Comparison of Tests for Streptococcal Pharyngitis

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Rapid streptococcal antigen detection tests are now an alternative to throat cultures for diagnosing group A streptococcal pharyngitis. By applying existing knowledge to 1,000 theoretical patients, this study compares the diagnostic accuracy, costs, and benefits of "gold standard" throat cultures, less specific office cultures, and rapid streptococcal tests. With the new rapid tests, appropriate treatment for streptococcal pharyngitis can be started promptly without waiting for a culture result. Benefit-cost analysis of existing data shows that rapid tests have the potential to be more efficient than throat cultures in minimizing medical costs and time lost because of illness. These conclusions remained true over widely ranging assumptions about streptococcal prevalence, carrier rate, rheumatic fever attack rate, test cost, and test accuracy.

The throat culture has long been the "gold standard" for diagnosing group A β-hemolytic streptococcal pharyngitis. Recently a number of rapid tests that detect group A streptococcal antigens directly from throat swabs have become available.[1-3] This article compares the costs and benefits of these new tests with those of throat cultures.

Deciding whether to use a gold standard throat culture, a less specific office throat culture, or a rapid antigen detection test involves compromises. None of them is perfectly accurate, and each has other disadvantages: serologically confirmed throat cultures processed in a reference laboratory have withstood the tests of time and remain the most accurate method for diagnosing group A β-hemolytic streptococcal pharyngitis, but there is a one- or two-day delay in obtaining the result, and the charge for the test is often considerably higher than for the other tests. When cultures are processed in the office laboratory, group A streptococci are usually identified presumptively on the basis of inhibition of colony growth by a bacitracin disk. This method is less expensive and less time consuming than serologic grouping, but it leads to some false-positive results. The new rapid streptococcal antigen detection tests allow treatment to be started immediately, and their cost falls between office cultures and reference laboratory cultures. However, the wide range in reported sensitivities of these tests has led some physicians to question whether the results are trustworthy.

The purpose of this article is to compare the three tests in terms of the expected results when testing 1,000 hypothetical patients. For each method of testing, the expected number of patients with undiagnosed streptococcal illness, the number receiving antibiotics unnecessarily, the total days of illness, and the financial costs of testing and of medical complications were calculated. These numbers are the results that concern physicians when they choose a test for streptococcal pharyngitis.

METHODS

The costs and benefits of testing 1,000 hypothetical patients were calculated in three steps. First, assumed values for the prevalence of streptococcal pharyngitis, the carrier frequency, and the accuracy of the diagnostic tests were used to calculate the expected number of patients in each of four groups. Those pa-

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tients with acute group A streptococcal pharyngitis have either a true-positive or a false-negative test. Carriers[4,5] and patients with nonstreptococcal pharyngitis have either a true-negative or a false-positive test. In the second step the number of patients in each group was multiplied by the costs of that outcome in time and money. Unlike previous benefit-cost analyses[6,7] of throat cultures, the utility of the patients' time was not converted to dollars. Finally, the costs of all four outcomes were totaled for each method of testing.

Reported culture sensitivities[8-13] range from 0.80 to 0.99. As up to 5 percent of group A β-hemolytic streptococci are consistently missed because they demonstrate no zone of inhibition around a bacitracin disk,[14,15] these measured sensitivities may be up to 5 percent too high.

Carriers also contribute to erroneous results, as they can have positive throat cultures and rapid tests but no acute streptococcal infection, ie, no delayed rise in serum antibodies.[4,5] While carriers complicate clinical studies, their effect was explicitly included in the benefit-cost analysis presented here. Reported carrier frequencies[4,6,16] vary from 0.05 to 0.6, expressed as a fraction of asymptomatic patients tested, so the percentage of positive cultures that result from carriers can be large.

