Management of Children with Acute Pharyngitis: A Decision Analysis

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Background. Although the incidence of acute rheumatic fever has declined in the last decades, a few outbreaks have recently been reported. A rapid latex agglutination test for group A streptococci seems reasonably accurate, and early treatment of acute pharyngitis seems to influence the pharyngitis itself. These factors have promoted uncertainty concerning the current best management of patients with sore throat.

Methods. Clinical decision analysis is used to compare the risks and benefits of symptomatic treatment, and oral and intramuscular penicillin as therapeutic options, and the throat culture and the rapid latex agglutination test as diagnostic strategies. Best estimates of the risk of streptococcal pharyngitis, its complications, the carrier rate, the accuracy of diagnostic tests, the efficacy of antibiotic treatment, allergic reactions, medication compliance, and health outcomes are combined into a management advisory. All results are subjected to a sensitivity analysis in order to check their strength against plausible changes in assumptions. Quality adjusted life days (QALD) lost are used as an outcome measure.

Results. The agglutination test combined with oral penicillin yielded the lowest expected loss (.50) of QALD for a typical child with a risk of harboring streptococci of .60. The other strategies, however, yielded losses that were only several hundredths of QALD higher.

Conclusions. For children with at least a 40% chance of harboring streptococci and a duration of complaints of less than 2 days before starting treatment, diagnostic testing and prescription of oral penicillin appear to be the best choice of initial management. The rapid latex agglutination test is more effective than the throat culture, because prompt penicillin treatment after a positive test result may shorten the duration of pharyngitis in infected children. High rates of acute rheumatic fever (over 5×10^{-4}) and low medication compliance change the best strategy to agglutination test with intramuscular administration of penicillin.

Key words. Decision analysis, streptococcal pharyngitis.
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During the last few years, research has provided new insights into the management of pharyngitis.[1–4] The incidence of acute rheumatic fever among children has declined in western countries,[5–9] but a few outbreaks have been reported recently.[10–14] An effect of oral penicillin therapy on the natural course of streptococcal pharyngitis has been demonstrated in patients who are treated early.[15] The new rapid agglutination tests for the detection of group A β-hemolytic streptococci make early treatment directed at streptococcal pharyngitis possible. In view of these developments, many clinicians may wonder whether their diagnostic and therapeutic approach to acute pharyngitis is optimal.

Clinical decision analysis can help in synthesizing the available information on this common but complex decision.

Steps in a decision analysis include[16,17]:

- Careful description of the available strategies and their possible consequences
- Quantitative assessment of all relevant probabilities and outcomes (in terms of utilities or utility losses)
- Calculations and sensitivity analyses (in order to identify the strategy with the lowest expected loss, and to check the strength of the analysis)
- Presentation of the conclusions in a clinically useful way

The method is explicit, it allows for detailed analysis, and it stimulates discussion among professionals.[16–20]

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Three therapeutic options (symptomatic treatment, treatment with penicillin given orally, and treatment with penicillin given intramuscularly) and two diagnostic strategies (throat culture and a rapid agglutination test) are compared. Best estimates of the risk of streptococcal pharyngitis, its complications, the rate of carriers, the accuracy of diagnostic tests, the efficacy of antibiotic treatment, allergic reactions, medication compliance, and health outcomes are evaluated and management guidelines are provided. A hypothetical patient is used to illustrate the analysis.

Management of Patient

Patient Scenario

A 14-year-old boy, who has suffered from a sore throat for 1 day, presents to a general practice office in the spring. He has a fever (38.5°C), and pain when swallowing; there is no cough or rhinitis. Physical examination reveals a red pharynx and tonsils with a heavy exudate. Cervical lymph nodes are enlarged and tender. The patient has never had acute rheumatic fever nor any allergy in the past.

Clinical Strategies

The clinical strategies that are considered are:

1. Symptomatic treatment
2. Direct treatment with penicillin
3. Agglutination test; if positive, treatment with penicillin
4. Culture; if positive, treatment with penicillin
5. Culture; start treatment immediately with oral penicillin; stop treatment if the culture turns out negative after a few days

In strategies 2 through 4, penicillin can be administered in a 10-day course either orally or intramuscularly. Beforehand it could be argued that implicit in strategy 5 is an inferior ratio of risks to benefits. The risks of penicillin given orally are concentrated in the first days of its use; therefore, it is better not to culture when penicillin is prescribed, in order to avoid false-negative results and the cost of the test. It is a commonly used strategy nevertheless,[6] and was therefore included in the analysis.

All strategies are represented by a decision tree (Figure 1). In this tree, the occurrence of suppurative complications, acute rheumatic fever and its sequelae, allergic complications, and a possible effect of penicillin on the natural course of the pharyngitis itself are modeled. Acute glomerulonephritis is not considered because there is no evidence that this complication can be prevented by early penicillin treatment.[21,22]

