

RHEUMATIC FEVER

Relevant Guidelines

ACC/AH 2020 guideline on valve disease

2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease *J Am Coll Cardiol*. 2020

Relevant Scientific Statements and Position Papers

ACC/AHA 2009 statement on rheumatic fever prophylaxis

AHA scientific statement: Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis. *Circulation*. 2009;119:1541-51.

AHA 2015 statement for revision of Jones criteria

Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015;131:1806-18.

RHEUMATIC FEVER

Definition

Acute rheumatic fever (ARF) results from an autoimmune response to infection with group A *Streptococcus pyogenes* (GAS). Although acute illness causes considerable morbidity and some mortality, the major clinical and public-health effects derive from the long-term damage to heart valves-*ie*, rheumatic heart disease (RHD).¹⁻³

Epidemiology

The incidence of acute rheumatic fever varies widely, mainly by socioeconomic development.² In the 2015 Global Burden of Disease Study, there were 33.4 million cases of rheumatic heart disease accounting for approximately 320,000 deaths. The health-related burden of rheumatic heart disease has declined worldwide, but high rates of disease persist in some of the poorest regions in the world.⁴ The annual incidence is estimated as ranging from 8 to 51 per 1000,000 among children and young people.² Rheumatic heart disease patients are usually young, and predominantly female.⁵ Acute rheumatic fever recurrences are highest in the first year after the initial episode, but low-level risk persists for >10 years. Progression to rheumatic heart disease is also highest in the first year, almost 10 times higher than acute rheumatic fever recurrence.⁶ Rheumatic heart disease is the most common cause of cardiovascular morbidity and early mortality in children and young adults worldwide.⁷

Aetiology

Infections of the pharynx with group A beta-hemolytic streptococci (GAS) are the precipitating cause of rheumatic fever. However, only one third of pharyngitis in young children is associated with GAS,⁸ and only 0.3-3% of people with GAS pharyngitis develop ARF.² Streptococcal skin infections (impetigo or pyoderma) have not been proven to lead to acute rheumatic fever, at least in non-tropical countries. Some strains of group A streptococci belonging to certain M serotypes are more likely to cause rheumatic fever, and HLA types and B-cell alloantigens have been associated with increased susceptibility to rheumatic fever and rheumatic carditis.⁹ Up to 0.3- 3% of untreated streptococcal pharyngitis are followed by rheumatic fever, 40-60% of patients with rheumatic fever end-up with carditis, and 60% of those with rheumatic heart disease.⁸ Appropriate therapy prevents rheumatic fever but at least one third of episodes of the disease result from inapparent streptococcal infections.¹

Pathophysiology

The autoimmune response that causes ARF is supposed to be triggered by molecular mimicry between 2 main streptococcal antigens, the surface M protein, and GlcNAc, the immunodominant epitope of the group A carbohydrate, and specific human tissues.³ The “neo-antigen” theory, a more recent development, suggests that the GAS organism gains access to the subendothelial collagen matrix, where M proteins binds to the CB3 region of type IV collagen, creating a neo-antigen that induces an autoimmune response against collagen.³ Valve damage in acute rheumatic fever occurs as a result of both humoral and cellular immune responses against valve proteins. Inflammation leads to neovascularization and healing by fibrosis, causing the characteristic valve lesions of rheumatic heart disease. Patients younger than 10 years predominantly have pure mitral regurgitation. In the second decade of life, rheumatic heart disease is characterized by mixed mitral valve disease. By the third decade, pure mitral stenosis dominates.¹⁰ Rheumatic heart disease is associated with high mortality at a median age of 28.7 years. Complications such as congestive heart failure and stroke affect one-fifth of patients over 2 years.¹¹

Several genes confer susceptibility to acute rheumatic fever and rheumatic heart disease, through alleles that code for proteins involved in both the innate and adaptive immune response to GAS infection. *TLR2* and *FCN2* are involved in pathogen recognition and elimination of bacteria. *MASP2*, *MBL2*, *MIF*, and *FCGR2A* are involved in clearing immune complexes. Several *HLADR* alleles are located in the short arm of chromosome 6 in the *DRB1* gene, of which *HLA-DR7* is the most commonly associated with acute rheumatic fever.²

