Principles of Appropriate Antibiotic Use for Acute Pharyngitis in Adults: Background

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The following principles of appropriate antibiotic use for adults with acute pharyngitis apply to immunocompetent adults without complicated comorbid conditions, such as chronic lung or heart disease, and history of rheumatic fever. They do not apply during known outbreaks of group A streptococcus.

1. Group A β-hemolytic streptococcus (GABHS) is the causal agent in approximately 10% of adult cases of pharyngitis. **The large majority of adults with acute pharyngitis have a self-limited illness, for which supportive care only is needed.**

2. Antibiotic treatment of adult pharyngitis benefits only those patients with GABHS infection. **All patients with pharyngitis should be offered appropriate doses of analgesics and antipyretics, as well as other supportive care.**

3. Limit antibiotic prescriptions to patients who are most likely to have GABHS infection. Clinically screen all adult patients with pharyngitis for the presence of the four Centor criteria: history of fever, tonsillar exudates, no cough, and tender anterior cervical lymphadenopathy (lymphadenitis). Do not test or treat patients with none or only one of these criteria, since these patients are unlikely to have GABHS infection. For patients with two or more criteria the following strategies are appropriate: a) Test patients with two, three, or four criteria by using a rapid antigen test, and limit antibiotic therapy to patients with positive test results; b) test patients with two or three criteria by using a rapid antigen test, and limit antibiotic therapy to patients with positive test results or patients with four criteria; or c) do not use any diagnostic tests, and limit antibiotic therapy to patients with three or four criteria.

4. Throat cultures are not recommended for the routine primary evaluation of adults with pharyngitis or for confirmation of negative results on rapid antigen tests when the test sensitivity exceeds 80%. **Throat cultures may be indicated as part of investigations of outbreaks of GABHS disease, for monitoring the development and spread of antibiotic resistance, or when such pathogens as gonococcus are being considered.**

5. The preferred antibiotic for treatment of acute GABHS pharyngitis is penicillin, or erythromycin in a penicillin-allergic patient.

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1.0 BACKGROUND

Sore throat is one of the most common chief complaints of adults treated in an outpatient setting. Although its differential diagnosis is large and includes many other causes that are important to recognize (**Table**), the vast majority of immunocompetent adults presenting with sore throat have acute infectious pharyngitis. Most of the widespread antibiotic use in such patients is based on an effort to treat bacterial (particularly streptococcal) pharyngitis. Recognition and specific treatment of some of these other sore throat entities are important but are beyond the scope of this paper, which addresses the treatment of nongonococcal, nondiphtherial acute pharyngitis in healthy adults.

1.1 Acute pharyngitis accounts for 1% to 2% of all visits to outpatient departments, physician offices, and emergency departments (1). A wide range of infectious agents, most commonly viruses, cause acute pharyngitis. Approximately 5% to 15% of cases in adults are caused by group A β-hemolytic streptococcus (GABHS) (2–7). In some patients, it can be important to identify an infectious cause other than GABHS (for example, gonococcal pharyngitis, Epstein–Barr virus, and acute HIV infection), but in the vast majority of cases, acute pharyngitis in an otherwise healthy adult is self-limited and rarely produces significant sequelae.

1.2 Antibiotics are prescribed to a substantial majority (approximately 75%) of adult patients with acute

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In addition to the Centers for Disease Control and Prevention, the principles outlined in this document have been endorsed by the American Academy of Family Physicians and the American College of Physicians–American Society of Internal Medicine.