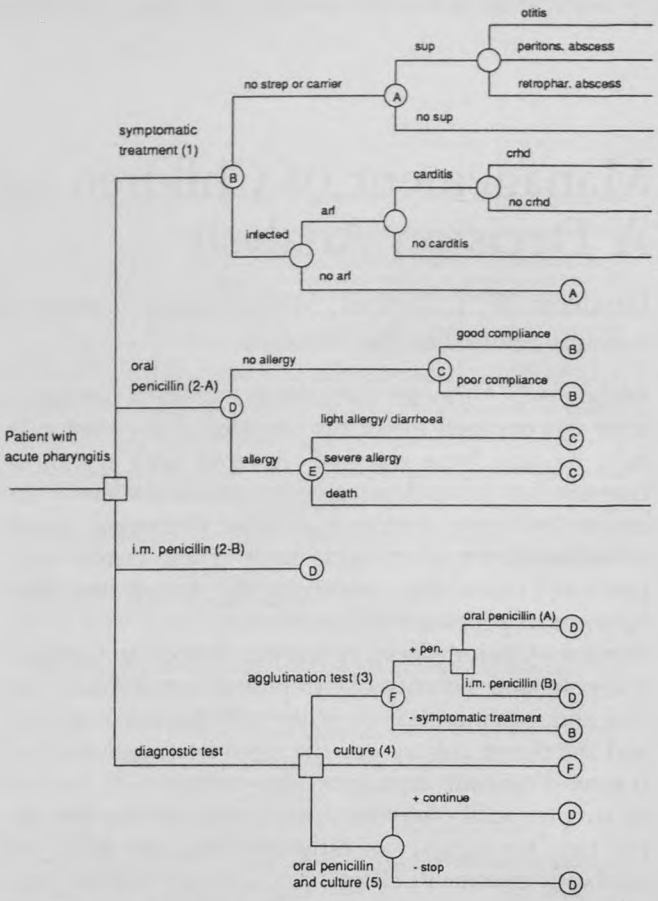

Figure 1. Decision tree for the management of acute pharyngitis in children. Five clinical strategies are represented: 1, symptomatic treatment; 2, treatment with either oral (A) or intramuscular (B) penicillin; 3 and 4, diagnostic testing using the rapid agglutination test (3) or the throat culture (4) with subsequent administration of oral (A) or intramuscular (B) penicillin in case of a positive test result; 5, culture; start immediately with oral penicillin; withdraw therapy if the culture turns out negative after a few days.

Strep denotes harboring streptococci; sup, suppurative complications; peritons, peritonsillar; retrophar, retropharyngeal; arf, acute rheumatic fever; crhd, chronic rheumatic heart disease; i.m., intramuscular; pen., penicillin. Upper case letters in chance nodes indicate that the corresponding subtree structure should be inserted, but probabilities in the subtree may differ.

In order to make an overall comparison of the strategies, outcomes are expressed in terms of quality adjusted life days (QALD) lost. QALD lost for each outcome are computed by estimating the number of days spent in each health state, and weighing these days by quality loss (L), a number between 0 and 1. This quality loss corre-

Table 1. Probabilities Used in the Decision Analysis of Acute Pharyngitis Management

Item	Point Value	Plausible Range
Probability of carrier	.3	.1–.4
Symptomatic treatment		
Otitis	.002	0–.005
Retropharingeal abscess	.002	0–.005
Peritonsillar abscess	.016	.01–.03
Acute rheumatic fever	36×10^{-5}	3×10^{-5}–360×10^{-5}
Carditis, after acute rheumatic fever	.7	.6–.8
CRHD after carditis	.25	.2–.3
Orally administered penicillin		
Mild allergic reaction	.02	.01–.03
Severe allergic reaction	2×10^{-5}	$1–4 \times 10^{-5}$
Death (anaphylaxis)	3×10^{-6}	$1–6 \times 10^{-6}$
Relative risk of suppurative complications	.3	.2–.5
Relative risk of acute rheumatic fever	.2	.1–.4
Diarrhea	.02	.01–.04
5 days' compliance	.7	.5–.9
9 days' compliance	.5	.3–.7
Intramuscularly administered penicillin		
Mild allergic reaction	.03	.02–.06
Severe allergic reaction	1×10^{-4}	$.5–2 \times 10^{-4}$
Death	2×10^{-5}	$1.5–2.5 \times 10^{-5}$
Relative risk of suppurative complications	.3	.2–.5
Relative risk of acute rheumatic fever	.1	.05–.2
Test characteristics		
Sensitivity of latex-agglutination test	.9	.80–.95
Probability of positive test in carriers	.8	.6–.9
Sensitivity of culture	.9	.85–.95
Probability of positive culture in carriers	.8	.6–.9

sponds to $1 - U$ (U = utility). Losses are easier to interpret because they directly reflect the impact of disease. The expected QALD lost for each strategy is computed by multiplying the losses for each outcome with the probability of that outcome. The strategy with the minimum expected number of QALD lost is the one preferred.

We chose to consider the benefits and risks of each strategy from the patient's viewpoint only. Financial costs (of diagnostic testing, treatment, complications, illness, and so forth) were ignored. Possible legal consequences of misdiagnosis and complications were not considered either.

Decision Analysis

All probability values used in the decision analysis are discussed in this section. They are summarized in Table 1.

Infection and Carrier State

Streptococcal infection is defined by the presence of group A β-hemolytic streptococci causing acute pharyngitis. A carrier is defined as a child with acute pharyngitis who harbors streptococci but is not truly infected. A carrier runs no risk of rheumatic fever, and penicillin treatment will not mitigate the symptoms of the pharyngitis. Several studies [23–25] have investigated the prevalence of streptococcal infection and of carriers among people with sore throat by looking for significant changes in antistreptococcal antibodies in serum. However, rather broad criteria of inclusion were used, ie, symptoms of sore throat only[23,25] and age up to 16 years.[25] This may account for the low prevalence of true streptococcal infections (20%). The frequency of carriers in these studies is about 30%. Some of the subjects in these studies were given penicillin during their illness; this may have resulted in an inaccurate estimate. Therefore, we allowed for a wide range of plausible values for the probability of carriers (.10 to .40).

Clinical scoring rules have been developed[26–30] that predict the result of a throat culture but not streptococcal infection. To link these concepts, we define four possible states (infected, carrier, streptococci, no streptococci), with the following relationship between their probabilities: P (streptococci) = 1 − P (no streptococci); and P (infected) = P (streptococci) − P (carrier). According to the rule of Breese[27] or Centor et al,[29] our patient would have a .60 probability of harboring streptococci. Breese's rule is the only one formulated for evaluating children. Unfortunately, Breese does not clearly state the proportion of positive cultures in the population on which his prediction rule was based, whereas Centor and colleagues suggest adjustment for different prevalences.

