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Rapid Diagnosis of Pharyngitis Caused by Group A Streptococci

Michael A. Gerber[1]* and Stanford T. Shulman[2]

Division of Infectious Diseases, University of Cincinnati College of Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 45229,[1] and Department of Pediatrics, The Feinberg School of Medicine, Northwestern University, and Division of Infectious Diseases, The Children's Memorial Hospital, Chicago, Illinois 60614[2]

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INTRODUCTION

Because the signs and symptoms of pharyngitis due to group A beta-hemolytic streptococci (GABHS) pharyngitis can be nonspecific, establishing an accurate clinical diagnosis often is difficult even for experienced physicians. Therefore, it has been standard practice to seek laboratory confirmation of the diagnosis. Culturing a throat swab on a sheep blood agar plate (BAP), as first described by Breese and Disney in 1954 (6), has been accepted as the standard for the diagnosis of GABHS pharyngitis for nearly five decades (3).

The major disadvantage of culturing throat swabs on BAPs is the delay (overnight or longer) in obtaining the results. In the early 1980s, commercial rapid antigen detection tests (RADTs) were developed for the rapid identification of GABHS directly from throat swabs. All such rapid tests involve an acid extraction step to solubilize GABHS cell wall carbohydrate and to identify its presence by an immunologic reaction. Although RADTs generally are more expensive than BAP cultures, the advantage they offer over the traditional procedure is the speed with which they can provide results. Rapid identification and consequent prompt treatment of patients with GABHS pharyngitis can reduce the risk of spread of GABHS, can allow the patient to return to school or work sooner, and may reduce the acute morbidity of this illness (23, 61).

* Corresponding author. Mailing address: Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave. MC5019, Cincinnati, OH 45229-3039. Phone: (513) 636-5594. Fax: (513) 636-7039. E-mail: Michael.gerber@cchmc.org.

The first RADTs used the latex agglutination technique. This is a relatively insensitive method with somewhat unclear end points. Newer tests based on enzyme immunoassay (EIA) techniques offered more sharply defined end points as well as increased sensitivity. More recently, a RADT using the optical immunoassay (OIA) technology has become available. Data suggest that this test may be more sensitive than other RADTs and perhaps may even be as sensitive as BAP cultures. However, there has been some reluctance to recommend the OIA for routine use without backing up negative test results with a confirmatory BAP culture.

The latest commercial RADTs for the diagnosis of GABHS pharyngitis to be developed are two tests that employ molecular biology methods. The first is a chemiluminescent single-stranded DNA probe that detects specific rRNA sequences unique to GABHS (Group A Streptococcus Direct Test; Gen-Probe, Inc., San Diego, Calif.) (10, 34, 35, 60, 73). Several investigations have demonstrated that this test has a sensitivity between 86 and 94.8% and a specificity between 95 and 100% compared to BAP cultures. This test takes approximately 2 h to complete; because of the multiple steps involved, the special equipment required, and the need to batch specimens, this is not a point-of-care test. The second test is a one-rapid-cycle, real-time PCR method (LightCycler Strep-A assay; Roche Applied Science, Indianapolis, Ind.) (79). In the only published report available, this test was demonstrated to have a sensitivity of 93% and a specificity of 98% compared to BAP culture. This test takes approximately 1.5 h to complete; because of the special equipment involved and the need to batch specimens, this also is not a point-of-care test. However, because only about 3 min of personnel time is required, this test would be

adaptable for use in smaller laboratories that are experienced in molecular biology-based testing.

Currently a wide variety of RADTs are available for diagnosing GABHS pharyngitis. In this paper, we review the available data with respect to the accuracy of these tests and their utilization. We also identify areas where gaps in knowledge exist.

PERFORMANCE CHARACTERISTICS

The results obtained with RADTs for GABHS are influenced by the skill, experience, and expertise of the individual who is actually obtaining the throat swab and performing the RADT (23, 43). In addition, with some RADTs that have a relatively subjective end point, strong observer bias can be apparent (36). When duplicate throat swabs obtained simultaneously from the same patient are studied, there is a relationship between the amount of growth on a BAP culture performed with one swab and the sensitivity of the RADT performed with the other (26, 46). That is, heavy growth is associated with very high RADT positivity rates while light growth is generally associated with lower RADT rates of positivity. Increasing the colony count and the quantity of antigen available by using two simultaneously collected throat swabs can increase the yield on the BAP culture significantly and also increases the sensitivity of the RADT (45). Increasing the colony count and the quantity of antigen present by using a 2-h broth culture enhancement of the throat swab before performing the RADT also increases the sensitivity significantly (5). In addition, it has been shown that the performance of RADTs increases as the pretest probability of GABHS being present (as predicted by the presence of specific clinical findings) increases (17). There is no single fixed value for the performance of a particular RADT for the diagnosis of GABHS pharyngitis; the performance is a function of the clinical characteristics of the illness of the patients selected for testing (17). Because of this "spectrum bias," RADT performance is not an absolute feature of a given test.