When throat cultures are processed in the office laboratory, identification of group A streptococci is usually made presumptively, based on sensitivity to bacitracin, and the final step of grouping the streptococci is omitted.[15] The price of this convenience is a small number of false-positive results: from 3 to 17 percent of non-group A streptococci are susceptible to bacitracin.[14,15] If the prevalence of group A β-hemolytic streptococci is 0.3 or less, the resulting specificity of an office culture[14,15] is between 0.93 and 1.0.

Clinical trials of two commercially available latex agglutination tests show sensitivities ranging from 0.81 to 0.95 and specificities from 0.91 to 1.0.[2,3,17]

The outcome for each group was estimated as follows:

True-negative results. The average number of days of illness for a patient with correctly diagnosed nonstreptococcal pharyngitis varied between two and seven days. The time lost depends on the prevailing nonstreptococcal illnesses. Also, if only those patients with more severe symptoms are tested,[18] the average time loss of those tested will be greater. Since from one to two days are required to obtain a culture result, the time lost by a patient with a true-negative result is independent of which test is used. (The use of bacitracin disks on the primary culture plate to reduce the delay in obtaining results greatly reduces the accuracy, so the majority of cultures require 24 to 48 hours.[19])

False-positive results. If a rapid test is positive, it is assumed the patient will be given an antibiotic immediately and instructed to wait at least one day before resuming normal activity. Thus, the average time loss per patient is the same as for a true-negative result. When a culture is used, there is usually a one- or two-day delay before diagnosis.

True-positive results. Recent studies have shown that early treatment with an antibiotic reduces the duration of symptoms by 24 to 48 hours.[3,20,21] It was assumed that waiting for a culture result before starting treatment extends the total duration of the illness by only one day. (Later, the consequences of eliminating this delay by starting antibiotic therapy before knowing the culture result are analyzed.) Although some patients contract rheumatic fever in spite of treatment, this complication is ten times less likely than when no treatment is given.[6]

False-negative results. Undiagnosed cases are subject to an increased number of complications, the most serious of which is rheumatic fever. The number of patients with this complication is the same when two tests have the same sensitivity. When tests with different sensitivities are compared, it is necessary to include the cost of the cases of rheumatic fever occurring because of additional false-negative results from the less sensitive test. False-negative results for patients who have taken antibiotics prior to testing are not included in the calculations because of a lack of data regarding the effect upon test results.

Because rapid tests are less specific than gold standard throat cultures, additional patients will receive antibiotics unnecessarily, and more allergic reactions will result. In the present analysis the probability estimates of Pantell and Bergman[7] for oral penicillin have been used, and their statements of medical costs have been increased by 15 percent, based on comparisons with current diagnosis-related grouping allowances. The chance of a severe reaction that results in hospitalization is 8.3 in 100,000 with an average cost per case of $1,472. The estimated average additional time lost is 14 days. The chance of a mild allergic reaction is 1.7 in 1,000 with no significant time loss on average.

The financial and time expenditures associated with the office visit need not be estimated because these costs are the same, whichever test is used. Regarding test costs, only the difference between the charges for a culture and a rapid test enters the analysis. Current costs of rapid tests[3] are approximately $2 per test, $1 more than the estimated cost of the materials for an office culture.[15,22] Although the cost of materials for a culture with streptococcal grouping is approximately $3,[23] more labor is required, and the charge by reference laboratories typically exceeds the cost of a rapid test by $5 to $15.

RESULTS

Gold Standard Throat Cultures vs Rapid Tests

The range of sensitivities of gold standard throat cultures, 0.80 to 0.99, is similar to that of the newer rapid tests, 0.81 to 0.95. Based on these data, cultures and

TABLE 1. OUTCOMES OF TESTING 1,000 PATIENTS FOR STREPTOCOCCAL PHARYNGITIS WHEN PREVALENCE AND CARRIER RATES ARE BOTH 0.2

	Rapid Test	Culture	Treat and Culture	Office Culture
Number of patients				
No streptococcus, treated	194	170	170	194
Steptococcus, treated	170	170	170	170
Streptococcus, not treated	30	30	30	30
Rheumatic fever	0.02	0.02	0.02	0.02
Allergic reactions				
Mild	0.62	0.58	1.7	0.62
Severe	0.03	0.03	0.08	0.03
Losses prevented with rapid test				
Time lost (patient-days)	—	340	0	364
Medical expenses	—	$9,830	$14,530	−$1,000*

Rapid test is more expensive

rapid tests are first assumed to have the same sensitivity, so there is no difference in the number of undiagnosed cases and associated complications. Later, this assumption is removed.

