What a Difference a Day Makes:

A Decision Analysis of Adult Streptococcal Pharyngitis

BRUCE E. HILLNER, MD, ROBERT M. CENTOR, MD

With the availability of group A beta-hemolytic streptococcal (GABHS) antigen detection tests, the management of adult pharyngitis is being reassessed. A decision analytic model was developed which considered four strategies: immediate treatment, no treatment, performing a rapid antigen test, or obtaining a bacterial culture. Patient outcomes were expressed in "well" days, which were reduced by the "sick" days associated with adverse reactions to treatment or complications of GABHS infection. When immediate test results are available, testing is the optimal strategy for probabilities of GABHS between 1 and 49 per cent. This range includes almost all patients, using probability estimates based on clinical criteria. The absolute benefit of testing was 0.1 days. The major advantage of a rapid test is the avoidance of penicillin reactions. Variations in the symptomatic benefits of treatment had minimal effects on the analysis. The analysis supports the use of an antigen test for adult patients with pharyngitis. Key words: pharyngitis; decision analysis; streptococcal antigen tests; utility theory. J GEN INTERN MED 1987;2:242–248.

THE MANAGEMENT of adult pharyngitis remains controversial. Some experts recommend antibiotic therapy only for patients with positive group A beta-hemolytic streptococcal (GABHS) cultures,[1] while others treat on the basis of clinical criteria.[2] In 1977, Tompkins et al. published a cost-effectiveness analysis of the prevention of primary acute rheumatic fever.[3] That analysis proposed that in endemic situations throat cultures be reserved for patients having a probability of GABHS between 5 per cent and 20 per cent.

In 1987, for various reasons, the Tompkins analysis may no longer be useful as a decision rule. First, the incidence of acute rheumatic fever has continued to decline,[4] without evidence of a concurrent decline in the incidence of GABHS infections. Second, although throat culture remains the "gold standard" for diagnosing infection with GABHS, a variety of rapid diagnostic tests based on latex agglutination testing for group A antigen have recently been developed and marketed.[5] The advantage of these tests is that the results are available within minutes to a few hours. Third, the Tompkins analysis did not consider the potential benefit of alleviation of symptoms by penicillin treatment. Last, all previous analyses concerning the management of GABHS infections have focused on society's rather than the patient's perspective.

Recently, Herman used the time-tradeoff method to estimate utilities for adults with sore throats and their potential consequences. He examined a patient's willingness to remain ill with pharyngitis compared with his or her willingness to risk two outcomes: a penicillin reaction or rheumatic fever.[6] Using these disutilities and published probabilities, we performed a decision analysis that determined the optimal strategy for the management of adult pharyngitis from an individual patient's perspective. The analysis specifically considered how rapid tests might alter the decision making process.

METHODS

Decision analysis is a modeling technique that systematically considers all possible management options of a problem.[7] Using a decision tree, the available choices and their potential outcomes are explicitly outlined. A decision tree consists of nodes, which describe choices, chances and outcomes. The tree is used to calculate the relative worth of each outcome. The numeric value of each outcome, or "utility," can be expressed using a defined scale. The option or strategy with the highest value is preferred. To answer questions of the form "What if. . . ?" a sensitivity analysis is performed. A sensitivity analysis varies one or several variables in a systematic manner and determines whether the optimal strategy changes. The point at which the optimal strategy changes is called a threshold.

Assumptions

Table 1 lists the assumptions made in structuring the analysis. Whenever "soft" data or assump-

TABLE 1

Assumptions of the Analysis

No history of acute rheumatic fever (ARF) or penicillin (PCN) allergy
A single rapid diagnostic test will be performed
Group A beta-hemolytic streptococcus (GABHS) is the only treatable pathogen
Acute rheumatic fever and a peritonsillar abscess cannot occur in the same patient
Penicillin is 100 per cent effective in preventing acute rheumatic fever
Oral penicillin will be given for ten days
Patient follow-up and compliance is 100 per cent

Received from the Division of General Medicine and Primary Care, Department of Internal Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia.

A preliminary version of this work was presented at the seventh annual meeting of the Society for Medical Decision Making, October 21, 1985.

Dr. Centor is a Teaching and Research Scholar of the American College of Physicians.

Address correspondence and reprint requests to Dr. Hillner: MCV Station, Box 170, Richmond, VA 23298-0001.

tions were required, the bias was consistently toward immediate penicillin treatment.

