Comparative Reliability of Clinical, Culture, and Antigen Detection Methods for the Diagnosis of Group A Beta-Hemolytic Streptococcal Tonsillopharyngitis

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Nearly every patient presenting to the primary care physician with a sore throat comes with the provisional diagnosis of streptococcal tonsillopharyngitis according to the patient, parent, or both. Various approaches have been advocated for dealing with this frequent clinical problem. Some advocate treating every patient with a sore throat with penicillin, others attempt to differentiate on clinical grounds those with nonstreptococcal pharyngitis and selectively culture only those patients demonstrating typical signs and symptoms of streptococcal infection, and others favor routine laboratory confirmation of possible group A beta-hemolytic streptococcal (GABHS) infection through a throat culture or an antigen detection test (rapid strep test). After studying this clinical dilemma for the past 10 years involving more than 65,000 throat cultures from actively ill children with pharyngitis (Table 1), the

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best approach has become clear to us: to diagnose GABHS tonsillopharyngitis accurately, you must take a throat culture. The other approaches should be discouraged through education of physicians regarding the shortcomings of the alternatives.

CULTURE NO ONE, TREAT EVERYONE

Sore throat is the third most common reason for physician office visits in the United States.1 The charge for an office throat culture varies. Our practice currently charges approximately $5 for a throat culture. In some communities, throat cultures can be processed by a local health department at no charge to patients. At the opposite extreme, if a throat culture is sent to a hospital microbiology laboratory for complete identification of all organisms isolated, a charge in excess of $35 (with antibiotic sensitivities, over $70) could be anticipated. Thus, there can be

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## Table 1

**Throat Cultures, Elmwood Pediatric Group, 1980 to 1990**

<table>
<thead>
<tr>
<th>Year</th>
<th>Primary Acute Cultures</th>
<th>Cultures Negative</th>
<th>Cultures Positive</th>
<th>% Positive</th>
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<tr>
<td>1980</td>
<td>5700</td>
<td>4733</td>
<td>1284</td>
<td>22.5</td>
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<tr>
<td>1981</td>
<td>5170</td>
<td>4418</td>
<td>1011</td>
<td>19.6</td>
</tr>
<tr>
<td>1982</td>
<td>5130</td>
<td>4243</td>
<td>1033</td>
<td>20.1</td>
</tr>
<tr>
<td>1983</td>
<td>5515</td>
<td>4573</td>
<td>1251</td>
<td>22.7</td>
</tr>
<tr>
<td>1984</td>
<td>5932</td>
<td>5939</td>
<td>1352</td>
<td>22.8</td>
</tr>
<tr>
<td>1985</td>
<td>5686</td>
<td>4657</td>
<td>1396</td>
<td>24.6</td>
</tr>
<tr>
<td>1986</td>
<td>5648</td>
<td>4653</td>
<td>1315</td>
<td>23.3</td>
</tr>
<tr>
<td>1987</td>
<td>5521</td>
<td>4052</td>
<td>1346</td>
<td>24.4</td>
</tr>
<tr>
<td>1988</td>
<td>6719</td>
<td>5581</td>
<td>1518</td>
<td>22.6</td>
</tr>
<tr>
<td>1989</td>
<td>7265</td>
<td>5980</td>
<td>1713</td>
<td>23.6</td>
</tr>
<tr>
<td>1990</td>
<td>7177</td>
<td>5984</td>
<td>1590</td>
<td>22.2</td>
</tr>
<tr>
<td>Total</td>
<td>65,463</td>
<td>54,813</td>
<td>14,809</td>
<td>22.6</td>
</tr>
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</table>

A significant cost associated with obtaining and processing throat cultures, and this cost could be eliminated by culturing no one and treating everyone with "a sore throat."

In the last published study of physician practices with regard to clinical management of tonsillopharyngitis, Cochi et al. found that:

- pediatricians are much more likely than family practitioners to obtain a culture from every patient with acute sore throat,
- only 20% of pediatricians (but more than 40% of all primary care physicians) always begin antibiotic treatment of tonsillopharyngitis before culture results are available,
- an additional 75% of pediatricians (and 55% of all primary care physicians) sometimes start antibiotic therapy before knowing culture results, and
- 74% of pediatricians (but only 58% of primary care physicians) who start treatment before knowing culture results discontinue therapy if the culture results are negative.

These findings support the position that the cost of a throat culture cannot be justified if it does not influence therapy.

