Empirical Validation of Guidelines for the Management of Pharyngitis in Children and Adults

Warren J. McIsaac, MD, MSc
James D. Kellner, MD, MSc
Peggy Aufricht, MD
Anita Vanjaka, MSc
Donald E. Low, MD

Context Recent guidelines for management of pharyngitis vary in their recommendations concerning empirical antibiotic treatment and the need for laboratory confirmation of group A streptococcus (GAS).

Objective To assess the impact of guideline recommendations and alternative approaches on identification and treatment of GAS pharyngitis in children and adults.

Design, Setting, and Participants Throat cultures and rapid antigen tests were performed on 787 children and adults aged 3 to 69 years with acute sore throat attending a family medicine clinic in Calgary, Alberta, from September 1999 to August 2002. Recommendations from 2 guidelines (those of the Infectious Diseases Society of America and of the American College of Physicians-American Society of Internal Medicine/American Academy of Family Physicians/US Centers for Disease Control and Prevention) were compared with rapid testing alone, a clinical prediction rule (ie, the modified Centor score), and a criterion standard of treatment for positive throat culture results only.

Main Outcome Measures Sensitivity and specificity of each strategy for identifying GAS pharyngitis, total antibiotics recommended, and unnecessary antibiotic prescriptions.

Results In children, sensitivity for streptococcal infection ranged from 85.8% (133/155; 95% confidence interval [CI], 79.3%-90.0%) for rapid testing to 100% for culturing all. In adults, sensitivity ranged from 76.7% (56/73; 95% CI, 65.4%-85.8%) for rapid testing without culture confirmation of negative results to 100% for culturing all. In children, specificity ranged from 90.3% (270/299; 95% CI, 86.4%-93.4%) for use of modified Centor score and throat culture to 100% for culturing all. In adults, specificity ranged from 43.8% (114/260; 95% CI, 37.7%-50.1%) for empirical treatment based on a modified Centor score of 3 or 4 to 100% for culturing all. Total antibiotic prescriptions were lowest with rapid testing (24.7% [194/787]; 95% CI, 21.7%-27.8%) and highest with empirical treatment of high-risk adults (45.7% [360/787]; 95% CI, 42.2%-49.3%), due to a high rate of unnecessary prescriptions in adults (43.8% [146/333]; 95% CI, 38.4%-49.4%).

Conclusions Guideline recommendations for the selective use of throat cultures but antibiotic treatment based only on positive rapid test or throat culture results can reduce unnecessary use of antibiotics for treatment of pharyngitis. However, empirical treatment of adults having a Centor score of 3 or 4 is associated with a high rate of unnecessary antibiotic use. In children, strategies incorporating throat culture or throat culture confirmation of negative rapid antigen test results are highly sensitive and specific. Throat culture of all adults or those selected on the basis of a clinical prediction rule had the highest sensitivity and specificity.

JAMA. 2004;291:1587-1595 www.jama.com

THE ARGUMENTS PUT FORTH FOR antibacterial treatment of pharyngitis caused by group A streptococcus (GAS) include relief of acute symptoms, prevention of rheumatic fever and suppurative complications, and reduced spread of disease. Treatment of suspected GAS pharyngitis at the time of initial clinical evaluation has a modest effect on acute symptoms and perhaps suppurative complications.[1] However, antibacterial treatment may be delayed for several days and still achieve the goal of preventing rheumatic fever and spread of disease. Due to the nonspecific clinical features of GAS pharyngitis, authorities have generally recommended laboratory confirmation of the presence of GAS before treatment in order to limit unnecessary antibiotic treatment of patients with GAS-negative sore throats.[2]

Recent guidelines from the Infectious Diseases Society of America (IDSA) reiterate 2 principles of management in cases of sore throat: (1) use of clinical and epidemiologic features to distinguish patients who may have GAS pharyngitis; and (2) antibacterial

See also Patient Page.

Author Affiliations are listed at the end of this article.
Corresponding Author: Warren J. McIsaac, MD, MSc, Ray D. Wolfe Department of Family Medicine, Mount Sinai Hospital, 600 University Ave, Toronto, Ontario, Canada M5G 1X5 (wmcisaac@mtsinai.on.ca).

Figure. Modified Centor Score and Culture Management Approach

Criteria	Points
Temperature >38° C	1
Absence of Cough	1
Swollen, Tender Anterior Cervical Nodes	1
Tonsillar Swelling or Exudate	1
Age	
3-14 Years	1
15-44 Years	0
45 Years or Older	−1

Score	Risk of Streptococcal Infection[8,9]	Suggested Management
≤0	1%-2.5%	No Further Testing or Antibiotic
1	5%-10%	
2	11%-17%	Culture All; Antibiotics Only for Positive Culture Results
3	28%-35%	
≥4	51%-53%	Treat Empirically With Antibiotics and/or Culture

The original Centor score[10] provides an estimate for the probability of a positive culture and applies to adults only. One point is assigned to each of 4 criteria: temperature >38°C; absence of cough; swollen, tender anterior cervical nodes; and tonsillar exudate. The probability of a positive culture result for a Centor score of 0 is 2.5%; for a score of 1, 6%-6.9%; for a score of 2, 14.1%-16.6%; for a score of 3, 30.1%-34.1%; and for a score of 4, 55.7%. Adapted with permission.[8]

treatment only for cases confirmed with a laboratory test (culture or rapid test).[3] In contrast, a position paper by the American College of Physicians–American Society of Internal Medicine/American Academy of Family Physicians/US Centers for Disease Control and Prevention (ASIM), while endorsing the IDSA approach in children, recommends a departure from the principle of laboratory confirmation of all adult cases with 2 new recommendations to use a clinical prediction rule (ie, the Centor score) to determine whom to test or treat directly.[1]

