Does Culture Confirmation of High-sensitivity Rapid Streptococcal Tests Make Sense? A Medical Decision Analysis

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ABSTRACT. *Objective.* **Since the 1990 publication of a decision analysis, in which the treatment of pharyngitis in children was evaluated, a number of assumptions important in that analysis have changed. Updating many of the assumptions and costs used in that analysis to reflect the conditions currently found in a large, suburban pediatric practice, a cost-effectiveness analysis was performed in which four strategies for the treatment of pharyngitis were considered: treat all, high-sensitivity antigen test, culture, and high-sensitivity antigen test with culture confirmation.**

Design. **Decision analysis.**

Results. **Using microbiology data from the 13 published studies in which a high-sensitivity antigen test (Strep A OIA; BioStar Inc., Boulder, CO) and blood agar plate culture were evaluated against a variety of gold standards, the sensitivity and specificity of the high-sensitivity antigen test were 89.1% and 95%, respectively. The sensitivity and specificity of blood agar plate throat culture were 83.4% and 99%, respectively. Penicillin V was used as the treatment of choice for uncomplicated pharyngitis; erythromycin was used in cases of penicillin allergy. Rates of suppurative and nonsuppurative complications reflect those currently seen in the United States. Other assumptions and cost data were taken from a large, suburban pediatric practice and its affiliated tertiary care medical center, except where noted.**

Despite the potential induction of resistance and the high number of allergic reactions associated with the treat-all strategy, this strategy had the lowest average cost per patient encounter and was the most cost-effective in terms of dollars per suppurative and nonsuppurative complication prevented. Of the strategies in which a diagnostic test was used, the high-sensitivity antigen test strategy had the lowest average cost and was the most cost-effective. The high-sensitivity antigen test with culture confirmation strategy had the highest average cost and was the least cost-effective.

In the sensitivity analyses, a number of assumptions used in the original model were varied within a reasonable range. Under most conditions, the treat-all strategy remained the most cost-effective strategy used. One notable exception: when the wholesale cost of the antibiotic exceeded $10.76, as would be seen if any cephalosporin were used as the primary therapy of uncomplicated pharyngitis, the high-sensitivity antigen test strategy became the most cost-effective strategy.

Under most conditions, the high-sensitivity antigen test strategy was the most cost-effective of the strategies in which a diagnostic test was used. Notable exceptions included: 1) conditions in which there was a low probability of streptoccal infection, 2) the use of an antigen test whose sensitivity is inferior to that of culture, and 3) during an epidemic of acute rheumatic fever.

Culture confirmation of a negative high-sensitivity antigen test is the most cost-effective testing strategy only under conditions in which the probability of acute rheumatic fever approaches those levels last seen in the United States more than 40 years ago.

Conclusions. **Although most cost-effective, the treat-all strategy is not recommended because of concerns about antibiotic resistance, which could not be included in the model, and the high number of allergic reactions found in children who did not have streptococcal infection. Use of the high-sensitivity antigen test without culture confirmation of all negative results was the most cost-effective strategy in which a diagnostic test was used with respect to prevention of suppurative and nonsuppurative complications of streptococcal pharyngitis. Culture confirmation of negative high-sensitivity antigen tests was not cost-effective under any of those conditions currently seen in the United States.** *Pediatrics* **1998;101(2). URL: http://www.pediatrics.org/cgi/content/full/101/2/e2;** ***streptococcal pharyngitis, decision analysis, antigen tests.***

ABBREVIATIONS. GABHS, group A β-hemolytic streptococci; BAP, blood agar plate; OIA, optical immunoassay.

Acute pharyngitis is one of the most common illnesses in children in the United States and one of the leading reasons for pediatric office visits. Although the majority of children presenting with acute pharyngitis are experiencing symptoms attributable to a viral infection, many are infected with group A β-hemolytic streptococci (GABHS). Accurate diagnosis of infections because of GABHS is important, as antibiotic therapy has been shown to shorten the clinical course,[1–3] reduce the rate of transmission, and prevent complications of GABHS such as peritonsillar abscess and acute rheumatic fever.[4,5]

Rapid and accurate diagnosis of pharyngeal infections attributable to GABHS can be difficult. Although blood agar plate (BAP) culture is widely held as the gold standard of diagnosis, this technique may demonstrate a sensitivity as low as 86% to 90% based on dual swab studies.[6] Because they require 24 to 48 hours to achieve a definitive result, throat cultures may also lead to incomplete initiation of therapy in

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those infected and delay the return to normal activities for the both child and caretaker.

In the 1980s, a number of rapid antigen tests for GABHS became available, with most of these tests relying on latex agglutination or enzyme immunoassay techniques. The advantages of these tests were rapid diagnosis and initiation of therapy. The main disadvantage was their sensitivity, which has been shown to be as low as 50% and 70%.[7] In 1994, the high-sensitivity optical immunoassay (OIA) (Strep A OIA; BioStar, Inc, Boulder, CO) became available, reporting sensitivity superior to BAP culture.[8]

Because of the low sensitivity seen with latex agglutination or enzyme immunoassay tests, the American Academy of Pediatrics and the American Heart Association have historically recommended that when a patient suspected of having pharyngitis attributable to GABHS has a negative rapid antigen test, a confirmatory culture should be obtained. The 1997 *Red Book* of the American Academy of Pediatrics states that "rapid diagnostic tests using new techniques, such as optical immunoassay and chemiluminescent DNA probes, have been developed recently. Available data suggest that these tests are as sensitive as standard throat cultures on sheep blood agar and more sensitive than other rapid tests for group A streptococci. However, additional corroborative information is needed before these tests can be recommended for routine use without confirmatory throat culture in patients with negative test results."[9]