Suppurative Complications

In the study by Valkenburg et al,[23] suppurative complications developed in approximately 2% of patients. The relative occurrence of retropharyngeal abscess, otitis, and peritonsillar abscess at 14 years of age is estimated at 1:1:8.[31,32] An equal probability of suppurative complications is assumed for streptococcal and nonstreptococcal pharyngitis.[33] Treatment with penicillin does not eliminate this risk completely because bacteria other than streptococci that are less sensitive to penicillin may cause these complications. We assume a two- to fivefold risk reduction.[6]

Acute Rheumatic Fever

A declining incidence of acute rheumatic fever has been demonstrated.[34,35] In the 1980s, an incidence of 0.5/100,000 per year among white suburban children in the United States and Scotland has been reported.[5,7,36,37] Penicillin seems to have played only a secondary role. Instead, the decline is attributed to socioeconomic improvements and changes in immunopathogenicity.[3,6,34] Veasy et al[11] reported a higher incidence in the US Intermountain area: 18 per 100,000 children in 1985. More outbreaks have been reported, but a catchment area for their cases was not given.[10,12–14] It is impossible to compute annual incidence rates from these studies. Estimates of the probability of acute rheumatic fever after streptococcal infection depend strongly on assumptions concerning the incidence of streptococcal pharyngitis among children. Children have an episode of sore throat about once every year.[38] Only approximately 10% (5% to 20%) are infected with streptococci. Thus, the probability of developing acute rheumatic fever for a patient with streptococcal infection of the pharynx may be as low as 3/100,000 or as high as 360/100,000, which is 120 times as great. This whole range was investigated. The upper estimate amply covers the rates reported.[10–14] A baseline estimate of 36/100,000 was used.

In a study of the natural course of acute rheumatic fever,[39] carditis was present in between two thirds and three quarters of all cases, with the first attack of acute rheumatic fever examined at the time of inclusion. Twenty-five percent of these patients developed chronic rheumatic heart disease. The immediate mortality for these patients is 0.05. The annual excess mortality of .015 (.01 to .02) is due to heart failure and related problems.[39]

The probability of acute rheumatic fever after streptococcal pharyngitis was estimated by dividing the population incidence of acute rheumatic fever by the incidence of streptococcal pharyngitis. This assumes that acute rheumatic fever is always preceded by symptomatic streptococcal pharyngitis. Thus, the estimate is probably biased toward too high values. The baseline estimate of the attack rate of acute rheumatic fever is taken arbitrarily, approximately midway between the extremes.

Penicillin Treatment

Several decades ago Denny et al[40] reported a tenfold decrease in the rate of acute rheumatic fever among recruits with streptococcal pharyngitis, who were treated with intramuscular penicillin. For oral penicillin, a five- to tenfold reduction in rate of attack seems plausible.[6]

Randolph and co-workers[15] reported the results of a double-blind randomized trial of oral penicillin, cefadroxil, and placebo in children with pharyngitis. A significantly larger proportion of the patients treated with antibiotics recovered after 1 day. Similar results have been reported in other studies.[41,42] We assumed a 1-day reduction in mean duration of illness for infected patients who are treated with penicillin and who have not been symptomatic for more than 48 hours.

Allergic complications of penicillin treatment are classified according to their severity and duration. Light allergy comprises cutaneous manifestations, such as erythematosquamous eruptions, pruritus, rashes, and urticaria. The probability of this complication is about .03 with penicillin administered intramuscularly.[43–46] For oral penicillin this probability may be lower.[44,46] Idsoe et al[47] estimate the risk of anaphylactic death due to intramuscular injection of penicillin at 1.5×10^{-5} to 2.5×10^{-5}. The probability of severe allergic reactions (nonfatal anaphylactic reactions, serum sickness–like manifestations, and hemolytic anemia) occurring following intramuscular injection of penicillin is approximately 1×10^{-4}. Anaphylactic reactions and severe allergy caused by oral administration of penicillin may also be less frequent or less severe or both.[43,47–50] Exact data are not available;

however, we assume a two- to tenfold lower probability of severe adverse reactions occurring from orally administered penicillin. Diarrhea (a nonallergic complication) occurs in 0.02 (0.01 to 0.04) of cases in which penicillin is administered orally.

Medication Compliance

Charney et al[51] investigated patient compliance with an orally administered regimen of penicillin in children by counting leftover pills and measuring penicillin activity in urine. Five days' compliance was 70%, and 50% of patients completed the full course. Compliance was related to the mother's perception of the severity of the disease. Colcher and Bass[52] concluded that counseling may enhance compliance. Gilbert and co-workers[53] showed that predicting compliance is difficult even in family practice where the influences of the patient's family and environment are considered.

It is assumed that when penicillin is taken for only 5 days, the incidence of suppurative complications will be reduced, but not the attack rate of acute rheumatic fever.

Throat Culture

Patients with throat culture positive for group A β-hemolytic streptococci receive treatment. The results of the blood agar culture are available after approximately 24 to 48 hours. This is too late to influence the natural course of the acute illness, but suppurative complications and acute rheumatic fever may still be prevented.

The sensitivity of throat cultures is taken at .90.[54] The probability of a patient who is not truly infected having a negative culture depends almost completely on the proportion of carriers.[25]

Agglutination Test

The results of the agglutination test for streptococci are available within 1 hour.[55] Use of this test for patients with symptoms of less than 2 days' duration influences the natural course of the acute illness in truly infected patients if treatment with penicillin is begun promptly. Complete data on the accuracy of this test are not available, but comparisons have been made with the throat culture.[56–60] The sensitivity of the latex agglutination test seems to be equal to or slightly lower than that of the throat culture (.80 to .95).[56,57,61] The test for streptococci is more often negative in cases that yield cultures with 10 colonies or less. Neither the throat culture nor the agglutination test can discriminate between carriers and truly infected persons.[25,58,61] A large plausible range of values for the probability of a positive test in carriers is suggested. Theoretically, antigenic cross-reactions with other microorganisms may also cause false-positives, but this effect is negligible.