Other approaches to the management of pharyngitis have also been proposed.[4-6] The use of high-sensitivity rapid antigen testing without confirmatory cultures for negative test results in children, as well as adults, has been suggested.[4,5] In a study of more than 30 000 children and adults managed on the basis of rapid testing alone, no difference was found in the rate of suppurative and nonsuppurative complications compared with cases managed on the basis of routine use of throat cultures.[4] Rapid testing without confirmatory cultures was also found to be cost-effective in children in whom the prevention of rheumatic fever was the primary goal.[5] Also, clinical prediction rules have been evaluated for use in the management of pharyngitis in children as well as adults.[6]

Prospective studies to compare the impact of various pharyngitis management strategies on clinically relevant outcomes have been recommended.[1,7] A particular focus of recent guidelines has been reducing overall use of antibiotics for treatment of pharyngitis in both children and adults in order to limit antibiotic resistance.[1,3] The objective of this study was to prospectively assess the impact of different clinical policies on the appropriateness of antibiotics prescribed, the proportion of GAS pharyngitis cases identified, and the use of throat cultures and rapid tests in a population of children and adults with a chief complaint of sore throat.

METHODS

Study Population, Subject Selection, and Procedures

This study was part of an unpublished clinical trial comparing 2 different antibacterial therapies for GAS pharyngitis in children and adults conducted at the Crowfoot Village Family Practice in Calgary, Alberta. The practice has 5 family physicians and serves approximately 11 500 people. Patients from 3 to 69 years of age with acute sore throat were screened for their eligibility for the trial by a physician or study nurse using clinical information obtained as part of routine care, and a throat swab was collected when the physician believed it was warranted. A second throat swab was collected at the same time to perform a rapid test. The clinical information was used to derive a clinical score result predicting the likelihood of a GAS-positive culture.[8,9] The results of the clinical score, rapid test, and throat culture were used in the present analysis. The study was approved by the University of Calgary Conjoint Health Research Ethics Board. Because data for this study were collected as part of routine care, informed consent was not required, although written informed consent was obtained for the clinical trial.

The clinical score used was a modification of the Centor score recommended in the ASIM guideline.[1] While the Centor score was developed for use in adults,[6,10] a modified Centor score has been validated for use in both children and adults with sore throat and provides similar results (FIGURE).[6,8,9] The probability of an adult with a Centor score of 1 or less having a culture positive for the presence of GAS is less than 10%.[10] An adult with a modified Centor score of 1 or less also has a less than 10% probability of a GAS-positive culture result.[8,9] In adults only, a Centor score of 2 to 4 is associated with a 14% to 56% probability for having a positive culture result,[10] compared with a 9% to 57% probability of a positive result with a modified Centor score of 2 to 5.[8]

Both the IDSA and the ASIM guidelines support the use of clinical scoring systems to identify persons at low risk for GAS pharyngitis such that further testing is unnecessary.[1,3] The ASIM guideline specifies a Centor score of 1 or less as an appropriate level for exclusion from further testing.[1] To be eligible for the trial, persons had to have an acute sore throat and a modified Centor score of 2 or more.

The rapid test used was the Abbott TestPack Plus Strep A w/OBC [On Board Controls] II (Abbott Laboratories, Montréal, Québec), a rapid enzyme-linked immunosorbent assay kit with a reported 89.9% sensitivity and 95.8% specificity for detecting GAS compared with a criterion standard of throat culture.[11] Throat cultures were performed by the Calgary Laboratory Services central microbiology laboratory using standard methods (streaking and stabbing sheep blood agar plates incubated anaerobically at 35°C, with confirmation of β-hemolytic colonies as GAS using latex agglutination [PathoDx Strep A Typing, Diagnostic Products Corp, Los Angeles, Calif] and amount of GAS growth quantified as scant to heavy).

Comparison of Pharyngitis Guidelines and Empirical Strategies

The strategies compared are shown in the BOX. The criterion standard against which each strategy was compared was a routine throat culture for each person with a sore throat (strategy 1). Because 3 approaches are possible under ASIM recommendations,[1] a separate strategy was modeled for each (strategies 2, 3, and 4). These approaches apply to adults only. For children, the ASIM report supports IDSA recommendations to perform rapid test on all children, treating those having positive test results and obtaining a throat culture for those with negative results.[1] Therefore, in assessing the ASIM strategies, the IDSA recommendations were applied to children in the cohort to determine the overall effect on prescribing and other outcomes for the entire study sample. Strategy 2 involves performing a rapid test on all adults and treating those having positive results without culture confirmation of negative results. Strategy 3 involves performing a rapid test on adults having a modified Centor score of 2 or 3 and treating those having positive results and those having a score of 4 or more without further testing. Strategy 4 proposes no further testing but treatment of all those having a modified Centor score of 3 or more. The final 2 strategies differ in their approach to children. Strategy 5 is similar to strategy 3, except that it uses a validated clinical score combined with selective use of throat culture for children as well as adults. Strategy 6 is similar to strategy 2 in the use of a high-sensitivity rapid test alone for children as well as adults.[4,5] For each strategy, it was assumed that antibiotics would have been prescribed to children and adults with a positive throat culture result, positive rapid test result, or modified Centor score of 3 or 4, as applicable.

Box. Management Strategies in Children and Adults Having Acute Sore Throat and Modified Centor Score of 2 or More

Strategy 1 (Standard Approach)

Obtain a throat culture in all children and adults with sore throat and treat only those having a positive culture result.

Strategy 2 (IDSA/ASIM$_1$)

Perform rapid test on all children and treat those having positive results; perform throat culture on those with negative rapid test results and treat any having positive culture results; perform rapid test on all adults and treat those having positive rapid test results without culture confirmation of negative results.