Since the publication of the 1997 *Red Book*, Gerber et al[10] have published an office-based, 2113 patient study in which the streptococcal OIA and BAP throat culture were compared with a gold standard of Todd Hewitt broth culture. Finding the streptococcal OIA to be more sensitive than BAP throat culture at all six pediatric office sites, the authors have suggested that "because the sensitivity of an office BAP culture is considered sufficient for use in the diagnosis of GABHS pharyngitis, it follows that another test with sensitivity equivalent to the office BAP and with adequate specificity should be equally acceptable when used alone for the diagnosis of GABHS pharyngitis." The authors have concluded that "with adequately trained personnel, negative OIA test results may not always need to be routinely confirmed with BAP cultures."[10]

In this article, medical decision analysis is used to examine the role of confirmatory culture after the use of a high-sensitivity rapid antigen test. This work draws heavily on the methods used by Lieu et al[11] in their excellent 1990 article, but updates this and other previously published analyses by including a new technology that was previously unavailable and may be superior to throat culture in the diagnosis and treatment of pharyngitis attributable to GABHS. This decision analysis also changes a number of the assumptions used by Lieu et al[11] to more appropriately reflect the conditions found in a private pediatric practice in the 1990s.

METHODS

Decision Analysis Model

The methods used in this decision analysis and sensitivity analyses are the same as those used by Lieu et al[11] and were performed on a computer using DATA version 2.5 (TreeAge Software, Williamstown, MA).

The decision tree is modified from the one used by Lieu et al[11] (Fig 1). The four strategies included in this analysis are 1) treating all patients who present with pharyngitis (treat all), 2) using throat culture in the diagnosis of GABHS pharyngitis with treatment of only those who are culture-positive (culture), 3) using a high-sensitivity antigen test without culture confirmation of the negative results and treatment of those who are antigen-test-positive (high-sensitivity antigen test), and 4) using a high-sensitivity antigen test with culture confirmation of all negative rapid tests and treatment of those positive by either technique (high-sensitivity antigen test plus culture).

Statistical Assumptions

Probability and cost assumptions are summarized in Table 1.

Test Characteristics

Using a variety of gold standards, there are 13 published studies in which BAP throat culture and the streptococcal OIA are compared.[10,12–23] The sensitivity and specificity of throat culture and the OIA were calculated by using a weighted average (based on sample size) of all available published studies. Throat culture demonstrated 83.4% sensitivity and 99% specificity. The streptococcal OIA demonstrated 89.1% sensitivity and 95% specificity (Table 2).

Prevalence of GABHS

In this analysis, the prevalence of GABHS in the oropharynx of those cultured was assumed to be 29%. This is the same prevalence used by Lieu et al[11] and is consistent with that observed in a suburban New England pediatric practice during the winter months. Although a positive throat culture may represent GABHS carriage and not be indicative of true infection, in this analysis it is assumed that treatment is initiated in any child presenting with symptomatic pharyngitis in whom a positive test for GABHS is obtained.

Treatment

Although Lieu et al[11] used intramuscular benzathine penicillin as initial therapy in their analysis of patients with pharyngitis seen in an inner-city emergency department, in this analysis oral penicillin V is used as initial therapy of uncomplicated GABHS pharyngitis, in keeping with the practice of most primary care pediatricians.

If a patient with pharyngitis has a positive antigen test for GABHS, it is assumed that 100% of them will be started on antibiotic therapy before leaving the office. By contrast, if a patient with pharyngitis has a positive throat culture follow-up and successful initiation of therapy may be incomplete. In this analysis, follow-up is assumed to be successful in 90% of patients after throat culture. This follow-up rate is much higher than the 57% follow-up rate found by Lieu et al[11] in their emergency room population. Follow-up rates would, of course, vary widely with practice type and patient demographics.

Although data are scarce, antibiotic therapy is probably not 100% effective in preventing adverse sequelae of GABHS.[4,5] In keeping with Lieu et al,[11] it is assumed that compliant antibiotic therapy is 90% effective in preventing adverse sequelae.

Complications

Data pertaining to allergic reactions to oral penicillin were reviewed by Tompkins et al[24] and have served as the basis for this and other decision analyses.[11,24–26] After reviewing the literature pertaining to rates of penicillin allergy, Tompkins[24] concluded that death after oral penicillin was extraordinarily rare, occurring in $<0.0003\%$ of patients treated. Because of the extreme rarity of this event and the inherent difficulty in assigning a valid dollar value to death of a child, this outcome is not included in this analysis. Serious allergic reactions occur in 0.025% of patients treated with