TABLE 1. Sensitivity and specificity of RADTs compared with cultures

Culture medium	RADT method	Sample size (no. of patients)	Sensitivity (%)	Specificity (%)	Reference
BAP	MM[a]	767	88.6	97.8	60
BAP	MM	277	86	95	73
BAP	MM	1,103	92.4	99.6	35
BAP	MM	318	91.4	97	34
BAP + THB	MM	520	94.8	100	10
BAP	MM	384	93	98	79
BAP + THB	OIA	200	80	89	42
BAP	OIA	301	91.4	95.6	62
THB	OIA	301	90.4	94.1	62
BAP	OIA	505	93.2	95.0	22
BAP	OIA	505	94.8	98.8	22
BAP	OIA	262	77	97	68
BAP	OIA	690	97	94	16
THB	OIA	690	95	97	16
THB	OIA	475	97.4	95.6	32
THB	OIA	800	98.9	98.4	32
THB	OIA	424	84.2	95.7	15
BAP	OIA	233	79.5	96.9	59
BAP	OIA	86	85	95	71
BAP + THB	OIA	363	89	96.5	45
BAP + THB	OIA	263	77	62	33
THB	OIA	413	89	93	75
BAP + THB	OIA	801	91.5	94.8	35
BAP + THB	OIA	500	83	89	63
BAP	OIA	77	78	90	1
BAP + THB	OIA	302	75.5	97.1	30
BAP + THB	OIA	2,113	84	93	24
BAP + THB	OIA	520	86.1	97.1	10
BAP + THB	EIA	302	92.6	92.8	30
BAP	EIA	182	95.5	96.3	41
BAP	EIA	777	89	96	20
BAP	EIA	1,449	52.6	98.2	86
BAP	EIA	258	95	100	70
BAP	EIA	258	87	100	70
BAP + RADT	EIA	322	80		64
BAP	EIA	351	96.9	97.4	18
BAP	EIA	454	89.9	95.8	47

[a] MM, molecular biology-based method.

CRITERION STANDARD

When one attempts to evaluate the sensitivity and specificity of a given RADT for GABHS by comparing the results obtained by the RADT to a criterion standard, the choice of standard is critical. If a relatively insensitive criterion standard is chosen, the RADT may be evaluated erroneously because the apparent sensitivity is elevated and the apparent specificity is lowered. Conversely, if the criterion standard is too sensitive (for example, one that is capable of detecting a single GABHS organism), the RADT may be evaluated erroneously because the apparent sensitivity is lowered and the apparent specificity is elevated.

In most clinical studies, RADTs for confirming the diagnosis of GABHS pharyngitis have been compared with BAP cultures as the criterion standard (see Table 1). However, comparisons of a RADT with a BAP culture are complicated by the fact that there is no universally accepted procedure for performing a BAP culture (23). The yield of GABHS from a BAP culture may vary with the type of medium, the atmosphere of incubation, the duration of incubation, the number of swabs obtained, the specific grouping procedure used, and whether the culture is performed in a physician's office or in a diagnostic laboratory (72). Fundamental questions about whether a RADT performed in a practice setting should be compared with a BAP culture performed in a similar setting or with a BAP culture performed in a diagnostic microbiology laboratory still remain unanswered (23). It has also been suggested in several studies that culturing the pledget (the plug separating the transport medium and swab in a transport tube) in Todd-Hewitt broth (THB) significantly increases the yield of GABHS compared with that obtained in standard BAP culture using the same throat swab (15, 16, 22, 32). However, in other studies, the yields of GABHS from BAP and THB cultures were comparable (62, 68). Because of the reported 5 to 10% discordance between duplicate throat cultures (23), the question also arises whether single or duplicate throat swab cultures should serve as the criterion standard against which a RADT is measured (23). Some have suggested that RADTs should be compared to a combination of an aerobically incubated BAP and an anaerobically incubated selective streptococcal agar plate (84, 85). Others, however, found that the use of an anaerobically incubated selective streptococcal agar plate added little to the yield of GABHS from a BAP culture incubated aerobically (18, 62).

Although the sensitivity of a BAP culture performed in a

clinical practice setting may be relatively low compared with a highly sensitive criterion standard (e.g., the BAP or THB culture performed in a diagnostic microbiology laboratory), it is important to consider how sensitive the BAP culture should be ideally to provide clinically valuable information. As an extreme example, it was proposed that a PCR procedure rather than a culture procedure be used as the criterion standard for RADT evaluations (42). However, it is not clear that identification of subjects with negative BAP cultures but positive RADT or PCR results would result in better clinical outcomes, since the clinical significance of very small numbers of GABHS organisms is doubtful.

BAP cultures are used frequently to confirm the clinical diagnosis of GABHS pharyngitis in U.S. office practice settings (37, 69). If a substantial number of children with GABHS pharyngitis were not being diagnosed and treated properly because of insufficient sensitivity of a single BAP culture, one would anticipate many cases of suppurative complications (e.g., peritonsillar abscess and retropharyngeal abscess) and many cases of one of the nonsuppurative complications of GABHS pharyngitis (e.g., acute rheumatic fever). Suppurative complications are rarely observed, and although there were several focal outbreaks of acute rheumatic fever in the mid to late 1980s in this country, there is little if any evidence to suggest that these outbreaks resulted from deficiencies in BAP culture procedures. There is also no evidence that the recent, well-publicized cases of invasive GABHS disease and GABHS toxic shock syndrome, which are usually unrelated to pharyngeal infections (74), resulted from deficiencies in BAP cultures. Because the sensitivity of an office BAP culture is generally considered sufficient for use alone in the diagnosis of GABHS pharyngitis (even with its variable methodology) (3, 12, 14), it follows that an alternate test with sensitivity approximating that of the office BAP and with adequate specificity should be equally acceptable when used alone for the diagnosis of GABHS pharyngitis.