Strategy 3 (ASIM$_2$)

Treat children per IDSA recommendations. Perform rapid test on all adults having a Centor score of 2 or 3 and treat those with positive rapid test results; treat all adults having a score of 4 or more empirically.

Strategy 4 (ASIM$_3$)

Treat children per IDSA recommendations. Test no adults and treat those having a Centor score of 3 or 4 empirically.

Strategy 5 (Modified Centor Score and Culture Approach)

Perform throat culture on all children and adults having a Centor score of 2 or 3 and treat those having positive culture results. Treat those having a score of 4 or more empirically.

Strategy 6 (Rapid Test Approach)

Perform rapid test on all children and adults and treat those having positive results without culture confirmation of negative results.

The modified Centor score[8,9] was used to approximate the Centor score.[10] ASIM indicates American College of Physicians–American Society of Internal Medicine/American Academy of Family Physicians/US Centers for Disease Control and Prevention; IDSA, Infectious Diseases Society of America.

Statistical Analysis

The main outcomes assessed were the sensitivity and specificity of each strategy for identifying GAS pharyngitis compared with a criterion standard of a single throat culture, the proportion of visits in which an antibiotic was prescribed, and the total proportion of unnecessary antibiotics prescribed to persons with GAS-negative culture results. Secondary outcomes included the proportion of cases requiring a throat culture or rapid test, the proportion of patients with GAS pharyngitis receiving an antibiotic prescription at the initial visit, and the proportion requiring a follow-up telephone call after a positive culture result if not initially treated. Statistical analysis included the use of proportions with exact binomial confidence intervals to describe categorical variables. All statistical analyses were performed using STATA release 6.0 (STATA Corp, College Station, Tex).

RESULTS

From September 1999 to August 2002, 918 persons were screened. Complete data were available for 787 (86%). The median age of the sample was 16 years (range, 3-69 years), with 454 persons (57.7%) aged 3 to 17 years and 333 persons (42.3%) aged 18 to 69 years. For this analysis, adults were considered to be those 18 years or older, consistent with the ASIM guideline.[1]

The prevalence of positive throat culture results overall was 29.0% (228/787) (TABLE 1). The proportion of positive culture results in children was 34.1% (155/454), compared with 21.9% (73/333) in adults. A higher proportion of children (67.8%) with positive culture results had a modified Centor score of 4 or 5 compared with published estimates (51.3%)[8]; among adults with positive culture results, the proportion was lower than published estimates (30.8% vs 57.1%).[8]

A positive rapid test result was obtained in 194 persons (24.7%). The sensitivity was 82.9%; specificity, 99.1%; and

negative predictive value, 93.4%. For the total study population, all strategies had a sensitivity of greater than 90% for identifying GAS pharyngitis (TABLE 2), except strategy 6 (rapid test only), which had a sensitivity of 82.9% (189/228). Sensitivities were lower (76.7%-78.1%) in adults for strategies not recommending throat cultures (strategies 2, 3, 4, and 6), compared with strategies that included a throat culture (strategies 1 and 5). The lowest sensitivity in children was 85.8% (133/155), which was observed for rapid testing without confirmation by throat culture (strategy 6). The specificities of all strategies were greater than 90%, except for strategy 4 (ie, in children, perform a rapid test and obtain a culture from those with negative results, but treat adults based on score results only), which had a specificity of 73.3% (410/559) for the total population. When only adults were considered, the specificity of this strategy was 43.8% (114/260).

The proportion of the total sample that would have received antibiotics with each approach ranged from 24.7% to 45.7% (TABLE 3). The highest prescribing rate (45.7% [360/787]) was associated with strategy 4 (ie, in children, perform a rapid test and obtain a culture from those with negative results, but treat adults based on score results only). In adults, this approach would result in 60.7% (202/333) being prescribed antibiotics. The highest prescribing rate in children (40.5% [184/454]) was associated with the modified Centor score (strategy 5) compared with culturing all children (34.1%; 155/454). Unnecessary antibiotic prescriptions were also highest with these strategies (18.9% for strategy 4; 4.8% for strategy 5). In adults, unnecessary prescribing was highest with strategy 4 (43.8% [146/333]), while in children unnecessary prescribing was highest with strategy 5 (6.4% [29/454]).

The modified Centor score (strategy 5) would result in the least number of tests (cultures and rapid tests) per person (0.87) but would require 96.1% (320/333) of adults to undergo a throat culture (TABLE 4). There was less difference in the proportion of children required to undergo throat culture testing with different strategies (70.0% [318/454] for strategies 2, 3, and 4 compared with 80.2% [364/454] for strategy 5 based on the clinical score). Strategies 2, 3, and 4 involved fewer throat cultures overall (40.4%, all children) but required more persons to undergo rapid testing, resulting in a greater number of tests per person (0.98-1.4). These strategies all required fewer telephone follow-up calls (2.8% [22/787]; all chil-

Table 1. Throat Culture Results for Children and Adults Having Acute Sore Throat, by Age Group and Clinical Score Result (Modified Centor Score ≥2)

	Total, No. (%)	GAS-Positive, No. (% [95% CI])
All ages (N = 787)		228 (29.0 [25.8-32.3])
Score 2	219 (27.8)	35 (16.0 [11.4-21.5])
Score 3	465 (59.1)	128 (27.5 [23.5-31.8])
Score 4-5	103 (13.1)	65 (63.1 [53.0-72.4])
Ages 3-17 y (n = 454)		155 (34.1 [29.8-38.7])
Score 2	88 (19.4)	18 (20.5 [12.6-30.4])
Score 3	276 (60.8)	76 (27.5 [22.4-33.2])
Score 4-5	90 (19.8)	61 (67.8 [57.1-77.2])
Ages ≥18 y (n = 333)		73 (21.9 [17.6-26.8])
Score 2	131 (39.3)	17 (13.0 [7.7-20.0])
Score 3	189 (56.8)	52 (27.5 [21.3-34.5])
Score 4-5	13 (3.9)	4 (30.8 [9.1-61.4])

Abbreviations: CI, confidence interval; GAS, group A streptococcus.