Table 2. Losses in Quality Adjusted Life Days (QALD) Resulting from Complications

Complication	Approximate Duration of Illness (days)	QALD Lost
Otitis	4	1.2
Retropharyngeal abscess	7	2.1
Peritonsillar abscess	7	2.1
Acute rheumatic fever		
No carditis	28	8.4
Carditis	182	54
Chronic rheumatic heart disease	9052	12,660
Mild allergic reaction	7	2.1
Severe allergic reaction	28	8.4
Anaphylactic death	—	21,714
Diarrhea	4	1.2

Outcome Values

In choosing between clinical strategies, small probabilities of serious consequences have to be traded off against high probabilities of negligible consequences. A decision analysis is not easy in such a case. A reasonable approach consists of counting the number of quality adjusted life days lost because of illness or death.

The quality loss of a day spent being ill is taken at .3, with a plausible range of 0 to .5. Using a quality loss of 0 implies that only survival, not the quality of life, is considered. In the baseline analysis, days spent being ill because of acute complications were assigned the same utility loss as days spent with chronic rheumatic heart disease. This is a chronic state with less acute pain and discomfort occurring at the beginning, but enduring long into adulthood. Therefore, the effect of assigning a three-times-higher or three-times-lower quality loss to this state is also investigated.

The smallest adverse health effect is experienced by a patient with an uncomplicated penicillin-treated streptococcal infection who does not experience side effects. This baseline loss was designated as 0. We estimated a 1-day longer duration of uncomplicated symptomatic illness for an infected patient who was not treated or for a patient who was not infected. In both situations excess loss (over the baseline loss) is .3 QALD. In Table 2

Table 3. Expected Number of Quality Adjusted Life Days (QALD) and the Contribution of Each Complication to the Expected Loss of Each Strategy

Strategy	QALD Lost	Contribution of Complications to QALD Lost			
		Duration of Complaints*	Acute Rheumatic Fever	Suppurative Complications	Allergy
1 Symptomatic treatment	.58	.30	.24	.04	—
2-A Penicillin (oral)	.55	.24	.14	.02	.14
2-B Penicillin (IM)	.74	.21	.02	.01	.50
3-A Agglutination test with penicillin (oral)	.50	.24	.16	.03	.07
3-B Agglutination test with penicillin (IM)	.55	.22	.05	.03	.25
4-A Culture with penicillin (oral)	.56	.30	.16	.03	.07
4-B Culture with penicillin (IM)	.63	.30	.05	.03	.25
5 Penicillin (oral), stop after negative culture	.63	.30	.16	.03	.14

**Before treatment.*
IM denotes intramuscular administration.

excess losses are given for all other complications. Loss from immediate death reflects the life expectancy of this patient: 59.5 years, or 21,714 days, according to the Dutch life tables.[62]

Results

Computation of Expected Loss

The probabilities and loss estimates were inserted into the decision tree, and expected loss was computed for each strategy (Table 3). The agglutination test with penicillin administered orally (strategy 3-A) yields the smallest expected loss, but symptomatic treatment (strategy 1), penicillin administered orally (2-A) and the agglutination test and intramuscularly administered penicillin (3-B) differ only by hundredths of quality adjusted days, ie, several quarters of hours! Therefore, a sensitivity analysis is needed to test the stability of strategy 3-A. Table 3 also shows the contribution of the duration of sore throat symptoms, acute rheumatic fever, suppurative complications, and allergy to the expected QALD loss of these strategies.

Sensitivity Analyses

In a sensitivity analysis, the probabilities and utilities are varied over the range mentioned in Table 1. The choice for strategy 3-A is only sensitive to changes in the carrier rate and in the attack rate of acute rheumatic fever and to medication compliance (Figure 2). In all of these cases the preferred strategy changes from 3-A to 3-B: agglutination test and intramuscular administration of penicillin.

The preferred strategy (3-A) does not change for changes in estimated quality loss (Figure 2), or for changes in the quality loss from chronic rheumatic heart disease (not shown).

Figure 3 shows that for patients with low risks of harboring streptococci (<.37), symptomatic treatment (strategy 1) is preferred. This test threshold is the probability for which the expected quality loss of symptomatic treatment (strategy 1) equals the expected quality loss of agglutination test and orally administered penicillin (3-A).[63] Likewise, the test treatment threshold (.88) is the risk for which the expected loss of strategy 3-A and strategy 2-A are equal. Assumptions about the probability of the carrier state strongly influence the test threshold. For example, with a probability of carriers of .10, the test threshold falls to .13. The impact of changes in test sensitivity on the threshold value of P (streptococci) is small. Studies demonstrating a lower proportion of carriers among children with streptococcal pharyngitis may warrant extending the range over which strategy 3-A is preferred.

The effect of changes in the attack rate of acute rheumatic fever on the test and treatment thresholds is presented in Figure 4. Very low values of the attack rate of acute rheumatic fever favor symptomatic treatment, and intermediate values up to more than two times the

