

Diagnosis and Management of Adults with Pharyngitis

A Cost-Effectiveness Analysis

Joan M. Neuner, MD, MPH; Mary Beth Hamel, MD, MPH; Russell S. Phillips, MD; Kira Bona, BS; and Mark D. Aronson, MD

Background: Rheumatic fever has become uncommon in the United States while rapid diagnostic test technology for streptococcal antigens has improved. However, little is known about the effectiveness or cost-effectiveness of various strategies for managing pharyngitis caused by group A β -hemolytic streptococcus (GAS) in U.S. adults.

Objective: To examine the cost-effectiveness of several diagnostic and management strategies for patients with suspected GAS pharyngitis.

Design: Cost-effectiveness analysis.

Data Sources: Published literature, including systematic reviews where possible. When costs were not available in the literature, we estimated them from our institution and Medicare charges.

Target Population: Adults in the general U.S. population.

Time Horizon: 1 year.

Perspective: Societal.

Interventions: Five strategies for the management of adult patients with pharyngitis: 1) observation without testing or treatment, 2) empirical treatment with penicillin, 3) throat culture using a two-plate selective culture technique, 4) optical immunoassay (OIA) followed by culture to confirm negative OIA test results, or 5) OIA alone.

Outcome Measures: Cost per lost quality-adjusted life-days (converted to life-years where appropriate) and incremental cost-effectiveness.

Results of Base-Case Analysis: Empirical treatment was the least effective strategy at a GAS pharyngitis prevalence of 10%

(resulting in 0.41 lost quality-adjusted life-day). Although the other four strategies had similar effectiveness (all resulted in about 0.27 lost quality-adjusted life-day), culture was the least expensive strategy.

Results of Sensitivity Analyses: Results were sensitive to the prevalence of GAS pharyngitis: OIA followed by culture was most effective when GAS pharyngitis prevalence was greater than 20%. Observation was least expensive when prevalence was less than 6%, and empirical treatment was least expensive when prevalence was greater than 71%. The effectiveness of strategies was also very sensitive to the probability of anaphylaxis: When the probability of anaphylaxis was about half the baseline probability, OIA/culture was most effective; when the probability was 1.6 times that of baseline, observation was most effective. Only at an OIA cost less than half of baseline did the OIA alone strategy become less expensive than culture. Results were not sensitive to other variations in probabilities or costs of diagnosis or treatment of GAS pharyngitis.

Conclusions: Observation, culture, and two rapid antigen test strategies for diagnostic testing and treatment of suspected GAS pharyngitis in adults have very similar effectiveness and costs, although culture is the least expensive and most effective strategy when the GAS pharyngitis prevalence is 10%. Empirical treatment was not the most effective or least expensive strategy at any prevalence of GAS pharyngitis in adults, although it may be reasonable for individual patients at very high risk for GAS pharyngitis as assessed by a clinical decision rule.

Ann Intern Med. 2003;139:113-122.

www.annals.org

For author affiliations, see end of text.

See editorial comment on pp 150-151.

Pharyngitis is a common and costly condition in adults. The National Ambulatory Medical Care Survey estimated that 18 million patients sought care for a sore throat in the United States in 1996, making it the sixth leading cause of visits to physicians (1). As many as four to six times more individuals may not seek care for a sore throat (2, 3).

Many organisms cause sore throat. Chief among them are group A β -hemolytic streptococcus (GAS), non-group A streptococcus, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and several respiratory viruses (4). With rare exceptions, such as with *Neisseria gonorrhoeae* infection or the acute antiretroviral syndrome, no compelling data indicate treatment for patients with pharyngitis not caused by group A streptococcus (5). Nevertheless, although only about 10% of adults with pharyngitis seen in primary care settings have group A streptococcal infection (6), 75% of patients seen by physicians receive antibiotics (7).

The potential morbidity of both allergic reactions and

antibiotic resistance must be considered in decisions about management of pharyngitis (8, 9). Thus far, GAS has remained sensitive to penicillin, which therefore remains the recommended treatment (10). However, despite expert recommendations, physicians prescribe broad-spectrum antibiotics to 70% to 75% of adults (7, 11). Widespread resistance to macrolides has already been documented in GAS (12-14).

Evidence for the effectiveness of GAS treatment has also become less compelling in recent years. Acute rheumatic fever, a sequelae of GAS pharyngitis, has become exceedingly rare in adults in industrial societies outside of sporadic outbreaks (15-17); as a result, prevention of that illness is not an important rationale for treatment. Little evidence suggests that treatment prevents glomerulonephritis (18-20). Pharyngitis treatment does shorten symptom duration and reduce the risk for infectious sequelae (21, 22), but the clinical significance of these benefits continues to be argued (22).

Clinicians have several tools to determine whether a patient with pharyngitis is likely to have GAS. Rapid diagnostic assays with excellent operating characteristics are available (23–33). Furthermore, clinical criteria or decision rules can help clinicians predict the likelihood of a positive throat culture (6, 34); a recent systematic review and clinical guideline (35, 36) recommended several strategies for diagnosis and management of pharyngitis based on one such decision rule (34).

Cost-effectiveness and decision analyses incorporating medical costs are useful in assessing management strategies when no definitive randomized clinical trials have compared these strategies (37). We performed a cost-utility analysis to examine five common strategies for testing and treatment in pharyngitis care. We also examined the effect of a decision rule (34) on those strategies.

METHODS

Decision Analytic Model

We developed a decision model (**Appendix Figure 1**, available at www.annals.org) to evaluate common strategies for managing adult patients with pharyngitis. We constructed this model to examine the short-term cost-effectiveness of five strategies: 1) observation only—neither test nor treat (observation); 2) empirical antibiotic treatment of all patients without any testing (empirical therapy); 3) throat culture for all patients, with antibiotic treatment for positive results (culture); 4) optical immunoassay (OIA) followed by culture to confirm negative OIA test result only, with antibiotic treatment for positive results on either test (OIA/culture); 5) OIA alone for all patients, with antibiotic treatment for positive results (OIA alone).

Our model examines several possible outcomes of pharyngitis, and we discuss the probabilities of each in the following section. In brief, we examined the effect of the preceding strategies for diagnosis or treatment with a 10-day course of penicillin (with erythromycin substituted in case of an allergic reaction to penicillin [10, 35, 36, 38, 39]) on each of four outcomes: acute rheumatic fever, peritonsillar abscess, duration of symptoms, and allergic reactions to antibiotics. All outcomes were appropriately treated, and the costs and effects of treatment were included in our model.

We made several simplifying conditions in creating our decision model. We considered only patients without a history of acute rheumatic fever or glomerulonephritis. Because a patient with a history of penicillin allergy would not receive penicillin and therefore would have no risk for allergic reaction, such patients were not included in our base-case model. We assumed that no patient would develop acute rheumatic fever with another complication (abscess or allergic reaction) and that patient adherence and follow-up (including ability to contact patients with culture results) were 100%. Finally, we assumed that all tests were done in an on-site reference laboratory; we did not

consider the cost of transporting specimens for either culture or OIA, and we assumed that OIA results would be available before the patient left the office.

In accordance with recent recommendations by an expert panel (40), the base-case analysis takes the societal perspective. We considered all outcomes and direct costs incurred within the first year of diagnosis except (as recommended for base-case analyses using quality-adjusted life-years [QALYs]) for costs such as work lost because of short-term illness (40, 41). These losses are assumed to be included in the decreased preference for illness, estimated as part of the utility for short-term illness. Three studies of adult pharyngitis that examined work days lost (42–44) did not find a significant difference between lost work days in patients treated and those not treated with penicillin; therefore, inclusion of lost productivity costs would probably not have affected our results appreciably.

We limited our analysis to the first year after diagnosis. Most of the costs associated with GAS pharyngitis occur within the first several weeks. A few patients will have late complications, such as rheumatic valve deformities, and will require treatments such as heart valve replacement 20 or more years after their episode of pharyngitis. Because these complications are rare and because discounting would eliminate most of these downstream costs, we joined pediatric investigators in limiting our analysis to health care costs incurred in the first year (45, 46).

The model output was quality-adjusted loss of life expectancy, measured as quality-adjusted life-days. Incremental cost-effectiveness analyses were performed by rank ordering all five competing strategies by increasing effectiveness, then calculating incremental cost-effectiveness strategies for each strategy (**Appendix**, available at www.annals.org). All analyses were performed by using a decision analysis software program (DATA, versions 3.5 and 4.0, TreeAge, Williamstown, Massachusetts).

Data Sources

We searched the published literature for probabilities, utilities, and costs, as described in the following section (and in more detail in the **Appendix**, available at www.annals.org).

The Clinical Examination

We examined the incorporation of the clinical examination into our strategies for management of pharyngitis. A recent systematic review of the clinical examination in adult pharyngitis (47) found that no individual element of the history or physical examination for a patient with pharyngitis is accurate enough to diagnose streptococcal pharyngitis (**Appendix**, available at www.annals.org). However, several clinical prediction rules have combined key findings as a tool in predicting the probability of sore throat in adults (6, 34, 48–50).

