Selective Utilization of Clinical Diagnosis in Treatment of Pharyngitis

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Exudate, adenopathy, and fever were used to predict clinically whether pharyngitis was streptococcal, nonstreptococcal, or questionable in 466 adults and 234 children. Clinical accuracy was: nonstreptococcal – adults 94.6 percent, children 86.9 percent; streptococcal – adults 44.2 percent, children 53.5 percent. Significance of results was determined by calculating the cost of routine cultures compared to risk of rheumatic fever. The economic justification of cultures was lowest in nonstreptococcal adults, streptococcal adults, and streptococcal children. Therapy of streptococcal patients presented an additional risk: anaphylaxis. The fatality risk after penicillin injection compared to the increased risk of rheumatic fever after oral penicillin is: adults 7.5 percent (clinical diagnosis), 3.3 percent (laboratory diagnosis); children 1.8 percent and 0.8 percent respectively. It is recommended that throat culture be obtained for all questionable patients and clinically nonstreptococcal children. Penicillin should be administered orally in the majority of adults.

The purpose of this study is to determine whether or not patients with pharyngitis should be treated solely on the basis of a clinical diagnosis. In order to make this determination, we first tried to achieve a high degree of accuracy in clinical diagnosis. From this data, we calculated the risk incurred when patients are treated on the basis of an incorrect clinical diagnosis. Next, we estimated the cost of eliminating the risk of an incorrect diagnosis by the routine use of throat cultures. Using the ratio of the *cost* of the throat cultures which would be required to eliminate the risk of an incorrect clinical diagnosis to the *risk* incurred by incorrect clinical diagnosis, recommendations are made as to whether or not the accuracy of clinical diagnosis of pharyngitis justifies the elimination of throat cultures.

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Methods and Materials

Criteria and Categories

The study was designed to be applicable to common clinical practice. Therefore, an accurate clinical diagnosis was defined as one which agreed with the results of a single throat culture. Repeat throat cultures and ASO titers were not done. Cultures which were reported as negative were grouped together with cultures which showed bacteria other than group A beta hemolytic streptococci (GABHS) in a category which we termed non GABHS.

In deciding what criteria would be used to establish a clinical diagnosis, the author reviewed the literature on clinical diagnosis of pharyngitis and chose the presence or absence of exudate, adenitis, and fever as being most diagnostic as to whether the etiology of pharyngitis was GABHS or non GABHS.[1-4]

No single finding was present in more than 60 percent of patients with GABHS and, conversely, not every patient with the findings had GABHS. We postulated that a combination of the most common findings might increase diagnostic accuracy. We also postulated that the degree of positivity of the findings would be proportional to prognostic significance. For example, one study found that a temperature over 102 F was highly diagnostic of the presence of GABHS.[1] However, it was evident that if a diagnosis of GABHS was limited to patients with highly positive findings, many false negatives would result while inclusion of minimal criteria would result in false positives.

We attempted to resolve this dilemma by not giving a definite diagnosis to patients with a solitary finding or with a combination of minimal findings, but placing them in a third category which we termed "questionable." A previous study[3] has confirmed that such a division increases the accuracy of clinical diagnosis. Minimal findings (1+) were defined as (1) temperature over 99 F, (2) one enlarged or tender node, or (3) one patch of exudate.

With two exceptions, the presence of any of the three criteria precluded a diagnosis of non GABHS. Patients with a mucoid exudate and multiple small nodes were diagnosed as infectious mononucleosis and given a clinical diagnosis of non GABHS. Patients with fever and myalgia but no exudate or adenitis were also diagnosed as non GABHS (influenzal syndrome) despite the presence of one of the criteria. The absence of all findings mandated a diagnosis of non GABHS.