Decision Tree

Figure 1 shows the decision tree. At the far left is a square node representing the choice of four strategies: 1) immediate treatment (TREAT NOW) without culture or testing; 2) withholding antibiotics and watching all patients (WATCH); 3) performing a rapid antibody test (RAPID TEST) and treating if positive; or 4) performing a traditional throat culture (CULTURE) and treating patients with positive cultures with antibiotics at follow-up visits.

For each strategy the initial node, shown as a circle, represents the chance or probability that the patient's pharyngitis is due to GABHS. Thereafter, each strategy has its own unique structure. In the upper branch (TREAT NOW), both STREP and NONSTREP branches have the possibility of a penicillin reaction (PCNRX and NO PCNRX). The branches of the decision tree shown have been reduced by using a subtree. A subtree represents elements of the main tree that have a common structure. In Figure 2*A*, the ALLERGY subtree shows the types of a penicillin reaction considered. If a penicillin reaction does occur, it may be a FATAL RX, SEVERE RX, or MILD RX. Excluding the FATAL RX branch, the possible formation of a peritonsillar abscess (ABSCESS) was considered. The STREP and NONSTREP nodes are symmetrical except that in the NONSTREP branch the probability of a peritonsillar abscess is zero. The disutility of a penicillin reaction or an abscess is expressed as an increase in the number of "sick" DAYS. If a patient has GABHS pharyngitis and does not have a penicillin reaction or abscess, antibiotics will reduce the duration of his or symptoms. This is shown as BENEFIT DAYS in the utility expression.

For the WATCH strategy, in which antibiotics are not prescribed, acute rheumatic fever with or without complications may occur following GABHS pharyngitis (Fig. 2*B* subtree, ACUTE RF). In the absence of acute rheumatic fever, a peritonsillar abscess may develop, as shown in the ABSCESS subtree (Fig. 2*A*). Compared with the TREAT NOW branch, the probability of peritonsillar abscess is increased since penicillin was not given. Non-GABHS pharyngitis is shown as the terminal node UNRX NONSTREP.

The RAPID TEST strategy shows that the rapid test may or may not correctly identify GABHS. If disease is present and the test is positive (DIS++), i.e., a true positive result, then the patient will receive penicillin. The remainder of this branch is as described earlier for the STREP branch of the TREAT NOW strategy except that when testing is done the amount of benefit from appropriate therapy is decreased by the turnaround time of the test. If the test is falsely negative (D+T−), the patient will not receive penicillin and will have the same possible outcomes shown in the UNRX STREP branch of the WATCH strategy. The RAPID TEST strategy's lower branch represents non-GABHS pharyngitis. Testing may confirm the absence of infection (D−T−), i.e., a true negative result, resulting in no antibiotic prescription. A false-positive (D−T+) test would result in unnecessary antibiotic exposure. This node and the NONSTREP branch of the TREAT NOW strategy have the same structure.

