Editorial

Streptococci, Sore Throats, and Uncertainty

Michael D. Hagen, MD
Lexington, Kentucky

What *are* we going to do about sore throats? Stillerman and Bernstein[1] stated in 1961, "If you are entirely comfortable selecting which pharyngitis patients to treat 10 days with penicillin, perhaps you don't understand the situation." In spite of scoring systems,[2–4] rapid diagnostic tests,[5–7] and improved culture media,[8] the search continues for the optimal approach to this common problem. Clinical treatment practices range from dogmatic to wholly empiric. Attempts to integrate throat culture, rapid tests, and prediction rules into a rational management approach have been directed mostly toward adults.[6,9] If prediction rules are to be applied in children, they must be adjusted for the higher likelihood that a child's sore throat is caused by *Streptococcus*.[10] Additionally, the *Streptococcus* carrier rate complicates throat culture interpretation in this age group.[11]

In this issue of the Journal, Dippel and colleagues[12] report a decision analysis that addresses these dilemmas. They investigated several management strategies for sore throats in children:

- Treat symptoms only
- Treat all patients with orally administered penicillin
- Treat all patients with intramuscularly administered penicillin
- Do an agglutination test and treat only patients whose tests are positive with either orally or intramuscularly administered penicillin
- Perform a throat culture and treat in 48 hours on the basis of the test result
- Perform a throat culture and begin treatment at the initial visit, but discontinue therapy if the culture is negative

Their model incorporates antibiotic cure rates, prevalence of streptococcal pharyngitis and carrier rates in children, the likelihood of acute rheumatic fever and the efficacy of antibiotic therapy in preventing this sequela, and the morbidities associated with treatment (penicillin-allergic reactions) and infection (peritonsillar abscess, retropharyngeal abscess, and otitis media).

How did they perform their analysis? Decision analysis is an explicit technique for exploring uncertainty in clinical practices, and consists of four steps[13,14]: (1) appropriate clinical strategies are identified and structured as a decision "tree"; (2) probability information is inserted in the tree for the uncertain "chance" events that occur in each strategy; (3) a value is assigned for each outcome that might occur in the various strategies (some typical outcome values, or "utilities," include life expectancy, lives saved or lost, and dollar costs); (4) the tree is "solved" by a process called "averaging out" and "folding back."[14] The strategy that yields the best outcome is selected as the most appropriate. Because the information used is frequently uncertain, the fourth step is repeated using different plausible values for the variables in the tree. This procedure is called "sensitivity analysis," and allows the analyst to examine the decision's susceptibility to model assumptions.

Let us review how Dippel and colleagues developed these four steps. The management strategies they chose to investigate are the options that emanate from the "choice" (square) node of their decision tree. (See Figure 1 of the article by Dippel et al.[12]) With each strategy, a number of events can occur subsequent to the strategy choice. These events are subject to chance and are therefore depicted as "chance" nodes (circles) in the model. For example, in the "treat symptoms only" strategy, patients followed expectantly have some probability of being carriers of streptococci. If they harbor streptococci, they also have some chance of developing suppurative complications (eg, peritonsillar abscess) and rheumatic fever. Similarly, in the other modeled strategies, Dippel et al have included the possibility of medication reactions, as well as streptococcal cure rates, for intramuscularly and orally administered penicillin. These chance events are all associated with probabilities for occurrence.

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From the Department of Family Practice, University of Kentucky College of Medicine, Lexington. Requests for reprints should be addressed to Michael D. Hagen, MD, Department of Family Practice, 820 South Limestone, Lexington, KY 40536-0226.

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The authors used estimates from the medical literature for their baseline probability estimates. The authors accomplished the third step, assignment of outcome values, in a somewhat unconventional manner. They chose to use "quality adjusted life days (QALD) lost" as their outcome measure. The best strategy is therefore defined as the one that minimizes QALD lost. This is reversed from the usual application of quality adjusted life expectancy[14,15] in which the analyst's objective is to maximize the outcome.