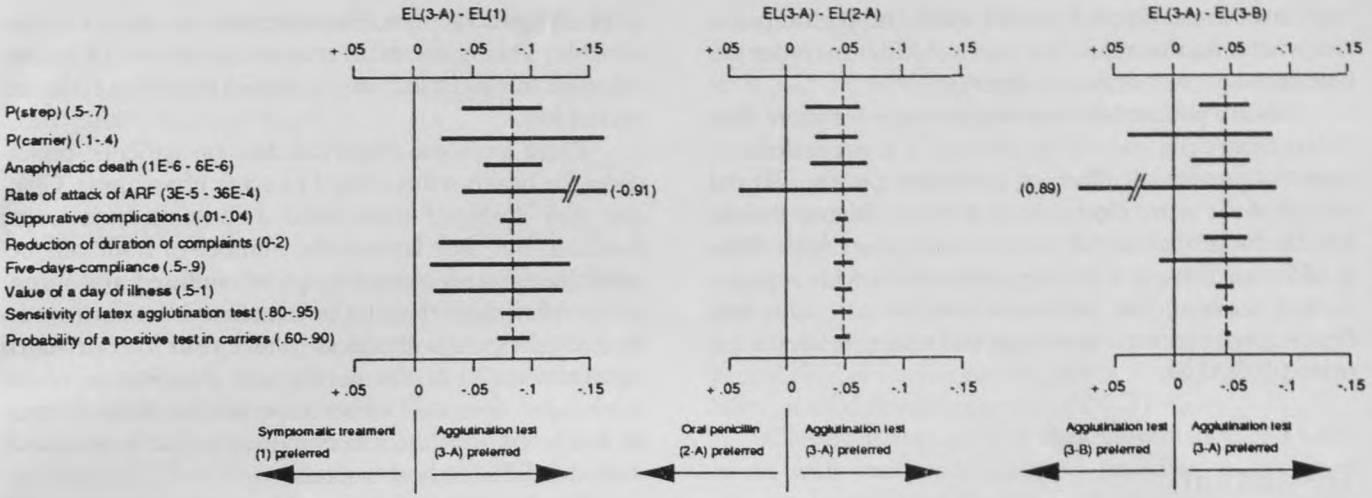

Figure 2. Sensitivity analyses for the key patient. The effect of plausible changes in estimated probabilities on the differences in quality adjusted life days (QALD) lost between symptomatic treatment (1) and the agglutination test combined with oral penicillin (3-A) is shown on the left graph; between oral penicillin (2-A) and strategy 3-A in the middle; and between the agglutination test combined with intramuscular penicillin and strategy 3-A on the right. The left column gives the items with their estimated range of plausible values. The dashed vertical lines show the difference in QALD lost resulting from the standard analysis (.09, .05, and .045, respectively).

baseline estimate favor the agglutination test combined with orally administered penicillin. When the attack rate is as high as suggested by Veasy et al,[11] the agglutination test with intramuscularly administered penicillin is the preferred strategy. Patients who also have a high risk of streptococcal pharyngitis benefit from direct treatment with intramuscularly administered penicillin.

Other Situations

When the test for streptococci is not available, direct treatment with orally administered penicillin is preferred over symptomatic treatment when the probability of streptococcal infection is over .55 (Figure 3). Culturing is never the best choice. The familiar strategy of prescribing orally administered penicillin and stopping it if a throat culture is negative is dominated by symptomatic treatment or orally administered penicillin, as long as at least 50% of the risk of allergic reactions is concentrated in the first 2 or 3 days of penicillin treatment. Low patient compliance (less than 30%) has the same effect as

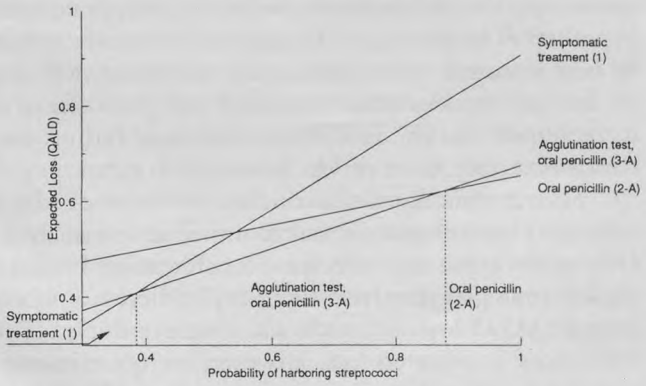

Figure 3. Dependency of the preferred strategy on the probability of streptococcal pharyngitis. Strategies with the lowest expected loss are indicated. Only three major clinical strategies are displayed: 1, symptomatic treatment; 2-A, treatment with oral penicillin; 3-A, rapid agglutination test with subsequent administration of oral penicillin in case of a positive test result.

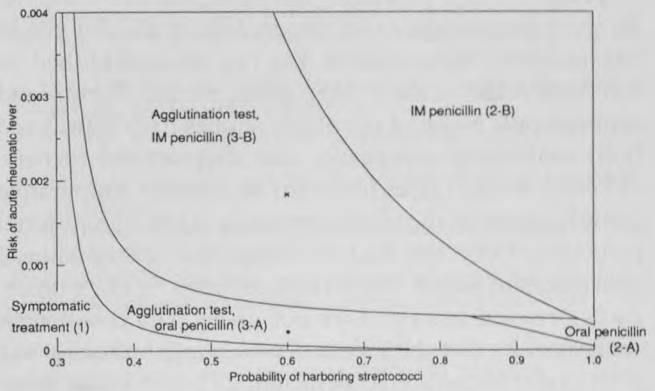

Figure 4. Two-way sensitivity analysis. The influence of changes in the estimated attack rate of acute rheumatic fever and in the probability of streptococcal pharyngitis on the recommended clinical strategy. The plane is subdivided according to the strategy with the lowest expected loss. On the boundary lines, two neighboring strategies have equal expected losses. The black dot indicates the baseline estimate for the key patient, and the asterisk indicates the estimates derived from the report of an outbreak of acute rheumatic fever.[11]

high acute rheumatic fever attack rates: the agglutination test with intramuscularly injected penicillin becomes the best strategy (not shown in figure).

When a patient has been symptomatic for more than 2 days before the start of the therapy, it is not realistic to expect a beneficial effect of penicillin on the natural course of the acute illness. In such a case the test threshold for the probability of streptococcal pharyngitis shifts to .55, but there is a strong competition with symptomatic treatment. The difference in expected quality loss between symptomatic treatment and testing is always less than .05 QALD.

Discussion

This is not the first decision analysis of sore throat management. In some studies this clinical problem was used as an example to illustrate theoretical concepts in teaching decision analysis.[16,64,65]

Almost a decade ago, Tompkins et al[54] performed a cost-benefit analysis to derive practical guidelines for the management of pharyngitis. The rapid agglutination test was not yet available at that time. The data concerning the attack rate of acute rheumatic fever used in this study are now obsolete. Other authors[66–68] also used the model of Tompkins et al for a cost-benefit analysis. Hillner[69] and Centor[70] and their co-workers report a decision analysis of the management of pharyngitis in adults. They recommended test thresholds and test treatment thresholds for the probability of streptococci of .11 and .46, respectively, in contrast with our figures of .40 and .85, respectively. This difference can be explained by the relatively high probability of carriers among the children in our analysis. Their analysis has not been published in sufficient detail to allow us to check the calculations and assumptions. None of the above studies have considered both medication compliance and streptococcal carriers. DeNeef's study[71] does not seem to consider suppurative complications or the use of intramuscularly administered penicillin. Only the best strategies for several clinical situations are noted, but estimated losses or exact differences between strategies are not given. The cost-benefit analysis of Lieu et al[72] recommends the agglutination test with orally administered penicillin as a reasonable strategy, but the combination of an agglutination test and culture is recommended the most. However, dependency between test results, and the carrier state is not considered. A strategy with only symptomatic treatment is not even considered.