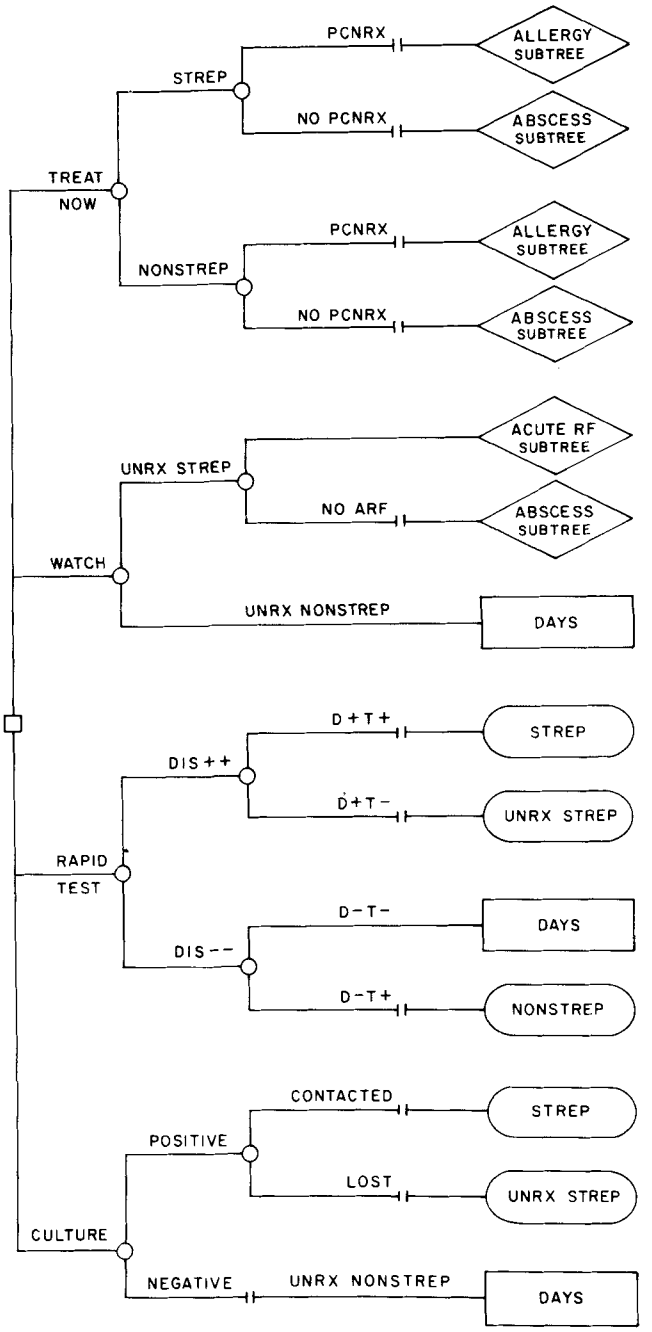

FIGURE 1. Decision tree for choice of four different strategies. The diamond-shaped boxes indicate paths leading to subtrees shown in Figure 2. The oval-shaped boxes represent a recursive link to a part of the tree previously defined.

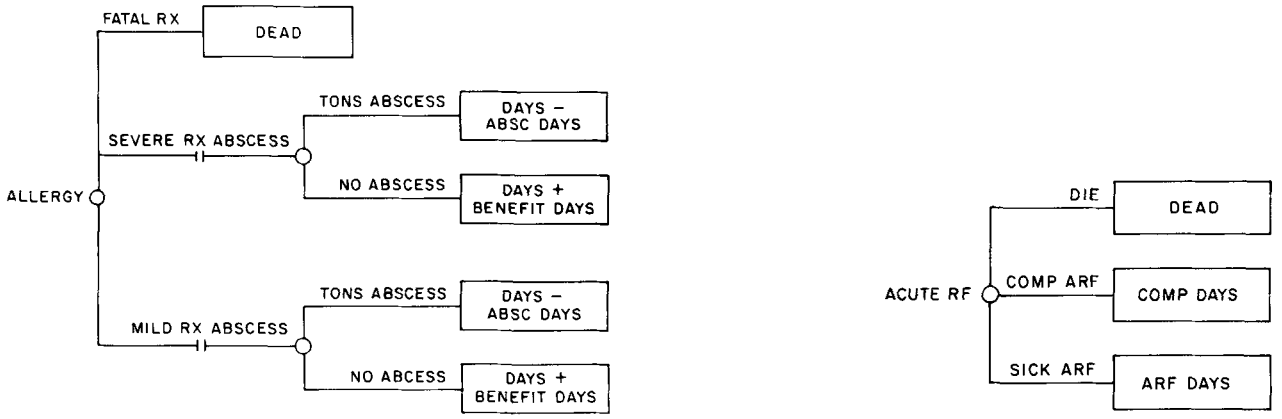

FIGURE 2. A (*left*), ALLERGY and ABSCESS subtree. Each node's value is expressed as a number of well days. *B* (*right*), ACUTE RF subtree. Each outcome reduces the number of well days by the sick-day equivalent.

The last branch (CULTURE) represents treating only after a positive throat culture. The initial chance node of POSITIVE and NEGATIVE refers to the throat culture for GABHS. If GABHS is present, the patient may be CONTACTED and receive penicillin as shown in the STREP branch of the TREAT NOW strategy. However, because of the delay in initiating therapy, the patient would receive no symptomatic benefit. If the patient cannot be followed, as shown in the LOST branch, the possible events are the same as in the UNRX STREP branch of the WATCH strategy. In our baseline analysis we assumed 100 per cent follow-up; however, lower follow-up rates must be considered in many settings.[8] In the sensitivity analyses we assessed various lower follow-up rates.

Data Summary

Table 2 lists the probabilities and utilities used in the analysis.