Table. **Differential Diagnosis of Sore Throat in the Immunocompetent Adult**

Epiglottitis
Ludwig angina
Retropharyngeal abscess
Peritonsillar abscess
Thyroiditis
Gastroesophageal reflux
Oropharyngeal or laryngeal tumor
Pharyngitis (infectious, traumatic)

pharyngitis (8). Physicians report that they prescribe unwarranted antibiotics because they believe that patients expect them, that patients will reconsult if antibiotics are not prescribed, that patients will be unsatisfied without a prescription, and that it is quicker to write a prescription than to explain why a prescription is not indicated (9–11). However, physicians are not very good at predicting which patients expect antibiotics (11, 12), and patient satisfaction depends less on whether an antibiotic is prescribed, or even whether preconsultation expectations are met, than on whether the physician shows concern and provides reassurance (9, 11–15). Delaying antibiotic prescriptions does not increase the chance that patients will return in the next few days for reconsultation. Prescribing antibiotics "medicalizes" the illness, and one study found increased likelihood that patients would return for the next similar illness (13, 15, 16). The inappropriate use of antibiotics can have significant negative consequences both to individual patients and to public health.

GOALS

This paper examines the available evidence regarding the diagnosis and treatment of acute GABHS pharyngitis in adult patients. It makes recommendations that balance concerns about the potential consequences of untreated GABHS and the goal of decreasing inappropriate antibiotic prescriptions. It discusses pharyngitis in adults (patients $\geq$ 18 years of age), a population in which GABHS accounts for only approximately 5% to 15% of cases (2–7) and in which such complications as acute rheumatic fever are much less common. These guidelines do not apply to patients with a history of rheumatic fever, valvular heart disease, immunosuppression, or recurrent or chronic pharyngitis (symptoms $>$ 7 days), or to patients whose sore throats have a cause other than acute infectious pharyngitis. They are not intended to apply during a known epidemic of acute rheumatic fever or streptococcal pharyngitis or in nonindustrialized countries in which the endemic rate of acute rheumatic fever is much higher than in the United States. Clinicians should always consider the epidemiologic circumstances when applying these recommendations in practice. Furthermore, these principles are not intended to comment on or contradict previous practice guidelines from other organizations (17, 18), which are primarily directed at sore throat evaluation in children.

2.0 METHODS

We conducted a systematic review of the literature from 1950 to 2000 for these evidence-based management principles. We identified all randomized, controlled trials or meta-analyses of randomized, controlled trials that contained clear definitions of criteria for inclusion, diagnosis, and outcomes, as well as studies evaluating diagnostic strategies for GABHS pharyngitis. We searched MEDLINE and the Cochrane Library, and we also searched the references of the inception articles to identify other studies. Our search strategy sought English-language articles and used the keywords *sore throat*, *group A streptococcus*, *pharyngitis*, *tonsillitis*, *streptococcal pharyngitis*, *throat culture*, and *strep*. Many of the identified articles had easily recognizable methodologic flaws (for example, use of convenience samples, exclusion of patients without a throat culture or those without a positive throat culture, and lack of an appropriate or clearly identified criterion standard), and we considered these limitations when evaluating the evidence and making our recommendations. Furthermore, the efficacy reported in the clinical trials may have been affected in part by repeated clinic visits, repeated cultures, and checks of patient adherence to pill ingestion, all of which would result in overestimation of the effect size of treatment. We did not mathematically summarize the various trials because of the variable quality of the cited evidence.

3.0 EVIDENCE FOR ANTIBIOTIC TREATMENT OF PHARYNGITIS CAUSED BY GABHS

Pharyngitis caused by GABHS is predominantly a disease of children 5 to 15 years of age. It has a prevalence of approximately 30% in pediatric pharyngitis but only 5% to 15% in adult pharyngitis in nonepidemic condi-

tions (2–7, 19, 20). Physicians may consider prescribing antibiotics for streptococcal pharyngitis to prevent rheumatic fever, prevent acute glomerulonephritis, prevent suppurative complications, decrease contagion, and relieve symptoms.

3.1 Acute Rheumatic Fever

Early randomized trials demonstrated that penicillin treatment of streptococcal pharyngitis is effective in preventing acute rheumatic fever (21–23) (relative risk, 0.28 [24]). This translated into a number needed to treat for benefit (NNT_B) of approximately 63 to prevent one case of acute rheumatic fever in the samples studied. These early trials were usually performed in populations with a much higher incidence of acute rheumatic fever in both the treated and control groups than is present today. The reported incidence per population was approximately 60 times greater in 1965 than in 1994 (the last year for which the Centers for Disease Control and Prevention reported statistics); therefore, the NNT_B today is undoubtedly much higher, in the range of approximately 3000 to 4000 (25–27).

