Diagnosis of Strep Throat in Adults: Are Clinical Criteria Really Good Enough?

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(See the IDSA Guideline by Bisno et al. on pages 113-25)

The clinical manifestations of group A streptococcal and nonstreptococcal pharyngitis overlap quite broadly. For this reason, the updated Infectious Diseases Society of America practice guideline for group A streptococcal pharyngitis, published in this issue of Clinical Infectious Diseases, recommends laboratory confirmation of the clinical diagnosis by means of either throat culture or a rapid antigen detection test. However, a recently published guideline, developed by a subcommittee of the American College of Physicians–American Society of Internal Medicine (ACP-ASIM) in collaboration with the Centers for Disease Control and Prevention, advocates use of a clinical algorithm alone, in lieu of microbiologic testing, for confirmation of the diagnosis in adults for whom the suspicion of streptococcal infection is high. In this discussion, we examine the assumptions of the ACP-ASIM guideline, question whether its recommendations will achieve the stated objective of dramatically decreasing excess antibiotic use, and suggest that its recommendations be confirmed by clinical trials before clinicians abandon long-held teachings regarding diagnosis and management of group A streptococcal pharyngitis.

Acute pharyngitis is one of the most common illnesses for which patients consult physicians in the United States [1]. A multitude of microbial agents are capable of inducing pharyngitis, either as a single manifestation or as part of a more generalized illness [2]. The sore throat, malaise, and fever associated with acute pharyngitis are distressing, but, with few exceptions, this illness is both benign and self-limited. Most cases of acute pharyngitis seen in primary care practice have a viral etiology [3]. Strategies for diagnosis and treatment of acute pharyngeal infection are primarily directed at identifying those patients who require specific antimicrobial therapy and avoiding administration of unnecessary and potentially detrimental treatment to the rest.

The β-hemolytic group A streptococcus (GABHS) is, by far, the commonest bacterial cause of acute pharyngitis, accounting for 15%–30% of cases in children [4] and 5%–10% of cases in adults [5, 6]. Antimicrobial therapy is indicated for “strep throat” to prevent suppurative sequelae and acute rheumatic fever, to limit secondary spread, and (if initiated early) to shorten somewhat the clinical course of the illness.

Given the frequency of strep throat and the voluminous medical literature devoted to this infection over so many decades, it is indeed surprising that so much controversy persists regarding the appropriate diagnosis and management of this common and ubiquitous infection. In this issue of CID, the Infectious Diseases Society of America (IDSA) has published an update of the guidelines for diagnosis and treatment of acute streptococcal pharyngitis [7] that were first published in 1997. The appearance of these revised guidelines brings into perspective important issues and some current controversies related to strep throat.

The clinical manifestations of group A streptococcal and nonstreptococcal pharyngitis overlap quite broadly [8]. Pharyngeal exudate, for example, may be present in more than one-third of patients with non–group A streptococcal pharyngitis [9]. For this reason, authoritative committees of the American Heart Association [10], the American Academy of Pediatrics [11], and the IDSA [7] recommend laboratory confirmation of the clinical diagnosis by means of either throat culture or a rapid antigen detection test (RADT). A positive culture or test result does not
definitively differentiate the acutely infected patient from the *Streptococcus* carrier, but it does prevent unnecessary treatment of the two-thirds or more of patients who test negative for streptococci.

Clinical prediction rules may assist practitioners in estimating the probability that an individual patient has GABHS pharyngitis, and a number of algorithms have been developed for this purpose for both pediatric [12, 13] and adult [5, 14–16] populations. A recently published clinical practice guideline has, however, gone much farther, indicating that a clinical algorithm may be used in lieu of microbiologic testing for confirmation of the diagnosis of GABHS pharyngitis in adults [17]. The guideline, developed by a subcommittee of the American College of Physicians–American Society of Internal Medicine (ACP-ASIM), is also endorsed by the Centers for Disease Control and Prevention (CDC) and the American Academy of Family Practice (AAFP). The authors maintain that the strategy they recommend will result in “dramatically decreasing excess antibiotic use” [17, p. 507]. This is a goal devoutly to be desired, because there are an estimated 6.7 million visits to primary care providers by adults who complain of sore throat each year in the United States, and antibiotics are prescribed at 73% of these visits [18].

It is, therefore, of considerable importance to examine the performance of such algorithms in clinical practice. Several investigators have focused on developing clinically based rules to aid in the diagnosis of GABHS pharyngitis in adults and to help predict the need for antibiotic therapy or further testing. Existing clinical algorithms vary in predictive strength. One model, for example, identified separate risk groups according to the presence or absence of 5 clinical findings [14]. Under the assumption that the true incidence of streptococcal infection among patients with pharyngitis in the population studied (i.e., the prior probability) was 15%, the probabilities of a GABHS-positive throat culture result for the high, medium, and low-risk groups were 28%, 15%, and 4%, respectively. Similarly, another study demonstrated that a relatively high proportion (42%) of patients presenting with tonsillar exudates, anterior cervical lymphadenitis, and fever had cultures positive for GABHS, whereas absence of these signs decreased the probability that the patient had acute streptococcal pharyngitis to 3.4% [5]. Only 2% of the patients, however, manifested all 3 clinical findings.

McIsaac et al. [15] studied children and adults with acute pharyngitis who were seen at a university-affiliated family medicine center. They assigned each patient a score of 0–4 on the basis of the patient’s age as well as the presence of anterior cervical lymphadenitis, tonsillar swelling or exudate, and temperature >38°C and the absence of cough. Of 413 patients in this study aged ≥15 years, 11% had a clinical score of 3 or 4. A score of 4 had a positive predictive value (PPV) of 57% for the presence of GABHS on culture, whereas a score of 3 was associated with a PPV of only 26.7%.