COST AND FEASIBILITY

Charges for various diagnostic tests for GABHS pharyngitis vary widely. In some settings, BAP cultures may cost as little as $5 or as much as $50 while RADTs may cost as little as $10 or as much as $60. Therefore, physicians should be aware of how much patients are charged for BAP cultures, RADTs, and the combination. Medicare and Medicaid reimbursement for RADTs for GABHS pharyngitis (CPT code 87430) is $16.01, reimbursement for a GABHS direct probe (code 87650) is $26.90, and reimbursement for a GABHS amplified probe such as PCR (code 87651) is $47.00. Because OIA-based RADTs are more expensive (with a physician's cost of reagents from $4 to $6.95 per test), time-consuming (approximately 12 min per test), and labor-intensive than many EIA procedures, it may not be acceptable for all practice settings. The chemiluminescent DNA probe test has multiple steps, requires special equipment, and takes at least 2 h to perform. Therefore, it is unacceptable for an office laboratory or an emergency room/clinic laboratory, but it could be practical for a large hospital or commercial laboratory that can batch specimens (35, 60).

The simplicity of some RADTs is exemplified by a study in which sixth- and seventh-grade students achieved a high level of performance with a RADT that is a polyclonal antibody membrane filter separation EIA, despite having no formal laboratory background, no previous method-specific training, and limited self-training (19).

The performance of RADTs by nurses and physicians in the office setting can decrease delays in specimen transport and shorten turnaround time. On the other hand, having experienced technologists performing RADTs may improve the accuracy of the results.

SENSITIVITY AND SPECIFICITY

The great majority of the RADTs that are currently available have a high specificity (i.e., 95% or greater) compared with BAP cultures (Table 1). This means that false-positive test results are unusual and therefore that therapeutic decisions can be made on the basis of a positive test with a great degree of confidence and without need for BAP culture confirmation. The sensitivity of most of the currently available RADTs is between 70 and 90% compared with BAP culture. Because of concerns about the adequacy of the sensitivity of many RADTs, it has been recommended that a negative RADT be confirmed with a BAP culture (3, 12, 14). A representative sample of published reports that address the sensitivity and specificity of RADTs is presented in Table 1.

Many patients with negative RADT results and a simultaneously obtained positive BAP culture have only small numbers of GABHS colonies on their BAP culture. Therefore, it has been suggested that most false-negative RADT results occur in patients who are merely chronic streptococcal carriers and not truly infected with GABHS. Because only patients with bona fide acute streptococcal infections (positive culture for GABHS and evidence of a serologic response to GABHS antigens) are at risk of developing acute rheumatic fever, this suggestion, if correct, would have important implications for the role of RADTs in the primary prevention of rheumatic fever. However, studies have demonstrated that a large proportion of patients with false-negative RADT results are actually infected with GABHS and are not merely streptococcal carriers (25). Therefore, it is often recommended that a negative RADT result be confirmed by a conventional BAP culture (3, 12, 14).

REASONS FOR FALSE-POSITIVE AND APPARENT FALSE-POSITIVE AND FALSE-NEGATIVE RADT RESULTS

False-positive RADT results are unusual. They may be produced by the presence in the pharynx of *Streptococcus milleri* group (SMG) strains that express the group A carbohydrate antigen. SMG strains are commensals that are frequently alpha-hemolytic or nonhemolytic and therefore are difficult to identify on a BAP culture (40, 65). It is not clear how often this phenomenon occurs because there are no published data on the prevalence of SMG strains that express the group A carbohydrate antigen. A recent report suggested that the false-positivity rate with RADTs may be as high as 15% compared with BAP cultures; however, the presence of an SMG strain expressing the group A carbohydrate or another explanation for the false-positive RADT results was identified in only a

very small proportion of these cases (40). Other reports have found much lower false-positivity rates (Table 1).

Apparent (but not true) false-positive RADT results are produced on rare occasions by either nutritional variants of group A streptococci or nonhemolytic group A streptococci (40, 66). Nutritional variants of group A streptococci and nonhemolytic group A streptococci possess the group A carbohydrate and therefore can produce a positive RADT result. However, because of their unusual nutritional requirements or absence of beta-hemolysis, such strains are not apparent on a BAP culture. Therefore, the BAP culture will be read mistakenly as negative for group A streptococci.

Apparent (but not true) false-negative RADT results may be produced on a BAP culture by the misidentification of beta-hemolytic organisms that lack group A carbohydrate antigen as group A streptococci. Large colonies of SMG that are beta-hemolytic, as well as large-colony, beta-hemolytic strains of group C or group G streptococci; may be bacitracin sensitive and thus may be misidentified as group A streptococci on a BAP culture if bacitracin sensitivity is utilized as the basis for categorizing organisms as members of group A. However, because of the absence of the group A carbohydrate antigen, these isolates produce a negative RADT result (31).