Table 2. Impact of Various Strategies for the Management of Sore Throat in Children and Adults on Identification of GAS Pharyngitis

	No. (% [95% CI])	
Outcome	Sensitivity (Cases of GAS Pharyngitis)	Specificity (Negative GAS Results)
Entire sample	n = 228	n = 559
Culture all (strategy 1)	228 (100.0)	559 (100.0)
IDSA/ASIM$_1$ (strategy 2)	211 (92.5 [88.3-95.6])	554 (99.1 [97.9-99.7])
ASIM$_2$ (strategy 3)	212 (93.0 [88.9-95.9])	545 (97.5 [95.8-98.6])
ASIM$_3$ (strategy 4)	211 (92.5 [88.3-95.6])	410 (73.3 [69.5-77.0])
Modified score and culture approach (strategy 5)	228 (100.0)	521 (93.2 [90.8-95.1])
Rapid test (strategy 6)	189 (82.9 [77.4-87.5])	554 (99.1 [97.9-99.7])
Children	n = 155	n = 299
Culture all (strategy 1)	155 (100.0)	299 (100.0)
IDSA/ASIM$_1$ (strategy 2)	155 (100.0)	296 (99.0 [97.1-99.8])
ASIM$_2$ (strategy 3)	155 (100.0)	296 (99.0 [97.1-99.8])
ASIM$_3$ (strategy 4)	155 (100.0)	296 (99.0 [97.1-99.8])
Modified score and culture approach (strategy 5)	155 (100.0)	270 (90.3 [86.4-93.4])
Rapid test (strategy 6)	133 (85.8 [79.3-90.9])	296 (99.0 [97.1-99.8])
Adults	n = 73	n = 260
Culture all (strategy 1)	73 (100.0)	260 (100.0)
IDSA/ASIM$_1$ (strategy 2)	56 (76.7 [65.4-85.8])	258 (99.2 [97.2-99.9])
ASIM$_2$ (strategy 3)	57 (78.1 [66.9-86.9])	249 (95.8 [92.6-97.9])
ASIM$_3$ (strategy 4)	56 (76.7 [65.4-85.8])	114 (43.8 [37.7-50.1])
Modified score and culture approach (strategy 5)	73 (100.0)	251 (96.5 [93.5-98.4])
Rapid test (strategy 6)	56 (76.7 [65.4-85.8])	258 (99.2 [97.2-99.9])

Abbreviations: ASIM, American College of Physicians–American Society of Internal Medicine/American Academy of Family Physicians/US Centers for Disease Control and Prevention; CI, confidence interval; GAS, group A streptococcus; IDSA, Infectious Diseases Society of America.

dren) for an untreated positive throat culture compared with either the modified Centor score (strategy 5) (20.7% [163/787]) or culturing all persons with a sore throat (strategy 1) (29.0% [228/787]) (TABLE 5). A greater proportion of children and adults with GAS pharyngitis would receive immediate antibiotic treatment under strategies 2, 3, and 4 or use of rapid tests alone (strategy 6) than with routine throat cultures or use of the modified Centor score.

COMMENT

Current guidelines for the management of GAS pharyngitis vary with regard to recommendations concerning empirical antibiotic therapy and the need for confirmatory testing using throat culture.[1,3] While the IDSA guideline supports omitting throat cultures in children or adults at a very low risk of streptococcal infection and in adults with a negative rapid test result, it recommends prescribing antibiotics to those with a positive rapid test or throat culture result only.[3] The ASIM guideline allows for empirical antibiotic treatment in adults based on clinical findings.[1] This study illustrates that there are tradeoffs between these and other management approaches in terms of unnecessary antibiotic prescriptions, the identification of GAS pharyngitis, the burden of office-based testing, convenience of immediate treatment, and the need for telephone follow-up. However, based solely on sensitivity and specificity, strategies for children that require a throat culture or culture confirmation of a negative rapid test result are 100% sensitive and 99% to 100% specific. In adults, strategies that recommend throat culture for all adults or only for those selected on the basis of a clinical prediction rule are 100% sensitive and 96% to 100% specific.

A major concern of recent guideline statements has been the volume of antibiotics prescribed to patients with pharyngitis.[1] An estimated 6.7 million health care visits are made by adults with a sore throat in the United States annually; between 1989 and 1999, 70% of adults presenting with sore throat received an antibiotic prescription.[12] While recent trends suggest a decline in use of antibiotics in children and adolescents with pharyngitis, 68.6% continued to receive a prescription in 1999-2000.[13] In contrast, the proportion of GAS pharyngitis cases in family practice settings has remained relatively constant at 10% to 20% over the last 25 years.[14-16] Under most strategies evaluated, antibiotic use for pharyngitis would be significantly reduced in both children and adults. However, the ASIM strategy of empirical antibiotic treatment of adults having a modified Centor score of 3 or greater without any testing (strategy 4) could result in 60% of adults with a sore throat continuing to receive antibiotics and 40% receiving a prescription unnecessarily. A previous analysis estimated that 60% of antibiotics prescribed to adults using this approach would be unnecessary.[7] All other strategies would result in levels of antibiotic use similar to what would result by obtaining a throat culture for every sore throat.