The pharyngitis decision rule by Centor and colleagues (34) (**Appendix Figure 2**, available at www.annals.org)

.org) is the only rule validated in several populations (47, 51–53). It is based on four clinical findings (tonsillar exudates, tender anterior cervical lymphadenopathy, absence of cough, and history of fever); each risk factor is weighted equally to give a score of 0 to 4 points. It can then be used as a likelihood ratio by applying it to a population with a known GAS pharyngitis prevalence (such as the patients seen in a practice) to determine the individual patient's probability of GAS pharyngitis.

Because this new probability estimate can be considered a “prevalence” of GAS pharyngitis for an individual patient, we examined the incorporation of the decision rule into our strategies (as described in the Results section under the heading “Application of a Clinical Decision Rule”).

Prevalence of GAS Pharyngitis

The prevalence of GAS pharyngitis in adults, defined as the proportion of throat cultures that grow GAS, varies between 5% and 26% in primary care and emergency department settings (6, 34, 54). It can also vary with the season of the year, exposure to children, and other factors (10). On the basis of a study done in Boston, Massachusetts, we used a GAS pharyngitis prevalence of 10% (6) for our model (Table 1).

GAS Test Characteristics

We modeled two-plate culture in the reference laboratory as the gold standard with 100% sensitivity and specificity. Although this is not an ideal gold standard, other possibilities (such as antibody titers) cannot be obtained when a treatment decision must be made. Culture is therefore generally considered the criterion standard (10, 46, 55, 56).

We identified studies of rapid antigen testing in September 2000 using the MEDLINE subject heading terms *pharyngitis* and *streptococcal infections, diagnosis* and found that most studies of OIA were of relatively good quality and used similar gold standards. Therefore, we averaged the sensitivity findings of the studies of OIA with weighting for the number of patients in each study to estimate an overall sensitivity of 0.884 (23–33) and specificity of 0.944 (23–33). We incorporated these test characteristics into our model by using Bayesian analysis.

Many enzyme immunoassays are available, and the test characteristics vary widely among different tests in published studies (57–59). Therefore, we did not directly examine these tests.

Penicillin Therapy

The risk for developing an allergic reaction to penicillin is 0.7% to 4.0% (8, 9); we set the probability at 2%. The probability of anaphylaxis is 1/10 000 persons, and the case-fatality rate from such a reaction is 10% (9).

Table 1. Baseline Probabilities, Utilities, and Costs for Cost-Effectiveness Analysis of Management of Group A β -Hemolytic Streptococcal Pharyngitis*

Variable	Value in Base-Case Analysis (Range in Sensitivity Analyses)
Probabilities	
Prevalence of GAS pharyngitis	0.097 (0.02–0.68)
OIA sensitivity	0.884 (0.70–0.99)
OIA specificity	0.944 (0.80–0.99)
Penicillin-induced rash	0.02 (0.005–0.04)
Penicillin-induced anaphylaxis	0.0001 (0.00005–0.0002)
Death from anaphylaxis	0.1 (0.05–0.2)
Acute rheumatic fever	0.0005 (0.0–0.03)
Complicated acute rheumatic fever	0.1 (0.05–0.2)
Death from acute rheumatic fever	0.01 (0.005–0.02)
Effectiveness of penicillin vs. acute rheumatic fever	0.70 (0.55–0.80)
Peritonsillar abscess	0.023 (0.0–0.056)
Penicillin effectiveness vs. abscess	0.84 (0.65–0.93)
Utilities, lost quality-adjusted life-days	
Untreated pharyngitis (5 d)†	0.25 (0–0.5)
Treated GAS pharyngitis	
After OIA (2-d reduction in sore throat)	0.15 (0.1–0.25)
After culture (1-d reduction in sore throat)	0.20 (0.15–0.25)
Penicillin-induced rash	0.625 (0.15–1.50)
Penicillin-induced anaphylaxis	9 (3–18)
Peritonsillar abscess	5 (1.65–10)
Uncomplicated rheumatic fever	76.5 (9–744)
Rheumatic fever resulting in valvular disease	744 (56–744)
Death from penicillin reaction or rheumatic fever	14 874 (–)
Costs (all in 2000 U.S. dollars), \$	
Tests	
OIA	7.67 (3.84–15.34)
Throat culture	2.83 (1.42–5.66)
Culture result notification	1.29 (0.65–2.58)
Calling in a prescription	1.28 (0.64–2.56)
Penicillin	10.05 (5.03–20.10)
Penicillin-induced rash‡	50.94 (25.47–102)
Anaphylaxis	1772.54 (886–3545)
Peritonsillar abscess	4369.16 (2185–8738)
Acute rheumatic fever	1883.98 (942–3768)

* GAS = group A β -hemolytic streptococcal; OIA = optical immunoassay.

† The median duration of the symptoms in several studies of pharyngitis is 5 days. Our estimate for the utility of sore throat is 0.95⁵⁷, meaning 1 sore throat day = 0.95 well day.

‡ Includes cost of switch to erythromycin therapy (see text).

Acute Rheumatic Fever and Suppurative Sequelae of GAS Pharyngitis

We used estimates derived from a systematic review of the literature and meta-analysis of outcomes of streptococcal pharyngitis performed for the Cochrane Collaboration (22), except where data were unavailable (as discussed in the following section).

Because the estimate from this Cochrane systematic review combined trials from four decades during which the population rates of acute rheumatic fever changed dramatically, we used an estimate of 5 cases/10 000 persons from recent epidemiologic literature for the probability of developing acute rheumatic fever after streptococcal pharyngitis (17). Ten percent of acute rheumatic fever cases result in complications, and 1% are fatal (60, 61).

Penicillin will prevent 70% of cases of acute rheumatic

fever even if the treatment is delayed while culture is performed (22). A 2-day delay in penicillin therapy to await culture results does not affect the effectiveness of therapy in preventing complications (22).

An estimated 2.4% of untreated patients will develop a peritonsillar abscess (22), which generally requires surgical drainage. Penicillin reduces the risk for peritonsillar abscess by 84% (from 2.4% to 0.4%) (22).

Symptoms

We used a baseline of 5 days of symptoms for all strategies (60). We assumed that the patient was seen within 3 days of symptom onset.

While the Cochrane systematic review (22) estimated that the duration of sore throat, fever, and headache was reduced by 1 day at day 3 of the illness, studies that enrolled only patients with culture-positive GAS (62) or patients with a high likelihood of GAS (42, 43, 63–65) showed greater reductions in symptoms. Since we wished to estimate the benefit for patients with GAS pharyngitis, we used the 2-day improvement in symptoms found in a recent study (42). We assumed that the delay of 24 to 48 hours before culture results become available reduced the benefit for patients who had a throat culture to 1 day.

Utilities

On the basis of published studies in which patients assigned a utility (or quality-of-life weight) of 0.95 to other common symptoms, such as diarrhea and dyspepsia (66), we estimated pharyngitis to be associated with a utility of 0.95. We estimated utilities for the other health states from a published patient survey comparing pharyngitis to other health states (60, 67). Since most outcomes occurred within several weeks, we converted them to lost quality-adjusted life-days (Table 1).

Costs

Where possible, cost estimates in this analysis represent actual resource costs rather than charges (Table 1) (68). All costs were converted to 2000 U.S. dollars by using the Medical Care Component of the Consumer Price Index (for detailed description of all costs, see the Appendix, available at www.annals.org).

We used previously published manufacturers' estimates to determine the costs for the OIA rapid test and culture with the necessary materials, quality control, and labor (23). We also assumed that the cost of culture included the test, notification of the patient, and calling in a prescription to the pharmacist.

We used wholesale (69) and pharmacy dispensing (70) costs to estimate the cost of penicillin (250 mg four times daily for 10 days), erythromycin (250 mg four times daily) for patients who had an allergic reaction to penicillin, and diphenhydramine (25 mg four times daily) to treat allergic reactions. We used the resource-based relative value scale

to estimate the costs of physician visits (71). We estimated the cost of treating anaphylaxis from a previous analysis (69).

We estimated the cost of acute rheumatic fever on the basis of the resource-based relative value scale and the Centers for Medicare & Medicaid (formerly the Health Care Financing Administration) clinical diagnostic laboratory fee schedule for eastern Massachusetts in 2000 (72). These costs included primary care physician and specialist visits, electrocardiography, and echocardiography and laboratory tests, all based on Jones criteria (73) (Appendix, available at www.annals.org).

We estimated costs for peritonsillar abscess from a hospital database, using an average of inpatient costs and adding the estimated physician costs to inpatient and surgical fees for a 2-day hospital stay.

Sensitivity Analyses and Base-Case Results after Application of a Decision Rule

In one-way sensitivity analyses, we varied all probabilities, costs, and utilities. We examined a range of estimates for each, with the range dictated by the published literature or 50% to 200% of the mean published result, whichever was larger.

We performed a Monte Carlo simulation (74) in which we simultaneously varied all of the values for the variables listed in Table 1 in the base case. Each variable was entered as a probability distribution based on reported 95% CIs (when available) or as a reasonable range. The logit normal distribution was assumed for all probabilities, and a normal distribution was assumed for the natural log of costs and utilities. New values from within each of the probability distributions were randomly selected during each of 10 000 iterations, and the likelihood that the incremental cost per QALY was less than \$50 000 for the comparison of the most effective strategy with the closest strategy was calculated. We repeated this for analyses stratified by varying prevalence estimates based on application of a decision rule.