RADT AND PHARYNGITIS DUE TO GROUP C AND GROUP G STREPTOCOCCI

A potential concern about using RADT alone without BAP culture confirmation of negative results is that patients with acute pharyngitis due to group C or group G streptococci will not be identified. The clinical features of pharyngitis due to both group C and group G streptococci are similar to those of GABHS pharyngitis with fever, mild to moderate sore throat, pharyngeal exudate, and cervical adenitis. Usually group C pharyngitis affects an older population, particularly teenagers and young adults. Several studies have demonstrated that group C streptococci are a relatively common cause of acute pharyngitis among college students and among adults seeking care in an emergency room (54, 78). In addition to endemic pharyngitis, group C streptococci can cause epidemic food-borne pharyngitis after ingestion of contaminated products such as unpasteurized cows' milk. Family and school outbreaks of pharyngitis due to group C streptococci also have been described (44). While there have been several well-documented food-borne outbreaks of pharyngitis due to group G streptococci and a single community-wide, respiratory outbreak in a pediatric population, the etiologic role of group G streptococci in acute, endemic pharyngitis remains unclear (29). Acute rheumatic fever has not been described as a complication of pharyngitis due to either group C or group G streptococci. Acute glomerulonephritis has been reported to be an extremely unusual complication of pharyngitis due to group C streptococci but a causal relationship between pharyngitis due to group G streptococci and acute glomerulonephritis has not been clearly established. Therefore, the primary reason for identification of either group C or group G streptococci as the etiologic agent of acute pharyngitis is to initiate antimicrobial therapy that may reduce the clinical impact of the illness. However, there is no convincing evidence from controlled studies of a clinical response to antimicrobial therapy in patients with acute pharyngitis and either group C or group G streptococci isolated from their pharynx. Therefore, the clinical significance of missing a case of pharyngitis due to group C or group G streptococci because of use of RADT appears to be limited.

CLIA AND ITS IMPACT ON RADTS

The Clinical Laboratory Improvement Act (CLIA) is federal legislation dating to 1967 but originally did not apply to physician office laboratories. CLIA 88 is a series of amendments to the previously existing law that were passed by Congress in 1988, to be effective in 1992 and to extend to physician office laboratories for the first time. CLIA 88 was stimulated in large part by inaccurate laboratory results, especially related to Pap smears. Since 1992, physician office laboratories have been required to meet certain standards in order to be certified to perform all laboratory tests, except for tests considered to be sufficiently uncomplicated to qualify as CLIA-waived tests.

As noted above, a variety of different technologies have been employed in the various RADTs, including latex agglutination, EIA, OIA, and chemiluminescent gene probes. For at least the first two technologies, many different configurations may be employed by various manufacturers. Some of these tests (primarily latex agglutination and EIA based) are CLIA waived, while the others are performed only in laboratories that have been certified to perform such tests. By definition, the latter tests are more complex and require more laboratory expertise while the former utilize few steps and require no special equipment or laboratory expertise.

The impact of the CLIA 88 legislation on practices related to the diagnosis of GABHS pharyngitis was swift. A study by Schwartz et al., published in 1994, documented that 24% of questionnaire respondents had discontinued streptococcal testing in the office since the implementation of CLIA 88 in 1992 (69). The effect was particularly noticeable in rural areas and in pediatric offices, with 72% of the latter indicating reduced test menus. Binns et al. surveyed Illinois pediatricians in 1988 and 1996 regarding the practices of their physician office laboratories (2). They identified a decline in the number of offices offering throat cultures for GABHS from 63 to 34% ($P < 0.001$) and a decline in the number performing RADTs from 77 to 64% ($P < 0.05$). For solo practitioners, the latter decline was from 66 to 39% ($P < 0.001$).

COMPARATIVE DATA

Remarkably few published studies have compared the performance of CLIA-waived tests for GABHS pharyngitis directly to that of CLIA-nonwaived tests. The published literature is composed almost exclusively of studies in which a specific test utilizing a specific method was compared to one or more culture techniques but not to other RADTs. In addition, relatively few studies have examined the performance of various RADTs in the office setting, as opposed to the hospital or diagnostic microbiology laboratory setting. In 1997, Schwartz published one of the few reports in which two RADTs, the OSOM Strep A test (Wyntek Diagnostics, San Diego, Calif.) and the QuickVue In-Line Strep A test (Quidel, San Diego, Calif.) were directly compared (70). Both tests were found to

be 100% specific compared to BAP cultures, with sensitivities of 95 and 87%, respectively. Sensitivity was related directly to the intensity of growth on the culture plate.

Pillai et al. presented data in abstract form in 1999 that compared the sensitivity, specificity, positive and negative predictive values, and overall accuracy of BAP cultures and RADTs as performed in 18 private pediatric offices in the greater Chicago area (S. Pillai, L. Dennis, B. Sehwarte, C. Ciesielski, and S. Shulman, Prog. Abstr. XIV Lancefield Int. Symp. Streptococci and Streptococcal Dis., abstr. 513, 1999). Results obtained in individual offices (using the procedures then standard in these offices) were compared with results for a simultaneously acquired throat swab that was shipped to a streptococcal research laboratory and processed by a broth culture technique. In this study, the performance of the RADTs appeared comparable to that of the BAP cultures when both were processed and interpreted in the office. Additionally, the CLIA-waived tests performed as well as the moderately complex tests, although the numbers were small and direct comparisons with duplicate specimens were not performed.

Roosevelt et al. compared the performance of a CLIA-waived RADT performed by nurses in the emergency room of a large children's hospital to a moderately complex test performed in the hospital microbiology laboratory (64). Duplicate throat swabs were obtained simultaneously for the two assays. In this study, there was a high degree of concordance of results ($P < 0.001$) and there was no significant difference in the performance of the tests.

RECOMMENDATIONS OF ADVISORY COMMITTEES

A number of advisory groups have formulated recent recommendations regarding the use of RADTs for the diagnosis of GABHS pharyngitis. For example, the Committee on Infectious Diseases of the American Academy of Pediatrics recommends that when a patient suspected of having GABHS pharyngitis has a negative RADT, a BAP culture should be performed to confirm the results of the RADT (12). However, because of the high specificity of RADTs, a positive test result does not require confirmation with a BAP culture. RADTs using newer technologies such as OIA or DNA probes may be more sensitive than earlier RADTs, and some experts think that these newer tests are sufficiently sensitive to be used without BAP culture backup. The Committee on Infectious Diseases suggests that physicians who use such tests without BAP culture backup compare their results with those of BAP culture to validate the presence of adequate RADT sensitivity in their practice (12).

