to 50% of their clinical time in this shared practice setting.

Data were collected on age, sex, the number of days since completion of antibiotics (for those who had recent streptococcal pharyngitis), and which antibiotic was used (recorded as penicillin, amoxicillin, erythromycin, other, or unknown). All patients who were given penicillin received oral penicillin V; to our knowledge none of the patients received intramuscular penicillin. Patients were requested by the nursing staff to give verbal informed consent at entry to the study. Institutional Review Board approval was sought and granted for the study. All patients who participated also agreed to sign a consent form to allow data collection for research purposes.

The study interval lasted 3.5 months, which was the amount of time required to collect data on a minimum of 200 cases and 200 controls. This number was determined by the statisticians designing the study to be necessary for statistically significant outcomes. When we designed the study, a false-positive rate of 5% or less was considered acceptable in our clinical practice. Assuming approxi-

mately one half of the 200 patients in the group with recently treated pharyngitis would have negative cultures, the study had a power of 0.9 to detect a false-positive rate of 15% or more compared with the fixed alternative of 5%. The power is higher for the combined group of 443 patients.

During the study, all specimens were screened by the rapid strep test (Abbott Testpack Plus Strep A Kit, Abbott Laboratories, Abbott Park, Ill) and by a definitive culture method (trypticase soy agar with 5% sheep blood – Beckton, Dickinson Microbiology Systems, Franklin Lakes, NJ) incubated at 35°C for 48 hours. Cultures positive for β-hemolytic streptococci were tested for *Streptococcus pyogenes* in a second step using a direct fluorescent antibody test (Dicfo Laboratories, Detroit). To determine whether the rapid strep test has a higher false-positive rate, these cultures included those that were positive by the rapid strep method from both patients who had and who had not had recent treatment for streptococcal pharyngitis.

Because we did not have data on how many days would constitute an antigen persistence effect, we studied time intervals of 0 to 1 day, l to 2 days, 2 to 3 days, 4 to 7 days, 7 to 14 days, 14 to 21 days, and 21 to 28 days since completion of treatment for streptococcal pharyngitis. Twenty-eight days was arbitrarily chosen as a cutoff for the upper limits of this effect, because 28 days coincides with our clinical triage rules requiring that patients who have had a streptococcal infection treated within 4 weeks be examined by a physician rather than receive treatment according to nurse-directed, throat-culture-only protocols.

Results

The original data set consisted of 464 observations—222 cases in which patients had recently been given antibiotics for streptococcal pharyngitis and 242 cases in which patients had not received treatment.

When study data were analyzed to comply with subsequent institutional requirements, 21 patients who had not given blanket authorization for research record review were excluded despite verbal consent having been obtained at study inclusion, leaving a total of 443 observations for analysis. There were 211 case observations of 194 patients and 232 control observations of 225 patients, with an overlap of 7 patients recorded as both cases and controls at different times during the study interval.

Table 1. Sensitivity and Specificity of Laboratory Culture and Rapid Strep Test in Patients With Recently Treated Cases of Streptococcal Pharyngitis.

Results	Culture Negative	Culture Positive
Rapid strep test negative	93	10
Rapid strep test positive	4	104
	Estimate	*95% CI*
Sensitivity	0.91	0.84, 0.96
Specificity	0.96	0.90, 0.99
Positive predictive value	0.96	0.91, 0.99
Negative predictive value	0.90	0.83, 0.95
False-positive rate	0.04	0.01, 0.10
False-negative rate	0.09	0.04, 0.15

Specificity and Sensitivity

The rapid strep test was not shown to have a higher false-positive rate in the setting of recent streptococcal infection (0.96 vs 0.98, $P = .468$). Rapid strep testing is equally specific regardless of whether a patient has had recent streptococcal pharyngitis. The rapid strep test appears to have a higher sensitivity in the recently treated group than in the control group (0.91 vs 0.70, $P < .001$) (Tables l and 2).

Other Variables

Linear regression modeling failed to find significant associations for the covariates of age, antibiotic choice, sex, or time since treatment for the case group. Because it was unclear how long an antigen persistence factor might last, time since completing treatment was divided into the following subsets for analysis: l day, 2 days, 3 days, 4 to 7 days, 8 to 14

Table 2. Sensitivity and Specificity of Laboratory Culture and Rapid Strep Test in Patients With No Recently Treated Cases of Streptococcal Pharyngitis.