RESULTS

Base-Case Analysis

Under baseline assumptions, probabilities, and cost estimates (including a baseline GAS pharyngitis prevalence of 9.7%), four of the five strategies were similar. The culture strategy was dominant (both most effective and least expensive), resulting in an average of 0.2668 quality-adjusted life-day lost and an average cost of \$6.66 per patient (Table 2). The next most effective strategies, in order, were OIA/culture, OIA alone, observation, and empirical therapy. Empirical therapy was considerably less effective than the other strategies. The most expensive strategy (OIA/culture) cost more than twice as much per patient as the least expensive strategy. The culture strategy was followed

in cost by observation, OIA alone, empirical therapy, and OIA/culture.

Sensitivity Analyses

Prevalence of GAS Pharyngitis

In the base-case analysis, the prevalence of GAS infection among patients with sore throat was 9.7%. If the prevalence of GAS pharyngitis was greater than 20%, OIA/culture was most effective. If the prevalence was less than 6%, observation was least expensive; at a prevalence greater than 71%, empirical treatment was least expensive. From a cost-effectiveness standpoint, for any prevalence between 6% and 20%, the culture strategy dominated all others (that is, was both more effective and less expensive).

Test Characteristics of OIA

Culture strategy remained most effective for OIA sensitivities between 70% and 100%. Only at a specificity greater than 98% did OIA (with or without culture) become more effective. Culture remained the least expensive strategy at all ranges of OIA test characteristics examined.

Acute Rheumatic Fever and Suppurative Sequelae

In the base-case analysis, we assumed the risk for acute rheumatic fever in untreated patients with GAS pharyngitis to be 0.05%, or 5/10 000 cases. At a risk for acute rheumatic fever of 0.008%, or 8/100 000 cases, observation became the most effective strategy. Culture remained the least expensive strategy for a prevalence up to 3% (the probability of acute rheumatic fever seen in epidemic conditions). No change in the probability of valvular complications or death from acute rheumatic fever altered results significantly. Furthermore, results did not change when the protective effect of penicillin was varied.

In the base-case analysis, the risk for developing a peritonsillar abscess was 2.3%. If the actual risk is less than 1.4%, the observation strategy becomes least expensive. The culture strategy remained most effective unless the risk for abscess falls below 0.23%, when observation became most effective. Culture remained the dominant strategy at all probabilities for the protection provided by penicillin against peritonsillar abscess.

Results did not change as the risk for rash was varied between 0% and 10%. Culture remained least expensive throughout a range of probabilities for anaphylaxis and death from anaphylaxis. However, the effectiveness of strategies was very sensitive to the probability of anaphylaxis, so that at a probability about half that of the baseline probability (4/100 000 cases, or 0.004%), OIA/culture was most effective. At a probability of 1.6 times baseline (1.6/10 000 cases, or 0.016%), observation was most effective.

Symptom Relief

In the base-case analysis, treatment of GAS with penicillin provided 2 days of symptom improvement if begun

Table 2. Cost-Effectiveness of Baseline Pharyngitis Management Strategies*

Strategy	Average Cost, \$†	Average Effectiveness, lost quality-adjusted life-days	Incremental Cost-Effectiveness
Culture	6.66	0.2668	—
Observation	9.84	0.2752	Dominated
OIA alone	11.73	0.2717	Dominated
Empirical therapy	12.74	0.4083	Dominated
OIA culture	15.15	0.2716	Dominated

* "Dominated" indicates that the strategy is less effective and more costly. For explanation of strategies, see the Methods section. OIA = optical immunoassay.
† In 2000 U.S. dollars.

immediately and provided only 1 day of improvement if treatment was delayed to await culture results. Culture remained cheapest under a variety of assumptions. Only at less than a 1-hour benefit of culture did OIA (with a 2-day benefit) become more effective.

Utilities

When symptoms of pharyngitis were given a utility (or quality-of-life weight) of more than 0.97 on a scale of 0 to 1, observation became the most effective strategy. No variation in other quality-of-life weights relative to pharyngitis (such as anaphylaxis) changed the results.

Costs

Only at an OIA cost less than half of current pricing (\$2.60) did OIA become less expensive than culture. Similarly, at a culture cost more than \$6.00 (twice the current costs), observation became least expensive. Among costs of treatment of complications, only the cost of abscess changed results: At a cost less than half our estimated cost (\$2382), observation was least expensive.

Application of a Clinical Decision Rule

Table 3 shows the effect of varying the prevalence as if a decision rule (34) were used on our base-case population, with its baseline prevalence of 10%. For example, at a prevalence of 3% (patients positive for one of four clinical criteria), observation was most cost-effective. Although the culture strategy was more effective (that is, resulted in fewer lost days of work), the additional cost per QALY was greater than \$250 000. At any higher prevalence, culture remained least expensive; when antigen testing with or without culture became more effective (when the prevalence exceeded 20%), the incremental cost of its use was greater than \$300 000/QALY.

Probabilistic Sensitivity Analysis

At our GAS pharyngitis baseline prevalence of 10%, culture dominated (that is, was less expensive and more effective than) all other options. When OIA/culture (the next most effective strategy) was compared with culture,

Table 3. Effect of Probability of Group A β -Hemolytic Streptococcal Pharyngitis from a Clinical Prediction Rule on Cost-Effectiveness of Pharyngitis Management*

Prevalence (Probability) of GAS Pharyngitis†	Cost, \$	Average Effectiveness, lost QALDs	Incremental Cost-Effectiveness
3% (1 of 4 criteria predictive of GAS pharyngitis)			
Observation	3.04	0.2578	–
Culture	4.91	0.2552	\$719/additional QALDs (\$262 519/QALY)
OIA alone	9.36	0.2630	Dominated
Empirical therapy	11.64	0.4109	Dominated
OIA/culture	13.11	0.2629	Dominated
8% (2 of 4 criteria predictive of GAS pharyngitis)			
Culture	6.22	0.2639	–
Observation	8.12	0.2708	Dominated
OIA alone	11.13	0.2695	Dominated
Empirical therapy	12.46	0.4089	Dominated
OIA/culture	14.64	0.2694	Dominated
19% (3 of 4 criteria predictive of GAS pharyngitis)			
Culture	9.10	0.2829	–
Empirical therapy	14.26	0.4047	Dominated
OIA alone	15.03	0.2838	Dominated
OIA/culture	18.03	0.2835	Dominated
Observation	37.03	0.2994	Dominated
41% (4 of 4 criteria predictive of GAS pharyngitis)			
Culture	14.87	0.3210	–
Empirical therapy	17.86	0.3961	Dominated
OIA alone	22.84	0.3124	\$926/additional QALDs (\$337 990/QALY)
OIA/culture	24.79	0.3119	\$3900/additional QALDs (\$1 423 500/QALY)
Observation	41.60	0.3567	Dominated

* GAS = group A β -hemolytic streptococcal; QALD = quality-adjusted life-day; QALY = quality-adjusted life-year.

† Criteria are tonsillar exudates, tender anterior cervical lymphadenopathy, absence of cough, and history of fever (34).

there was a 0% chance that it was associated with an incremental cost-effectiveness ratio less than \$50 000/QALY (10% chance that OIA/culture was more effective but more expensive with incremental cost-effectiveness ratio > \$50 000/QALY; 90% chance that OIA/culture was less effective and more expensive).

When we used a GAS pharyngitis prevalence of 3%, culture was more effective but more expensive than observation. In probabilistic sensitivity analysis, there was a 49% chance that culture was dominant or was associated with an incremental cost-effectiveness ratio less than \$50 000/QALY when compared with observation (15% chance that culture was more effective and less expensive; 34% chance that culture was more effective and more expensive, but with an incremental cost-effectiveness ratio < \$50 000/QALY; 29% chance that culture was more effective but more expensive, with an incremental cost-effectiveness ratio > \$50 000/QALY; 19% chance that culture was less

effective and more expensive; and 3% chance that culture was less effective and less expensive).

In our analysis at a GAS pharyngitis prevalence of 41%, OIA alone was more effective but more expensive than culture. In probabilistic sensitivity analysis, there was a 14% chance that OIA was dominant or was associated with an incremental cost-effectiveness ratio less than \$50 000/QALY when compared with culture (4% chance that OIA was more effective and less expensive; 10% chance that OIA was more effective and more expensive, but with an incremental cost-effectiveness ratio < \$50 000/QALY; 23% chance that OIA was more effective and more expensive, with an incremental cost-effectiveness ratio > \$50 000/QALY; 59% chance that OIA was less effective and more expensive; and 3% chance that OIA was less effective and less expensive).

DISCUSSION

Expert panels have traditionally recommended routine laboratory diagnosis of pharyngitis, with the principal goal of preventing acute rheumatic fever (10). Throat cultures have traditionally been the preferred diagnostic method and the gold standard (10). More recently, however, the American College of Physicians retreated from that stance and recommended selective diagnosis and therapy based on clinical findings and adoption of rapid diagnostic tests to replace the standard throat culture (35, 36). Our study supports use of clinical findings in ways similar to those recommended by the panel, but suggests that several strategies, including culture, are reasonable.