In decision analysis, outcome values should ideally be derived from utility measurements.[16] However, the very small chances of death and permanent disability due to pharyngitis or penicillin treatment are almost inconceivable. This is the main reason for the use of quality adjusted life days lost as an approximation of the expected loss.

There are some empirical data on patients' preferences for health states related to acute pharyngitis. Giauque and Peebles[64] formulated a multiattribute utility function, but they limited the number of trade-offs because participants tended to grow confused and inconsistent after more than 10 assessments. Herman[73] investigated "patients' willingness to take risks in pharyngitis management," but the nature and duration of health states were described rather superficially. Neither study took into account the excess mortality that is associated with the different health states.

The attitudes of the parents were not considered explicitly in this analysis. We believe, however, that adding these would not have affected our results much, because QALD lost may just be regarded as "parent's QALD lost," and the analysis was not very sensitive to changes in the quality loss of chronic rheumatic heart disease compared with acute complications.

It is impossible to consider all possibilities in a decision analysis. For example, we did not consider the possibility of our patient becoming sensitized to penicillin, thus placing him at risk of future allergic complications. Also, a relatively higher vulnerability to future streptococcal infections because of unnecessary penicillin treatment was not considered. On the other hand, the occurrence of allergic reactions to penicillin depends on the constitution of the particular patient. Therefore, a choice for symptomatic treatment does not exclude the possibility of a future allergic complication. Actually, this complication may only be postponed until the patient is treated with penicillin for another reason. Thus, an even more complete decision-analysis could incorporate such hypothetical future events. The first two scenarios would be best managed with symptomatic treatment, whereas the last one would warrant treatment with penicillin. It is to be hoped that the probabilities of these various scenarios occurring more or less balance each other.

Several clinically useful conclusions (some of which contradict current practice) were drawn in our analysis. One might argue that attempts to differentiate between clinical strategies that have such small differences in expected QALD loss is "much ado about nothing." The differences in expected loss, however, are quite insensitive to plausible changes in estimated data. Moreover, they gain importance when one considers the number of patients involved. In The Netherlands, the incidence of sore throat episodes among people under 20 years of age is about once per person per year.[38] One tenth of these cases are evaluated by general practitioners.[74] This means

a total annual number of new visits of 250,000. Why should these patients not receive the treatment that best balances risks and benefits, even when the stakes are (fortunately) not very high?

Conclusions

Intramuscular administration of penicillin offers the largest reduction in attack rate of acute rheumatic fever, and it has the advantage that its effects do not depend on patient compliance. Its risks, however, clearly outweigh these benefits in many patients. Furthermore, we did not even consider the pain and discomfort caused by an intramuscular injection. Thus, a choice should be made between oral administration of penicillin and symptomatic treatment. The current notion that early treatment with orally administered penicillin influences the natural course of the acute illness in patients with a real streptococcal infection is important. Without this benefit, symptomatic treatment should be preferred over a wide range (up to .60) of values for the risk of streptococcal pharyngitis.

Claims that the agglutination test discriminates between carriers and truly infected patients are not justified. Still the test's rapid performance results in the possibility of treating a patient with a sore throat in time to influence the natural course of the acute illness. This makes it the diagnostic strategy of choice. This conclusion is enhanced by our assumption that a child returns with certainty for treatment in case of a positive throat culture, which biases the analysis in favor of culturing. Strategy 5 (empirically prescribing orally administered penicillin and discontinuing it when the culture turns out negative) is always dominated by symptomatic treatment, the agglutination test, or orally administered penicillin, even when stopping penicillin treatment after 2 days would reduce the risk of allergic complications by 50%.

The widely accepted assumption that patients with streptococcal pharyngitis without serologic response to group A β-hemolytic streptococci are never infected is important in this analysis. Without it, the culture and agglutination test would have a much higher reliability. The "carrier assumption" has been challenged by Gerber et al,[75] who report an equal effect on the pharyngitis in patients who test positive with and without serologic evidence of streptococcal infection. However, a comparison with a placebo group was not made.

The risk of acute rheumatic fever is an important factor in the analysis. Values as observed in Scotland and certain areas of the United States favor use of the agglutination test and treatment with orally administered penicillin, whereas very high values, such as those reported by Veasy et al,[11] favor the more aggressive approach using the agglutination test and intramuscularly administered penicillin. However, although several other studies report increased numbers of cases of rheumatic fever, their results do not suggest a higher incidence than our baseline estimate.

If it were possible to predict whether an individual patient would complete his or her course of orally administered penicillin, a more diverse range of clinical strategies should be considered. The agglutination test in combination with intramuscularly administered penicillin would be a good alternative for patients with a high probability of harboring streptococci and a low probability of medication compliance (<.3).

Overall, it appears that the agglutination test combined with orally administered penicillin is the most effective strategy for children with pharyngitis, a probability of harboring streptococci between .40 and .85, and symptoms of less than 2 days' duration before starting treatment.