A diagnosis of GABHS was made when a combination of two or more moderately positive (2+) criteria were present. Moderately positive was defined as (1) temperature over 99 F, (2) two or more enlarged or tender nodes, or (3) two or more patches of exudate. A diagnosis of GABHS was also made when a confluent, purulent exudate (3+) was present. Exudate was the only finding which could be used

Table 1. Diagnostic Criteria

GABHS	"QUESTIONABLE"	non GABHS
3+ exudate	solitary finding	no findings
or	or	or
2+ exudate & fever	any combination of	flu syndrome
2+ exudate & 2+ adenitis	1+ adenitis, 1+ exudate, fever	mono syndrome
2+ adenitis & fever		

in the absence of confirmatory findings to make a definite diagnosis of GABHS. Table 1 summarizes the diagnostic criteria used in this study.

It has also been shown that accuracy of clinical diagnosis increases with patient age.[3] As our final step in our attempt to produce a high degree of diagnostic accuracy we therefore divided patients into adult (15 and over) and pediatric (14 and under). These divisions resulted in six possible categories of clinical diagnosis: adult GABHS, adult non GABHS, adult "questionable," pediatric GABHS, pediatric non GABHS, and pediatric "questionable."

Primary Study Group

The criteria were applied by the author to 140 consecutive patients who presented with (1) an unsolicited complaint of sore throat of less than one week's duration, and (2) no history of antibiotic administration in the preceding two weeks. A clinical diagnosis was recorded on the basis of the aforementioned criteria. Then a vigorously obtained pharyngeal swab was streaked on a blood agar plate, incubated, and sent to a laboratory with rigid quality control.

The accuracy of a clinical diagnosis (cl dx) was calculated from the following:

# of cl dx "confirmed" by culture/ # of cl dx "confirmed" by culture + # of unconfirmed cl dx

This was done for the GABHS and the non GABHS categories in adults and children. A negative culture was considered confirmation that the diagnosis was non GABHS.

Reproducibility

If the criteria were valid predictors of the presence or absence of GABHS on culture, then other physicians had to be able to achieve a similar degree of accuracy using the criteria. Ideally this should have been checked by comparing the accuracy achieved by different observers on the same patients. This was impractical for a large series so we attempted to verify the reproducibility of the author's results by having two groups of physicians provide comparison series.

The first group of physicians attempted to apply the criteria to a similar patient population – 140 consecutive patients who presented with sore throat of less than one week's duration and had not received antibiotics in the preceding two weeks. (Comparison Group I).

Comparison Group II recorded a clinical diagnosis only on those patients (250) whom the clinician would have cultured in his normal practice routine. For a few physicians, this meant all patients. For the majority, this meant only those patients whom the physician felt were likely to have GABHS because of clinical findings, a history of contact, or a history of repeated GABHS infection. The purpose of this group was to provide an estimate of the extent to which population selection influenced the accuracy of diagnosis.

The number of pediatric patients in the series of the author and the two comparison groups was too small (58 total) to permit valid comparisons between the groups. Therefore, four pediatricians were asked to contribute a series (176 children aged 14 and under) comprised of patients selected with the same restrictions as those used for the primary group.

Comparability

If the results were to be considered valid, it had to be established that the populations being studied were comparable. Comparability was established in the three series of consecutive patients by calculating the occurrence rate of GABHS. A similarity in the occurrence rate was considered presumptive evidence that the populations were similar.

Significance of Results

If it were established that results were reproducible in comparable series, it still had to be demonstrated that the accuracy achieved was acceptable. In order to provide objective proof that clinical accuracy was acceptable, we attempted to quantitate the risk involved in relying on a clinical diagnosis.

The major impetus for increased accuracy of diagnosis is to reduce the risk of rheumatic fever. Other factors such as the need to reduce the overuse of antibiotics are secondary and difficult to quantitate. The number of cases of rheumatic fever which will occur is a product of the number of GABHS present and the attack rate of rheumatic fever:

RISK = occurrence rate GABHS x attack rate

Prior studies have shown that the attack rate of rheumatic fever averages 0.005.[5] The occurrence rate of GABHS will depend on the category of clinical diagnosis. When the category is non GABHS, the occurrence rate will equal the percent of incorrect diagnoses (error rate). For questionable patients, occurrence rate will equal the percent GABHS found on culture. For clinically GABHS patients, the occurrence rate will equal the percent accuracy.