Of the five strategies we studied, culture was by a slight margin the most effective and least expensive strategy at our baseline GAS pharyngitis prevalence of 9.7%. More notably, empirical treatment was substantially less effective than the other four strategies (culture, OIA alone, OIA/culture, and observation), which had very similar effectiveness. Because empirical treatment of patients likely to have GAS pharyngitis is considered acceptable (35, 36), we used the prediction rule for GAS pharyngitis created by Centor and colleagues (34) and cited by the American College of Physicians to examine the cost-effectiveness of empirical treatment over a range of probabilities of GAS pharyngitis. Only at a 71% probability of GAS pharyngitis, one unlikely to be reached except perhaps after use of a decision rule in an emergency department, does empirical therapy become the least expensive strategy. Even then it remains less effective than culture.

Our results were unchanged by most of the sensitivity analyses in which we varied our probabilities, utilities, and costs. Because four strategies were so similar at baseline, the changes we did see might be expected. Furthermore, they generally made observation of more patients a more cost-effective strategy than culture. For example, if the probability of acute rheumatic fever (a probability particularly difficult to estimate in 2002) was one fifth of our estimate

or less, observation would be more effective. Similarly, if the likelihood of anaphylaxis is higher or the quality of life with pharyngitis is slightly better, observation is more effective.

Few studies have examined the cost-effectiveness of testing and treatment strategies for pharyngitis in adults, and these were performed before the development of rapid testing (75) or examined only effectiveness without costs (60). Previous analyses in children used an appropriately higher baseline GAS pharyngitis prevalence. The most recent analysis and the only one to account for both allergic reactions and GAS pharyngitis complications in its primary results (55) had findings similar to ours.

The key dilemmas in diagnosing and treating pharyngitis have previously been well summarized (35, 36, 38, 47), and several of these may have led to differences between our findings and guideline recommendations. First, throat culture, the traditional diagnostic gold standard, is not a perfect test and does not provide point-of-care results. Some of the concerns regarding its sensitivity and specificity probably arise from the many variations in technique that can theoretically affect this deceptively simple test (10); its test behavior in trials does appear to vary (27, 76, 77). Next, the existence of a carrier state, in which a positive culture does not necessarily mean that GAS is the cause of a patient's sore throat, adds to the difficulty of evaluating the test (78, 79). Finally, some have interpreted the length of time needed for culture results as unacceptable for symptom relief (35, 36). Despite these limitations and concerns, we chose to examine two-plate culture because it is the traditional gold standard, is widely available, and has been shown in randomized trials (43, 44) to provide results in primary care settings in time to allow treatment for symptom relief. In settings where the two-plate culture is not available, other strategies or careful attention to the technique chosen for one-plate culture (Appendix, available at www.annals.org) might be preferred.

The similarities and differences between our results and the American College of Physicians' guideline (35, 36) can be further examined by using the results of our stratified examination of the estimated probabilities of GAS pharyngitis likely to be encountered with use of the College-recommended decision rule (Table 3) (34). The College guideline recommends against use of culture and recommends use of a decision rule (Appendix Figure 2, available at www.annals.org) for all patients. Because we found that OIA is less effective than culture if the patient is positive for fewer than four criteria and that the test is not cost-effective even when the patient meets four criteria, our analyses do not support the guideline recommendations for eliminating the use of culture. However, if culture is ignored, the other guideline recommendations can be examined: 1) When patients are positive for one criteria (clinical characteristic), the guideline recommends no testing or treatment. Our analysis agreed that observation is less effective and cheaper than OIA for patients positive for one

criteria. 2) When patients are positive for two criteria, the guideline recommends observation or rapid antigen testing. In our analysis, antigen testing became more effective than observation when patients met at least two criteria, but the incremental cost-effectiveness ratio was high (\$845 115/QALY). 3) When patients are positive for three or four criteria, the guideline recommends antigen testing or empirical treatment. We found that empirical therapy was less expensive than OIA, but the incremental cost-effectiveness of OIA compared with empirical treatment was reasonable (\$2325/QALY for three criteria and \$17 356/QALY for four criteria).

Our findings should be interpreted in the context of the limitations of many cost-effectiveness analyses. Many of the variables we examined were not drawn from randomized trials or were from trials performed before the probability of acute rheumatic fever decreased substantially. As a result, the uncertainty surrounding each of these estimates is large. Furthermore, our study examined small differences in cost-effectiveness and effectiveness of various strategies, and readers may disagree with our conclusions regarding the clinical significance of these differences. However, we attempted to thoroughly survey the literature, and we performed sensitivity analyses over wide ranges to examine the effects of that uncertainty and put them into perspective. Our use of QALYs also allows comparison to interventions for many other diseases.

Our findings should also be interpreted in the context of several other limitations particular to our analysis. First, we did not directly measure the utilities (quality-of-life weights) associated with the relevant health states. Second, we did not directly incorporate patients' preferences for antibiotic treatment (vs. observation) into our analysis. Many patients have strong opinions about whether they should take an antibiotic when they get a sore throat, and these opinions often influence physicians' prescription decisions (80). However, surveyed patients (67) who reported their preferences for various pharyngitis outcomes (which we incorporated into our analyses as utility estimates) are likely to have taken these preferences at least partially into account. Furthermore, patient satisfaction in pharyngitis treatment has recently been shown to be more strongly related to their physicians' "understanding their concerns" than to receipt of antibiotics (65). Finally, we examined five common approaches to the management of pharyngitis, but we could not study every possible treatment strategy. For example, a further strategy many clinicians use—obtaining the culture and empirically treating—does not reduce the risk for therapy in the first few days of treatment and thus would be as effective as empirical treatment.

We conclude that four strategies in managing streptococcal pharyngitis are reasonable and cost-effective. For a disease as common as pharyngitis, current variations in clinicians' approaches are striking. Often in such cases, no compelling data support one strategy over another, and our analysis of the data suggests that this continues to be true

for pharyngitis in adults. Empirical therapy is the exception—it is reasonable only when probabilities approach 70%: that is, in cases of epidemics of streptococcal infection and perhaps when streptococcal pharyngitis is being spread among family members or patients are at very high probability of having the condition after application of the Centor decision rule.

From Medical College of Wisconsin, Milwaukee, Wisconsin, and Beth Israel Deaconess Medical Center, Boston, Massachusetts.

Presented in part at the annual meeting of the Society of General Internal Medicine, San Diego, California, May 2001.

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Mark D. Aronson, MD, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Rose Building, Room 118, Boston, MA 02215.

Current author addresses are available at www.annals.org.