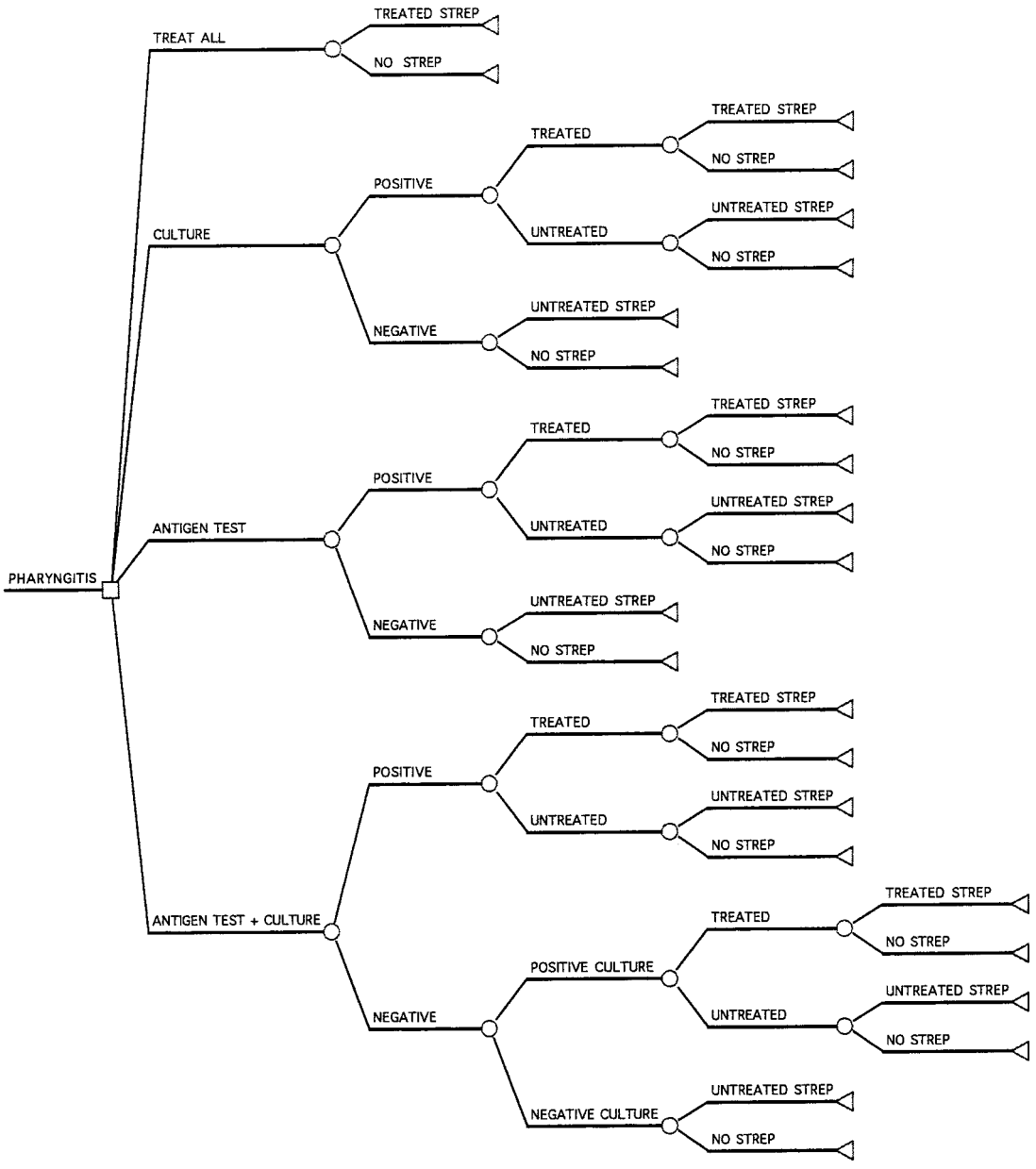

Fig 1. Decision tree of alternative diagnostic and therapeutic strategies.

oral penicillin. Mild allergic reactions occur in 0.525% of patients treated with oral penicillin.[24]

Although Bennicke et al[4] observed that 9 (5.1%) of 175 untreated and 1 (0.6%) of 174 penicillin-treated patients with sore throats developed peritonsillar abscesses in 1951, more recent incidence data are unavailable. Previously published analyses[11,25] have estimated that suppurative complications occur in only 0.5% to 2% of patients with untreated GABHS pharyngitis. In this analysis, peritonsillar abscess is assumed to occur in 1% of untreated patients.

Recent incidence data for acute rheumatic fever is also unavailable. Between 1935 and 1960, the incidence of acute rheumatic fever in the United States ranged from 40/100 000 to 65/100 000.[27] By the 1980s, the incidence rate of acute rheumatic fever had fallen to approximately 1 to 2/100 000 in the United States with sporadic local epidemic rates as high as 18 to 45/100 000.[28,29] In their decision analysis, Lieu et al[11] assumed a rate of acute rheumatic fever after untreated pharyngitis of 0.288%, a high rate that may have been justified by the sporadic local epidemics of acute rheumatic fever seen in the mid-1980s. Since that time, however, sporadic epidemics of acute rheumatic fever have not been widely reported in this country. In this analysis, it is estimated that the probability of a child developing acute rheumatic fever after an untreated GABHS pharyngitis is 0.03%, one tenth of that used by Lieu et al.[11]

Costs

In this analysis, total costs of treatment (encounter plus complication costs) are considered. The wholesale cost of an office visit is estimated to be $27, obtained by multiplying the usual and customary compensation of $45 for an established level 3 visit with 60% office overhead costs ($45 × .6 = $27). The cost of performing the OIA is based on the wholesale cost of the test kit and the direct and indirect costs of performing the test in our office-based laboratory. The costs of throat culture and subsequent follow-up are assigned the same dollar values as those chosen by Lieu et al[11] in 1988. Pharmaceutical costs are wholesale costs to a large New England pharmacy chain. Costs of severe allergic and suppurative complications are based on charge data for patients treated for these conditions at Baystate Medical Center, the second largest tertiary care medical center in Massachusetts, in 1996.