Let us digress for a moment to examine how quality adjusted life expectancy is calculated. Consider a familiar example: assume that a physician is treating a 50-year-old man for chronic ischemic heart disease. The patient has been diagnosed as having triple-vessel coronary disease and chronic stable angina. What is this man's quality adjusted life expectancy if he receives medical therapy? The average age-specific life expectancy for a 50-year-old man is about 26 years.[16] This number must be adjusted for both the patient's disease process (coronary artery disease) and the effect that his symptoms have on his perceived quality of life. Triple-vessel coronary disease is associated with an *excess* mortality rate of about 2.1% per year.[17] Using a life expectancy approximation technique known as the declining exponential approximation of life expectancy (DEALE),[18,19] the average life expectancy of a 50-year-old man with medically treated triple-vessel coronary disease is estimated to be about 16.8 years. This corrected life expectancy can be further adjusted to reflect how greatly chronic, stable angina reduces the patient's perceived quality of life. Ideally, the patient would be questioned (using techniques such as standard reference gambles and time tradeoffs[14] to gain insight into his or her perceptions of quality of life. If this is not possible, literature estimates might be used. Weinstein and Stason[20] suggest that life with chronic angina is associated with a perceived quality of life that is about 70% of that attributed to full health. We now have enough information to calculate this 50-year-old man's *quality adjusted* life expectancy. Assuming that the patient's perception of the quality of his life is constant throughout his remaining years, his disease-specific life expectancy (16.8 years) is multiplied by the quality factor (0.70 or 70%) to yield about 11.8 quality adjusted life years. This value could then be used as the outcome measure in a decision model.

Let us view this same problem now from the perspective taken by Dippel et al. From their point of view, chronic stable angina would be associated with a 30% decrement in quality adjusted life expectancy; every day spent with angina would be worth 30% less than a day spent in full health, ie, each day spent with angina would represent a loss of 0.3 quality adjusted days. Projected over his total life expectancy, this would represent about 1840 quality adjusted days lost (16.8 years × 365 days × 0.3).

Where do we get quality values? As mentioned earlier, several techniques are used to assess patients' preferences. Two commonly used methods are the standard reference gamble and the time-tradeoff.[16] Alternatively, population-based instruments such as the Quality of Well Being scale[21] and the Sickness Impact Profile[22] can be used. Unfortunately, values obtained from the same patient or patients using different methods seldom agree. Which one is correct? That is an issue of continued research and active discourse.[23,24] If a decision analysis incorporates patient preferences, the reader should discern carefully how these values were obtained. This is particularly important if comparisons are to be made with other analyses of the same topic. If the authors use different methods to assess outcome preferences (as expressed in the quality values applied to each outcome), divergent conclusions may be due to the disparate utility structures rather than to the inherent superiority of one strategy over another.

For use in their model, Dippel and colleagues assumed that the quality of life with acute illness is 70% of that of life spent in full health, ie, "Q" equals 0.7. This means that a day with illness is associated with a 30% loss of a full-quality life day; hence, 0.3 QALD lost. The authors do not clearly describe how this value was derived, but apparently they, acting as proxies for the patient, assigned this value based on their clinical judgment. While such assignments are not unusual in the decision analysis literature, they should be viewed cautiously unless supporting documentation is provided to justify the assignment. Seckler and colleagues[25] demonstrated that, in the context of resuscitation decisions, physicians "did no better than chance in predicting the wishes of their patients." The pharyngitis decision is complicated further by the patient's age: not only must a child's preferences be determined, but also the parents' opinions must be considered. Because of the difficulties inherent in assessing children's utilities (as noted by the authors), it is not unreasonable to use proxy judgments, but these values must be explored extensively with sensitivity analysis to ensure that small variations in this value do not affect the results. This brings us to the fourth step in the decision analysis process, averaging out and folding back the tree, and testing the results with sensitivity analyses to determine which values are uncertain.

When the pharyngitis decision tree is folded back (or solved), the strategy that yields the smallest number of quality adjusted life days lost is the optimal selection. For the clinical scenario chosen (a 14-year-old boy who has had a sore throat for 1 day, fever, exudative pharyn-

gitis, and no cough or rhinorrhea), the optimal strategy would be to perform an agglutination test and begin treatment with orally administered penicillin if the result is positive. The baseline scenario is important to the outcome: according to the authors' estimates, there is a 60% chance that the patient is harboring streptococci. There would be a substantially lower probability that an adult patient with similar symptoms would be harboring streptococci; therefore, early antibiotic treatment would be of less benefit to an adult.