The Practice Guidelines for the Diagnosis and Management of Group A Streptococcal Pharyngitis of the Infectious Diseases Society of America also states that positive RADT results do not require culture confirmation (3). However, for children and adolescents, they recommend that a negative RADT result be confirmed with a BAP culture unless the physician has determined in his or her own practice that the RADT utilized performs comparably to a BAP culture. The Infectious Diseases Society of America guidelines suggest that because adults have both a lower incidence of GABHS pharyngitis than children and adolescents and an extremely low risk of contracting acute rheumatic fever, negative RADT results for adults need not be confirmed with BAP cultures (3).

The Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the American Heart Association published recommendations in 1995 for the diagnosis and treatment of streptococcal pharyngitis (14). These recommendations indicate that RADTs are useful and can be utilized diagnostically, especially when positive results are obtained. These 8-year-old recommendations include the suggestion that negative RADTs be confirmed by BAP cultures.

The Centers for Disease Control and Prevention, the American College of Physicians—American Society of Internal Medicine, and the American Academy of Family Physicians have recently published a clinical practice guideline for acute pharyngitis in adults (13). This guideline recommends that all adults with pharyngitis be screened for the presence of the four "Centor criteria": history of fever, tonsillar exudate, absence of cough, and tender anterior cervical lymphadenopathy. Those with none or one of these criteria need not be tested or treated. The appropriate options for adults with two or more criteria are the following: (i) test by RADT and treat only those with positive results; (ii) use a RADT for those with two or three criteria and treat only those with a positive result or with four criteria; or (iii) use no RADT and treat only those with three or four criteria. In contrast to other guidelines directed primarily at children (12), but consistent with recent guidelines directed primarily at adults (3), this guideline recommends that BAP cultures not be required for confirmation of negative RADT results (13). Some have expressed concern that this approach might result in the administration of antimicrobial therapy to an unacceptably large number of adults with nonstreptococcal pharyngitis (4). In addition, it has been suggested that these recommendations should be confirmed by clinical trials before clinicians abandon long-held teachings regarding the need for bacteriologic confirmation in patients suspected to have GABHS pharyngitis on the basis of clinical and epidemiologic findings before antimicrobial therapy is provided (4).

ACTUAL PRACTICES

There is relatively little published information about how physicians in practice actually use RADTs for the diagnosis of GABHS pharyngitis. In 1994, Schwartz et al. (69) sent surveys to 1,060 board-certified pediatricians in seven western states. There were 679 responses, of which 531 were appropriate for comparison with contemporaneous recommendations from the American Academy of Pediatrics. An optimal approach (defined as RADT alone when the results were positive and RADT backed up by BAP culture when the results were negative) for at least 80% of patients was employed by only 44% of the responding pediatricians. Of the pediatricians who responded, 17% used RADT in an appropriate manner for fewer than 50% of their patients. In 1997, Hofer et al. (37) reported the results of a survey sent to 1,000 board-certified pediatricians throughout the United States from September to November 1991. Of the 510 respondents, 20% used RADTs for the diagnosis of GABHS pharyngitis in a manner not consistent with contemporaneous recommendations from the American Academy of Pediatrics.

These studies demonstrate that many physicians do not fol-

low recommended guidelines for using RADTs to diagnose GABHS pharyngitis, particularly including the confirmation of negative RADT results with BAP cultures. The implementation of CLIA in 1996 served as an incentive for manufacturers of diagnostic test to develop new RADTs that did not require CLIA certification (CLIA-waived tests). Over the past several years, numerous CLIA-waived RADTs for the diagnosis of GABHS pharyngitis have been marketed in the United States; however, there are virtually no published data about how physicians are using these CLIA-waived tests in practice.

MEDICAL DECISION MAKING

It has been estimated that approximately 18 million patients sought care for a sore throat in the United States in 1996, making it the sixth leading reason to visit a physician (67). Unfortunately, some physicians perform a BAP culture or RADT for almost every patient with an upper respiratory tract infection. Such indiscriminate use of these diagnostic tests not only contributes to the excessive cost of health care but also does not serve patients well.

Whether one uses a BAP culture or a RADT, it is important that they be used selectively in order to remain useful and cost-effective diagnostic procedures. When attempting to decide whether to perform a test such as a BAP culture or RADT on a particular patient, the epidemiologic and clinical findings should be considered (80). For example, in temperate climates, GABHS pharyngitis is a disease of the winter and early spring and primarily affects children between 3 and 18 years of age. Therefore, physicians should have a lower threshold for performing throat cultures or RADTs in the winter and spring and for children aged 3 to 18 years. Awareness of much GABHS in the community or the presence of a specific viral agent of pharyngitis at a particular time can also be helpful in deciding whether to perform a diagnostic test for GABHS, as is a history of close contact with a well-documented case of GABHS pharyngitis. In addition, there are certain clinical findings which strongly suggest either a GABHS (tender anterior cervical lymph node, palatal petechiae) or a nonstreptococcal (rhinorrhea, cough, hoarseness, diarrhea) etiology of pharyngitis (80).