Probability of GABHS Pharyngitis. Reported prevalences of GABHS in adult sore throat patients range from 7 per cent to 25 per cent.[9] Our initial estimate of 20 per cent is based on the data obtained in our emergency room.[10] An individual patient's probability of GABHS pharyngitis can be estimated by combining prevalence information with a clinical score derived from a logistic regression model based on four clinical signs.[9, 11]

Acute Rheumatic Fever. In 1987 it is difficult to provide an accurate estimate of the probability of acquiring rheumatic fever after a GABHS infection. In 1961 Siegel et al.[12] found that 2/311 (0.004) school children developed acute rheumatic fever (ARF) after untreated streptococcal pharyngitis. In recent years, the incidence of ARF has dropped at least fiftyfold.[4] This dramatic reduction in the incidence of ARF has occurred without evidence of a decline in the incidence of GABHS throat infections.[13] The reason for the reduction is probably multifactorial and has been reviewed elsewhere.[14] Based on a review of published expert opinions, we estimate the conditional probability of ARF associated with untreated GABHS pharyngitis to be one in 2,000 cases.[15] In the sensitivity analyses we assess multifold changes in this probability. Rheumatic heart disease and death per case were estimated at 10 per cent and 1 per cent, based on rates reported in the 1960s.[16]

Peritonsillar Abscess. A peritonsillar abscess is a serious complication of GABHS pharyngitis not considered in previous analyses of sore throats. When a peritonsillar abscess develops, it usually presents days after the sore throat and often necessitates hospitalization and surgical drainage. The available incidence data are meager. Bennicke observed that 9/175 untreated and 1/174 penicillin-treated patients with sore throats developed peritonsillar abscesses.[17] We estimate that 2 per cent of untreated persons with GABHS pharyngitis develop peritonsillar abscesses.

Penicillin Allergy. The probabilities of mild and severe penicillin allergy were abstracted from those used by Tompkins et al.[3, 18] The probabilities of

TABLE 2

Probabilities of Chance Events

	Baseline	Range
Absolute probabilities		
(GABHS) as source of pharyngitis	0.20	0.0–0.50
Penicillin allergy	0.005	0.0–0.01
Conditional probabilities		
GABHS infections that develop into acute rheumatic fever (ARF)	0.0005	0.0–0.001
ARF that is complicated	0.10	0.0–0.20
ARF that is fatal	0.01	0.0–0.02
GABHS infections that develop into peritonsillar abscess	0.02	0.0–0.10
Severe penicillin reaction	0.005	0.0–0.01
Fatal penicillin reaction	0.0005	0.0–0.005

allergic reactions appear to differ in children and adults. Given the bias of the analysis towards immediate treatment, the estimated probability of a penicillin allergy was conservative—0.005, or 1/200. The number of severe penicillin reactions (serum sickness and true anaphylactic reactions) was estimated as a conditional probability, i.e., as a relative amount of the total number of allergic reactions: 0.005 or 1/200 severe reactions and 0.001 or 1/1,000 fatal reactions. Therefore, the baseline estimates were 2.5×10^{-4} risk of a severe reaction and 2.5×10^{-6} of a fatal reaction.

Benefits of Therapy. Thirty-five years ago, Denny et al.[19] demonstrated the importance of antibiotic therapy in decreasing the risk of rheumatic fever after GABHS pharyngitis. Given the current low incidence of ARF, we have assumed that penicillin therapy is 100 per cent effective in preventing ARF in cases in which GABHS pharyngitis is identified and treated. Others[20] have made this assumption based on medical and legal reasons. The prevention of peritonsillar abscess formation attributable to antibiotics has not been documented but was estimated to be 75 per cent.

In most studies the duration of morbidity or "sickness" from GABHS pharyngitis is reduced by about a day when antibiotics are promptly given.[21] Accordingly, we have used a one-day symptom benefit if GABHS is treated. However, some experts do not think that this conclusion can be extrapolated to the current endemic conditions, particularly in adults. As part of the sensitivity analyses, the analysis was repeated excluding a symptomatic benefit.

Test Characteristics. Several new latex agglutination tests for detecting group A antigen from throat swabs have been developed.[22] These tests have processing times of 10–120 minutes. Most published studies have indicated that the new tests are very specific (96–100 per cent). However, relative sensitivities of different products vary widely. When performed by an experienced technician, the rapid diagnostic test has a sensitivity of at least 95 per cent and specificity of least 98 per cent for adults. These values were used as the initial estimates. In the sensitivity analysis lower test sensitivities were evaluated. We have conservatively estimated an effective turnaround time or delay in the initiation of antibiotic therapy of three hours. These test characteristics are summarized in Table 3.