Carditis is the most serious complication associated with acute rheumatic fever. In recent outbreaks of acute rheumatic fever, carditis was seen in 50% to 91% of pediatric cases (28–31). These data probably reflect diagnosis of subclinical cases by echocardiography. Carditis occurred in approximately one third of adult cases of acute rheumatic fever (32, 33). The most important consequence of carditis, permanent valvular dysfunction, is most common after clinically severe carditis (28). Given that acute rheumatic fever is rare in adults, that carditis is not a common feature of adult cases of acute rheumatic fever, and that most cases of carditis in adults are mild or asymptomatic, the likelihood of permanent cardiac dysfunction seems to be very small. Thus, the NNT_B to prevent a single case of clinically significant carditis is substantially greater than the NNT_B to prevent a single case of acute rheumatic fever.

During the 1980s, several outbreaks of acute rheumatic fever occurred, causing concern about reemergence of the disease (29–32, 34, 35). It is important to consider local epidemics. Physicians should be prepared to revise their treatment approaches if evidence suggests an outbreak.

3.2 Acute Glomerulonephritis

Although poststreptococcal acute glomerulonephritis occurs, it is extremely rare, even in the absence of antibiotic treatment (36–41). Furthermore, no evidence shows that antibiotic therapy for pharyngitis decreases the incidence of this complication (36–41).

3.3 Peritonsillar Abscess

The incidence of suppurative complications, regardless of treatment with antibiotics, is also low (42–45). A review of randomized trials from the 1950s and 1960s indicates that antibiotics decrease the incidence of peritonsillar abscess ("quinsy") complicating streptococcal pharyngitis (24), with a best estimate for NNT_B of 27. Modern clinical trials (44, 45) provide some evidence that targeting antibiotics to a subset of patients with higher clinical likelihood of GABHS may prevent peritonsillar abscess. However, in another recent review of GABHS pharyngitis in practice, Little and Williamson (46) reported that the risk for peritonsillar abscess was not reduced because many patients did not present for care until after the complication had developed (46). A recent retrospective study of more than 30 000 patients confirms these findings (47). Among patients who developed suppurative complications, 31 of 71 (44%) had them at first presentation (47). Of the other 56% who presented with pharyngitis before subsequent development of peritonsillar abscess, only approximately 25% showed GABHS on culture or rapid antigen test, and most (67%) had been treated with antibiotics that effectively eradicated GABHS.

3.4 Prevention of Spread of Disease

Streptococcal infection often occurs in epidemics, and contagion is a problem in areas of overcrowding or close contact. Although treatment must continue for 10 days, 24 hours of antibiotic therapy greatly reduces the recovery of GABHS from pharyngeal cultures (41, 48–50). While antibiotics are recommended as a means of reducing spread in schools and other closed settings (20), the impact of treatment on disease spread in noninstitutionalized adult populations is unknown. Nevertheless, for clinical decision making, it is reasonable to consider whether an adult is living in close quarters with others, especially small children.

3.5 Relief of Symptoms

Relief of suffering is an appropriate concern of both physicians and patients. Antibiotic therapy instituted within 2 to 3 days of symptom onset hastens symptomatic improvement by 1 to 2 days in patients whose throat cultures ultimately grow GABHS or in populations that have a high likelihood of GABHS pharyngitis identified clinically; however, antibiotics do not have this effect in patients with a negative culture (37, 43–45, 49–52). Few studies have examined the effect of antibiotic treatment on other clinical indicators, such as return to work or to normal activity.

One recent trial among unselected patients with acute pharyngitis found that symptom duration was strongly related to patient satisfaction (13). Satisfaction, in turn, was far more closely related to whether the physician addressed the patient's concerns than to use of antibiotics (15). This further supports limiting antibiotics to the patients most likely to benefit and reemphasizes the importance of the quality of the physician–patient interaction.