Selective use of these diagnostic tests not only increases their rate of positivity but also increases the percentage of test-positive patients who are truly infected while reducing the percentage of test-positive patients who are merely chronic streptococcal carriers. Consequently, there is an increase in the percentage of test-positive patients who would benefit from antimicrobial therapy and a reduction in the percentage of those who, as carriers, would not benefit from such therapy. In addition, because of the presence of a selection bias with RADTs, selective use of these tests may also increase their sensitivity.

To evaluate the potential clinical impact of RADTs for the diagnosis of GABHS pharyngitis, one should consider carefully the specific reasons for diagnosing and treating GABHS pharyngitis. One important reason is to prevent acute rheumatic fever (81). Prevention of acute rheumatic fever is thought of in terms of primary prevention (prevention of the initial episode) and secondary prevention (prevention of recurrent episodes). Primary prevention depends on identification of all patients with GABHS infections of the upper respiratory tract and their treatment with a course of antimicrobials that will eradicate GABHS (9). Rapid diagnosis is not essential; antimicrobial therapy can be initiated as late as 9 days after the onset of GABHS pharyngitis and still effectively prevents acute rheumatic fever (9). However, effective primary prevention requires that the diagnostic test used have a high degree of sensitivity in order to identify all patients with GABHS pharyngitis at risk of developing acute rheumatic fever.

A second reason to diagnose and treat GABHS pharyngitis is to reduce the associated acute morbidity. Children with GABHS pharyngitis who have received immediate treatment with the appropriate antibiotic demonstrate significantly faster resolution of clinical signs and symptoms than do those for whom antimicrobial therapy was temporarily withheld (61). Additional evidence suggests that the earlier in the course of GABHS pharyngitis that antimicrobial therapy is initiated, the greater is the potential impact (8). In contrast to their relatively low sensitivity, the currently available RADTs consistently show high specificities of about 95 to 100% (23, 26). At such high specificities, RADTs can identify patients with GABHS pharyngitis who would benefit from early antimicrobial therapy and would consequently be able to return to school or work more quickly.

GABHS are spread by respiratory secretions and droplets, and another reason for diagnosing and treating GABHS pharyngitis is to prevent the spread of GABHS to others. Even untreated patients become asymptomatic within a few days and, on return to normal activities, may serve as an occult source for spread of GABHS to others. In contrast, 95% of treated patients are culture negative within 24 h of the initiation of appropriate therapy and may return safely to school or work (61). Evidence from school-, military-, and family-based investigations suggests that the sooner antimicrobial therapy is initiated, the lower the risk of transmission of GABHS to others (23, 26). Because of their high specificity, RADTs can rapidly identify patients with GABHS pharyngitis who pose a transmission risk and who could return to normal activities sooner with timely initiation of antimicrobial therapy.

Finally, diagnosing and treating GABHS pharyngitis can prevent the development of suppurative complications such as peritonsillar and retropharyngeal abscesses, as well as cervical lymphadenitis. Although the use of antimicrobials to treat GABHS pharyngitis clearly reduces the incidence of these suppurative sequelae, it is not clear that speed is essential (39). Therefore, there is little or no advantage to RADTs over BAP cultures in this respect.

Are there any potential disadvantages to prompt diagnosis and early initiation of antimicrobial therapy for GABHS pharyngitis? The concern has been raised that this approach might interfere with the development of immunity and consequently could result in a higher recurrence rate as well as an older population of susceptible patients (52). Although antimicrobial therapy can interfere with the production of type-specific (anti-M protein) antibodies, there is no well-documented evidence that early therapy results in a shift in the age-related incidence of GABHS pharyngitis to an older population (7). Pichichero et al. reported that patients with GABHS pharyngitis who were treated immediately with penicillin had significantly more recurrences than did patients treated more than 48 h after diag-

nosis (57). However, this investigation was weakened by a lack of GABHS serotyping of isolates and an inability to distinguish recurrences from new infections. It was not confirmed by other investigators (27). In addition, there is some evidence that non-type-specific immunity may be important in preventing recurrent GABHS infections (21).

Taking all these issues into consideration, physicians should examine their threshold for testing for GABHS in patients with acute pharyngitis. Both cost-effectiveness and positive predictive value may be unacceptably low when the prevalence of GABHS is low. Physicians also should note that the greater the likelihood of problems with follow-up, the lower the threshold should be for using a RADT. Even a relatively insensitive RADT may be superior to clinical judgment alone. Studies indicate that even experienced clinicians diagnose GABHS pharyngitis correctly only 75 to 80% of the time when the diagnosis is based on clinical assessment alone (6, 7).

Despite their limitations, the use of RADTs in certain populations significantly increases the treatment rate for patients with GABHS pharyngitis compared with BAP cultures. For example, in a report by Lieu et al. (48), 255 children who presented to a busy urban emergency room with acute pharyngitis were evaluated. A BAP culture and RADT were simultaneously performed for each patient. The RADT had a sensitivity of only 55% compared with the BAP culture. However, 80% of patients with positive BAP cultures received appropriate antimicrobial therapy when RADTs were used as an adjunct to the BAP cultures, compared with a 57% treatment rate among patients who had GABHS pharyngitis diagnosed on the basis of a positive BAP culture alone ($P < 0.05$). This difference, at least in part, reflects the fact that the need to call back patients after BAP cultures have been incubated is eliminated for many by the use of RADTs

It is important to note that the majority of patients with acute pharyngitis have nonstreptococcal infection and therefore do not benefit from antibiotic therapy (61). Nevertheless, many physicians treat pharyngitis patients with antibiotics while awaiting results of the BAP culture; in two surveys, approximately 40% of physicians admitted to continuing antibiotic treatment even after the BAP culture was reported as negative (11, 38). Rapid exclusion of GABHS pharyngitis by a negative RADT could avoid the use of unnecessary antibiotics in many patients. However, before a practice decides to use a RADT without BAP culture backup, it should compare the RADT and BAP culture results to validate adequate RADT sensitivity in the practice. This is particularly important in areas of the country that are experiencing a resurgence of acute rheumatic fever.