Utility Estimates. The utilities assigned to individual health outcomes were based on patient preferences expressed as "sick-day equivalents." The sick-day equivalents for penicillin reaction and acute rheumatic fever were based on Herman's results.[6] Herman used a time-tradeoff method to establish these sick-day equivalents using a descriptive questionnaire for two different categories of patients. One category was patients with acute pharyngitis and the other consisted of patients with non-acute health care needs. Outcome risks were estimated for 5 per cent, 50 per cent, and 100 per cent risks of each adverse outcome. The sick-day equivalents for a peritonsillar abscess and for death were arbitrarily assigned. The disutility of a peritonsillar abscess was chosen to be greater than that of a mild and less than that of a severe penicillin reaction. The sick-day equivalents for death of 20,000 days (about 55 years) was made by doubling the reported result for complicated rheumatic fever. Table 4 lists the sick-day equivalents used in the analysis and the ranges considered.

TABLE 3

Rapid Test Characteristics

	Baseline	Range
Sensitivity	0.95	0.75–1.00
Specificity	0.98	0.90–1.00
Turnaround time (days)	0.125	0.00–1.00

The final results of the analysis were expressed as the number of "well" days using a ten-day time frame by the formula

$$\text{Net well days} = 10 \text{ well days} - \text{sick-day equivalents}$$

Calculations. All calculations were performed with a commercially available decision analysis computer program written in the Pascal language.[23]

RESULTS

The baseline analysis resulted in an average expected utility of 4.93 well days for immediate-treatment strategy, 5.00 well days for the rapid-test strategy, 4.87 well days for the culture-only strategy,

TABLE 4

Utility Estimates

Outcome	Sick-day Equivalents	Range
Benefit of treated group A beta-hemolytic streptococcal (GABHS) pharyngitis	−1*	−1–0
Change in symptom benefit due to testing	0.25	0–1
Untreated pharyngitis	5	5–10
Mild penicillin reaction	15	7–30
Peritonsillar abscess	100	30–180
Severe penicillin reaction	180	60–360
Uncomplicated rheumatic fever	1,000	360–3,600
Complicated rheumatic fever	10,000	3,600–20,000
Death from penicillin allergy or acute rheumatic fever	20,000	10,000–30,000

*This outcome is negative since it is a reduction in sick days.

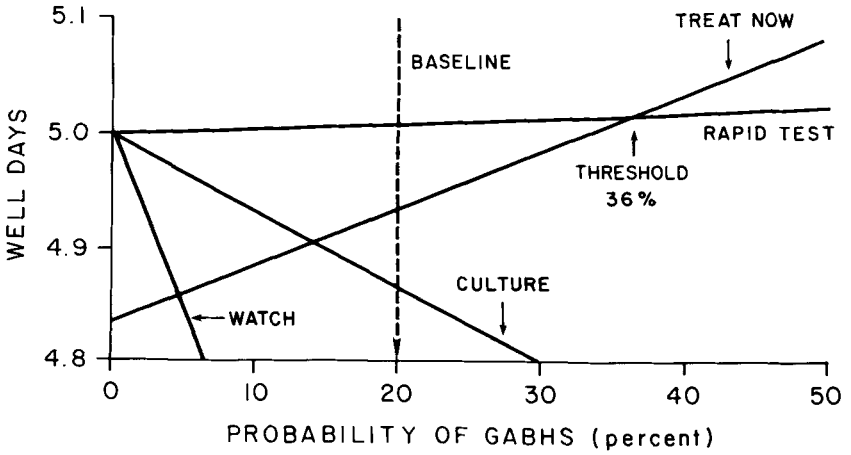

FIGURE 3. One-way sensitivity analyses. The expected utility in well days (vertical axis) for a range of probabilities of infection with group A beta-hemolytic streptococcus (GABHS) (*horizontal axis*). Each line represents a clinical strategy. The baseline estimate and threshold value between the TREAT NOW and RAPID TEST strategies are marked with arrows.

and 4.39 well days for the withhold-all-treatment strategy.

Sensitivity Analyses. Sensitivity analyses were performed to determine the impacts of changes in the baseline probability estimates, utility assignments, and structural assumptions.