Calculating the risk of rheumatic fever in clinically GABHS patients involves more than the accuracy since patients would presumably receive antibiotics and eliminate their risk. The risk would still be present in contacts if cultures were not taken, the diagnosis confirmed, and routine cultures taken in contacts of culture positive patients. Hence, physicians who culture contacts should know the relative risk of rheumatic fever developing in a contact.

The rate of GABHS infection in contacts is approximately 25 percent.[6] However, the patients who would really require cultures are the 40 percent

of GABHS infections which are asymptomatic.[1,5] Since not every patient who presents with a sore throat will have GABHS, the occurrence rate in contacts of patients with clinical GABHS will be:

% accuracy clinical diagnosis GABHS x 25% x 40%

There is also a risk of rheumatic fever if the clinician elects to treat with oral and not injectable penicillin because the diagnosis was not confirmed by culture and the clinician is unwilling to risk an unjustifiable anaphylactic death. This risk occurs because the eradication rate with oral penicillin is less than with injectable. Well controlled studies show that the difference in eradication rates ranges from three percent to ten percent depending on whether or not the patient was specifically encouraged to complete oral therapy.[7,8] We used an estimate of six percent as the difference in eradication rates. This would correspond to the occurrence rate of GABHS when therapy is with oral and not injectable penicillin, and permits calculation of the risk of oral therapy.

Injecting penicillin on the basis of an incorrect clinical diagnosis carries the risk of an unjustifiable anaphylactic death. This risk is one in 100,000 in adults, and one in 400,000 in children.[9,10] Hence, after clinical diagnosis, the risk of anaphylactic death in a culture negative patient is:

RISK = anaphylaxis rate x error rate

These last two calculations can be combined to determine the mortality rate when injectable penicillin is given to achieve a greater reduction in rheumatic fever than that which is possible with the less effective but less dangerous alternative of oral therapy:

$$\frac{\text{unjustified death}}{\text{rheumatic fever prevented}} = \frac{\text{anaphylaxis rate} \times \text{error rate}}{6\% \times \text{attack rate}}$$

Theoretically, the above risks can be eliminated if the diagnosis is confirmed by culture before treatment is begun. A major reason for resistance to routine cultures of pharyngitis is the cost. We used $5 as the cost of a throat culture and expressed cost and risk as a ratio:

Cost of Routine Throat Cultures/Risk of Incorrect Clinical Diagnosis

This permits evaluation of the accuracy achieved by clinical diagnosis in an objective fashion. We compared cost/risk for throat cultures/rheumatic fever in the different categories of clinical diagnosis. As our standard for comparison, we used $500 – the cost/risk ratio for polio immunization/polio prevention.

Results

Comparability

The incidence of GABHS was 15.7 percent (19/121) in the primary group of adults and 14.2 percent (17/116) in Comparison Group I or 15.1 percent overall. These figures are statistically comparable (p = 0.9) and indicate that the populations to which the criteria were applied are similar and consequently that comparisons should be valid.

The occurrence rate of GABHS in children (32.4 percent or 12/38) in the primary group and Comparison Group I taken together was statistically comparable (p = 0.78) to the incidence in the pediatricians' patients (30.4 percent or 53/176). This indicates that the family physicians did not see an atypical pediatric population. Consequently the differences in the incidence of GABHS seen in adults and children is real.[5]

Table 2. Correlation of Clinical and Culture Diagnosis

		Adults			Children		
		Culture		CLINICAL ACCURACY	Culture		CLINICAL ACCURACY
		NON GABHS	GABHS		NON GABHS	GABHS	
Clinical Diagnosis	Group						
NON GABHS	Primary (Author's)	82	2	97.6%	4	0	
	Comparison I	56	3	94.9	6	3	
	Comparison II	106	9	92.1	4	0	
	Pediatrician				79	11	
		244	14	94.6%	93	14	86.9%
GABHS	Primary (Author's)	4	11	73.3%	3	1	
	Comparison I	26	10	27.7	4	4	
	Comparison II	47	40	45.9	5	3	
	Pediatrician				27	37	
		77	61	44.2%	39	45	53.5%
"QUESTIONABLE"	Primary (Author's)	16	6		3	1	
	Comparison I	17	4		5	3	
	Comparison II	20	7		6	3	
	Pediatrician				17	5	
		53	17		31	12	
	%GABHS	24.3%			27.9%		