Because it is an extremely rare disease in the United States, the cost of acute rheumatic fever and rheumatic heart disease in this country is unknown. In their decision analysis, Lieu et al[11] used

TABLE 1. Probability Assumptions and Costs

Assumptions		Costs	
Probability of GABHS	.29	Visit	$ 27
High-sensitivity antigen test		Oral penicillin	$ 2
Sensitivity	.891	High-sensitivity antigen test	$ 7
Specificity	.950	Culture	$ 5
Culture		Follow-up	$ 5
Sensitivity	.834	Mild allergic reaction	$ 35
Specificity	.990	Day of illness	$ 0
Treatment rates		Severe allergic reaction	$ 4194*
After positive antigen test	1.00	Suppurative complication	$ 4564*
After positive throat culture	.90	Acute rheumatic fever	$20 000†
Treatment efficacy	.90		
Complication rates (after untreated infection)			
Acute rheumatic fever	.0003		
Peritonsillar abscess	.01		
Allergic reactions (after oral penicillin)			
Mild	.00525		
Severe	.00025		

* Based on charges at Baystate Medical Center, Springfield, MA.
† Based on Tompkins et al[24] (1977) and North et al[30] (1993), adjusted at 3.5% inflation.

TABLE 2. Summary of All Published Streptococcal OIA Data

Source	Gold Standard	Subjects	Sensitivity		Specificity	
			OIA	Culture	OIA	Culture
Harbeck[12]	Broth	1275	97.4	75.4	95.6	99.2
Della-Latta[13]	Broth	690	95	78	97	99
Harris[14]	Agar	519	96	75.2	94	—
Smith[15]	Broth	483	95	—	98	—
Fries[16]	Broth	505	94.8	92.5	98.8	99.4
Heiter[17]	Broth	801	91.5	97.1	94.8	100
Roddey[18]	Broth	301	90.4	94.8	94.1	96.2
Daly[19]	Broth	424	84.2	82.9	95.7	98.6
Roe[20]	Broth	500	83	91	89	—
Dale[21]	Agar or broth or 2 antigen tests positive	746	81	92.3	97.5	98.3
Schlager[22]	Agar	262	77	—	97	—
Baker[23]	Agar	77	78	—	90	—
Gerber[10]	Broth	2113	84	78	93	99
Weighted average			89.1	83.4	95	99

the 1977 assumptions of Tompkins et al[24] and adjusted them for inflation, obtaining a 1988 per patient cost of $14 674. Using the same method, if Tompkins' assumptions are adjusted at a constant 3.5% annual inflation rate until 1997, the per-patient cost of acute rheumatic fever and rheumatic heart disease in 1997 is estimated to be $21 012. In 1993, North et al[30] performed an intensive analysis of the cost of acute rheumatic fever and rheumatic heart disease in Auckland, New Zealand, obtaining an average per patient cost of New Zealand dollars $19 226. If North's estimate is converted into United States dollars and adjusted at 3.5% annual inflation rate, the per patient cost in 1997 is estimated to be $18 600. In this analysis, the cost of acute rheumatic fever and rheumatic heart disease is estimated as $20 000.

Finally, because parental or patient preferences have a large impact on clinical decision-making, it would be desirable to include them in the model. Recent evidence has demonstrated that proper antibiotic therapy has a demonstrable effect on the clinical course of patients infected with GABHS, with most patients showing clinical improvement within 24 hours of the initiation of therapy.[1–3] Proper treatment of GABHS pharyngitis also renders the patient noncontagious within 24 hours of the initiation of therapy. It is therefore not surprising that most parents and patients desire the immediate result obtained with antigen testing, such that normal activities may be more quickly resumed for both child and caretaker. An attempt to integrate a financial proxy of parent and patient preferences into the model is made, despite the fact that these costs do not represent direct medical costs, per se. However, because many readers would balk at its inclusion, the value of a day of illness is initially set at $0. This value was increased in the sensitivity analyses.

Sensitivity Analyses

Sensitivity analysis is a test of the stability of the conclusions of a decision analysis throughout a range of reasonable probability and cost estimates. Sensitivity analyses were performed for a number of the statistical assumptions detailed above.

RESULTS

Total Costs and Public Health Outcomes for Each Strategy

In Table 3, the total per patient costs and complications of each strategy for a hypothetical cohort of 100 000 children with pharyngitis are shown.

The ability of each testing strategy to prevent suppurative and nonsuppurative complications is given by the product:

Percent of complications avoided
= test sensitivity × follow-up rate × treatment efficacy

Because the treat-all strategy would, by definition, treat all patients with pharyngitis attributable to GABHS, the effectiveness of the treat-all strategy is limited only by the effectiveness of penicillin therapy in preventing complications attributable to GABHS. The treat-all strategy would prevent 90% of streptococcal complications and is the most cost-effective of

TABLE 3. Total Costs, Benefit, and Harm Associated with Each Strategy Using a Hypothetical Cohort of 100 000 Symptomatic Children

	Strategy			
	Treat	Culture	OIA	OIA Plus Culture
Total costs per patient	$31.73	$38.83	$37.92	$40.93
Benefits: patients with disease prevented				
% of potential cases prevented	90%	68%	80%	88%
Number of patients with acute rheumatic fever prevented	7.8	5.9	7.0	7.7
Number of suppurative complics prevented	261	197	232	255
Harm: patients with penicillin allergy				
Mild	525 (373)*	117 (4)	154 (19)	170 (19)
Severe	25 (18)	5.6 (.2)	7.3 (.9)	8.1 (.9)

* Number in parentheses denotes number of allergic reactions in patients without pharyngitis due to GABHS and therefore treated inappropriately.

the four strategies analyzed. This strategy would, however, lead to a high number of allergic reactions, including 373 minor and 18 severe allergic reactions among the 71 000 patients who did not have pharyngitis attributable to GABHS and were therefore treated inappropriately.