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References

1. Gerber MA, Markowitz M. Management of streptococcal pharyngitis reconsidered. Pediatr Infect Dis J 1985; 4:518–26.
2. Gerber MA. Culturing of throat swabs: end of an era. J Pediatr 1985; 107:85–8.
3. Bass JW. Treatment of streptococcal pharyngitis revisited. JAMA 1986; 256:740–3.
4. Shulman ST, Amren DP, Bisno AL. Prevention of rheumatic fever. A statement for health professionals by the committee on rheumatic fever and infective endocarditis of the Council on Cardiovascular Disease in the Young. Circulation 1984; 70:118A–122A.
5. Land MA, Bisno AL. Acute rheumatic fever: a vanishing disease in suburbia. JAMA 1983; 249:895–8.
6. Shulman ST. The decline of rheumatic fever. Am J Dis Child 1984; 138:426–7.
7. Bisno AL. The rise and fall of rheumatic fever. JAMA 1985; 254:538–41.
8. Bisno AL. Acute rheumatic fever: forgotten but not gone. N Engl J Med 1987; 316:476–8.
9. Fulginiti VA. Still more on streptococcal pharyngitis: an important disease with yet unresolved clinical issues. JAMA 1985; 253: 1302.
10. Hosier DM, Craenen JM, Teske DW, et al. Resurgence of acute rheumatic fever. Am J Dis Child 1987; 131:730–3.
11. Veasy LG, Wiedmeyer SE, Orsmond GS, et al. Resurgence of acute rheumatic fever in the intermountain area of the United States. N Engl J Med 1987; 316:421–7.
12. Wald ER, Dashefskey B, Feidt C, et al. Acute rheumatic fever in western Pennsylvania and the tristate area. Pediatrics 1987; 80: 371–4.
13. Wallace MR, Garst PD, Papadimos TJ, et al. The return of acute rheumatic fever in young adults. JAMA 1989; 262:2557–61.
14. Mason T, Kujala G. Acute rheumatic fever in West Virginia: not just a disease of children. Arch Intern Med 1991; 151:133–6.
15. Randolph MF, Gerber MA, DeMeo KK, Wright L. Effect of

antibiotic therapy on the clinical course of streptococcal pharyngitis. J Pediatr 1985; 106:870–5.
16. Weinstein MC, Fineberg HV, Elstein AS, et al. Clinical decision analysis. Philadelphia: WB Saunders, 1980.
17. Habbema JDF, Van der Maas PJ, Dippel DWJ. A perspective on the role of decision analysis in clinical practice. Ann Med Intern 1986; 137:267–73.
18. von Winterfeldt D, Edwards W. Decision analysis and behavioral research. New York: Cambridge University Press, 1986.
19. McNeil BJ, Keeler E, Adelstein SJ. Primer on certain elements of medical decision making. N Engl J Med 1975; 293:221–6.
20. Kassirer JP, Moskowitz J, Lau J, Pauker SG. Decision analysis: a progress report. Ann Intern Med 1987; 106:275–91.
21. Weinstein L, LeFrock J. Does antimicrobial therapy of streptococcal pharyngitis or pyoderma alter the risk of glomerulonephritis? J Infect Dis 1971; 124:229–31.
22. Drummond KN. Acute glomerulonephritis. In: Behrman RE, Vaughan VC, eds. Nelson textbook of pediatrics. Philadelphia: WB Saunders, 1983:1330–4.
23. Valkenburg HA, Haverkorn MJ, Goslings WRO, Lorrier JC, De Moor CE, Maxted WR. Streptococcal pharyngitis in the general population. J Infect Dis 1971; 124:348–58.
24. Siegel AC, Johnson EE, Stollerman GH. Controlled studies of streptococcal pharyngitis in a pediatric population. N Engl J Med 1961; 565:559–71.
25. Kaplan EL, Top FH, Dudding BA, Wannamaker LW. Diagnosis of streptococcal pharyngitis: differentiation of active infection from the carrier state in the symptomatic child. J Infect Dis 1971; 123:490–501.
26. Walsh BT, Bookheim W, Johnson RC, Tompkins RK. Recognition of streptococcal pharyngitis in adults. Arch Intern Med 1975; 135:1493–7.
27. Breese BB. A simple scorecard for the tentative diagnosis of streptococcal pharyngitis. Am J Dis Child 1977; 131:514–7.
28. Centor RM, Witherspoon JM, Dalton HP, Brody CE, Link K. The diagnosis of strep throat in adults in the emergency room. Med Decis Making 1981; 1:239–46.
29. Centor RM, Meier FA, Dalton HP. Throat cultures and rapid tests for diagnosis of group A streptococcal pharyngitis in adults. In: Sox HC Jr, ed. Common diagnostic tests. Use and interpretation. 2nd ed. Philadelphia: American College of Physicians, 1990:253.
30. Komaroff AL, Pass TM, Aronson MD, et al. The prediction of streptococcal pharyngitis in adults. J Gen Intern Med 1986; 1:1–7.
31. Teele DW. The mouth, pharynx and esophagus. In: Bluestone CD, Stool SE, Arjona SK, eds. Pediatric otolaryngology. Philadelphia: WB Saunders, 1983:978–91.
32. Behrman RE. The respiratory system: inflammatory disease. In: Behrman RE, Vaughan VC, eds. Nelson textbook of pediatrics. Philadelphia: WB Saunders, 1983:1024–9.
33. Valkenburg HA. Streptococcal pharyngitis and tonsillitis. In: Braude AI, Davis CE, Fierer J, eds. Infectious diseases and medical microbiology. Philadelphia: WB Saunders, 1986:715–8.
34. Markowitz M. Rheumatic fever. In: Behrman RE, Vaughan VC, eds. Nelson textbook of pediatrics. Philadelphia: WB Saunders, 1983:588–94.
35. Annegers JF, Pillman NL, Widman WH, Kurland LT. Rheumatic fever in Rochester, Minnesota, 1935–1978. Mayo Clin Proc 1982; 57:753–7.
36. Schwartz RH, Hepner SI, Ziai M. Incidence of acute rheumatic fever: a suburban community hospital experience during the 1970s. Clinical Pediatrics 1983; 22,12:798–801.
37. Howie JGR, Foggo BA. Antibiotics, sore throats and rheumatic fever. J R Coll Gen Pract 1985; 35:223–4.
38. Bots AW. De keelontsteking in de huisartsenpraktijk. Leiden; Stenfort Kroese, 1965.
39. The natural history of rheumatic fever and rheumatic heart disease. Ten-year report of a cooperative clinical trial of ACTH, cortisone and aspirin. Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association. Circulation 1965; 32:457–76.
40. Denny FW, Wannamaker LW, Brink WR, Rammelkamp CH, Custer EA. Prevention of rheumatic fever. JAMA 1950; 143: 151–3.
41. Krober MS, Bass JW, Michels GN. Streptococcal pharyngitis: placebo controlled double-blind evaluation of clinical response to penicillin therapy. JAMA 1985; 253:1271–4.
42. Merenstein JH, Rogers KD. Streptococcal pharyngitis. Early treatment and management by nurse practitioners. JAMA 1974; 227: 1278–82.
43. DeSwarte RD. Drug allergy. In: Patterson R, ed. Allergic diseases. Diagnosis and management. Philadelphia: JB Lippincott, 1984: 505–661.
44. Arndt KA, Jick H. Rates of cutaneous reactions to drugs. A report from the Boston Collaborative Drug Surveillance Program. JAMA 1976; 235:918–23.
45. Herman R, Jick H. Cutaneous reaction rates to penicillin—oral versus parenteral. Cutis 1979; 24:232–3.
46. Shapiro S, Siskind V, Slone D, Lewis GP. Drug rash with ampicillin and other penicillins. Lancet 1969; 1:969–72.
47. Idsoe O, Guthe T, Willcox RR, De Weck AL. Nature and extent of penicillin side-reactions. Bull WHO 1968; 38:159–88.
48. Erffmeyer JE. Adverse reactions to penicillin. Ann Allergy 1981; 47:288–300.
49. James LP, Austen KF. Fatal systemic anaphylaxis in man. N Engl J Med 1964; 270:597–603.
50. Spark RP. Fatal anaphylaxis due to oral penicillin. Am J Clin Pathol 1971; 56:407–11.
51. Charney E, Bynum R, Eldrege D, et al. How well do patients take oral penicillin? A collaborative study in private practice. Pediatrics 1967; 40:188–95.
52. Colcher IS, Bass JW. Penicillin treatment of streptococcal pharyngitis. A comparison of schedules and the role of specific counselling. JAMA 1972; 222:657–9.
53. Gilbert JR, Evans CE, Haynes RB, Tugwell P. Predicting compliance with a regimen of digoxin therapy in family practice. J Can Med Assoc 1980; 123:119–22.
54. 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.
55. Radetsky M, Wheeler RC, Roe MH, Todd JK. Comparative evaluation of kits for rapid diagnosis of group A streptococcal disease. Pediatr Infect Dis J 1985; 4:274–81.
56. Berkowitz CD, Anthony BF, Kaplan EL, Wolinsky E, Bisno AL. Cooperative study of latex agglutination to identify group A streptococcal antigen on throat swabs in patients with acute pharyngitis. J Pediatr 1985; 107:89–92.
57. Gerber MA, Spadaccini LJ, Wright LL, Deutsch L. Latex agglutination tests for rapid identification of group A streptococci directly from throat swabs. J Pediatr 1984; 105:701–5.
58. Gerber MA, Randolph MF, Chanatry J et al. Antigen detection test for streptococcal pharyngitis: evaluation of sensitivity with respect to true infections. J Pediatr 1986; 108:654–8.
59. Wright A, Crabtree B, O'Connor P. Evaluation of a rapid method for diagnosing streptococcal pharyngitis in an office laboratory. J Fam Pract 1987; 25:505–8.
60. Yu PKW, Germer JJ, Torgerson CA, Anhalt JP. Evaluation of TestPak Strep A for the detection of group A streptococci in throat swabs. Mayo Clin Proc 1988; 63:33–6.
61. Haverkorn MJ, Valkenburg HA, Goslings WRO. Streptococcal pharyngitis in the general population. I. A controlled study of streptococcal pharyngitis and its complications in the Netherlands. J Infect Dis 1971; 124:339–47.
62. CBS (Central Bureau of Statistics). Lifetables for The Netherlands 1986. Mdnstat Bevolk 1987; 11:30–1.
63. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. N Engl J Med 1980; 302:1109–17.
64. Giauque WC, Peebles TC. Application of multidimensional utility theory in determining optimal test-treatment strategies for strep-