Table 3. Adjustment for Carrier State (Theoretical)

Diagnosis	Adult Accuracy	Pediatric Accuracy
non GABHS	94.6 + 2 = 96.6%	86.9 + 10 = 96.9%
GABHS	44.2 – 2 = 42.2%	53.5 – 10 = 43.5%

Table 4. Cost of Cultures per Rheumatic Fever Prevented		
Clinical Diagnosis	**Adults**	**Children**
non GABHS	$18,500	$ 7,500
"Questionable"	$ 4,000	$ 3,500
GABHS (contact risk)	$23,500	$19,000
(oral ℞ risk)	$37,500	$31,500

Reproducibility

Table 2 displays the correlation of clinical diagnosis with culture diagnosis. The author's accuracy in making a clinical diagnosis using the criteria he proposed was reproducible in adults by Comparison Groups I and II when the clinical diagnosis was non GABHS (97.6 percent vs 94.9 percent vs 92.1 percent; $p = 0.24$) but not when the clinical diagnosis was GABHS (73.3 percent vs 27.7 percent vs 45.9 percent; $p = 0.01$).

The author's accuracy was not reproduced in children when the diagnosis was either non GABHS or GABHS (97.6 percent vs 86.9 percent; 73.3 percent vs 53.5 percent). This may be more apparent than real since a positive throat culture does not distinguish between a true GABHS infection and a carrier. About two percent of adults and ten percent of children are carriers.[4] If we assume that positive throat cultures due to carriers are equally distributed between the GABHS and non GABHS categories and compare average accuracy, we find that the accuracy of a clinical diagnosis becomes almost identical in adults and children as shown in Table 3.

Significance of Results

Using the average accuracy achieved and making no correction for the carrier state, cost/risk analyses (rounded) were calculated as shown in Table 4.

We also calculated the number of anaphylactic mortalities for every 100 cases of rheumatic fever prevented by the use of injectable rather than oral penicillin. The mortality rate after clinical diagnosis: 7.5 percent (adult), 1.8 percent (child); after culture diagnosis: 3.3 percent (adult), 0.8 percent (child). The cost of preventing mortality in a patient with an incorrect clinical diagnosis: $1,000,000 (adult); $4,000,000 (child).

Discussion

Were the criteria which were presented useful in predicting the etiology of pharyngitis?

The absence of exudate, adenitis, and fever, and the presence of the influenza syndrome of fever and myalgia without exudate or adenitis both correlated well (97.6 percent) with the finding of negative throat cultures in adults in the author's series. Accuracy was highly reproducible in the other adult series (94.9 percent and 92.1 percent. It was expected that accuracy would be lower in Group II where patients were preselected because of being at high risk). Hence, the criteria for a clinical diagnosis of non GABHS can be accepted as being an accurate predictor in adults.

The same criteria were less accurate in children (86.9 percent) but, as previously stated, this discrepancy may be due to the high prevalence of carriers in children. Hence, while the criteria are probably highly accurate predictors of *true* GABHS infection in children, we must at this time conclude that they are only moderately accurate predictors of a negative culture.

The presence of specific combinations of exudate, adenitis, and fever correlated with the presence of GABHS on culture in 73.3 percent of adults in the author's series. Reproducibility was low in the other adult series (27.7 percent and 45.9 percent) and in the pediatric patients (53.5 percent). Retrospective discussions with participating physicians indicate that they experienced difficulty in grading the findings at the beginning of the study. What the author termed a 2+ exudate was often classified as 3+ by others. Injection of the pharynx was included as a diagnostic criteria when it was not in the protocol. Hence, the poor reproducibility represented an inability to formulate criteria which could be precisely applied and also represented a tendency to lapse into personal diagnostic criteria.