With its 89.1% sensitivity and its 95% specificity, the high-sensitivity antigen test strategy would prevent 80% of complications of pharyngitis attributable to GABHS. In terms of streptococcal complications prevented, this strategy is superior to the culture strategy because of its better sensitivity and superior follow-up rates. It is also better than the culture strategy in terms of cost-effectiveness. By contrast, the culture strategy is superior to the high-sensitivity antigen test in terms of allergic complications for two reasons: 1) culture has a slightly higher specificity than the OIA, and 2) fewer patients are treated using the culture strategy because of its inferior sensitivity and follow-up.

Addition of culture confirmation to all negative high-sensitivity antigen tests would prevent more streptococcal complications than either of the single test strategies, preventing 88% of streptococcal complications. Because more patients are treated when using this strategy, the number of patients with allergic complications would be slightly higher than was seen with either of the single test strategies. Additionally, the total per-patient costs of this strategy are much higher than those costs associated with any of the other strategies.

Cost-effectiveness

Cost-effectiveness ratios are shown in Table 4.

Cost-effectiveness is measured in two ways: 1) number of allergic reactions per case of acute rheumatic fever prevented, and 2) total costs per streptococcal complication prevented. In terms of allergic complications per case of acute rheumatic fever prevented, the three strategies in which a test is used are far superior to the treat-all strategy. In terms of total costs per complication prevented, the treat-all strategy was the most cost-effective. The high-sensitivity antigen test strategy has the lowest costs per complication prevented of the three strategies in which a diagnostic test is used. It should be noted, however, that for all strategies analyzed, the costs per complication prevented far exceeds the expected costs of the complications themselves, particularly the rare complication of acute rheumatic fever.

Sensitivity Analysis

Probability of Streptococcal Infection

In previous decision analyses, the optimal treatment strategy has varied with the rate of streptococcal infection.[11,24–26] In this sensitivity analysis, the probability of pharyngitis attributable to GABHS was varied from 0% to 100% (Fig 2). All treatment strategies became more expensive as the prevalence of streptococcal pharyngitis increased, because of higher rates of treatment and complications. At all probabilities of streptococcal pharyngitis, the treat-all strategy was the most cost-effective, because of the low cost of oral penicillin. At a low probability of infection with GABHS (probability $<.20$), such as is seen during the summer months or among patients whose clinical picture is atypical for streptococcal infection (including those who are probable carriers), the culture strategy is the most cost-effective of any strategy in which a test is performed. Only at a very high probability of infection with GABHS (probability $>.60$) was the sequential test strategy more cost-effective than either of the single test strategies.

Sensitivity of the Streptococcal OIA

Because the sensitivity of the streptococcal OIA has varied from a low of 77% to a high of 97.4% in the 13 published studies in which it was evaluated (Table 1), the sensitivity of the antigen test was varied

TABLE 4. Cost-effectiveness Ratios for Each Strategy

	Strategy			
	Treat	Culture	OIA	OIA Plus Culture
Number of allergic reactions/case acute rheumatic fever prevented	70.5	20.8	23	23.1
Cost/complication prevented acute rheumatic fever	$371 795	$571 017	$494 143	$497 273
Suppurative complication	$ 11 111	$ 17 102	$ 14 909	$ 15 016

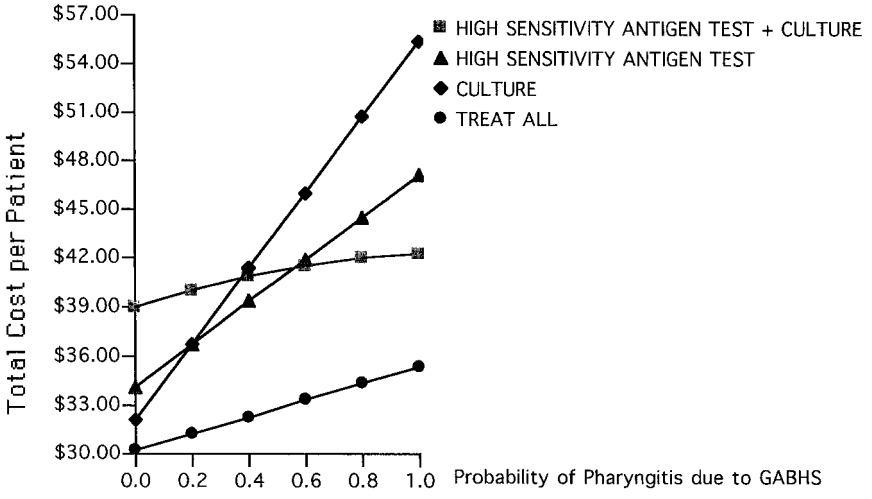

Fig 2. The effect of varying streptococcal pharyngitis probability on total patient costs using each of the alternative diagnostic and therapeutic strategies.

from 75% to 100% (Fig 3). At an antigen test sensitivity of <.82, as was demonstrated by 3 of the studies in which the streptococcal OIA was studied[21–23] and as is typical of lower-sensitivity antigen tests currently available, the culture strategy was more cost-effective than the high-sensitivity antigen test strategy. At no point in the sensitivity analysis range was the sequential strategy, high-sensitivity antigen test plus culture, more cost-effective than a strategy using only one test.