tococcal sore throat and rheumatic fever. Operations Res 1976; 24:933–50.
65. Murphy TF. Sore throat management. Decision analysis using pleasant hour equivalents. Comp Biomed Res 1979; 12:203–19.
66. Cebul RD, Poses RM. The comparative cost-effectiveness of statistical decision rules and experienced physicians in pharyngitis management. JAMA 1986; 256:3353–7.
67. Komaroff AL, Pass TM, Pappius EM. Cost-effectiveness of alternate strategies for management of sore throat. Clin Res 1983; 31:299A.
68. Pantell RH, Bergman DA. Strategies for pharyngitis management: who benefits? who pays? who decides? In: Shulman ST, ed. Management of pharyngitis in an era of declining rheumatic fever. Columbus, Ohio: Ross Laboratories, 1984:203–12.
69. Hillner BE, Centor RM, Clancy CM. What a difference a day makes: the importance of the turnaround time of diagnostic tests in sore throats. Med Decis Making 1985; 5:363.
70. 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.
71. DeNeef P. Selective testing for streptococcal pharyngitis in adults. J Fam Pract 1987; 25:347–51.
72. Lieu TA, Fleisher GR, Schwartz JS. Cost-effectiveness of rapid latex agglutination testing and throat culture for streptococcal pharyngitis. Pediatrics 1990; 85:246–56.
73. Herman JM. Patients' willingness to take risks in the management of pharyngitis. J Fam Pract 1984; 19:767–72.
74. Evans CE, McFarlane AH, Norman GR, et al. Sore throats in adults: who sees a doctor? Can Fam Physician 1982; 28:453–8.
75. Gerber MA, Randolph MF, Mayo DR. The group A streptococcal carrier state. A reexamination. Am J Dis Child 1988; 142:562–5.

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