Although reducing unnecessary use of antibiotics for treatment of pharyngitis has become a priority as a result of the problem of antibiotic resistance, the appropriate treatment of cases of GAS pharyngitis remains a relevant consideration.[2,3] Not all of the strategies evaluated were optimal in detecting cases of GAS pharyngitis. Only the standard approach of obtaining a throat culture for every sore throat and the modified Centor score and culture approach (strategy 5) would result in all cases of GAS pharyngitis being identified. While the IDSA and ASIM strategies would identify all cases of GAS pharyngitis in children, almost one quarter of cases in adults would be missed using any of the strategies with

Table 3. Impact of Various Strategies for Management of Children and Adults Having Sore Throat on Overall Antibiotic Prescriptions and Unnecessary Use of Antibiotics

Outcome	No. (% [95% CI])	
	Total Antibiotic Prescriptions	Unnecessary Antibiotics*
Entire sample (N = 787)		
Culture all (strategy 1)	228 (29.0 [25.8-32.3])	0
IDSA/ASIM$_1$ (strategy 2)	216 (27.4 [24.4-30.7])	5 (0.6 [0.2-1.5])
ASIM$_2$ (strategy 3)	226 (28.7 [25.6-32.0])	14 (1.8 [1.0-3.0])
ASIM$_3$ (strategy 4)	360 (45.7 [42.2-49.3])	149 (18.9 [16.3-21.8])
Modified score and culture approach (strategy 5)	266 (33.8 [30.5-37.2])	38 (4.8 [3.4-6.6])
Rapid test (strategy 6)	194 (24.7 [21.7-27.8])	5 (0.6 [0.2-1.5])
Children (n = 454)		
Culture all (strategy 1)	155 (34.1 [29.8-38.7])	0
IDSA/ASIM$_1$ (strategy 2)	158 (34.8 [30.4-39.4])	3 (0.7 [0.1-1.9])
ASIM$_2$ (strategy 3)	158 (34.8 [30.4-39.4])	3 (0.7 [0.1-1.9])
ASIM$_3$ (strategy 4)	158 (34.8 [30.4-39.4])	3 (0.7 [0.1-1.9])
Modified score and culture approach (strategy 5)	184 (40.5 [36.0-45.2])	29 (6.4 [4.3-9.0])
Rapid test (strategy 6)	136 (30.0 [25.8-34.4])	3 (0.7 [0.1-1.9])
Adults (n = 333)		
Culture all (strategy 1)	73 (21.9 [17.6-26.8])	0
IDSA/ASIM$_1$ (strategy 2)	58 (17.4 [13.5-21.9])	2 (0.6 [0.1-2.2])
ASIM$_2$ (strategy 3)	68 (20.4 [16.2-25.2])	11 (3.3 [1.7-5.8])
ASIM$_3$ (strategy 4)	202 (60.7 [55.2-65.9])	146 (43.8 [38.4-49.4])
Modified score and culture approach (strategy 5)	82 (24.6 [20.1-29.6])	9 (2.7 [1.2-5.1])
Rapid test (strategy 6)	58 (17.4 [13.5-21.9])	2 (0.6 [0.1-2.2])

Abbreviations: ASIM, American College of Physicians-American Society of Internal Medicine/American Academy of Family Physicians/US Centers for Disease Control and Prevention; CI, confidence interval; IDSA, Infectious Diseases Society of America.
*Defined as the proportion of visits in which an antibiotic was prescribed and the throat culture was negative for group A streptococcus.

rapid testing without throat culture confirmation of negative results. However, this is likely an underestimate of the true proportion of missed cases in adults, as the study population was selected on the basis of having had a modified Centor score of 2 or more.

Previous studies have found that as many as 25% to 30% of all GAS-positive culture results in adults with pharyngitis may occur in those with a modified Centor score less than 2.[8,9] This suggests that if those with a score of 2 or less are omitted from further testing, the IDSA and ASIM strategies of not confirming negative rapid test results in adults may identify no more than 60% of GAS-positive cultures that occur in unselected adults presenting with a sore throat. Current opinion is that the clinical impact of not confirming negative rapid test results in adults is limited.[3,4] However, if only 60% of GAS cases are being identified, the risk of missing rare suppurative or nonsuppurative complications (eg, rheumatic fever) in adults may be greater than assumed. Alternatively, the risk of such complications may be so low that treatment of 50% or even 40% would be sufficient if prevention of rheumatic fever is the goal of treatment of adult pharyngitis. Symptom relief is another justification for antibiotic treatment in adults, but the benefit is likely confined to those with fevers occuring early in their illness.[17] This is primarily those adults with a Centor score of 3 or 4. Rapid testing only this group, with treatment for positive rapid test results, would likely result in substantial reductions in unnecessary use of antibiotics for adults. However, this would be predicated on the absence of rheumatic fever in adults in a given community.

Table 4. Impact of Various Strategies for the Management of Children and Adults Having Sore Throat on Use of Diagnostic Tests*