Clinical studies on the prevalence of GABHS tonsillopharyngitis in pediatric and adult populations are quite relevant to consideration of the "treat everyone" philosophy. Widely quoted prevalence rates of GABHS tonsillopharyngitis in children indicate that 30% of the pediatric age group with sore throats harbor GABHS. However, because these studies were performed during the streptococcal season and generally in the peak pediatric age population (children aged 6 to 12 years), they overestimate the prevalence of disease for all children at all seasons of the year. At the Elmwood Pediatric Group, we generally obtain cultures from children of any age, but particularly from age 3 years to age 18 years if GABHS is suspected on clinical grounds. Our suspicion level is generally high, especially in the streptococcal season (September through May), in children and adolescents with sore throat and exudative tonsillitis, who have no cough, coryza, or hoarseness. Using these criteria, our track record at Elmwood Pediatric Group (a practice of pediatricians with a long history of research in streptococcal disease) indicates that we suspect GABHS pharyngitis in our suburban pediatric practice far more often than it actually occurs (Table 1).

These are sobering statistics since they would indicate that the philosophy of culturing no one and treating everyone would over treat 85% of the pediatric population. Furthermore, among patients with acute pharyngitis and a positive GABHS throat culture are carriers suffering from acute viral sore throat with GABHS colonization. Therefore, treating everyone with sore throat results in overtreating approximately more than 90% of children who are at risk for GABHS sequelae.

The “cost-effectiveness” argument of the “treat everyone” approach can be challenged on several fronts. Unnecessary treatment with penicillin costing $5 to $10 of 90% or more of patients with sore throat is of problematic value. Perhaps the proper price for a throat culture obtained in a physician’s office in any given community should be low enough so as not to be a significant burden to the patient or to be a deterrent to the cost-conscious physician from procur-
Widely quoted prevalence rates of GABHS tonsillopharyngitis in children indicate that 30% of the pediatric age group with sore throat harbor GABHS.

It is not good medicine to treat a disease without having made a diagnosis. However, there are other issues beyond the strictly financial considerations relating to the consequences of indiscriminate penicillin use in the treatment of presumed streptococcal sore throat. These are: 1) the risks of penicillin side effects including anaphylaxis, 2) unnecessary pressure on the indigenous flora resulting in the production of tolerant or resistant bacteria, and 3) unnecessary alterations in human ecology (changing the natural state of balance between natural flora and potential pathogens).

Regarding the risk of penicillin side effects and anaphylaxis, this risk is seen as so trivial or unlikely to the pediatrician as to not generally be given much weight. Yet 2% to 5% of patients receiving penicillin experience an adverse event. Typically, this involves gastrointestinal upset, rash, neutropenia, thrombocytopenia, and mucusitis. The possibility of indiscriminate penicillin use producing the emergence of resistant or tolerant streptococci has also long been ignored as an extremely unlikely occurrence. Unfortunately, tolerant streptococci have now been described in three GABHS outbreaks.4-6 The influence of penicillin on the indigenous throat flora favoring the emergence of beta-lactamase (penicillinase) producing “co-pathogenic” strains has been a third long-ignored possible consequence of excessive penicillin treatment. Yet Brook7 has shown that even a single course of penicillin can produce a doubling of the number of beta-lactamase producing strains in the oropharynx. Colonization with these beta-lactamase producing strains may result in subsequent upper and lower respiratory infections that can only be successfully treated with broader spectrum antimicrobial agents. More recently, studies by Roos et al8 have shown that alpha streptococci compete with GABHS for pharyngeal epithelial cell colonization. These alpha streptococci through elaboration of bacteriocins are part of the natural host defense against GABHS pathogenic colonization. Penicillin eradicates these "protective" alpha streptococci providing an enhanced opportunity for colonization with pathogenic GABHS.

What are the downside risks of not giving penicillin treatment to all patients with tonsillopharyngitis? The most widely discussed reason is the loss of patient satisfaction. The patient wants penicillin for his or her sore throat, and the physician feels compelled to satisfy that desire. Receiving a prescription for an antibiotic makes the patient feel like the visit was worthwhile. On the contrary, we would argue that with appropriate patient education, this expectation can be overcome and used to the advantage of physician and patient alike. Due to the influence of Breese and Disney,9 in Rochester, nearly all pediatricians obtain throat cultures on patients with possible GABHS tonsillopharyngitis. If one does not take a throat culture, then the physician is open to the criticism of being "unscientific" and indiscriminate in his or her use of antibiotics. As such, through patient and physician education, a mutual understanding has emerged that a "quality" physician obtains throat cultures and an educated patient expects throat cultures for proper diagnosis of GABHS tonsillopharyngitis and doesn’t expect to be given an antibiotic for every "sore throat" complaint.