References

- Schappert SM. Ambulatory Care Visits to Physician's Offices, Hospital Outpatient Departments, and Emergency Departments: United States, 1996. Hyattsville, MD: National Center for Health Statistics; 1998.
- Horder J, Horder E. Illness in general practice. *Pract*. 1954;173:177-87.
- Goslings WR, Valkenberg HA, Bots AW, Lorrier JC. Attack rates of streptococcal pharyngitis, rheumatic fever and glomerulonephritis in the general population. A controlled pilot study of streptococcal pharyngitis in one village. *N Engl J Med*. 1963;268:687-94.
- Huovinen P, Lahtonen R, Ziegler T, Meurman O, Hakkarainen K, Miettinen A, et al. Pharyngitis in adults: the presence and coexistence of viruses and bacterial organisms. *Ann Intern Med*. 1989;110:612-6. [PMID: 2494921]
- Petersen K, Phillips RS, Soukup J, Komaroff AL, Aronson M. The effect of erythromycin on resolution of symptoms among adults with pharyngitis not caused by group A streptococcus. *J Gen Intern Med*. 1997;12:95-101. [PMID: 9051558]
- Komaroff AL, Pass TM, Aronson MD, Ervin CT, Cretin S, Winickoff RN, et al. The prediction of streptococcal pharyngitis in adults. *J Gen Intern Med*. 1986;1:1-7. [PMID: 3534166]
- Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. *JAMA*. 1997;278:901-4. [PMID: 9302241]
- Mandell GL, Petri WA Jr. Antimicrobial agents: penicillins, cephalosporins, and other β -lactam antibiotics. In: Hardman JG, Limberd LE, eds. Goodman and Gilman's The Pharmacologic Basis of Therapeutics. New York: Churchill Livingstone; 1995:272-8.
- deShazo RD, Kemp SF. Allergic reactions to drugs and biologic agents. *JAMA*. 1997;278:1895-906. [PMID: 9396651]
- Bisno AL, Gerber MA, Gwaltney JM Jr, Kaplan EL, Schwartz RH. Diagnosis and management of group A streptococcal pharyngitis: a practice guideline. Infectious Diseases Society of America. *Clin Infect Dis*. 1997;25:574-83. [PMID: 9314443]
- Linder JA, Stafford RS. Antibiotic treatment of adults with sore throat by community primary care physicians: a national survey, 1989-1999. *JAMA*. 2001;286:1181-6. [PMID: 11559262]
- Stollerman GH. Global changes in group A streptococcal diseases and strategies for their prevention. *Adv Intern Med*. 1982;27:373-406. [PMID: 7041547]
- Seppala H, Nissinen A, Jarvinen H, Huovinen S, Henriksson T, Herva E, et al. Resistance to erythromycin in group A streptococci. *N Engl J Med*. 1992;326:292-7. [PMID: 1728733]
- Martin JM, Green M, Barbadora KA, Wald ER. Erythromycin-resistant group A streptococci in schoolchildren in Pittsburgh. *N Engl J Med*. 2002;346:1200-6. [PMID: 11961148]
- Wallace MR, Garst PD, Papadimos TJ, Oldfield EC III. The return of acute rheumatic fever in young adults. *JAMA*. 1989;262:2557-61. [PMID: 2681847]
- Veasy LG, Tani LY, Hill HR. Persistence of acute rheumatic fever in the intermountain area of the United States. *J Pediatr*. 1994;124:9-16. [PMID: 7802743]
- 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.
- Chamovitz R, Stetson CA, Rammelkamp CH. Prevention of rheumatic fever by treatment of previous streptococcal infections. *N Engl J Med*. 1954;251:466-71.
- Brink WR, Denny FW, Wannamaker LW. Effect of penicillin and aureomycin on the natural course of streptococcal tonsillitis and pharyngitis. *Am J Med*. 1951;10:300-8.
- Brumfitt WS, Slater DH. Treatment of acute sore throat with penicillin: a controlled trial among young soldiers. *Lancet*. 1957;1:8-11.
- Del Mar C. Managing sore throat: a literature review. II. Do antibiotics confer benefit? *Med J Aust*. 1992;156:644-9. [PMID: 1625619]
- Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for sore throat. *Cochrane Database of Systematic Reviews*. 2002;2.
- Baker DM, Cooper RM, Rhodes C, Weymouth LA, Dalton HP. Superiority of conventional culture technique over rapid detection of group A Streptococcus by optical immunoassay. *Diagn Microbiol Infect Dis*. 1995;21:61-4. [PMID: 7628193]
- Daly JA, Korgenski EK, Munson AC, Llausas-Magana E. Optical immunoassay for streptococcal pharyngitis: evaluation of accuracy with routine and mucoid strains associated with acute rheumatic fever outbreak in the intermountain area of the United States. *J Clin Microbiol*. 1994;32:531-2. [PMID: 8150968]
- Fries SM. Diagnosis of group A streptococcal pharyngitis in a private clinic: comparative evaluation of an optical immunoassay method and culture. *J Pediatr*. 1995;126:933-6. [PMID: 7776098]
- Gerber MA, Tanz RR, Kabat W, Dennis E, Bell GL, Kaplan EL, et al. Optical immunoassay test for group A beta-hemolytic streptococcal pharyngitis. An office-based, multicenter investigation. *JAMA*. 1997;277:899-903. [PMID: 9062328]
- Harbeck RJ, Teague J, Crossen GR, Maul DM, Childers PL. Novel, rapid optical immunoassay technique for detection of group A streptococci from pharyngeal specimens: comparison with standard culture methods. *J Clin Microbiol*. 1993;31:839-44. [PMID: 8463394]
- Heiter BJ, Bourbeau PP. Comparison of two rapid streptococcal antigen detection assays with culture for diagnosis of streptococcal pharyngitis. *J Clin Microbiol*. 1995;33:1408-10. [PMID: 7615768]
- Kaltwasser G, Diego J, Welby-Sellenriek PL, Ferrett R, Caparon M, Storch GA. Polymerase chain reaction for *Streptococcus pyogenes* used to evaluate an optical immunoassay for the detection of group A streptococci in children with pharyngitis. *Pediatr Infect Dis J*. 1997;16:748-53. [PMID: 9271035]
- Kuhn S, Davies HD, Katzko G, Jadavji T, Church DL. Evaluation of the Strep A OIA assay versus culture methods: ability to detect different quantities of group A Streptococcus. *Diagn Microbiol Infect Dis*. 1999;34:275-80. [PMID: 10459477]
- Pitetti RD, Drenning SD, Wald ER. Evaluation of a new rapid antigen detection kit for group A beta-hemolytic streptococci. *Pediatr Emerg Care*. 1998;14:396-8. [PMID: 9881982]
- Schlager TA, Hayden GA, Woods WA, Dudley SM, Hendley JO. Optical immunoassay for rapid detection of group A beta-hemolytic streptococci. Should culture be replaced? *Arch Pediatr Adolesc Med*. 1996;150:245-8. [PMID: 8603215]
- Smith JM, Bauman MC, Fuchs PC. An optical immunoassay for the direct detection of group A strep antigen. *Laboratory Medicine*. 1995;26:408-10.
- 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. [PMID: 6763125]

35. Cooper RJ, Hoffman JR, Bartlett JG, Besser RE, Gonzales R, Hickner JM, et al. Principles of appropriate antibiotic use for acute pharyngitis in adults: background. *Ann Intern Med.* 2001;134:509-17. [PMID: 11255530]
36. Snow V, Mottur-Pilson C, Cooper RJ, Hoffman JR. Principles of appropriate antibiotic use for acute pharyngitis in adults. *American Academy of Family Physicians, American College of Physicians–American Society of Internal Medicine, Centers for Disease Control and Prevention. Ann Intern Med.* 2001;134:506-8. [PMID: 11255529]
37. Hillner BE, Smith TJ, Desch CE. Efficacy and cost-effectiveness of autologous bone marrow transplantation in metastatic breast cancer. Estimates using decision analysis while awaiting clinical trial results. *JAMA.* 1992;267:2055-61. [PMID: 1552641]
38. Gonzales R, Bartlett JG, Besser RE, Cooper RJ, Hickner JM, Hoffman JR, et al. Principles of appropriate antibiotic use for treatment of acute respiratory tract infections in adults: background, specific aims, and methods. *Ann Intern Med.* 2001;134:479-86. [PMID: 11255524]
39. Dajani A, Taubert K, Ferrieri P, Peter G, Shulman S. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association. *Pediatrics.* 1995;96:758-64. [PMID: 7567345]
40. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-Effectiveness in Health and Medicine. New York: Oxford Univ Pr; 1996.
41. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA.* 1996;276:1253-8. [PMID: 8849754]
42. Zwart S, Sachs AP, Ruijs GJ, Gubbels JW, Hoes AW, de Melker RA. Penicillin for acute sore throat: randomised double blind trial of seven days versus three days treatment or placebo in adults. *BMJ.* 2000;320:150-4. [PMID: 10634735]
43. Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. Open randomised trial of prescribing strategies in managing sore throat. *BMJ.* 1997;314:722-7. [PMID: 9116551]
44. Dagnelie CF, van der Graaf Y, De Melker RA. Do patients with sore throat benefit from penicillin? A randomized double-blind placebo-controlled clinical trial with penicillin V in general practice. *Br J Gen Pract.* 1996;46:589-93. [PMID: 8945796]
45. Webb KH. Does culture confirmation of high-sensitivity rapid streptococcal tests make sense? A medical decision analysis. *Pediatrics.* 1998;101:E2. [PMID: 9445512]
46. Tsevat J, Kotagal UR. Management of sore throats in children: a cost-effectiveness analysis. *Arch Pediatr Adolesc Med.* 1999;153:681-8. [PMID: 10401800]
47. Ebell MH, Smith MA, Barry HC, Ives K, Carey M. The rational clinical examination. Does this patient have strep throat? *JAMA.* 2000;284:2912-8. [PMID: 11147989]
48. Hoffman S. An algorithm for a selective use of throat swabs in the diagnosis of group A streptococcal pharyngo-tonsillitis in general practice. *Scandinavian Journal of Primary Health Care.* 1992;10:295-300.
49. Walsh BT, Bookheim WW, Johnson RC, Tompkins RK. Recognition of streptococcal pharyngitis in adults. *Arch Intern Med.* 1975;135:1493-7. [PMID: 1103766]
50. Dobbs F. A scoring system for predicting group A streptococcal throat infection. *Br J Gen Pract.* 1996;46:461-4. [PMID: 8949324]
51. Wigton RS, Connor JL, Centor RM. Transportability of a decision rule for the diagnosis of streptococcal pharyngitis. *Arch Intern Med.* 1986;146:81-3. [PMID: 3510600]
52. Meland E, Digraanes A, Skjaerven R. Assessment of clinical features predicting streptococcal pharyngitis. *Scand J Infect Dis.* 1993;25:177-83. [PMID: 8511511]
53. Poses RM, Cebul RD, Collins M, Fager SS. The importance of disease prevalence in transporting clinical prediction rules. The case of streptococcal pharyngitis. *Ann Intern Med.* 1986;105:586-91. [PMID: 3530079]
54. Holmberg SD, Faich GA. Streptococcal pharyngitis and acute rheumatic fever in Rhode Island. *JAMA.* 1983;250:2307-12. [PMID: 6355522]
55. Gerber MA. Comparison of throat cultures and rapid strep tests for diagnosis of streptococcal pharyngitis. *Pediatr Infect Dis J.* 1989;8:820-4. [PMID: 2687791]
56. 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. [PMID: 3535604]
57. Savoia D, Francesetti C, Millesimo M, Dotti G, Gatti G, Rurali C. Evaluation of the diagnostic accuracy of a kit for the rapid detection of group A streptococci. *Microbios.* 1994;77:253-9. [PMID: 8208140]
58. Hoffmann S. Detection of group A streptococcal antigen from throat swabs with five diagnostic kits in general practice. *Diagn Microbiol Infect Dis.* 1990;13:209-15. [PMID: 2200635]
59. Wegner DL, Witte DL, Schrantz RD. Insensitivity of rapid antigen detection methods and single blood agar plate culture for diagnosing streptococcal pharyngitis. *JAMA.* 1992;267:695-7. [PMID: 1731138]
60. Hillner BE, Centor RM. What a difference a day makes: a decision analysis of adult streptococcal pharyngitis. *J Gen Intern Med.* 1987;2:244-50. [PMID: 3302145]
61. Feinstein AR, Harrison FW, Spagnuolo M, Taranta A, Jonas S, Kleinberg E, et al. Rheumatic fever in children and adolescents: a long-term epidemiologic study of subsequent prophylaxis, streptococcal infections, and clinical sequelae. *Ann Intern Med.* 1964;60:87-123.
62. De Meyere M, Mervielde Y, Verschraegen G, Bogaert M. Effect of penicillin on the clinical course of streptococcal pharyngitis in general practice. *Eur J Clin Pharmacol.* 1992;43:581-5. [PMID: 1493837]
63. Valkenburg HA, Haverkorn MJ, Goslings WR, Lorrier JC, De Moor CE, Maxted WR. Streptococcal pharyngitis in the general population. II. The attack rate of rheumatic fever and acute glomerulonephritis in patients. *J Infect Dis.* 1971;124:348-58. [PMID: 5143843]
64. Denny LW, Hahn EO. Comparative effects of penicillin, aureomycin and terramycin on streptococcal tonsillitis and pharyngitis. *Pediatrics.* 1953;11:7-14.
65. Little P, Gould C, Williamson I, Warner G, Gantley M, Kinmonth AL. Clinical and psychosocial predictors of illness duration from randomised controlled trial of prescribing strategies for sore throat. *BMJ.* 1999;319:736-7. [PMID: 10487997]
66. Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. *Med Care.* 2000;38:583-637. [PMID: 10843310]
67. Herman JM. Patients' willingness to take risks in the management of pharyngitis. *J Fam Pract.* 1984;19:767-72. [PMID: 6502081]
68. Finkler SA. The distinction between cost and charges. *Ann Intern Med.* 1982;96:102-9. [PMID: 7053682]
69. Drug Topics Red Book. Montvale, NJ: Medical Economics; 2000.
70. Tsevat J, Duke D, Goldman L, Pfeffer MA, Lamas GA, Soukup JR, et al. Cost-effectiveness of captopril therapy after myocardial infarction. *J Am Coll Cardiol.* 1995;26:914-9. [PMID: 7560617]
71. Kirschner CG, Burkett RC, Kotowicz GM, et al. eds. Physicians' Current Procedural Terminology: CPT '97. Chicago: American Medical Assoc; 1997.
72. Health Care Financing Administration, Public Use Datafiles. 30 December 2000. Accessed at <http://cms.hhs.gov/surveys/hos/pufs.asp> on 1 December 2001.
73. Goldman L, Bennett JC, eds. Cecil Textbook of Medicine. 21st ed. Philadelphia: WB Saunders; 2000.
74. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. *Med Decis Making.* 1985;5:157-77. [PMID: 3831638]
75. 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. [PMID: 403842]
76. Wegner DL, Witte DL, Schrantz RD. Insensitivity of rapid antigen detection methods and single blood agar plate culture for diagnosing streptococcal pharyngitis. *JAMA.* 1992;267:695-7. [PMID: 1731138]
77. Roddey OF Jr, Clegg HW, Martin ES, Swetenburg RL, Koonce EW. Comparison of throat culture methods for the recovery of group A streptococci in a pediatric office setting. *JAMA.* 1995;274:1863-5. [PMID: 7500536]
78. Kaplan EL, Top FH Jr, 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. [PMID: 5115179]
79. Gunnarsson RK, Holm SE, Soderstrom M. The prevalence of beta-haemolytic streptococci in throat specimens from healthy children and adults. Implications for the clinical value of throat cultures. *Scand J Prim Health Care.* 1997;15:149-55. [PMID: 9323783]