Outcome	No. (% [95% CI])
Throat cultures	
Entire sample (N = 787)	
Culture all (strategy 1)	787 (100.0)
IDSA/ASIM$_1$ (strategy 2)	318 (40.4 [37.0-43.9])
ASIM$_2$ (strategy 3)	318 (40.4 [37.0-43.9])
ASIM$_3$ (strategy 4)	318 (40.4 [37.0-43.9])
Modified score and culture approach (strategy 5)	684 (86.9 [84.4-89.2])
Rapid test (strategy 6)	0
Children (n = 454)	
Culture all (strategy 1)	454 (100.0)
IDSA/ASIM$_1$ (strategy 2)	318 (70.0 [65.6-74.2])
ASIM$_2$ (strategy 3)	318 (70.0 [65.6-74.2])
ASIM$_3$ (strategy 4)	318 (70.0 [65.6-74.2])
Modified score and culture approach (strategy 5)	364 (80.2 [76.2-83.7])
Rapid test (strategy 6)	0
Adults (n = 333)	
Culture all (strategy 1)	333 (100.0)
IDSA/ASIM$_1$ (strategy 2)	0
ASIM$_2$ (strategy 3)	0
ASIM$_3$ (strategy 4)	0
Modified score and culture approach (strategy 5)	320 (96.1 [93.4-97.9])
Rapid test (strategy 6)	0
Rapid tests	
Entire sample (N = 787)	
Culture all (strategy 1)	0
IDSA/ASIM$_1$ (strategy 2)	787 (100.0)
ASIM$_2$ (strategy 3)	774 (98.3 [97.2-99.1])
ASIM$_3$ (strategy 4)	454 (57.7 [54.1-61.2])
Modified score and culture approach (strategy 5)	0
Rapid test (strategy 6)	787 (100.0)
Children (n = 454)	
Culture all (strategy 1)	0
IDSA/ASIM$_1$ (strategy 2)	454 (100.0)
ASIM$_2$ (strategy 3)	454 (100.0)
ASIM$_3$ (strategy 4)	454 (100.0)
Modified score and culture approach (strategy 5)	0
Rapid test (strategy 6)	454 (100.0)
Adults (n = 333)	
Culture all (strategy 1)	0
IDSA/ASIM$_1$ (strategy 2)	333 (100.0)
ASIM$_2$ (strategy 3)	320 (96.1 [93.4-97.9])
ASIM$_3$ (strategy 4)	0
Modified score and culture approach (strategy 5)	0
Rapid test (strategy 6)	333 (100.0)

*See Table 2 footnote for abbreviations.

The timely treatment of GAS pharyngitis was considered a secondary outcome, as antibiotic treatment within 9 days is sufficient to prevent rheumatic fever.[3] However, strategies that incorporate rapid testing can provide patients with immediate treatment, which may offer symptom relief for those with fevers or those early in their illness.[17-19] Physicians and their staffs are saved the work of contacting patients with a positive throat culture result in order to initiate treatment. However, the reduction in telephone follow-up may be offset by the additional work of conducting rapid tests in an office setting. Only 1 out of 5 patients with sore throat would have required a telephone follow-up call with the score approach, but 58% to 100% of patients would need rapid testing with the IDSA or ASIM strategies. Nonetheless, rapid testing may be advantageous in settings such as emergency departments, where follow-up may be difficult.

The IDSA strategy requires all children and adults to undergo rapid test-

ing. In addition, 70% of children will require confirmatory throat cultures for negative rapid test results. However, one study reported that a diagnostic test was performed in only 22% of office encounters for tonsillopharyngitis in children, and in 36% of the cases of sore throat.[20] Fewer than 1% of encounters included both rapid tests and throat cultures. Family physicians may be even less likely than pediatricians to use diagnostic tests in the evaluation of pharyngitis.[21] In addition, a study of 790 laboratories found that more than half do not confirm negative rapid test results with throat cultures.[22] Despite these practices, rheumatic fever remains rare in developed countries.[23] This may raise questions about the necessity of proposing high levels of diagnostic testing and about the likelihood that such recommendations will be followed. The modified Centor score approach may provide a compromise in that it required the least level of diagnostic testing, provided a sensitivity of 100% and a specificity of greater than 90% in both children and adults, and was associated with significant reductions in unnecessary use of antibiotics compared with current practices.[12,13]

A limitation of the study was the inclusion of only children and adults with a modified Centor score of 2 or more. However, the IDSA guideline supports the use of clinical scoring systems to exclude patients from testing,[3] and the ASIM guideline advises physicians not to test or treat adult patients having fewer than 2 Centor criteria.[1] The modified Centor score used in this study provides estimates for the probability of a GAS-positive culture similar to those provided by the recommended Centor score.[8-10] As a result, the population studied was appropriate to estimate the impact of these guidelines. The effects of these approaches on testing and antibiotic use in clinical practice may be less than those estimated in this study if physicians rely on clinical judgment to determine which children and adults have a high enough likelihood of GAS for application of the guidelines. In particular, clinical judgment has a reduced sensitivity for identifying GAS pharyngitis in children.[9,24,25]

The proportion of persons with a positive throat culture result who would be recommended for empirical antibiotic treatment under the score approach (modified Centor score of 4 or more) differed somewhat from published estimates.[8,9] Children were more likely to have a GAS-positive culture result than was estimated in an earlier study (68% vs 51%),[8] while adults were less likely to have a positive result (31%

Table 5. Impact of Various Strategies for the Management of Children and Adults Having Sore Throat on Early Antibiotic Treatment of GAS Infection and Need for Telephone Follow-up*