CLINICALLY DIAGNOSING GABHS PHARYNGITIS

The signs and symptoms of GABHS tonsillopharyngitis are nonspecific. This makes the clinical diagnosis of this infection difficult even for the most experienced physician. This was the conclusion of the Elmdoor Pediatric Group founding partners, Breese and Disney, in 1954 in the publication of their landmark paper, “The Accuracy of Diagnosis of Beta Streptococcal Infections in Clinical Grounds.”9 Using throat cultures on every patient to confirm or refute their clinical diagnosis in a prospective study, these investigators were able to clinically predict positive and negative throat cultures for GABHS with 75% and 77% accuracy, respectively. The classical symptoms of GABHS tonsillopharyngitis were established to be sore throat, dysphagia, fever, headache, abdominal pain, vomiting, and the absence of cough, coryza, and hoarseness. Classical signs were described to include moderately to very inflamed tonsillar pharyngeal tissues associated with a moderate to large amount of yellowish exudate, and in some cases, palatal petechiae. An important associated laboratory finding was elevation of the white blood cell count in excess of 12 500/cu mm.

Epidemiologically, the age incidence of infection was shown to peak between 5 and 11 years, the peak months to be September through May (in Rochester, New York), and the typical onset of symptoms to be acute (less than 24 hours from the onset of sore throat to significant discomfort). In 1961, Stillerman and Bernstein reevaluated the prospects of making a clinical diagnosis of streptococcal pharyngitis.10 Their conclusions were virtually identical to those of Breese and Disney, and an accompanying editorial comment continued on page 802.
The most widely used test for the differentiation of GABHS from non-GABHS strains is the bacitracin sensitivity test. With that publication is noteworthy: "If you are entirely comfortable selecting which pharyngitis patients to treat 10 days with penicillin, perhaps you don't understand the situation!"

In 1971, Honikman and Massell evaluated 6093 respiratory and febrile illnesses experienced by children to devise simple guidelines that would allow for the detection of most GABHS infections while eliminating the need for taking throat cultures in the majority of non-GABHS illnesses. The results of their analysis led to the recommendation that throat cultures be taken in all illnesses with pure or predominant sore throat and fever of any degree, and also in all other illnesses with an oral temperature of ≥101°F even in the absence of sore throat.11

In 1977, Breeze described a simple scoring system for the diagnosis of GABHS pharyngitis following an evaluation of 20,000 acute respiratory illnesses in children studied in the Elmwood Pediatric Group.12 The scoring system included the following nine factors:

- Season of the year,
- Age of the patient,
- Presence or absence of fever,
- Sore throat,
- Cough,
- Headache,
- Abnormal pharynx,
- Abnormal anterior cervical glands, and
- Total white blood cell count.

Patients with few points (18-25) and with many points (30-38) could be predicted to not have GABHS infection (94% accuracy) or to have GABHS infection (78% accuracy). Unfortunately, the vast majority of children presenting with sore throat fell in the intermediate point group (25-30) where the accuracy was approximately 50%. When the Breeze scoring system was validated in a teaching hospital13 in 892 patients, it was found that the system was most useful in predicting culture-negative patients (80% accurate). However, although not highlighted in this article, it is noteworthy that the white blood cell count as part of the scoring system was infrequently used and that the prevalence of GABHS in the population studied was low (50% in the Elmwood Pediatric Group population and 24% in the teaching hospital population).

In a more recent study by Poses et al,14 10 physicians...
recorded their treatment decision and estimated probability of GABHS infection. For patients at a University Student Health Service who presented with a sore throat, 4.9% of throat cultures were positive for GABHS. The physicians overestimated the probability of a positive culture for 81% of their patients, and their estimates and treatment decisions were strongly associated. Of 104 patients treated before culture results were available, only 8 had positive cultures. The physicians' gross overestimation of GABHS infection appeared due to the failure to recognize the low culture positivity rate in the young adult population, their giving undue importance to weakly predictive or highly intercorrelated clinical features, and a bias favoring treatment.

At the Elmwood Pediatric Group, considerable weight is given to the white blood cell count in the clinical differentiation of viral and GABHS tonsillopharyngitis. Patients with sore throat and a low or normal white blood cell count may have a throat culture taken, but are less frequently found to be infected with GABHS. In contrast, in a prospective 1-year study of acute febrile exudative tonsillitis in 110 children in Finland, the white blood cell count and erythrocyte sedimentation rate were not helpful in differentiating bacterial from viral tonsillitis.12 However, review of all the previously cited papers9-12 involving more than 27,000 patients seems to support the concept that a patient with a low white blood cell count is very unlikely to have GABHS tonsillopharyngitis and that the majority of patients with GABHS tonsillopharyngitis have an elevated white blood cell count.