80. Butler CC, Rollnick S, Pill R, Maggs-Rapport F, Stott N. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *BMJ*. 1998;317:637-42. [PMID: 9727992]
81. Steinhoff MC, Abd el Khalek MK, Khallaf N, Hamza HS, el Ayadi A, Orabi A, et al. Effectiveness of clinical guidelines for the presumptive treatment of streptococcal pharyngitis in Egyptian children. *Lancet*. 1997;350:918-21. [PMID: 9314870]
82. Kljakovic M. Sore throat presentation and management in general practice. *N Z Med J*. 1993;106:381-3. [PMID: 8367095]
83. McIsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. *CMAJ*. 1998;158:75-83. [PMID: 9475915]
84. Komaroff AL, Pass TM, Aronson MD, Ervin CT, Cretin S, Winickoff RN, et al. The prediction of streptococcal pharyngitis in adults. *J Gen Intern Med*. 1986;1:1-7. [PMID: 3534166]
85. Crawford G, Brancato F, Holmes KK. Streptococcal pharyngitis: diagnosis by gram stain. *Ann Intern Med*. 1979;90:293-7. [PMID: 85421]
86. Moyer NP, Quinn PJ, Showalter CA. Evaluation of the Directigen 1,2,3 Group A Strep Test for diagnosis of streptococcal pharyngitis. *J Clin Microbiol*. 1990;28:1661-3. [PMID: 2199526]
87. Kellogg JA. Suitability of throat culture procedures for detection of group A streptococci and as reference standards for evaluation of streptococcal antigen detection kits. *J Clin Microbiol*. 1990;28:165-9. [PMID: 2179252]
88. Kellogg JA, Manzella JP. Detection of group A streptococci in the laboratory or physician's office. Culture vs antibody methods. *JAMA*. 1986;255:2638-42. [PMID: 3517397]
89. Wegner DL, Witte DL, Schrantz RD. Insensitivity of rapid antigen detection methods and single blood agar plate culture for diagnosing streptococcal pharyngitis. *JAMA*. 1992;267:695-7. [PMID: 1731138]
90. Bellon J, Weise B, Verschraegen G, De Meyere M. Selective streptococcal agar versus blood agar for detection of group A beta-hemolytic streptococci in patients with acute pharyngitis. *J Clin Microbiol*. 1991;29:2084-5. [PMID: 1774341]
91. Lauer BA, Reller LB, Mirrett S. Effect of atmosphere and duration of incubation on primary isolation of group A streptococci from throat cultures. *J Clin Microbiol*. 1983;17:338-40. [PMID: 6339551]
92. Graham L Jr, Meier FA, Centor RM, Garner BK, Dalton HP. Effect of medium and cultivation conditions on comparisons between latex agglutination and culture detection of group A streptococci. *J Clin Microbiol*. 1986;24:644-6. [PMID: 3095365]
93. Anhalt JP, Heiter BJ, Naumovitz DW, Bourbeau PP. Comparison of three methods for detection of group A streptococci in throat swabs. *J Clin Microbiol*. 1992;30:2135-8. [PMID: 1500522]
94. Fries SM. Diagnosis of group A streptococcal pharyngitis in a private clinic: comparative evaluation of an optical immunoassay method and culture. *J Pediatr*. 1995;126:933-6. [PMID: 7776098]
95. Roddey OF Jr, Clegg HW, Martin ES, Swetenburg RL, Koonce EW. Comparison of throat culture methods for the recovery of group A streptococci in a pediatric office setting. *JAMA*. 1995;274:1863-5. [PMID: 7500536]
96. 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. [PMID: 3534175]
97. Siegel AC, Johnson EE, Stollerman G. 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.
98. Cantanzaro FJ, Morris AJ, Chamovitz R, Rammelkamp CH, Stolzer B, Perry WD. Symposium on rheumatic fever and rheumatic heart disease. The role of streptococcus in the pathogenesis of rheumatic fever. *Am J Med*. 1954;17:749-56.
99. Denny LW, Brink WR, Rammelkamp CH, Custer EA. Prevention of rheumatic fever: treatment of the preceding streptococcal infection. *JAMA*. 1950;143:151-3.
100. Wannamaker LW, Rammelkamp CH, Denny FW, Brink WR, Houser HB, Hahn EO. Prophylaxis of acute rheumatic fever by treatment of the preceding streptococcal infection with various amounts of depot penicillin. *Am J Med*. 1951;10:673-94.
101. Kirschner CG, Burkett RC, Kotowicz GM, et al., eds. *Physicians' Current Procedural Terminology: CPT '95*. Chicago: American Medical Assoc; 1994.
102. Tsevat J, Wong JB, Pauker SG, Steinberg MH. Neonatal screening for sickle cell disease: a cost-effectiveness analysis. *J Pediatr*. 1991;118:546-54. [PMID: 1901081]

APPENDIX Model

The model output was loss of quality-adjusted life expectancy measured as quality-adjusted life-days. Incremental analyses were performed by rank ordering all five competing strategies by increasing effectiveness after eliminating strategies that were more costly and less effective than another strategy (that is, ruled out by simple dominance). We then calculated the incremental cost-effectiveness ratio for each strategy (additional cost divided by additional benefit) compared with the next least expensive strategy. If a strategy was less effective and had a higher incremental cost-effectiveness ratio than another strategy, it was ruled out by weak dominance and eliminated from the list as the incremental cost-effectiveness strategies were recalculated. This process was continued until no more weakly dominated strategies were left.