Outcome	No. (% [95% CI])
Early Antibiotic Treatment of GAS Infection	
Entire sample (N = 228)	
Culture all (strategy 1)	0
IDSA/ASIM$_1$ (strategy 2)	189 (82.9 [77.4-87.5])
ASIM$_2$ (strategy 3)	190 (83.3 [77.8-87.9])
ASIM$_3$ (strategy 4)	189 (82.9 [77.4-87.5])
Modified score and culture approach (strategy 5)	65 (28.5 [22.7-34.8])
Rapid test (strategy 6)	189 (82.9 [77.4-87.5])
Children (n = 155)	
Culture all (strategy 1)	0
IDSA/ASIM$_1$ (strategy 2)	133 (85.8 [79.3-90.9])
ASIM$_2$ (strategy 3)	133 (85.8 [79.3-90.9])
ASIM$_3$ (strategy 4)	133 (85.8 [79.3-90.9])
Modified score and culture approach (strategy 5)	61 (39.4 [31.6-47.5])
Rapid test (strategy 6)	133 (85.8 [79.3-90.9])
Adults (n = 73)	
Culture all (strategy 1)	0
IDSA/ASIM$_1$ (strategy 2)	56 (76.7 [65.4-85.8])
ASIM$_2$ (strategy 3)	57 (78.1 [66.9-86.9])
ASIM$_3$ (strategy 4)	56 (76.7 [65.4-85.8])
Modified score and culture approach (strategy 5)	4 (5.5 [1.5-13.4])
Rapid test (strategy 6)	56 (76.7 [65.4-85.8])
Need for Telephone Follow-up	
Entire sample (N = 787)	
Culture all (strategy 1)	228 (29.0 [25.8-32.3])
IDSA/ASIM$_1$ (strategy 2)	22 (2.8 [1.8-4.2])
ASIM$_2$ (strategy 3)	22 (2.8 [1.8-4.2])
ASIM$_3$ (strategy 4)	22 (2.8 [1.8-4.2])
Modified score and culture approach (strategy 5)	163 (20.7 [17.9-23.7])
Rapid test (strategy 6)	0
Children (n = 454)	
Culture all (strategy 1)	155 (34.1 [29.8-38.7])
IDSA/ASIM$_1$ (strategy 2)	22 (4.8 [3.1-7.2])
ASIM$_2$ (strategy 3)	22 (4.8 [3.1-7.2])
ASIM$_3$ (strategy 4)	22 (4.8 [3.1-7.2])
Modified score and culture approach (strategy 5)	94 (20.7 [17.1-24.7])
Rapid test (strategy 6)	0
Adults (n = 333)	
Culture all (strategy 1)	73 (21.9 [17.6-26.8])
IDSA/ASIM$_1$ (strategy 2)	0
ASIM$_2$ (strategy 3)	0
ASIM$_3$ (strategy 4)	0
Modified score and culture approach (strategy 5)	69 (20.7 [16.5-25.5])
Rapid test (strategy 6)	0

*See Table 2 footnote for abbreviations.

vs 57%).[8] However, the latter may have been due to the small number of adults in this category. While the decision to prescribe antibiotics in children would not likely be altered owing to the high probability of a positive culture result, a 31% probability of infection in adults may not warrant empirical treatment. This group accounts for only 3% to 10% of adults with a sore throat, however,[8,10] and both overall and unnecessary prescribing of antibiotics in adults under the modified Centor approach were similar to prescribing practices under other strategies. Nonetheless, further validation of the Centor score and the modified Centor score may be appropriate.

An additional limitation may have been the sensitivity of the rapid test used. The sensitivity of the rapid test in the current study was 83%. However, the ASIM guideline advises that throat cultures are unnecessary when the sensitivity of a rapid antigen test exceeds 80%.[1] Similarly, a sensitivity of 80% was used in an analysis of children with pharyngitis that concluded that rapid testing was cost-effective.[5] While higher sensitivities have been reported for some rapid tests,[26] varying test sensitivity between 70% and 100% did not alter one study's conclusion that routine throat cultures were the most cost-effective option in adults.[27] This conclusion was, however, sensitive to the prevalence of GAS pharyngitis in the population, although not within the range generally reported for adult populations.[27]

We were not able to assess the impact of a higher or lower prevalence of GAS pharyngitis because the throat culture reports used to determine the outcomes associated with a given strategy were from individual children and adults. Studies that use decision-analysis simulations generally assume a prevalence of infection for the population as a whole, rather than for individuals, and vary the population prevalence of infection within a plausible range.[5,27] However, when only those with a modified Centor score of 2 or more are considered, the 29% prevalence of GAS pharyngitis in the current study was similar to the rates of 26% to 32% observed in 2 other studies of children and adults.[8,9] These studies had an overall prevalence of GAS pharyngitis similar to that found in other general practice settings,[14-16] which suggests the results are likely applicable to settings with endemic rates of GAS pharyngits.

The selective use of throat cultures as advocated in guidelines for the management of pharyngitis is compatible with a goal of reducing overall and unnecessary use of antibiotics for treatment of pharyngitis. However, empirical antibiotic treatment of adults with a Centor score of 3 or greater as proposed in the ASIM guideline may result in 40% of adults being prescribed antibiotics unnecessarily. Throat cultures, or throat culture confirmation of negative rapid test results, continue to be necessary in children to ensure optimal identification of GAS pharyngitis. While the feasibility of proposing high levels of diagnostic testing may need further assessment, the IDSA guidelines are highly sensitive and specific in children and result in the lowest levels of unnecessary antibiotic use compared with other strategies. Guideline recommendations to not test adults with a low clinical likelihood of GAS pharyngitis and to omit confirmation of negative rapid antigen test results using throat culture may result in a large proportion of cases of GAS pharyngitis being missed.

Author Affiliations: Ray D. Wolfe Department of Family Medicine (Dr McIsaac) and Department of Microbiology (Dr Low), Mount Sinai Hospital, Toronto, Ontario; Departments of Family and Community Medicine (Dr McIsaac) and Laboratory Medicine and Pathobiology (Dr Low), University of Toronto; Department of Pediatrics, Alberta Children's Hospital, and University of Calgary, Calgary, Alberta (Dr Kellner); Department of Family Medicine, Foothills Hospital, Calgary (Dr Aufricht); and Abbott Laboratories, Montréal, Québec (Ms Vanjaka).