**ACCURACY OF THE THROAT CULTURE**

In 1954, Breese and Disney first reported the use of the throat culture in an office setting.3 Since then, the use of a throat culture as a common office practice has grown steadily, such that by the early 1980s the Centers for Disease Control estimated that between 28 and 36 million throat cultures were performed annually in the United States. The value of this simple office laboratory test in avoiding unnecessary antibiotic therapy motivated physicians and patients alike to protest the federal government’s initiative to curtail and eliminate office laboratory testing such that proposed regulations requiring periodic accreditation of office laboratories that performed GABHS cultures were modified after further study (Clinical Laboratory Improvement Amendment [CLIA] regulations).

**False-Positive Throat Cultures**

False-positive throat cultures in most cases represent misidentified beta-hemolytic streptococci belonging to Lancefield groups B, C, F, or G, or beta-hemolytic *Streptococcus aureus*. The most widely used test for the differentiation of GABHS from non-GABHS strains is the bacitracin sensitivity test: it provides a presumptive identification of GABHS based on the observation that 95% to 100% of GABHS demonstrate a zone of inhibition around a disk containing 0.04 units of bacitracin, whereas 83% to 97% of non-GABHS do not.16,17 If there are sufficient numbers of GABHS in the area of the disk, the test can be interpreted adequately on a primary blood agar plate.

**False-Negative Throat Cultures**

Moffett et al18 and Krober et al19 have shown that 3.6% to 17% of children symptomatic with sore throat will develop an antibody rise to GABHS antigens despite negative throat cultures. Discordance between duplicate throat cultures obtained at the time of an office visit has been offered as evidence that the throat culture is unreliable as a diagnostic test. However, discordance is actually quite uncommon. Breese and Disney found an 8% discordance rate (7 of 85 positive cultures).20 Stillerman a 1% discordance rate (2 of 152 throat cultures),10 and Kaplan et al a 9% discordance (11 of 133 positive cultures).3 In a recent study, Macknin et al21 obtained three simultaneous throat cultures in 103 consecutive patients between the ages of 2 and 20. Concordance of positive or negative culture on all three swabs was seen in 102 (99%) of 103 patients.

To explain this limited problem of false-negative throat cultures, three possibilities might be considered: 1) faulty culture technique, 2) occult antibiotic therapy, and 3) faulty bacteriologic methods.21 Brien and Bass22 evaluated the optimal site for throat culture in a small study involving 12 children. The general teaching that the tonsil surface is the optimal

**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>Hospital-Based</th>
<th>Office-Based</th>
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<tbody>
<tr>
<td>N</td>
<td>7767</td>
<td>2798</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>87* (75%-95%)</td>
<td>45% (93%)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>96 (86%-100%)</td>
<td>90 (75%-98%)</td>
</tr>
<tr>
<td>Overall accuracy (%)</td>
<td>92 (75%-99%)</td>
<td>86 (66%-97%)</td>
</tr>
</tbody>
</table>

*Numbers represent mean value; ranges are given in parentheses. For hospital-based studies 15 publications included, for office practice-based studies 11 publications included.*

**Abbreviations:** GABHS = group A beta-hemolytic streptococci.
TABLE 3

<table>
<thead>
<tr>
<th>Recommendation for Use of Rapid GABHS Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain duplicate swabs from acutely ill patients</td>
</tr>
<tr>
<td>If positive, presume the patient has GABHS infection and treat; discard second swab</td>
</tr>
<tr>
<td>If negative, presume the patient does not have GABHS infection, don't treat; send second swab for confirmatory cultures</td>
</tr>
</tbody>
</table>

| Abbreviations: GABHS = group A beta-hemolytic streptococci. |

size from which the throat culture should be obtained in patients suspected of having GABHS pharyngitis was confirmed, and the posterior pharyngeal wall was consistently positive for heavy growth of GABHS in all patients positive for tonsillar infection.

In a study of 200 patients at the Elmwood Pediatric Group, two culture methods were compared: vigorous swabbing of both tonsillar surfaces as well as the posterior pharyngeal wall and placement of the throat culture swab to the posterior pharyngeal wall and then rotation of the swab 90°. The isolation rate was identical with both techniques (Elmwood Pediatric Group. Unpublished data). In contrast, Brock found that both tonsils must be sampled since cultures taken from one tonsil were negative in up to 20% of children in whom the other tonsil was positive.