Cost of Antibiotics

Some authors have maintained that penicillin is no longer the treatment of choice for streptococcal pharyngitis because of increasing rates of treatment failure after a course of oral penicillin.[31] In this analysis, oral penicillin was chosen as the treatment of choice because of its low cost and proven effectiveness in the reduction of adverse sequelae attributable to GABHS. If a first- or second-generation cephalosporin were used instead of penicillin V, pharmaceutical costs would increase dramatically. In this sensitivity analysis, the cost of antibiotic was varied from $0 to $50 (Fig 4). At an antibiotic cost of $10.76 per treatment course, the high-sensitivity antigen test strategy became less expensive than the treat-all strategy. At an antibiotic cost of greater than $15.05, the culture strategy became less costly than the high-sensitivity antigen test strategy. This paradoxical result is explained by the high cost of antibiotics becoming more expensive than the costs of the additional streptococcal complications prevented by the high-sensitivity antigen test strategy.

Probability of Acute Rheumatic Fever

In their 1961 study, Siegel et al[32] calculated the probability of a child developing acute rheumatic fever after an untreated streptococcal pharyngitis as 0.643%. Because the current probability is unknown, the probability of acute rheumatic fever was varied from 0.01% to 1% of cases of untreated pharyngitis attributable to GABHS (Fig 5). Not surprisingly, as the probability of acquiring acute rheumatic fever increases, the cost of treatment using any of the four strategies increases. Within this range of probabilities, the high-sensitivity antigen test strategy was always more cost-effective than the culture strategy. The sequential strategy of high-sensitivity antigen test plus culture became more cost-effective than culture at a probability of .16% and more cost-effective than the high-sensitivity antigen test alone at a probability of .58%, a level comparable to that observed by Siegel et al.[32] Although this probability of developing acute rheumatic fever is rarely seen in

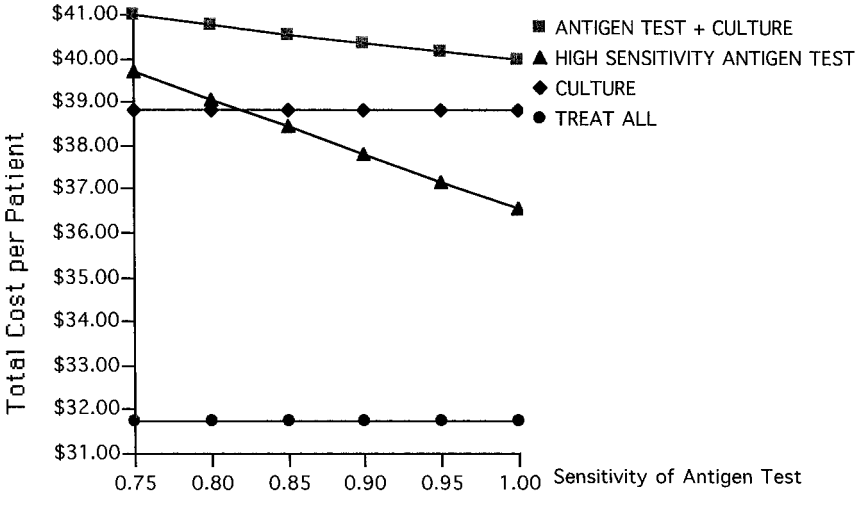

Fig 3. The effect of varying antigen test sensitivity on total patient costs using each of the alternative diagnostic and therapeutic strategies.

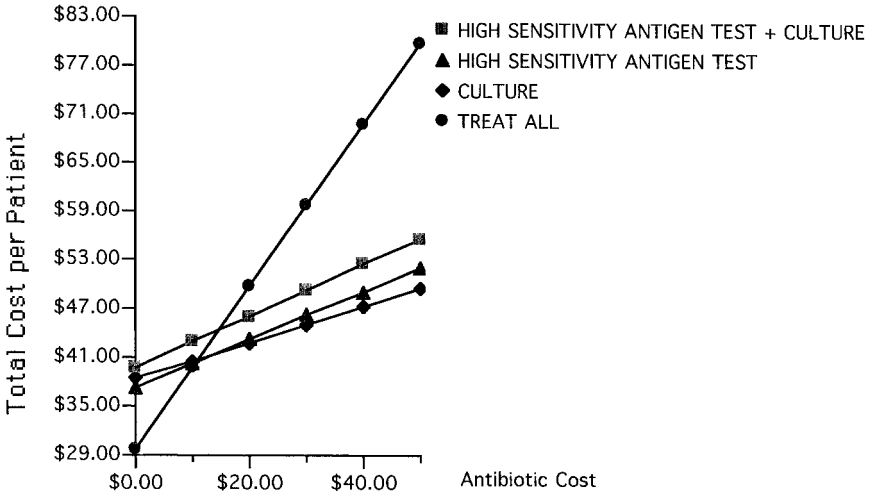

Fig 4. The effect of varying antibiotic cost on total patient costs using each of the alternative diagnostic and therapeutic strategies.