Data Sources

Clinical Findings

Several investigators have examined the sensitivity and specificity of clinical examination findings in pharyngitis (47, 81–85). These findings were statistically summarized in a recent review and meta-analysis, in which positive and negative likelihood ratios and the area under the receiver-operating characteristic (ROC) curve were calculated for history and physical examination findings (47). The positive likelihood ratio (sensitivity/[100 – specificity]) is a measure of how well a positive result rules in disease, while a negative likelihood ratio ($[100 - \text{sensitivity}]/\text{specificity}$) is a measure of how well a negative result rules out disease. The greater a positive likelihood ratio is above 1, the higher the likelihood of ruling in a disease. For negative likelihood ratios, the closer a likelihood ratio is to 0, the greater the likelihood of ruling out disease. By one assessment (47), a likelihood ratio between 2 and 5 (negative likelihood ratios of 0.5 to 0.2) is weak evidence, between 5 and 10 (negative likelihood ratios of 0.1 to 0.2) is moderate evidence, and greater than 10 (negative likelihood ratio < 0.1) is strong evidence for (or against) a hypothesis. While no individual sign or symptom of pharyngitis is accurate enough by itself to diagnose GAS pharyngitis, several symptoms and signs perform better than others in “ruling in” disease (higher positive likelihood ratio). These include the presence of tonsillar exudate (positive likelihood ratio, 3.4), pharyngeal exudate (positive likelihood ratio, 2.1), and GAS pharyngitis exposure in the previous 2 weeks (positive likelihood ratio, 1.9). The absence of findings is not efficient in ruling out disease (the lowest negative likelihood ratio is 0.60 for the absence of tender anterior cervical lymph nodes). The variables with the greatest diagnostic accuracy, or ability to discriminate between patients with and without GAS pharyngitis (that is, with the greatest area under the ROC curve), are pharyngeal or tonsillar exudate, fever by history, tonsillar enlargement, tenderness or enlargement of the anterior cervical lymph nodes, and absence of cough.

GAS Test Characteristics (Culture, Enzyme Immunoassay, and OIA Rapid Tests)

The sensitivity and specificity of GAS culture have been controversial (27, 35, 86–89).

Some of the concerns about GAS culture arise from the many variables in technique that can at least theoretically affect this deceptively simple test, and it is important that careful technique be followed. Testing for GAS begins with specimen collection. Throat swabs are collected by passing a sterile swab over the tonsillar fossae and posterior pharynx, and the area that is sampled can vary a great deal. Single or double swabs can also be used. Swabs can either be transported directly to the laboratory dry or transported in a transport medium before inoculation onto plates. Although none of these variables has been clearly linked to sensitivity and specificity of culture, some researchers have speculated that they may be important factors (87).

Once the swabs are ready to be plated, there are three additional variables in commonly practiced laboratory or office culture techniques: the duration of incubation, the atmosphere used to incubate the culture, and the medium in which the culture is plated. Investigators have reached the consensus that a longer incubation period (that is, examination of culture plates at both 24 and 48 hours) is advantageous for detecting GAS (87, 89–91). However, studies of the optimal atmosphere (air, air enriched with 5% to 10% CO₂, and anaerobic atmospheres) have produced conflicting results, as have studies of the optimal media (from one blood agar plate to two-plate cultures with selective blood agar with broth-enhanced media) (90, 92–94). Several recent studies that examined single-plate culture methods have found particularly poor sensitivity (27, 89). However, at least in laboratories (and perhaps in offices [95]), several media-atmosphere combinations are likely to produce sensitivity similar to that of a rapid antigen test (at least 90% to 95%) (9): blood agar incubated anaerobically, blood agar incubated aerobically with a cover glass or with swabs dried before “stabbing” of the agar (95), blood agar with sulfamethoxazole incubated aerobically with CO₂, or blood agar with sulfamethoxazole incubated anaerobically. More selective agar (such as selective streptococcal agar, which contains colistin and crystal violet in addition to sulfamethoxazole) or broth-enhanced cultures (such as Todd–Hewitt broth) may improve culture sensitivity, as may the use of two plates.

Most of the specificity concerns for GAS culture arise from the “carrier state” (78, 79). Because of the carrier state, a positive culture does not necessarily mean that GAS is the cause of a patient’s sore throat. This has led to problems with determining the specificity of throat culture. However, Centor and colleagues (96) examined asymptomatic adults in an emergency department setting and found that 1.22% had positive culture results, suggesting a specificity of 99%. In a more recent study of children with pharyngitis symptoms that used polymerase chain reaction as the comparative standard, Kaltwasser and coworkers reported a specificity of 98% (29).

Rapid tests also have similar problems with performance (23–33). Enzyme immunoassays and OIAs are the current common methods available in the United States. These rapid assays

detect GAS antigens directly from the throat swab and minimize the time needed for diagnosis. Enzyme immunoassays implement agents to extract antigens from a throat swab and antibodies to visualize these antigens. The methods for visualization vary by test and include agglutination of antibody-coded latex particles; changes in color caused by an enzymatic reaction; or binding of color colloids, latex particles, or lipids to the antibody. Enzyme immunoassays are so varied that their overall sensitivity and specificity are difficult to estimate.

Because all studies of OIA examined the same assay (Thermo BioStar, Louisville, Colorado), its sensitivity and specificity are more certain. This test works by allowing direct visualization of a physical change in the thickness of thin films. This change is produced by the binding reactions between antigens and antibodies. The OIA tests possess an initial stationary monolayer to which antigens present in a throat swab may bind. If binding occurs, a second antigen layer is produced atop the existing monolayer. The resulting increased thickness affects the reflection of light through the films and causes a change in color (27). All OIA studies we reviewed were of acceptable quality, although study samples were sometimes not well described and blinding of investigators was not always noted. A few studies (29, 31) found sensitivities for OIA less than 80%; however, even when we incorporated these studies, on average OIA had a sensitivity of 88%. Although enzyme immunoassays have never been compared in head-to-head studies with OIAs, they appear on average to have lower sensitivity and specificity.

Both enzyme immunoassays and OIAs probably also suffer from many of the same problems as culture: variable collection technique and the uncertainty regarding colonization (34). Serologic testing is the only way to determine whether a positive result on culture or rapid test for GAS actually represents a true infection. However, these tests may take weeks to complete and thus have no practical application to the management of patients with pharyngitis.

Acute Rheumatic Fever and Suppurative Sequelae of GAS Pharyngitis

The probability of GAS pharyngitis in nonepidemic conditions in the 1980s is estimated to be 5/10 000 (17), and we, like others (45, 60, 75), used this as our baseline probability. Much higher prevalences were reported in the 1960s (3, 63, 97). During the epidemics in the Rocky Mountains in the 1980s (15, 16), and in studies in the 1950s (18–20, 63, 64, 98–100), the prevalence was as high as 3%. No trials and few studies followed patients over the long term or reported systematically on complications of acute rheumatic fever. However, one cohort study estimated that 10% of cases caused complications and that 1% were fatal (27, 31).

Untreated streptococcal infections can result in a variety of complications, including peritonsillar abscess, otitis media, sinusitis, and life-threatening complications such as bacteremia or necrotizing fasciitis. The risk for developing one of the life-threatening complications is not well established, and other complications can themselves be treated with antibiotics. However,

2.3% of untreated patients will develop a peritonsillar abscess (22), which generally requires surgical drainage. We focused on this common but morbid suppurative complication for our analysis.

Duration of Symptoms

Symptoms related to streptococcal pharyngitis are self-limiting unless complications develop. Even without antibiotics, 29% of patients with pharyngitis are free of sore throat by the third day and 82% are free by the seventh day (22).

Utilities

Utilities, or quality-of-life weights, are used in cost-effectiveness analyses to account for the quality of time spent in various health conditions. This allows analyses to consider not only length of life but also quality of life. Utilities are generally expressed as a number between 0 and 1.0, where 1.0 represents excellent health. The utility associated with pharyngitis has not been directly assessed. We estimated that pharyngitis was associated with a utility of 0.95, which is the utility associated with other minor symptoms, such as diarrhea and dyspepsia (66). On the basis of a survey (67) that assessed how patients valued pharyngitis relative to mild penicillin reaction, severe penicillin reaction, and acute rheumatic fever, we assigned utilities to these other outcomes. Study participants in this survey study who received sick pay were more likely to be willing to risk the chance of a penicillin reaction, suggesting that the participants took lost pay into account in estimating the utilities for certain outcomes. This survey did not assess the utility associated with peritonsillar abscess; we based our utility estimate for peritonsillar abscess on a previous decision analysis that used expert opinion (60). Because most of our outcomes occurred within several weeks, we then converted them to lost quality-adjusted life-days.

Costs

Tests

We based our estimate of the costs of performing the OIA rapid test and throat culture on a previous analysis (46), with information obtained from Biostar. The cost of the OIA rapid test with the necessary quality control is \$7.67. The cost of pharyngeal culture, including materials, quality control, and labor, is \$2.83.

Notifying Patients of Culture Results, Calling in Prescriptions

Because GAS culture takes 2 days, we calculated the costs of calling patients with results and calling pharmacies with penicillin prescriptions. We surveyed eight nurses in our office and estimated that it takes an average of 5.2 minutes to inform patients of culture results and 5.1 minutes to call in an antibiotic prescription for a patient with a positive culture. At an estimated salary for an office nurse of \$15 per hour (46), these costs would be \$1.30 and \$1.28, respectively.