The first two columns of Table 1 show the expected outcomes when 1,000 hypothetical patients with pharyngitis are tested with a rapid test and a gold standard throat culture assuming the prevalence and carrier rates are 0.2, the sensitivities of both tests are 0.85, the specificity of rapid tests is 0.96, the average nonstreptococcal illness lasts two days, culture results are available in two days, and test cost difference is $10.

The frequency of allergic reactions is also listed in the table, showing that the probable total time loss for all of the patients is less than one day. Use of the rapid test will result in one additional severe reaction for every 500,000 patients tested and one additional mild reaction for every 24,000 tested. The financial cost of the severe reactions is $2.94 per 1,000 patients tested. This cost, plus that of treating an extra 24 patients with penicillin ($7 each for a 10-day course), is a small amount compared with the savings of $10,000 in test costs using rapid tests. Column 2 shows that using a rapid test also saves 340 patient-days per 1,000 patients tested. The savings is 170 patient-days for a culture taking one day.

Other reasonable assumptions were used in the calculations (sensitivity analysis) to determine whether they change the conclusions. Varying the prevalence and carrier rates from 0.05 to 0.5, test sensitivity from 0.81 to 0.95, rapid test specificity from 0.91 to 1.0, length of nonstreptococcal illness from two to seven days, and test cost difference from $5 to $15 demonstrates that using a rapid test saves a minimum of 40.5 patient-days per 1,000 people tested. A minimum of $5,000 is saved in test costs, and the maximum increase in expense resulting from severe allergies is $9.86 per 1,000 tested (.0067 extra severe allergies). Thus, the rapid test offers better benefit-cost performance for all situations evaluated.

Treating Everyone While Waiting for the Culture

Starting antibiotic therapy before the culture result is available eliminates the delay in treating patients with true-positive results. Column 3 in Table 1 shows the outcomes of this strategy. Compared with a rapid test that has the same sensitivity as the culture (0.85), there is no significant difference in the time lost. However, more than 2.5 times as many severe allergic reactions can be expected from treating everyone with antibiotics pending the culture result. The additional test cost savings with a rapid test is $10,000, and 636 fewer prescriptions for penicillin are written.

Office Cultures vs Rapid Tests

Column 4 in Table 1 shows the outcomes for an office culture with specificity 0.96. The number of patients treated, and thus the number of allergic reactions, is the same as with a rapid test. Using the culture saves $1,000 in test costs, but an extra 364 patient-days are lost, so the rapid test is more cost effective. If the culture results are available in one day, 170 patient-days are lost, so the rapid test remains cost effective.

Using a Less Sensitive Rapid Test

The sensitivities of cultures and rapid tests have been assumed to be equal. To determine how using a less sensitive test affects the conclusions, the sensitivity of the rapid test was reduced to 0.80, and the culture sensitivity was raised to 0.95. In this case it is necessary to estimate the attack rate of rheumatic fever for the 30 additional patients with false-negative rapid tests. This risk is subject to considerable uncertainty.

If the risk is 6.4 in 10,000 as used by Thompkins,[6] more than 52,000 patients must be tested for the rapid test to lead to one additional case of rheumatic fever. In testing that number of patients, the rapid test would save (1) 48 person-years for the uncomplicated outcomes, (2) $520,000 in test costs, and (3) 15 percent fewer allergic reactions. These advantages must be compared with the potential consequences of a single case of rheumatic fever. An estimate[7] of the probable value of preventing one case of rheumatic fever, including the risks and monetary equivalents for disability and death from cardiac involvement, is $19,244.