Probability of GABHS Pharyngitis. Figure 3 shows a one-way sensitivity analysis of the effects of changes in the probability of GABHS pharyngitis. The baseline 20 per cent probability of GABHS pharyngitis is shown with an arrow on the horizontal axis. When the probability of GABHS pharyngitis is less than 0.5 per cent, CULTURE is the optimal strategy. When the probability of GABHS pharyngitis is between 0.5 per cent and 36 per cent, the RAPID TEST strategy is optimal. When the probability of GABHS pharyngitis exceeds 36 per cent, immediate treatment (TREAT NOW) is optimal. Through the range considered, the maximal benefit is less than 0.1 days. The analysis could be considered a "toss-up."[24]

Acute Rheumatic Fever. The analysis is insensitive to changes in the probability of acute rheumatic fever per GABHS infection. If the probability of acute rheumatic fever were increased fivefold ($p = 0.0025$), the threshold of the CULTURE strategy would remain under 1 per cent and that for immediate treatment (TREAT NOW) would decrease only to 25 per cent. A tenfold increase in the probability of acute rheumatic fever, which would require a major change in the rheumatogenicity of GABHS, would narrow the window in which the RAPID TEST strategy is optimal to a probability of GABHS pharyngitis between 1.4 per cent and 17 per cent.

Test Sensitivity and Time. The baseline analysis was biased against the use of a rapid diagnostic test by reducing the benefits of treatment by three hours. This reduction in benefit may be incorrect since the rapid diagnostic tests are intended for use to guide therapy before the patient leaves the health care office. If the effective test turnaround time is zero, the threshold value of GABHS pharyngitis increases to 49 per cent.

Major reservations about the use of rapid tests have been based on questions of their sensitivity. Given the initial assumptions, the test sensitivity threshold is 0.84. Using a lower probability of GABHS of 10 per cent, the test sensitivity threshold decreases to 0.59. Each of these thresholds is below the sensitivities found for most rapid tests. If testing does not decrease the benefit of therapy, then the test sensitivity thresholds decrease slightly to 0.81 (pGABHS = 0.20) and 0.56 (pGABHS = 0.10).

Penicillin Allergy. The analysis is quite sensitive to modest changes in the probability of penicillin allergy and allergic death. When penicillin is given intramuscularly, the probability of an allergic reaction is approximately doubled. In this situation the threshold for immediate treatment increases from 36 per cent to 54 per cent. If the lowest reported rate for penicillin anaphylaxis of 0.0025 is used, the threshold for immediate treatment decreases to 22 per cent. If the possibility of a fatal penicillin reaction is excluded, the threshold for immediate treatment decreases to 18 per cent. Therefore, in generalized terms, the immediate-treatment strategy is preferred only when the probability of GABHS pharyngitis is high and the rapid test sensitivity is low and has a long turnaround time.

Treatment Benefit and Follow-up. Some experts do not believe antibiotics will reduce the duration of symptoms. Therefore, the analysis was repeated varying the benefit of therapy between zero and one day as shown in Figure 4. When no reduction in symptoms resulted from therapy, the CULTURE strategy is optimal, since 100 per cent follow up was assumed. This is shown at the left of the graph where the lines intersect the vertical axis. The threshold between the CULTURE and RAPID TEST strategies is 0.26 days, i.e., the point where the two lines cross. Therefore, when the benefit of treatment is less than 0.26 days, CULTURE is the optimal strategy. When separately considering the CULTURE and TREAT NOW strategies, the threshold was a benefit of 0.66 days.

Repeating the analysis using a reduction in

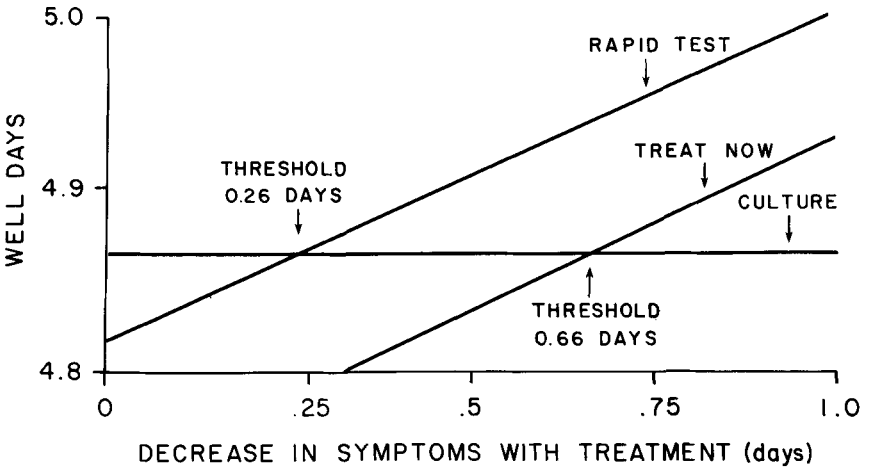

FIGURE 4. One-way sensitivity analyses of the decrease in symptoms with treatment of group A beta-hemolytic streptococcal (GABHS) pharyngitis. The probability of GABHS was 20 per cent. The threshold values between the CULTURE and RAPID TEST (*left*), and the CULTURE and TREAT NOW (*right*) strategies are marked with arrows. Throughout the range shown TREAT NOW is never the optimal strategy.