Since the accuracy of both the author and the participating physicians tended to increase from the first half of each study to the second half (21 percent on the average), it may be that other criteria such as degree of discomfort or speed of onset were unconsciously utilized as the physicians gained diagnostic skill. Increased skill probably results from the knowledge gained when laboratory results are carefully correlated with clinical impressions.

The author's greater accuracy is probably due to the fact that he had the largest series and hence the greatest training. It is probable that a clinical accuracy of 70 to 80 percent is generally obtainable in diagnosing GABHS. However, it is questionable whether written criteria can be devised which can be applied de novo to achieve this accuracy. To reach such a level will probably require an initial training period in which the physician learns to grade the degree of exudate and adenitis. To maintain this level may require periodic "refresher" series.

Further studies will be required to see if the criteria can be improved. However, even at the relatively low average accuracy achieved here, the use of a cost risk analysis shows that clinical diagnosis is preferable to culture diagnosis.

At a cost of $4,000,000 in children and $1,000,000 in adults per mortality prevented, cultures are obviously not indicated as a method of eliminating mortality secondary to injectable penicillin anaphylaxis in a patient with an incorrect clinical diagnosis. The cost of cultures to identify GABHS in asymptomatic contacts is similarly excessive (over $30,000). The cost of cultures as justification for penicillin injection in order to provide superior prevention of rheumatic fever is also high ($20,000). Since ten percent of patients with streptococcal infection have negative cultures, the justification for relying on a culture in treating clinically GABHS patients is questionable. To do so would subject a larger percent of patients to the risk of rheumatic fever than are at risk because of failure to culture clinically non GABHS adults.

The data cast doubt on current recommendations on treatment of phar-

yngitis as well as diagnosis. Adults given injectable penicillin on the basis of a culture diagnosis will experience 3.3 deaths for every 100 cases of rheumatic fever prevented. Considering the relatively low immediate mortality of rheumatic fever, such a risk seems unjustified.

The risk of anaphylactic mortality is substantially less in children given penicillin injections whether the diagnosis is clinical (1.8 percent) or by culture (0.8 percent). When we consider that most research on rheumatic fever prevention has been on pediatric populations, the reason for the current recommendations is clear. The high carrier rate in children led to the impression that a clinical diagnosis of non GABHS is relatively inaccurate. The low mortality and morbidity of injectable penicillin in children led to recommendations that patients with a positive throat culture or who were likely to be noncompliant be treated with penicillin by injection. This study demonstrates that physicians who deal with both adults and children must diagnose and treat pharyngitis differently in each age group.

If a patient is at above average risk of rheumatic fever because of a previous history of rheumatic fever or because of the presence of a virulent strain of GABHS in the community, then the risk would rise and the use of throat cultures and injectable penicillin would become more advantageous. If these conditions are lacking, the following recommendations seem justified:

Clinically non GABHS adults: do not culture; treat symptomatically

Clinically non GABHS child: culture; treat symptomatically

Clinically GABHS adult: do not culture; give oral penicillin

Clinically GABHS child: do not culture; give oral penicillin but use injectable more freely

Clinically "questionable": culture; treat symptomatically

Had the above recommendations been followed in this study, our results would have been as follows:

In adults, three percent of those complaining of a sore throat would have had a GABHS infection which was undiagnosed because of failure to take routine cultures; 16.5 percent would have received unnecessary antibiotics; 77.7 percent would have received the correct treatment on their initial visit; 85 percent would not have required cultures.

In children, zero percent would have had an undiagnosed GABHS infection; 14.6 percent would have received unnecessary antibiotics; 63.5 percent would have received the correct treatment on their initial visit; 33.4 percent would not have required cultures.

These results (1) would be superior to those achieved in other antibiotic treated illness, such as otitis and pneumonitis, insofar as the unnecessary use of antibiotics is concerned; (2) would result in an extremely small risk of rheumatic fever; (3) would be superior on a cost basis to the routine use of cultures. Since throat cultures are subject to false negatives and false positives, the actual superiority of clinical diagnosis is probably even more impressive. Future data may show that only the "questionable" patient requires a culture.

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