Penicillin Therapy

On the basis of wholesale and pharmacy dispensing costs, we estimated that the cost for penicillin at a dosage of 250 mg four times a day for 10 days is \$3.29 wholesale (69) plus pharmacy dispensing costs of \$6.76 (70), for a total cost of \$10.05.

Penicillin-Induced Rash

We estimated that treating a drug-induced rash incurs the charges for the following: 1) \$24.65 in physician time based on the resource-based relative value scale reimbursement rate in Boston for Physicians' Current Procedural Terminology (CPT) code 99212 (101); 2) 2-day course of diphenhydramine, 25 mg four times a day as needed (\$8.08); and 3) 10-day course of erythromycin, 250 mg orally four times a day (\$13.37) (69).

Anaphylaxis

On the basis of a previous analysis (102), the cost of treating anaphylaxis was estimated to be \$1772.54.

Acute Rheumatic Fever

The cost of acute rheumatic fever was first estimated by Tompkins and colleagues (75) in a cost-minimization analysis in 1977. As others (46) have noted, their estimate includes the cost of premature death, which we have not included in our analysis. We believe most cases of acute rheumatic fever are treated on an outpatient basis, because only one case of acute rheumatic fever was identified in a search of a database of our hospital discharges from 1990 to 2000. Therefore, instead of using this case, we estimated costs for acute rheumatic fever as follows:

Physician Costs. We estimated physician fees using resource-based relative value scale outpatient reimbursement rates (101) as follows: 1) one level 4 visit, established patient 99214 = \$57.34; 2) one level 3 visit, established patient 99213 = \$35.64 (follow-up); 3) physician charge for reading of electrocardiogram (\$33.09) and echocardiogram (\$177.75); 4) two of the following: rheumatology, cardiology, or neurology consult 99244 = \$136.05.

Laboratory/Procedure Costs. We estimated costs for labora-

tory tests, medications, and procedures for diagnosing and treating acute rheumatic fever from the Centers for Medicare & Medicaid clinical diagnostic laboratory fee schedule for 2000 (72). We selected tests on the basis of revised Jones criteria for acute rheumatic fever (73) and our assessment of laboratory tests that a clinician is likely to order when faced with an undiagnosed patient with the most common symptoms and signs of acute rheumatic fever: 1) laboratory tests: chemistries and liver function tests (\$14.61), complete blood count (\$11.71), urinalysis (\$3.10), antistreptolysin O titer (\$10.09), rheumatoid factor (\$7.85), C-reactive protein (\$7.15), and erythrocyte sedimentation rate (\$4.91); 2) medications: penicillin, if not already given (\$10.05); 3) procedures: electrocardiogram (\$92) and echocardiogram (\$1213).

Penicillin-Induced Rash. We estimated that treating a drug-induced rash incurs the following charges: 1) physician time based on the resource-based relative value scale reimbursement rate in Boston for CPT code 99212 (\$24.65) (101); 2) 2-day course of diphenhydramine, 25 mg four times a day as needed (\$8.08); 3) 10-day course of erythromycin, 250 mg orally four times a day (\$18.21) (69).

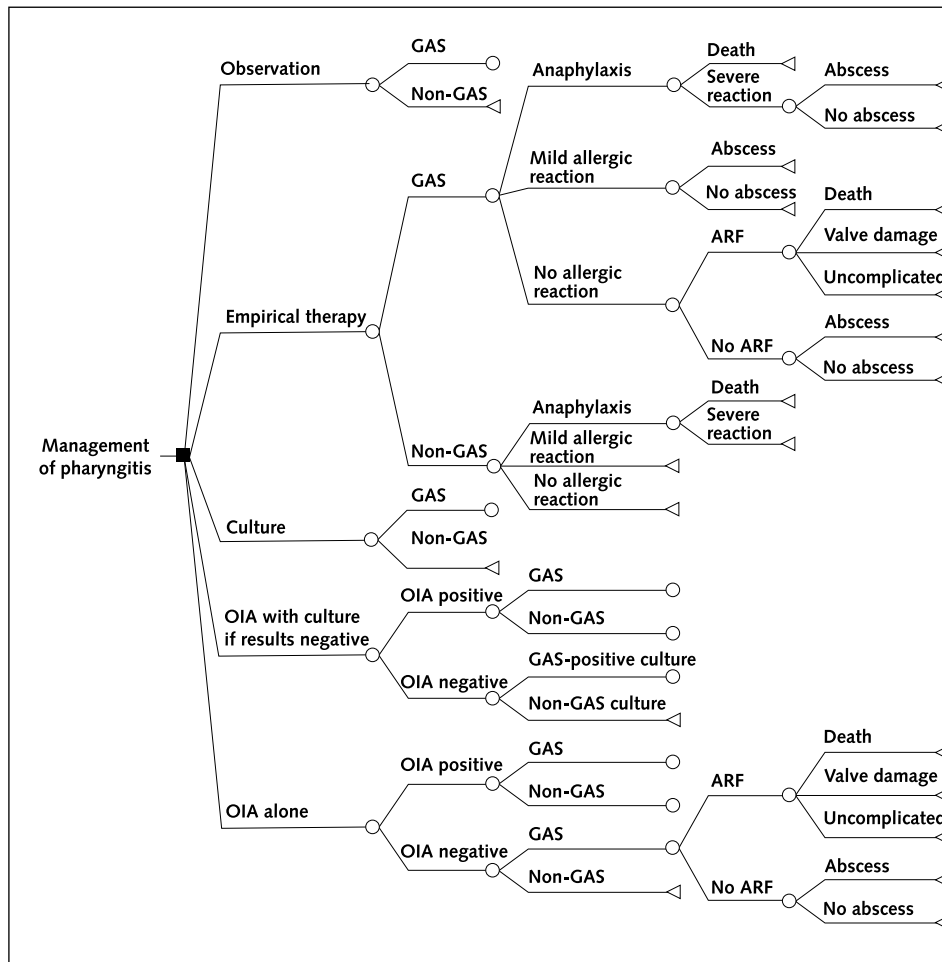
Sensitivity Analyses

In one-way sensitivity analyses, we varied all probabilities, costs, and utilities for which we found either large variation or single reports in the published literature. We examined a range of probabilities or costs for each, with the range dictated by either the published literature or 50% to 200% of the mean published result, whichever was larger. Because culture and antigen tests and penicillin were used in most patients in all strategies except observation, we varied these costs widely between \$0 and approximately five times our estimates.

Current Author Addresses: Dr. Neuner: Center for Patient Care and Outcomes Research, Medical College of Wisconsin, HRC H2755, 8701 Watertown Plank Road, Milwaukee, WI 53226.

Drs. Hamel, Phillips, and Aronson and Ms. Bona: Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Rose Building, Room 118, Boston, MA 02215.

Appendix Figure 1. The decision model.



The tree represents the possible outcomes of an adult with group A β -hemolytic streptococcal (GAS) pharyngitis. The node on the left represents a choice among five alternative strategies. All other nodes are chance nodes (*circles*) or terminal nodes (*triangles*) representing events that might occur (with a certain probability estimated as described in the text) after each strategy is chosen. For example, a patient with pharyngitis could receive penicillin without any testing (*branch 2*). That patient would then either have GAS pharyngitis (*upper branch*) or non-GAS pharyngitis (*lower branch*). If the patient had GAS pharyngitis, he or she could have only symptoms or also have complications shown in the subsequent branches: anaphylaxis, rash, peritonsillar abscess, acute rheumatic fever (ARF), or none of these. If the patient did not have GAS pharyngitis, then he or she would still be subject to the risk for anaphylaxis or rash from penicillin given, but no other sequelae. For all other branches that end in a circle, the complete tree is not shown; the complete tree shown for empirical therapy would be followed by using the appropriate branch (labeled either GAS or non-GAS). Note that the tree also shows the consequences of false-positive results on optical immunoassay (OIA) antigen tests. For example, a patient with pharyngitis could undergo OIA alone (*bottom branch*). If that test result were positive, the patient could have GAS pharyngitis (that is, have a true-positive result) and thus might develop the sequelae of pharyngitis; the other possibility is that the patient has a false-positive result and thus faces only the risks of treatment as shown in the empirical therapy branches.

Appendix Figure 2. Centor clinical prediction rule for the diagnosis of group A β -hemolytic streptococcal (GAS) pharyngitis in adults.

1. Assign 1 point for each of the following clinical characteristics: 1) history of fever, 2) anterior cervical adenopathy, 3) tonsillar exudate, and 4) absence of cough.
2. Find the column that most closely matches the pretest probability of GAS pharyngitis in the patient and look down the column to the row that matches the patient's number of points to determine the probability of GAS pharyngitis.

Points	Likelihood Ratio	Pretest Probability of GAS Pharyngitis, %						
		5	10	15	20	25	40	50
0	0.16	1	2	2	3	5	10	14
1	0.3	2	3	5	7	9	17	23
2	0.75	4	8	12	16	20	33	43
3	2.1	10	19	27	34	41	58	68
4	6.3	25	41	53	61	68	81	86

Adapted from Ebell et al. (47). Copyright 2000, American Medical Association.