In 1998, Needham et al. performed an investigation to determine whether the availability of results from a RADT for GABHS improved the management of patients with acute pharyngitis (55). Physician's intent to prescribe antimicrobial therapy based on clinical impression alone was compared to physician's intent once the result of the RADT was known for 465 consecutive pediatric and adult patients with acute pharyngitis. They found that use of the particular RADT they studied (which had a sensitivity and specificity of 87 and 97%, respectively, compared with BAP culture) substantially improved physicians' decisions to prescribe appropriate therapy. Had the RADT alone guided therapeutic choice at the initial encounter, physicians would have prescribed appropriate antimicrobial therapy for 95% of the patients. The investigators concluded that neither clinical assessment nor BAP culture would add significantly to the outcome achieved when a RADT, with performance characteristics like those of the test used in this study, is used to assist in management of patients with acute pharyngitis.

In 1990, Meier et al. investigated the impact of the introduction of a RADT in an inner-city community health center on the use of antimicrobials in patients with negative test results (53). They compared antimicrobial-prescribing behavior for a 7-month period during which BAP cultures were the primary diagnostic tests for patients with acute pharyngitis to a 7-month period during which a RADT was the primary diagnostic test. They found that use of the RADT significantly reduced the rate of antimicrobial therapy in patients with negative test results. In a limited analysis, the investigators also found that the savings in antimicrobial therapy avoided in patients with negative test results offset the increased cost of RADT compared to BAP cultures.

Webb et al. examined the incidence of suppurative and nonsuppurative complications of GABHS pharyngitis in a population served by a large suburban medical center during two different periods (83). During the first 2-year period, diagnosis of GABHS pharyngitis was made almost exclusively on the basis of BAP cultures, while during the second 2-year period, this diagnosis was made almost exclusively on the basis of a sensitive RADT without BAP culture confirmation of negative results. A total of 30,036 patients were evaluated for pharyngitis during the 4-year period, and there was no difference in the incidence of either suppurative or nonsuppurative complications of GABHS pharyngitis between the two study periods.

Cost-Effectiveness

In 1998, Webb performed a decision analysis using conditions in a large, suburban, pediatric practice to determine which of four strategies for the management of children with acute pharyngitis (treat all, use RADT alone, use BAP culture alone, use RADT with BAP culture confirmation of negative results) was most cost-effective (82). Using data from 13 published studies in which this particular RADT (an OIA) and BAP culture were evaluated against a variety of criterion standards, this RADT was assumed to have a sensitivity and specificity of 89.1 and 95%, respectively, while the BAP culture was assumed to have a sensitivity and specificity of 83.4 and 99%, respectively. Although the strategy of treating all children with acute pharyngitis with antimicrobial therapy was the most cost-effective, this strategy was not recommended because of concerns about the promotion of antimicrobial resistance (which could not be included in the model) and about the large number of allergic reactions induced in children who did not have confirmed GABHS pharyngitis. Of the strategies in which a diagnostic test was employed, use of a RADT with performance characteristics similar to those of the test used in the model without BAP culture confirmation of all negative RADT results was the most cost-effective.

In 1999, Tsevat and Kotagal performed a decision analysis to determine the cost-effectiveness of seven different strategies for managing children with acute pharyngitis: no testing or

treatment, treat all, BAP culture only, RADT #1 with sensitivity of 85.9% and specificity of 94.3% only, RADT #2 with sensitivity of 80.8% and specificity of 89.5% only, RADT #1 with backup BAP culture for negative results, and RADT #2 with backup BAP culture for negative results (77). At a baseline prevalence of 20.8% for GABHS pharyngitis and with all tests performed at a local reference laboratory, BAP culture only was the most cost-effective strategy. When all testing was office based, BAP culture only was still the most cost-effective strategy.

In 1993, Majeed et al. in Kuwait performed a decision analysis to determine the cost-effectiveness of four different strategies for managing children with acute pharyngitis: treat all with benzathine penicillin G, treat with benzathine penicillin G on the basis of clinical diagnosis, treat with benzathine penicillin G on the basis of RADT, and treat with oral penicillin on the basis of RADT (49). The last strategy, using RADT and treating positive patients with a 10-day course of oral penicillin, was determined to be the most cost-effective.

Neuner et al. recently reported a detailed cost-effectiveness analysis of the diagnosis and management of adults with acute pharyngitis. The investigators compared five management strategies: no diagnostic testing or treatment, empirical treatment with penicillin with no diagnostic testing, BAP culture using a two-plate selective technique, OIA testing with BAP culture confirmation of negative results, and OIA testing alone. Assuming a 10% prevalence of GABHS among adults with pharyngitis, empirical treatment without diagnostic testing was the least effective strategy. Although the other strategies were similarly effective, the BAP culture was the most cost-effective (56).