In the sensitivity analysis of Pantell and Bergman,[7] the attack rate of rheumatic fever is varied up to 0.003, which is higher than they think is likely. If this upper limit is used, an extra $110,000 in test costs and 10 person-years in time lost in uncomplicated cases would be spent for each case of rheumatic fever prevented by using a culture rather than a rapid test.

DISCUSSION

Fortunately for the purposes of choosing a test, the analysis shows that, even with conservative assumptions about the value of early treatment and the attack rate of rheumatic fever, the conclusions are not especially sensitive to the particular numbers chosen. Over a wide range of assumptions, rapid tests are more efficient than throat cultures in minimizing expected medical costs and time lost because of illness.

The outcomes of testing using throat cultures and rapid tests depend on more than simply the cost and accuracy of each test. For example, the number of carriers unnecessarily receiving antibiotics depends on the carrier rate, and it differs for tests with different sensitivities. Other influences used in predicting the outcomes of testing include the prevalence of group A β-hemolytic streptococcal pharyngitis, the duration of nonstreptococcal illnesses, the delay for processing cultures, the effect of early treatment on the duration of symptoms, the frequency of allergic reactions, the attack rate of rheumatic fever, and the length of time a patient remains contagious after treatment has been started. Also complicating the analysis, rheumatic fever and allergic reactions are rare but serious outcomes, making it difficult to use clinical experience as a guide in weighing the relative risk of each. The benefit-cost calculation presented here allows all of these influences to be taken into account.

Priorities differ regarding the compromises made in choosing a method of testing. For example, some physicians may place the highest value on minimizing unnecessary antibiotic use or on minimizing the number of missed cases of streptococcal illness. To be of value to physicians with different priorities, the outcomes of testing have been expressed in practical terms: cost, time lost from activities, and the number of patients in each clinical group.

One important assumption in the analysis is that early treatment reduces the duration of streptococcal pharyngitis by at least one day. Recent studies have supported this estimate,[1,20,21] but it has been a controversial subject.[1] If early treatment has no effect on the duration of symptoms, one of the major assumed advantages of rapid tests would be lost.

A number of criticisms of the sensitivity of rapid tests have been published.[2,3,23,24] Three principal concerns have been stated:

First, the sensitivities of two rapid tests were only 0.62 and 0.64 when an inhibitory (antibiotic-containing) culture medium was used as the standard of comparison.[23,24] However, the standard noninhibitory cultures used in many laboratories also miss 30 percent or more of patients with positive inhibitory cultures.[24] To be consistent, criticisms based on studies using selective media should also advise against the use of culture materials frequently used in reference laboratories. The clinical significance of the additional positive cultures found with selective media is unknown.[15]

Second, rapid tests may be less accurate when performed by office staff rather than trained laboratory technicians. It has been assumed here that in practice rapid tests and office cultures achieve the accuracy demonstrated in published studies. The example of a low sensitivity rapid test presented earlier emphasizes the importance of operating these tests with careful attention to technique. The accuracy of any office test, whether it is a culture or a new rapid test, should be verified in a clinical trial in the office where it will be used.

Third, among trials of rapid tests, wide variations in sensitivity have been found. Review of the literature shows, however, that similarly wide variations in culture techniques and sensitivities are also reported. The physician is faced with a choice among different methods of testing, each with a large range of reported sensitivities. With such uncertainty, there is no substitute for a careful office trial before deciding whether to use a rapid test.

Finally, advice based only on test sensitivity neglects the other issues discussed in this analysis.

In summary, benefit-cost analysis based on the results of clinical trials shows that for patients with no special risk factors, rapid antigen detection tests have the potential to be more efficient than throat cultures in minimizing the expected medical costs and the time lost because of streptococcal pharyngitis. Choosing a test involves compromises that have been made explicit by this analysis.

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