Several of the values used in the model were considered to be fairly "soft." For this reason, the authors repeated the analysis multiple times using a range of values for each of the pertinent variables. They have presented the results of these *sensitivity analyses* in Figures 2, 3, and 4 of their article. Figure 2 merits some discussion. In this figure, the sensitivity analyses for 10 variables are presented. The left-most graph compares treatment with orally administered penicillin on the basis of agglutination test results (strategy 3-A of Dippel et al) with symptomatic treatment (strategy 1). In this graph, negative numbers indicate that strategy 3-A is preferred to symptomatic treatment. These results show that the optimal decision (strategy 3-A) is remarkably stable over plausible ranges for the examined variables. The middle graph shows how treatment with orally administered penicillin as indicated by a positive agglutination test compares with prescribing orally administered penicillin to all patients (strategy 2-A). Again, negative numbers indicate that the test-treat strategy is preferred unless the rheumatic fever attack rate approaches the upper limits of established values. The right-most graph contrasts intramuscularly and orally administered penicillin therapy for patients whose agglutination tests are positive. This chart demonstrates again that orally administered penicillin therapy for patients with positive tests is preferred unless the compliance with treatment is as low as 50% or the acute rheumatic fever attack rate is equivalent to the highest reported values.

The results presented in Figure 2 are all *one-way* sensitivity analyses. In a one-way sensitivity analysis, one factor is varied while all other variables in the model are held constant. Figure 3 presents graphically a one-way sensitivity analysis of the probability of harboring streptococci. This variable appears on the horizontal axis, and expected loss (in quality adjusted life days lost) is shown on the vertical axis. On this graph, small Y-axis values are preferred. If the probability of harboring streptococci is anywhere between .37 and .88, the patient with a positive agglutination test should be treated with orally administered penicillin. For probabilities below .37, symptomatic treatment is preferred. Above .88, treatment with penicillin, without testing, is the optimal strategy.

Figure 4 is a *two-way* sensitivity analysis. Here two variables are applied throughout their plausible ranges while all other factors are held constant. In this figure, the probability of harboring streptococci appears on the X-axis and the risk of acute rheumatic fever on the Y-axis. As the probabilities for harboring streptococci and contracting acute rheumatic fever increase, more aggressive treatment strategies are preferred. The band labeled "agglutination test, oral penicillin" corresponds to combinations of acute rheumatic fever and streptococci probabilities for which the test–oral penicillin strategy is best. Notice that where the risk of rheumatic fever is higher, intramuscularly administered penicillin is the preferred treatment. This is due to the higher losses that might be expected because of less than full compliance with orally administered antibiotic treatment regimens.

The sensitivity analyses demonstrate how issues such as the streptococcal carrier state, cure rates, rheumatic fever attack probabilities, and compliance rates all affect the choice of an optimal treatment strategy. The dominant result (antigen testing followed by treatment of patients with positive tests) is consistent with other recommendations for managing streptococcal pharyngitis,[26] but how does this compare with other decision analyses of this topic? Since antigen tests became widely available, one other analysis of streptococcal pharyngitis in children has appeared. Lieu and colleagues[27] performed a cost-effectiveness analysis of four possible strategies: (1) treat all patients, (2) culture and treat patients 2 days later if they have positive cultures, (3) perform an antigen test and immediately treat patients whose results are positive, and (4) combine antigen testing with culture confirmation of negative tests. These authors chose not to incorporate the issue of carrier rate, and did not include the impact of early treatment on symptom duration. In spite of these differences, Lieu et al also found the antigen test strategy to be optimal for test sensitivities similar to those assumed by Dippel et al.

The optimal approach to treating children's sore throats will continue to be controversial until we have clinical tests that both provide immediate results and accurately identify streptococcal infection (not just the presence of the organism). Until such a test is available, analyses such as the one presented by Dippel et al can direct our management efforts. If the streptococcal prevalence is markedly different or high rheumatic fever attack rates prevail, the clinician can use the sensitivity analysis results to modify his or her treatment recommendations as appropriate.

Dippel and colleagues have tackled a common but vexing primary care problem. They have defined explicitly the data and assumptions on which their results are based. Even if we assumed perfect tests, well over 78,000

subjects would be required in a randomized trial to demonstrate convincingly (assuming a two-tailed test with $\alpha = .05$ and $\beta = .2$) a 50% reduction in acute rheumatic fever using the strategies examined.[28] Even if such a study were to be undertaken immediately, the results would not be available to direct our decision making for quite some time. In the absence of such definitive clinical trials, decision analyses can integrate the best available information to aid the decision maker.

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See article on page 149.