In a recent investigation designed specifically to address the cost-effectiveness of using a RADT without BAP culture confirmation of negative test results, Mayes and Pichichero retrospectively reviewed the experience in their private pediatric practice with two different RADTs during a 3-year period from January 1996 through May 1999 (51). During this 3-year period, 11,427 RADTs were performed: 8,385 were negative and 3,042 were positive. A confirmatory BAP culture was performed for 8,234 (98.2%) of the negative RADTs; only 200 (2.4%) of the 8,234 patients with negative RADTs had a positive confirmatory BAP culture. A cost analysis showed that while the cost of performing confirmatory BAP cultures was high, the cost of complications arising from missed GABHS infections would be very low because false-negative RADT results and sequelae are infrequent and rare, respectively. The investigators concluded that BAP culture confirmation of negative RADT results in patients with acute pharyngitis is costly and may not be medically necessary for most patients, given the current availability of highly sensitive RADTs.

RADT AND SUSCEPTIBILITY TESTING

One of the problems with using RADTs rather than BAP cultures to diagnose GABHS pharyngitis is that the isolates of GABHS causing the pharyngitis are not available to test for antibiotic susceptibility. Despite the use of penicillin for almost 50 years to treat GABHS infections, there has been no significant change in the in vitro susceptibility of GABHS to penicillin, nor has there been a single, well-documented report of a clinical isolate of GABHS that is resistant to penicillin (28). Although erythromycin resistance among GABHS had been a major problem in Japan and in Finland, it has not been a problem in the United States (28). However, Martin et al. recently reported a clonal outbreak of erythromycin-resistant GABHS pharyngitis in the Pittsburgh area in which 48% of the isolates of GABHS from the children in one school were erythromycin resistant (50). While focal outbreaks of GABHS infections due to erythromycin-resistant strains have been described in the United States in the past, there is no evidence of widespread erythromycin resistance among strains of GABHS. In fact, Tanz et al. recently reported the results of a national surveillance of 972 pharyngeal isolates of GABHS collected during the 2000 to 2001 season and almost 2,000 isolates collected during the 2001 to 2002 season, in which only 4.4% of the isolates were erythromycin resistant (R. R. Tanz, W. Kabat, K. Kabat, B. Beall, and S. Shulman, Prog. Abstr. 40th Annu. Meet. Infect. Dis. Soc. Am., abstr. 110, 2002). Although it is important to continue national surveillance for resistance to macrolides among pharyngeal isolates of GABHS, susceptibility testing on a routine basis is not indicated. Therefore, the inability to perform antibiotic susceptibility testing in cases of GABHS pharyngitis diagnosed solely on the basis of a RADT result should not be clinically significant.

GAPS IN KNOWLEDGE

Currently available published data are inadequate to allow definitive conclusions to be made regarding the relative performance characteristics of the various RADTs for GABHS pharyngitis. In the very few published studies available, striking differences between performance characteristics of CLIA-waived and moderately complex tests were not apparent. However, more office-based studies are needed to adequately address this issue.

In addition to the paucity of peer-reviewed publications in this area, another major problem is the variability of the criterion standard against which individual RADTs have been compared.

The clinical setting may also dictate the way in which comparative data should be considered. For example, the performance of a RADT compared to a BAP cultures in the setting of an emergency room of a large hospital with a microbiology laboratory that is fully staffed by certified microbiology technologists may be different from the performance in the setting of a private physician office that lacks such highly skilled laboratorians. Therefore, recommendations regarding back-up BAP cultures when RADTs are reported to be negative may need to vary with the setting in which care is delivered. This is also an area in need of additional well-designed studies.

There is an obvious paucity of clinical studies that have directly compared various rapid tests and culture techniques for diagnosing GABHS pharyngitis. This has resulted in a vacuum of information, with resulting confusion about the relative merits of various diagnostic modalities.

It is apparent that there is a need for direct comparative studies of CLIA-waived and moderately complex RADTs for GABHS pharyngitis by using a standardized method. In addition, the rarity of serious life-threatening consequences of acute GABHS pharyngitis in the United States today suggests

the need for careful cost-benefit and risk-benefit analyses of different diagnostic strategies in various clinical settings. The individual office laboratory should take care to verify the performance in that office of its chosen diagnostic method compared to standard BAP cultures performed in that office.

CONCLUSION

The development of easy-to-perform RADTs for the diagnosis of GABHS pharyngitis has altered clinical practice substantially. Although very high specificity is apparent with virtually all of the various available RADTs, the sensitivities of these assays vary. Assessment of performance characteristics, especially sensitivity, is highly unstandardized, with variously performed culture techniques used as comparators, and this accounts for much of the reported variability in sensitivity among different RADTs. Studies in which CLIA-waived and moderately complex RADTs are compared directly are lacking. Recommendations for the clinical utilization of RADTs should reflect the clinical setting in which they are performed (hospital, private office, or clinic), cost issues (managed care, cost of individual tests), and the availability and expense of non-RADT tests (throat cultures). Only limited cost-effectiveness data exist, and they are markedly influenced by the assumptions made regarding test performance as well as the risks and costs associated with certain outcomes. It would be prudent for clinicians to establish that a specific RADT performs satisfactorily with respect to throat cultures in their own practices before relying solely on RADTs for the diagnosis of GABHS pharyngitis. This can be done by performing both culture and RADT on duplicate or the same specimens and assessing the level of concordant results. This is particularly important in communities in which cases of acute rheumatic fever continue to occur. Because many physicians apparently do not follow recommended guidelines for using RADTs to diagnose GABHS pharyngitis, particularly the confirmation of negative RADT results with BAP cultures, the availability of a RADT that does not require BAP culture confirmation could improve patient care.

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