TREATING PHARYNGITIS CAUSED BY GABHS: SUMMARY

Antibiotic treatment of GABHS pharyngitis decreases the risk for an extremely rare disease (acute rheumatic fever), decreases the risk for a rare complication (peritonsillar abscess), and decreases duration of some symptoms by 1 to 2 days. Symptomatic improvement seems to depend on whether treatment begins within 48 hours of symptom onset. Because acute rheumatic fever is rare in the United States, patients who decline antibiotic treatment are very unlikely to have measurable adverse consequences. Therefore, it is most appropriate to limit antibiotic therapy to the few adults with a high likelihood of GABHS pharyngitis who are likely to benefit; the epidemiologic circumstances of the patient should also be considered. For example, it may be appropriate to test for and treat GABHS pharyngitis in health care or child care workers, teachers, and parents of young children. Group A β-hemolytic streptococcus is more likely to spread in environments frequented by these patients, and those at risk for exposure may be at greater risk for complications of GABHS infection.

4.0 DIAGNOSING GABHS

The diagnostic accuracy of any test (including a clinical examination) reflects both its sensitivity and specificity. Investigators typically attempt to define the variables of tests to attain high accuracy. At the same time, however, clinicians generally value sensitivity (and the ability to rule out disease) more than specificity. This type of strategy, which minimizes false-negative results at the expense of increased false-positive results, can be appropriate when the consequences of failure to diagnose disease are substantial, and thus the primary goal is to miss the least number of cases.

For a population in which the prevalence of disease is low, a small change in specificity has a far greater effect on overall accuracy than even large changes in sensitivity, because the number of cases is small and the number of patients without disease is large. For example, when the prevalence of disease is 10%, as it is for GABHS in adult pharyngitis, a strategy that evenly sacrifices 1% in specificity to gain 1% in sensitivity would increase the number of false-positive results by nine times as much as it would decrease the number of false-negative results. Pharyngitis caused by GABHS is not highly prevalent in adults, is not life-threatening, rarely has serious sequelae, and is often overtreated in current practice. Therefore, it seems appropriate to design a diagnostic strategy that sacrifices a small degree of sensitivity and allows substantial gains in specificity.

4.1 Diagnosis of GABHS remains a subject of controversy, partly because the best standard for diagnosis has not been definitively established. In addition, tests for significant increases in antistreptolysin titers and use of throat swab cultures cannot provide "real-time" results—that is, results that are available when a decision regarding antibiotics must be made. Because only patients with pharyngitis resulting from GABHS (and a few other rare bacterial causes) benefit from antibiotic therapy, the goal of the diagnostic evaluation is to predict which patients are highly likely to have GABHS pharyngitis.

Recovery of GABHS from throat cultures is reported in many clinical trials and may be the best available predictor of treatment response. Yet the physician should also be aware that results of throat swab cultures vary according to technique, the site in which the sample is obtained and plated (53–55), the culture medium

(56–58), the conditions in which the culture is incubated (53, 56, 58–60), and whether results are checked at 24 or 48 hours (53, 56). Throat swab cultures also fail to distinguish acute infection from the carrier state (37–39, 50, 61, 62). Although we no longer recommend throat swab cultures for routine use, they may be indicated to help investigate outbreaks of GABHS disease and to monitor the development and spread of antibiotic resistance.

4.2 There are several reasonable approaches to the diagnosis of GABHS in an otherwise healthy adult, such as use of rapid antigen testing as an adjunct to clinical screening or use of clinical criteria alone. Either of these strategies is associated with reasonable diagnostic accuracy (approximate sensitivity $\geq 70\%$, specificity $\geq 70\%$) and allows treatment decisions to be made early in the course of illness, when patients can receive symptomatic therapy. In a low-prevalence population, the additional increase in sensitivity obtained by performing throat culture in patients with negative results on rapid antigen tests translates into a small absolute gain in identified GABHS cases. To detect one additional case of GABHS infection, approximately 30 throat cultures would need to be performed on persons with negative results on rapid antigen tests who had at least two clinical signs suggestive of GABHS infection. These data assume that the prevalence of GABHS is 10%, that the sensitivity of the rapid antigen test is 70%, and that 70% of adults have pharyngitis with at least two clinical signs suggestive of GABHS. Furthermore, culture results are not available at the time of the index visit, and a delayed decision about use of antibiotics eliminates the primary benefit of antibiotic therapy in adults, namely symptom relief.