Thus, the performance of these algorithms was similar. They were effective in identifying low-risk patients—that is, those whose chance of having a positive culture result approximated the anticipated asymptomatic carriage rate in the population studied. In contrast, the algorithms were only modestly successful in differentiating streptococcal from non-streptococcal pharyngitis in adults with more-prominent clinical signs and symptoms.

The ACP-ASIM guidelines employ a prediction rule developed by Centor and associates [16]. Those investigators evaluated 234 individuals aged >15 years who presented to the emergency department of the Medical College of Virginia (Richmond) from February through April 1980 with the complaint of sore throat [16]. Throat cultures were found to be positive for GABHS for 17% of patients. The investigators evaluated the predictive value of 4 clinical features (history of fever, tonsillar exudate, anterior cervical lymphadenitis, and absence of cough) and determined PPVs, which ranged from 56% (for patients with all 4 findings present) to 2.5% (for patients with none of the findings present).

The ACP-ASIM guideline for adults is presented in 2 companion articles, in which the management recommendations actually vary slightly [17, 19]. In the article by Snow et al. [17], the recommendations for adult patients with acute pharyngitis are as follows: (a) empirical antibiotic treatment should be administered to adults who meet at least 3 of 4 Centor criteria and should not be administered to all other adults, and (b) empirical antibiotic treatment should be administered to adults who meet all 4 clinical criteria, rapid antigen testing should be performed for patients who meet 3 (or, perhaps, 2) clinical criteria, and administration of antibiotic treatment should be limited to those with positive RADT results.

We agree that adults who meet none or only 1 of the 4 Centor criteria should not be tested or treated because of the very low probability of streptococcal infection, and we agree that results of a highly sensitive RADT may be used as a basis for diagnosis without confirmatory culture results for adult patients. The latter conclusion takes into consideration the relatively low incidence of GABHS pharyngitis in adults, the extremely low risk of a first attack of acute rheumatic fever in adults in the United States at the present time, and the rarity of serious supplicative sequelae. It should be kept in mind, however, that the risk of GABHS pharyngitis is apt to be higher for parents of school-aged children and for adults whose occupation brings them into close association with children.

The ACP-ASIM recommendations regarding management of patients who present with 3 or 4 of the Centor criteria are, however, more problematic, in that they advocate treatment for all adults who have 3 or 4 predictive factors without the requirement for any corroborating microbiologic test results. The authors of the

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ACP-ASIM guideline state that a major goal of their guideline is “dramatically decreasing antibiotic use” [17, p. 507]. In the Centor study, however, only 10% of “adult” patients (i.e., those aged >15 years) with pharyngitis who presented to an urban emergency department manifested all 4 predictive factors [16]; in this group, the probability that a patient would have a throat culture positive for group A streptococci was 56%, a finding almost identical to those of the later study by McIsaac et al. [15]. In the 20% of subjects exhibiting 3 predictive factors, the probability of a positive culture result was only 30%–34%. Therefore, the PPV associated with having either 3 or 4 predictive clinical factors would be ~40%. Consequently, 60% of patients for whom antibiotics are prescribed on the basis of this guideline would have negative results of microbiologic tests (throat culture and/or RADT). Yet the major strategic consideration, surely, should be limitation of excessive and unnecessary prescription of antimicrobials to this age group [18].

Although it is true that the ACP-ASIM guideline allows options for the use of the RADT, it is extremely unlikely that clinicians will elect to perform such a test if statements bearing the imprimatur of the ACP-ASIM, the CDC, and the AAFP allow a decision to be made on clinical grounds alone. Moreover, the message perceived by the practicing community may be simply that microbiologic tests are no longer necessary for adults with acute pharyngitis, even when strict clinical prediction rules are not observed.

Admittedly, this effect may be ameliorated somewhat if further experience with the Centor algorithm determines that it overestimated the number of patients likely to present with 3 or 4 criteria. Indeed, such an overestimation is suggested by findings for the other aforementioned algorithms for adults. It must also be kept in mind, however, that the positive or negative predictive value of an algorithm or a test is strongly influenced by prevalence. Thus, with regard to clinical predictors, the probability of a positive culture might be overestimated for populations with a lower prevalence of streptococcal pharyngitis. For a population with a GABHS prevalence of 5%, for example, the posterior probability of infection was only 24% among patients with all 4 Centor criteria [20]. This finding stands in contrast to a PPV of 56% demonstrated in a population for which 17% of throat cultures were positive for GABHS [16]. Formulae exist that allow correction for differences in prevalence [21]. However, clinicians would have to be familiar with the prevalence of GABHS in the population of interest to predict the effect of pretest probability on predictive values. In contrast, likelihood ratios are less influenced by prior probability and, thus, seem to be more suitable for comparison of the strength of clinical predictors. Unfortunately, only few studies have determined likelihood ratios for comparison of prediction rules.

We must conclude, therefore, that the algorithm-based strategy proposed in the ACP-ASIM guideline would result in the administration of antimicrobial treatment to an unacceptably large number of adults with nonstreptococcal pharyngitis. This is a particularly undesirable result in an age group with low prevalence of streptococcal pharyngitis and its nonsuppurative sequelae. It should be pointed out that the ACP-ASIM clinical practice guideline was not endorsed by the IDSA and, indeed, is at variance with the IDSA’s updated official recommendations [7]. The authors of the ACP-ASIM guideline themselves suggest that “prospective studies should be conducted to compare these strategies in terms of relevant patient outcomes and cost” [19, p. 514]. Should not such studies be completed before established methods of diagnosis and treatment of GABHS pharyngitis in adults are abandoned?

References