Results	Culture Negative	Culture Positive
Rapid strep test negative	165	19
Rapid strep test positive	4	44
	Estimate	*95% CI*
Sensitivity	0.70	0.57, 0.81
Specificity	0.98	0.94, 0.99
Positive predictive value	0.92	0.80, 0.99
Negative predictive value	0.90	0.84, 0.94
False-positive rate	0.02	0.01, 0.06
False-negative rate	0.30	0.19, 0.43

days, 15 to 21 days, 21 to 28 days, and a small subset of unknown number of days.

A surprising finding turned up in the analysis of the group of patients who recently had treatment with antibiotics. Ninety percent of the false-negatives occurred in those treated with penicillin, approaching statistical significance ($P = .06$). Dosing regimens for penicillin V were twice a day, for amoxicillin three times a day, and for erythromycin four times a day. Despite this finding, the combined sensitivity of the rapid strep test overall was still substantially higher in the case than in the control groups.

Discussion

This study has shown in a statistically valid manner that rapid strep testing performs as well for the subgroup of patients who have recently had treatment for streptococcal pharyngitis as it does for patients who have not had recent streptococcal pharyngitis, if not better. We were reassured that the findings appeared equally valid across the variables of age, sex, and time since treatment. We do not have an explanation for the higher predictive value of the rapid strep test in the group with recently treated streptococcal pharyngitis. Perhaps antigen levels could be higher in this group, because those patients with recurrence start from a higher inoculum. It would also be possible that those with recurrent streptococcal infection might have more intense exposure from family contacts compared with community contacts.

We were able to instruct our nursing staff that all patients with recently treated pharyngitis who complained of a new episode of pharyngitis could be tested by the rapid strep method. This new directive saved nursing time and expedited patient care, because nurses no longer had to seek out the physician to determine which test to do. It has also decreased friction at work and conflicting messages to patients about our testing procedures.

The finding of a higher false-negative rate in patients who had been given penicillin V approached statistical significance ($P = .06$). All but one patient with false-negative findings in the case group had taken penicillin, whereas none had taken amoxicillin or erythromycin. We have no plausible explanation for this finding and assume it was a random event, although certainly it would bear further investigation if other studies had similar findings. The literature suggests that other agents, particularly cephalosporins and possibly expanded spectrum macrolides, might have higher eradication rates than penicillin.[11,12]

Controversy still surrounds the question of whether early treatment is more or less desirable than delayed therapy for group A β-hemolytic streptococcal pharyngitis.[13–15] The nonsuppurative sequelae are either treated adequately by both approaches, as in the case of rheumatic fever, or are not well prevented by either approach, as in the case of post-streptococcal acute glomerulonephritis.[2] Preventing rheumatic fever still remains the primary and most convincing reason to treat streptococcal pharyngitis.

Compassion to reduce suffering and improve symptoms, population-based concern to diminish transmission, and the potential to decrease such suppurative complications as abscess formation are interpreted by many clinicians to favor early treatment. Combined with the economic and social incentives for patients to return to work, school, and daycare, there are compelling reasons that push some clinicians toward earlier treatment when laboratory-based evidence is available.

The findings of this study indicate that the rapid strep test is both sensitive and specific in the setting of recent group A β-hemolytic streptococcal pharyngitis and might allow earlier treatment in this subgroup of patients for those clinicians who believe early treatment is appropriate.[16] Our findings show that there are still substantial false-negative rates with rapid antigen testing. Thus, our protocols require backup culturing of all specimens that test negative by a current rapid antigen method. It is possible that this substantial false-negative rate for the antigen test, especially in the control group, is partially offset by data suggesting delaying treatment might help decrease recurrence rates for streptococcal pharyngitis.

This degree of accuracy clearly leaves room for protocol revision as antigen detection methods improve and approach the accuracy of culture techniques. We also welcome further evidence-based research on whether early or delayed treatment of streptococcal pharyngitis is optimal for patient outcomes.

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