4.2.1 Clinical Prediction

Several clinical findings have some discriminative value in distinguishing GABHS from other causes of acute pharyngitis. The ability of experienced physicians to predict positive throat cultures is moderate, with estimated sensitivity ranging from 55% to 74% and estimated specificity ranging from 58% to 76% (39, 63–65). In an attempt to improve clinical sensitivity and specificity, investigators have developed and tested clinical decision rules based on various constellations of historical and physical signs and symptoms (6, 63, 64, 66, 67). Depending on threshold or cutoff scores, these rules in academic and community practices have a sensitivity of 64% to 83% and a specificity of 67% to 91% for predicting positive throat cultures (6, 7, 45, 64, 68). Although some prediction rules that have nine or more variables with differential weighting may be slightly more accurate than rules containing four or five elements, they are much less practical to remember and use.

The most reliable predictors of GABHS pharyngitis are the Centor criteria (63). These include tonsillar exudates, tender anterior cervical lymphadenopathy or lymphadenitis, absence of cough, and history of fever. The positive and negative predictive values will vary depending on the prevalence of GABHS in the population. However, several studies of adults with pharyngitis indicate that the presence of three or four of these criteria has a positive predictive value of 40% to 60%, and the absence of three or four criteria has a negative predictive value of approximately 80%. Compared with throat culture, the sensitivity and specificity of three or four clinical criteria for identifying GABHS pharyngitis are 75% and 75% (45, 63, 68).

Although clinical screening alone would leave some patients with GABHS untreated and result in overtreatment for other patients, most patients with GABHS would be treated and excess antibiotic use would substantially decrease (69). National estimates suggest that antibiotics are prescribed for approximately three quarters of adults with pharyngitis in the United States (8). A recent study reported that clinical screening could decrease overall antibiotic prescriptions to adults with pharyngitis by 81.5%, thereby decreasing inappropriate antibiotic use by almost 88% (7).

4.2.2 Rapid Antigen Tests

Rapid antigen tests for GABHS, when compared with the "criterion standard" of throat culture, have reported sensitivities of 65% to 91% and specificities of 62% to 97%, depending on the type of test and the practice setting (57, 68, 70–72). These tests can be done during the office visit and allow real-time treatment decisions. The potential advantage of the rapid antigen tests compared with clinical models is that they have approximately the same sensitivity and greater specificity for predicting results of throat culture. The disadvantage is that many patients must be tested to reduce antibiotic

use more than clinical criteria alone. Although rapid antigen testing would further decrease antibiotic prescribing, it would "medicalize" pharyngitis because patients would need to see a physician for the test to be performed.

Limited evidence suggests that rapid antigen tests could be effectively added to clinical criteria in a Bayesian manner, to increase specificity, although this is unlikely to be the case (68). If it is assumed that there is no association between the two prediction methods (although this is unlikely to be the case), performing a rapid antigen test only in patients with an intermediate clinical probability of GABHS (with two or three of the four clinical variables) and withholding antibiotics from those with negative test results would decrease antibiotic use, compared with a clinical decision alone, at the cost of potentially undertreating an additional small group of patients with GABHS. Assuming a rapid antigen test with 80% sensitivity and 90% specificity and a GABHS prevalence of 10%, an antibiotic prescription rate of approximately 10.6% and a testing rate of 70% would be expected if a rapid antigen test was applied to all adults with two or more Centor criteria. This strategy would correctly treat approximately 6 to 7 of 10 patients with GABHS pharyngitis. If adults with four Centor criteria were treated with antibiotics empirically, and only those with two or three Centor criteria were tested, an antibiotic prescription rate of 25% and a testing rate of 55% would be expected. This strategy would correctly treat approximately 7 to 8 of 10 patients with GABHS pharyngitis. In comparison, using similar assumptions, the estimated antibiotic prescription rate would be 33% if patients with three or four criteria were empirically treated.