symptoms of one-half day minimally altered the analysis. The threshold between the CULTURE and RAPID TEST strategies increased from 0.5 per cent to 1.4 per cent, and that between the RAPID TEST and TREAT NOW strategies from 36 per cent to 38 per cent. The absolute range in which RAPID TEST is optimal actually increased.

In few clinical situations is 100% patient follow up guaranteed. Therefore, we performed a two-way sensitivity analysis looking at the concurrent effect of changes in test sensitivity and follow-up rates. A threshold line with a slope of approximately 1 was found. For example, if the follow-up probability is assumed to be 80 per cent, then if the rapid test has a sensitivity greater than 81 per cent the RAPID TEST strategy is optimal.

COMMENTS

The appropriate management of acute pharyngitis remains controversial because of the changing incidence of acute rheumatic fever and improvements in diagnostic procedures. In this analysis we have incorporated these changes and have approached the problem from the patient's perspective. By explicitly including the symptomatic benefit of therapy and patient preferences, we have built a model that we believe closely resembles the problems facing health care providers. Our analysis shows that the use of a rapid test is the strategy of choice in most clinical settings.

The analysis reveals that using a rapid antigen test is superior to the immediate-treatment strategy principally because of the reduction in the number of cases of penicillin allergy and/or anaphylaxis. Since the baseline estimates for adverse reactions to penicillin were relatively low, the analysis strongly supports the use of a rapid antigen test for almost all reported probabilities of GABHS pharyngitis observed in adult populations. The analysis underscores the importance of avoiding treatment morbidity as well as disease complications.

The prevention of ARF is relatively unimportant in the analysis. The conditional risk of ARF per case of GABHS pharyngitis would have to approximate the endemic rates reported over 30 years ago before testing is no longer the approach of choice. At such high rates of ARF, the optimal strategy would be immediate treatment and not culturing. Treatment is preferred because patients who would have had a false-negative test are treated, and because the duration of symptoms is reduced by treatment. Immediate treatment would be preferred at even lower probabilities of GABHS pharyngitis if follow up were less than 100 per cent.

One of the major criticisms of the rapid antigen detection tests is their relatively poor sensitivity.[22] Our analysis shows that when the test sensitivity exceeds 85 per cent the test strategy is optimal under almost all assumptions. This was found even when we biased the analysis against testing by reducing the benefit of therapy. However, such a delay in benefit is probably unrealistic since a rapid test would be performed during the same patient encounter and any delay in therapy would be minimal. When the delay is excluded, the test strategy is optimal even at very high probabilities of GABHS pharyngitis.

The amount of symptomatic benefit from prompt antibiotic therapy has been debated. The analysis shows that when the symptoms are reduced by even six hours, testing is preferred to culturing. A reduction in benefit of more than six hours but less than a full day does not significantly change the test/immediate treatment thresholds.

Advocates of performing a throat culture assume that all patients who have positive cultures will receive antibiotics, and that those with negative cultures will have antibiotics stopped. In practice both of these assumptions have been shown to be false.[8] Even excluding any benefit from therapy, if the sen-

sitivity of the test exceeds the follow-up rate, then the testing is optimal compared with the culture strategy. This linear relationship may prove to be a useful rule for physicians.

Our analysis is the first in which patient preferences are used as the basis for the values of each outcome. The values for peritonsillar abscess and death were arbitrarily assigned but were consistent with the other utilities. The analysis was repeated using the extremes of the utility values of an allergic reaction or rheumatic fever. The threshold values of the probability of GABHS pharyngitis and test sensitivity were minimally changed.

Our analysis shows that the rapidity of the antigen test defines the diagnostic window of the probability ranges of GABHS pharyngitis in which the test should be used. The benefit of testing is primarily the result of avoiding penicillin reactions. Prevention of ARF or peritonsillar abscess has little effect on the analysis.