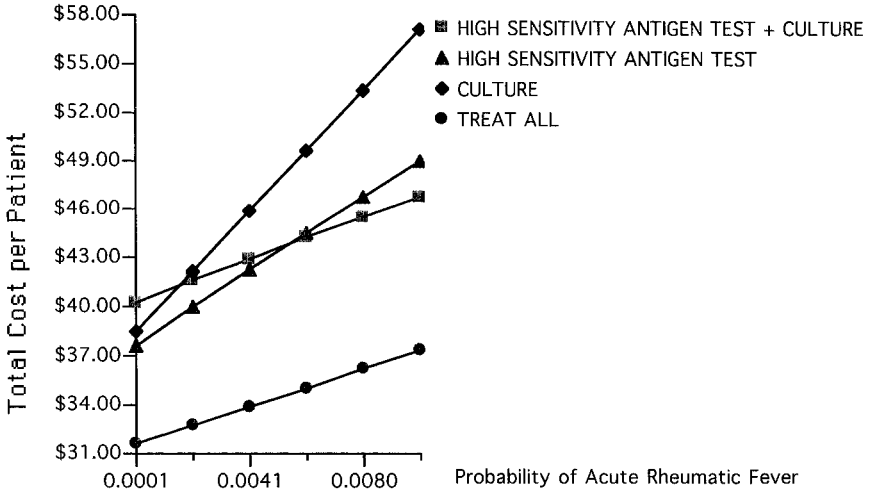

Fig 5. The effect of varying rates of acute rheumatic fever on total patient costs using each of the alternative diagnostic and therapeutic strategies.

the United States, the sequential strategy advocated by the *Red Book* is the most cost-effective and should be considered during epidemics of acute rheumatic fever.

Value of an Additional Day of Illness

In this sensitivity analysis the value of an additional day of illness is increased from the initial value of $0 (Fig 6). Because a strategy using throat culture requires a delay in diagnosis and treatment, an additional day of illness is defined as time spent waiting for the result of a diagnostic test such that therapy can be initiated, symptoms can improve, and normal activities can be resumed. Although the dollar value of a day is controversial, one may estimate it by dividing the per capita personal income of individuals in the United States ($23 193 in 1995) by 365 days in a year to obtain a value of $63.54 per day.[33] This is less than the value of $106 per day that has been used in another decision analysis.[34] Figure 6 clearly demonstrates the high societal costs of those strategies relying on culture in establishing the diagnosis of pharyngitis attributable to GABHS.

DISCUSSION

Medical decision analysis is a valid, quantitative modeling technique in which all treatment options of a problem are systematically considered. Medical decision analysis may be used to facilitate making complex treatment choices amid diagnostic uncertainty and demonstrate cost-effectiveness. For these reasons, decision analysis is used here. This is not the first decision analysis to be applied to the treatment of streptococcal pharyngitis, but it differs from those previously published in that it includes the option of using a new, rapid diagnostic technique that may have sensitivity superior to that of sheep blood agar throat culture in most settings. It is also the first study to use current probability estimates for acute rheumatic fever, a nonsuppurative complication of GABHS infections that has become rare in the United States. This study is also the first to include the value of patient time spent waiting for a diagnostic result.

As a decision analysis relies completely on the accuracy of the data used in its creation, all data must be scrutable. In this analysis, care was taken to use the best cost and probability assumptions available. As this analysis sought to update many of the cost and probability assumptions used in a previously published pediatric decision analysis, the assumptions of this earlier analysis were used wherever appropriate. Updated cost and microbiology assumptions accurately represent those found in our office and its affiliated tertiary care medical center,

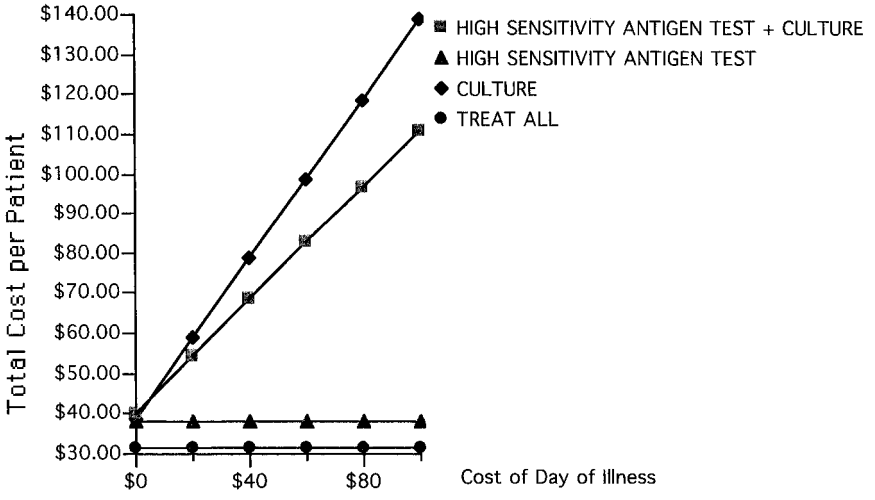

Fig 6. The effect of varying values assigned to a day of illness on total patient costs using each of the alternative diagnostic and therapeutic strategies.

except where stated. In circumstances in which recent, accurate probability data were not available, such as the probability of suppurative and nonsuppurative complications of GABHS, conservative estimates based on expert opinion or national incidence data were used.

Previous decision analyses on this subject have concluded that under most circumstances, treat all is the most cost-effective strategy in the treatment of pharyngitis potentially attributable to GABHS.[11,24–26] The analysis presented here concurs with those conclusions. Under almost all conditions, the treat-all strategy was the most cost-effective strategy of those analyzed. This relationship held up under all conditions studied in the sensitivity analyses except one: when the wholesale cost of the antibiotic exceeded $10.76, the high-sensitivity antigen test strategy became the most cost-effective of the strategies studied.

Although least expensive, the treat-all strategy is not advocated here and is probably not acceptable to most physicians. This strategy is associated with a much higher rate of allergic reactions than any of the other strategies studied. Greater than 70% of these allergic reactions would occur in patients who did not have pharyngitis attributable to GABHS, including 18 unnecessary severe allergic reactions per 100 000 patients treated in this way.