5.0 Principles

We recommend the following strategies to select patients for antibiotic therapy. These strategies achieve the goal of treating a substantial proportion of true-positive patients while limiting unnecessary antibiotic use. For these strategies, projected antibiotic prescription rates for adults with sore throats in a low-prevalence practice setting are between 10.6% and 33%, much lower than current rates, which exceed 65%. Prospective studies should be conducted to compare these strategies in terms of relevant patient outcomes and cost. The Centers for Disease Control and Prevention strongly recommend that rapid antigen testing remain a reimbursable diagnostic test. The empirical strategy and a test-and-treat strategy, both based on clinical criteria, should provide the clinician with some flexibility to tailor evaluation and treatment strategies to individual patients and practice settings.

Principle 1. Clinically screen all adult patients with pharyngitis for the presence of the four Centor criteria: history of fever, tonsillar exudates, no cough, and tender anterior cervical lymphadenopathy (lymphadenitis) [A]. (Letters in square brackets are evidence ratings. See the background document in this issue [pp 479-486] for explanation. Levels of evidence for treatment strategies reflect efficacy of treatment among selected groups of patients; none of the strategies discussed in this paper have been evaluated prospectively to determine the impact of the selection strategy on adverse outcomes.)

Principle 2. Do not test or treat patients with none or only one of these criteria. These patients are unlikely to have GABHS infections [A].

Principle 3. For patients with two or more criteria, the following strategies are appropriate: a) Test patients with two, three, or four criteria by using a rapid antigen test, and limit antibiotic therapy to patients with positive test results [D]; b) test patients with two or three criteria by using a rapid antigen test, and limit antibiotic therapy to patients with a positive test result or patients with four criteria [D]; or c) do not use any diagnostic tests, and limit antibiotic therapy to patients with three or four criteria [B].

Principle 4. Do not perform throat cultures for the routine primary evaluation of adults with pharyngitis or for confirmation of negative rapid antigen tests when the test sensitivity exceeds 80% [A]. Throat cultures may be indicated as part of investigations of outbreaks of GABHS disease, for monitoring the development and spread of antibiotic resistance, or when such pathogens as gonococcus are being considered [A].

Principle 5. Administer appropriate analgesics, antipyretics, and supportive care to all patients with pharyngitis [A].

6.0 Preferred Choice of Antibiotics

To be precise, all of the evidence showing that treatment of streptococcal pharyngitis prevents acute rheumatic fever was derived from studies involving administration of intramuscular penicillin (21–23). However, other routes of administration are assumed to be equally

efficacious. The appropriate antibiotic for presumed GABHS should be one with a narrow spectrum of action that includes GABHS. Penicillin is therefore the first choice for patients selected for antibiotic therapy. No evidence indicates GABHS resistance to or tolerance of penicillin (73–76). If patients are allergic to penicillin, erythromycin is the preferred alternative in countries where erythromycin-resistant GABHS is uncommon, such as the United States (73). If patients are unable to tolerate erythromycin, a variety of treatment regimens have been proven effective in eradicating GABHS. These regimens have been well summarized in other documents (18, 77) and are beyond the scope of this paper. Issues regarding duration of therapy have been reviewed by others (18) and will not be commented on here. Patients with suspected GABHS pharyngitis should receive 1) a single dose of intramuscular penicillin (1.2 MU for adults) or 2) standard penicillin VK, 500 mg orally twice or three times daily for 10 days.

7.0 Conclusion

In conclusion, the indiscriminate use of antibiotic therapy for adults with pharyngitis is not endorsed. A diagnostic and therapeutic rationale that limits antibiotic therapy to patients most likely to benefit must consider the low prevalence of GABHS pharyngitis in adults, the magnitude of the benefits, and the risks for allergic reaction to therapy and excessive prescribing of antibiotics.

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