The utility or value of each outcome in the analysis was expressed in days. What constitutes a clinically "significant" difference between strategies is unknown. When such short time-frames are considered, fractions of a day may or may not be important. To restate our results, the analysis shows that in aggregate all patients derive a benefit from testing of a fraction of a day, but a correctly identified patient will benefit by a full day. From a decision analytic perspective the results may represent a toss-up. To others the symptomatic benefit of therapy is so important that the phrase "what a difference a day makes" is appropriate.

REFERENCES

1. Lowe R, Hedges JR. Early treatment of streptococcal pharyngitis. Ann Emerg Med 1984;13:440-8
2. Reilly BM. Practical strategies in outpatient medicine. Philadelphia: W. B. Saunders, 1984;71-100
3. Tompkins RK, Burnes DC, Cable WE. An analysis of the cost-effectiveness of pharyngitis management and acute rheumatic fever prevention. Ann Intern Med 1977;86:481-92
4. Land MA, Bisno AL. Acute rheumatic fever: a vanishing disease in suburbia. JAMA 1983;249:895-8
5. Infectious Disease and Immunization Committee, Canadian Paediatric Society. Rapid identification of group A beta-hemolytic streptococci in throat swabs. Can Med Assoc J 1986;134:228-9
6. Herman JM. Patients' willingness to take risks in the management of pharyngitis. J Fam Pract 1984;6:767-72
7. Pauker SG, Kassirer JP. Decision analysis. N Engl J Med 1987;316:250-8
8. Centor RM, Witherspoon JM. Treating sore throats in the emergency room: the importance of followup in decision making. Med Decis Making 1982;2:463-9
9. Walsh BT, Bookheim WW, Johnson RC, Tompkins RK. Recognition of streptococcal pharyngitis in adults. Arch Intern Med 1975;135:1493-7
10. Centor RM, Dalton HP, Campbell MS, Lynch MR, Watlington AT, Garner BK: Rapid diagnosis of streptococcal pharyngitis in adult emergency room patients. J Gen Intern Med 1986;1:248-51
11. Centor RM, Meier FA, Dalton HP. Throat cultures and rapid tests for diagnosis of group A streptococcal pharyngitis. Ann Intern Med 1986;105:892-9
12. Siegel AC, Johnson EE, Stollerman GH. Controlled studies of streptococcal pharyngitis in a pediatric population. 1. Factors related to the attack rate of rheumatic fever. N Engl J Med 1961;265:559-66
13. Holmberg SD, Faich GA: Streptococcal pharyngitis and acute rheumatic fever in Rhode Island. JAMA 1983;250:2307-12
14. Bisno AL. The rise and fall of rheumatic fever. JAMA 1985;254:538-41
15. Sanford JP. Management of pharyngitis in an era of declining incidence of rheumatic fever: an overview and synthesis. In: Shulman ST, ed. Pharyngitis: management in an era of declining rheumatic fever. New York, Praeger, 1984:251-4
16. Feinstein AR, Wood HF, Spagnuolo M, et al: Rheumatic fever in children and adolescents. A long-term epidemiologic study of subsequent prophylaxis, streptococcal infections, and clinical sequelae. VII. Cardiac changes and sequelae. Ann Intern Med 1964:60(suppl 5):87-123
17. Bennicke T, Brochner-Mortensen K, Kjaer E, Skadhange K, Trolle E. Penicillin therapy in acute tonsillitis, phlegmonous tonsillitus and ulcerative tonsillitis. Acta Med Scand 1951;139:253-74
18. Idsoe O, Guthe T, Willcox RR, et al: Nature and extent of penicillin side-reactions with particular reference to fatalities from anaphylactic shock. Bull WHO 1968;38:158-88
19. Denny FW, Wannamaker LW, Brink WR, Rammelkamp CH, Custer EA. Prevention of rheumatic fever: treatment of the preceding streptococci infection. JAMA 1950;143:151-3
20. Hedges JR, Lowe RA. Streptococcal pharyngitis in the emergency department: analysis of therapeutic strategies. Am J Emerg Med 1986;4:107-15
21. Nelson JD: The effect of penicillin therapy on the symptoms and signs of streptococcal pharyngitis. Pediatr Infect Dis 1984;3:10-3
22. Kellogg JA, Manzella JP. Detection of group A streptococci in the laboratory or physician's office: culture vs antibody methods. JAMA 1986;255:2638-43
23. Hollenberg JP. Smltree 1.5, copyright 1986.
24. Kassirer JP, Pauker SG. The toss-up. N Engl J Med 1981; 305:1467-8