Experienced pediatricians know that patients frequently do not take the full amount of prescribed antibiotic. Leftover antibiotic is saved for the next occurrence of similar symptoms. In a hospital emergency room study, 10% of patients who forthrightly denied antibiotic use on direct questioning by a physician had antibacterial activity detected in their urine. Because GABHS isolation is extremely difficult after one or two doses of antibiotic, the role of occult antibiotic use as a cause of false-negative throat cultures may be significant.

Quality assurance methods should be incorporated into office laboratory routines. (These will now be mandated by CLIA regulations.) A known isolate of GABHS should be inoculated onto a plate and incubated concurrently as a positive control with throat swabs obtained on patients suspected of GABHS infection. Depending on the volume of cultures processed in the office, monthly, quarterly, or semiannually, a sample of duplicate swabs should be processed in a reference lab (hospital) to corroborate the office lab findings.

ANTIGEN DETECTION METHODS FOR DIAGNOSING GABHS

Antigen detection tests (ADTs; rapid antigen tests) for the rapid identification of GABHS directly from throat swabs are now used by many pediatricians. The first ADTs used latex agglutination as a detection method. Subsequently, tests employing enzyme immunoassay techniques have become available. Rapid strep tests are appealing to physicians who are uncomfortable with the accuracy of their office microbiology techniques for the culture identification of GABHS. Antigen detection tests are also of value in those clinical situations where a diagnosis within 10 to 15 minutes is desirable in contrast to the obligatory 18 to 24 hours incubation time required for a throat culture. The advantages of immediate diagnosis of GABHS tonsillopharyngitis with ADTs include faster elimination of contagion, shortening of the duration of acute illness, and possible reduction in unnecessary antibiotic use. The disadvantages of immediate treatment focus primarily on a reduction or elimination of the natural antibody response to the GABHS infection, thereby predisposing the patient to a relapse or recurrence.

Because antibiotic therapy can be delayed for up to 9 days from the onset of symptoms without compromising the beneficial effects of precluding the development of acute rheumatic fever, there is more than enough time to allow 24 to 48 hours to pass for throat culture incubation without compromising this important therapeutic effect. Furthermore, Woodin et al recently have shown that patients who experience a bona fide relapse with homologous (same serotype) GABHS shortly following a primary infection may experience minimal or no symptoms. That is, patients who seek treatment within 24 hours of onset of symptoms (as is frequently the case) have an ADT performed on a throat swab, and if positive, have immediate antibiotic therapy initiated, expose themselves to an increased likelihood of an asymptomatic bona fide GABHS relapse, and when this relapse occurs, they are likely to be minimally symptomatic, thereby seeking no care and receiving no treatment, which could lead to significant consequences.

Review of the published reports comparing latex agglutination and enzyme immunoassay ADTs with throat culture allows their categorization into hospital-based and office-based studies (Table 2). More than 7700 patients have been studied by hospital microbiology laboratories. In this setting, the average sensitivity, specificity, and overall accuracy of the tests have been 87%, 96%, and 92%, respectively. When these studies have been performed in office practice-based populations, the sensitivity, specificity, and overall accuracy decline to 79%, 90%, and 86%, respectively. More importantly, the range of accuracy broadens such that in some studies the sensitivity has dropped below 50%. This would indicate that obtaining an ADT can be little better than flipping a coin. Poor sensitivity of ADTs may occur when ADTs are performed under hurried office circumstances, without proper attention to detail, including the use of
positive and negative concurrent controls.
As a consequence of concern for the inferior sensitivity of ADTs compared with the gold standard of throat culture, authorities in streptococcal research have developed a consensus on recommending an approach to the use of ADTs in office practice. This approach permits ADTs to replace throat cultures if desired in 75% to 85% of patients (Table 3).
In considering which ADT to use in a specific office setting, we have found that the enzyme immunosay (the color change kits as opposed to the latex bead tests) are easier for office personnel to interpret. However, the best test is the one that your own personnel prefer. Slight differences in cost should be given secondary importance to ease and accuracy in the hands of the person(s) performing the tests.

CONCLUSION
The use of throat cultures and antigen detection tests in office practice have become the standard of medical care in the United States for pediatricians. To culture no one and treat everyone is a disservice to the patient and the population at large and a compromise in quality medical care. To rely on the differentiation of GABHS tonsillitis/angitis from nonstreptococcal infection on clinical grounds leads to missed diagnosis or overdiagnosis. The throat culture remains the gold standard for the laboratory diagnosis of GABHS. Antigen detection tests have a role in the laboratory confirmation of GABHS tonsillitis/angitis, but negative ADTs should be confirmed with a throat culture.

REFERENCES