Author Contributions: Dr Kellner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.
Study concept and design; statistical expertise: McIsaac, Kellner.
Acquisition of data: McIsaac, Kellner, Aufricht, Vanjaka.
Analysis and interpretation of data: McIsaac, Kellner, Low.
Drafting of the manuscript: McIsaac.
Critical revision of the manuscript for important intellectual content: McIsaac, Kellner, Aufricht, Vanjaka, Low.
Obtained funding: Kellner, Vanjaka.
Administrative, technical, or material support: Vanjaka, Low.
Study Supervision: Kellner, Aufricht.
Funding/Support: This study was funded by Abbott Laboratories, Montréal, Québec.
Role of the Sponsor: Abbott Laboratories had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the review or approval of the manuscript. The contract with Abbott Laboratories required its approval of the manuscript through Ms Vanjaka, but Abbott requested no changes to the manuscript.
Previous Presentation: An abstract of this study was presented at the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 27-30, 2002; San Diego, Calif.
Acknowledgment: Curtis Bell, MD, Stephanie Kubik, MD, Deborah Putnam, MD, and Richard Ward, MD, were the physician coinvestigators. Lorraine Bucholtz, BSc, RN, and Barbara Henwood, RN, were nurse coordinators. Hiu-Yee Kwok managed the database. We thank the clinic staff for their assistance and especially the patients of the Crowfoot Village Family Practice for their willingness to participate in the study.

REFERENCES

1. Cooper RJ, Hoffman JR, Bartlett JG, et al. Principles of appropriate antibiotic use for acute pharyngitis in adults: background. *Ann Intern Med.* 2001; 134:509-517.
2. Dajani A, Taubert K, Ferrieri P, Peter G, Shulman S, and the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, American Heart Association. Treatment of acute streptococcal pharyngitis and prevention of rheumatic fever: a statement for health professionals. *Pediatrics.* 1995;96:758-764.
3. Bisno AL, Gerber MA, Gwaltney JM Jr, Kaplan EL, Schwartz RH. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. *Clin Infect Dis.* 2002;35:113-125.
4. Webb KH, Needham CA, Kurtz SR. Use of a high-sensitivity rapid test without culture confirmation of negative results: 2 years' experience. *J Fam Pract.* 2000; 49:34-38.
5. Ehrlich JE, Demopoulos BP, Daniel KR, Ricarte MC, Glied S. Cost-effectiveness of treatment options for prevention of rheumatic heart disease from group A streptococcal pharyngitis in a pediatric population. *Prev Med.* 2002;35:250-257.
6. Ebell MH, Smith MA, Barry HC, Ives K, Carey M. The rational clinical examination: does this patient have strep throat? *JAMA.* 2000;284:2912-2918.
7. Bisno AL, Peter GS, Kaplan EL. Diagnosis of strep throat in adults: are clinical criteria really good enough? *Clin Infect Dis.* 2002;35:126-129.
8. 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.
9. McIsaac WJ, Goel V, To T, Low DE. The validity of a sore throat score in family practice. *CMAJ.* 2000; 163:811-815.
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: 239-246.
11. Laubscher B, Van Melle G, Dreyfuss N, De Crousaz H. Evaluation of a new immunologic test kit for rapid detection of group A streptococci, the Abbott Testpack Strep A Plus. *J Clin Microbiol.* 1995;33:260-261.
12. Linder JA, Stafford RS. Antibiotic treatment of

adults with sore throat by community primary care physicians: a national survey, 1989-1999. *JAMA.* 2001; 286:1181-1186.
13. McCaig LF, Besser RE, Hughes JM. Trends in antimicrobial prescribing rates for children and adolescents. *JAMA.* 2002;287:3096-3102.
14. Hart WJ. Streptococcal pharyngitis: a demonstration of the inaccuracy of clinical diagnosis without culture. *Can Fam Phys.* 1976;22:34-39.
15. Shank JC, Powell TA. A five-year experience with throat cultures. *J Fam Pract.* 1984;18:857-863.
16. Kljakovic M. Sore throat presentation and management in general practice. *N Z Med J.* 1993;106: 381-383.
17. 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;46:589-593.
18. Randolph MF, Gerber MA, De Meo KK, Wright L. Effect of antibiotic therapy on the clinical course of streptococcal pharyngitis. *J Pediatr.* 1985;106:870-875.
19. El-Daher NT, Hijazi SS, Rawashdeh NM, al-Khalil IA, Abu-Ektaish FM, Abdel-Latif DI. Immediate vs delayed treatment of group A beta-hemolytic streptococcal pharyngitis with penicillin V. *Pediatr Infect Dis J.* 1991;10:126-130.
20. Mainous AG III, Zoorob RJ, Kohrs FP, Hagen MD. Streptococcal diagnostic testing and antibiotics prescribed for pediatric tonsillopharyngitis. *Pediatr Infect Dis J.* 1996;15:806-810.
21. Watson RL, Dowell SF, Jayaraman M, Keyserling H, Kolczak M, Schwartz B. Antimicrobial use for pediatric upper respiratory infections: reported practice, actual practice and parent beliefs. *Pediatrics.* 1999; 104:1251-1257.
22. Dale JC, Novak R, Higgens P, Wahl E. Testing for group A streptococci. *Arch Pathol Lab Med.* 2002; 126:1467-1470.
23. Stollerman GH. Rheumatic fever in the 21st century. *Clin Infect Dis.* 2001;33:806-814.
24. Poses RM, Cebul RD, Collins M, Fager SS. The accuracy of experienced physicians' probability estimates for patients with sore throats: implications for decision making. *JAMA.* 1985;254:925-929.
25. McIsaac WJ, Butler CC. Does clinical error contribute to unnecessary antibiotic use? *Med Decis Making.* 2000;20:33-38.
26. Gerber MA, Tanz RR, Kabat W, et al. Optical immunoassay test for group A beta-hemolytic streptococcal pharyngitis: an office-based, multicenter investigation. *JAMA.* 1997;277:899-903.
27. Neuner JM, Hamel MB, Phillips RS, Bona K, Aronson MD. Diagnosis and management of adults with pharyngitis: a cost-effectiveness analysis. *Ann Intern Med.* 2003;139:113-122.

Security is mostly a superstition. It does not exist in nature. . . . Life is either a daring adventure or nothing.
—Helen Keller (1880-1968)