Additionally, as we live in an era of increasing antibiotic resistance, haphazard use of antibiotics, such as that advocated by the treat-all strategy, is medically unacceptable. Although it would have been desirable to include the impact of the treat-all strategy on the rate and costs of increasing antibiotic resistance in this model, data that would inform the probability assumptions necessary for their inclusion are unavailable.

Because a treatment strategy in which all cultured patients are given antibiotics pending culture results would similarly lead to a high rate of needless allergic reactions, the option of initiating therapy with 1 to 2 days of antibiotics to all patients upon whom a culture is performed is not considered in this analysis. Because this strategy involves only partial treatment with antibiotics, one might theorize an even greater contribution to the growing antibiotic resistance problem in the United States. In an era in which a number of inexpensive rapid streptococcal antigen tests are widely available, it is felt that immediate, empirical therapy with 1 to 2 days of antibiotics pending culture results should be viewed as suboptimal care.

The high-sensitivity antigen test strategy was more expensive than the treat-all strategy, but it leads to <6% of the needless allergic reactions seen with the treat-all strategy. Use of the high-sensitivity antigen test was the least expensive of the strategies using a diagnostic test, in terms of total (encounter plus complication) costs. In terms of cost per streptococcal complications prevented, the high-sensitivity antigen test strategy was also the most cost-effective under most circumstances currently seen in the United States. Notable circumstances in which the use of the culture strategy might be more cost-effective include: 1) with low rates of streptococcal infection, as may be seen during summer months or among populations that are at low risk for infections attributable to GABHS, or 2) with use of lower sensitivity antigen tests.

Whereas the strategy of high-sensitivity antigen test plus culture is superior to either single test strategy in terms of complications avoided, this modest gain more than the strategy utilizing the high-sensitivity antigen test alone comes at a high cost. Utilizing a sequential strategy such as that recommended by the *Red Book*,[9] more than 70 000 cultures would have to be done to prevent 1 additional case of acute rheumatic fever. In dollar amounts, an additional $528 571 would have to be spent in an effort to prevent 1 additional case of rheumatic fever, a disease valued in this analysis at $20 000.

Finally, it should be noted in Table 4 that the cost per case of acute rheumatic fever prevented by any of the strategies is 18 to 27 times the estimated cost of a case of acute rheumatic fever. The cost per suppurative complication prevented by any of the strategies is 3 to 4 times the estimated cost of a suppurative complication. Given the low rates of suppurative and nonsuppurative complications of GABHS currently seen in the United States, perhaps it is time that we rethink the traditional wisdom that physicians diag-

nose and treat GABHS pharyngitis primarily in an effort to prevent acute rheumatic fever. Although this was no doubt true in the 1950s, acute rheumatic fever is currently such a rare disease in the United States that its prevention through diagnosis and treatment of GABHS pharyngitis may no longer be cost-effective. The same may be said for suppurative complications.

Perhaps it is time that physicians view GABHS pharyngitis for what it is: an acute and, for the most part, self-limited infectious disease. In a country and an era in which the incidence of acute rheumatic fever is estimated to be <1/100 000, it seems more logical that diagnosis and treatment of GABHS pharyngitis should focus on the alleviation of symptoms and the diminution of its spread through prudent and rapid use of antibiotics.

Use of the high-sensitivity antigen test leads to more rapid initiation of therapy, relief from symptoms, and potentially decreased transmission of GABHS than does culture. As has been shown in this analysis, culture confirmation of all negative high-sensitivity antigen tests in an effort to prevent additional relatively rare suppurative and nonsuppurative complications is not cost-effective.

CONCLUSION

Streptococcal pharyngitis is a common disease among school-aged children. It is a self-limited disease in the majority of cases with streptococcal complications occurring in 1% of patients infected. Because the morbidity and mortality associated with GABHS infections are almost entirely preventable through the judicious use of antibiotics, rapid accurate diagnosis and treatment of these infections should be attempted. The lack of diagnostic specificity, as is seen when using a treat-all strategy, will lead to the overtreatment of those children not infected with GABHS and a larger number of allergic reactions. The lack of diagnostic sensitivity will lead to the undertreatment of those children infected with GABHS and a larger number of bacterial complications. In this analysis, it was shown that throat cultures are a costly diagnostic method in the treatment of streptococcal pharyngitis. Routine exclusive use of throat cultures may lead to a relatively high number of suppurative and nonsuppurative complications because of their imperfect sensitivity and the potential for lost follow-up. Additionally, throat cultures neither are in keeping with patient and parent desires for an immediate diagnostic result, nor do they most expeditiously lead to treatment, relief from symptoms, or decreased spread of disease. Finally, as shown in this analysis, throat cultures are also less cost-effective than the high-sensitivity antigen test alone in the prevention of suppurative and nonsuppurative complications attributable to GABHS.

Use of a sequential strategy, high-sensitivity antigen test plus culture, as is advocated by the *Red Book*,[9] is not cost-effective under any of the circumstances studied. We agree with Gerber et al[10] in their assessment that with adequately trained personnel, negative high-sensitivity antigen test results do not usually need to be confirmed with blood agar plate cultures. The one notable exception to this conclusion would be during an epidemic of acute rheumatic fever. Under this circumstance, treatment should utilize whichever diagnostic option most effectively identifies patients with GABHS pharyngitis and leads to their successful initiation of treatment.

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