Presentation

Group A streptococcal pharyngitis is primarily a disease of children 5-15 years of age, usually occurring in winter and early spring. Acute pharyngitis is caused considerably more often by viruses than by bacteria. Viruses that commonly cause pharyngitis include influenza virus, parainfluenza virus, rhinovirus, coronavirus, adenovirus, respiratory syncytial virus, Epstein-Barr virus, enteroviruses, and herpesviruses. Other causes of acute pharyngitis include groups C and G streptococci, *Neisseria gonorrhoeae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Arcanobacterium hemolyticum*, and human immunodeficiency virus (HIV).¹ There is typically sudden onset sore throat, pain on swallowing, fever, headache, and possibly nausea or vomiting. Polyarthralgia and carditis follow afterwards.

Clinical Forms

Carditis, associated with a murmur of valvulitis, occurs in 50-70% of patients and is the most specific manifestation of ARF (Table 1). Approximately 20% of patients with symptomatic rheumatic heart disease are in AF, whereas heart failure may ensue with advanced disease especially with aortic

involvement or dominant regurgitant lesions.³

Polyarthritis is the most common but least specific major manifestation. The classic migratory polyarthritis of the major joints of RF should be distinguished from the post-streptococcal reactive arthritis of the small joints of the hand that does not carry a risk of carditis. However, mono- and polyarthralgia are common, highly nonspecific manifestation of a number of rheumatologic disorders.¹²

Chorea (Sydenham chorea, St Vitus dance, or chorea minor) occurs in about 20% of cases. It is a delayed manifestation of ARF usually appearing ≥ 3 months after the onset of the precipitating streptococcal infection.

Erythema marginatum and *subcutaneous nodules* in the elbows, knees and the occipital portion of the scalp are rare ($<5\%$).

Diagnosis

The differential diagnosis of arthritis, carditis, and chorea is presented in Table 1. The AHA revised Jones criteria and a diagnostic strategy are presented in Table 2, and Figure 1. To avoid over-diagnosis, AHA recommends to consider individuals to be at low risk for ARF if they come from a setting or population known to experience low rates of ARF or rheumatic heart.¹² Children not clearly from a low-risk population are at moderate to high risk depending on their reference population (AHA 2015 statement, IIa-C). Low risk should be defined as having an ARF incidence $<2/100\ 000$ school-aged children (usually 5–14 years old) per year or an all-age prevalence of RHD of ≤ 1 per 1000 population per year.

Echocardiography with Doppler

It is mandatory (AHA 2015 statement, I-B) (Table 3). Echo/Doppler findings not consistent with carditis should exclude that diagnosis in patients with a heart murmur otherwise thought to indicate rheumatic carditis (AHA 2015 statement, I-B).

Throat culture

Microbiological confirmation with either a throat culture or a rapid antigen detection test (RADT) is required for the diagnosis (Class I-B, AHA 2009 statement).¹ In untreated patients with GAS pharyngitis, a properly obtained throat culture (by vigorous swabbing of both tonsils and posterior pharynx) is almost always positive (Table 4). A positive throat culture may reflect chronic colonization by GAS, and cannot be used to differentiate carriage from infection. A negative throat culture permits the physician to withhold antibiotic therapy from the large majority of patients with sore throats. When deciding whether to perform a microbiological test for a patient with acute pharyngitis, the clinical and epidemiological findings in Table 2 need to be considered (AHA 2009 statement, I-B). For patients with acute pharyngitis and clinical and epidemiological findings suggestive of a viral origin, the pretest probability of GAS is low, and testing usually does not need to be performed (AHA 2009 statement, IIb-B).

The use of clinical algorithms without microbiological confirmation has been recently recommended as an acceptable strategy for diagnosing GAS pharyngitis in adults. This approach could result in the receipt of inappropriate antimicrobial therapy by an unacceptably large number of adults with nonstreptococcal pharyngitis and is not recommended (AHA 2009 statement, III-B). However, a strategy of culturing all patients may be prohibitively expensive. Treating all children presenting with pharyngitis in urban primary care clinics in South Africa with intramuscular penicillin was the least costly.¹³ It seems that a strategy of using a clinical decision rule without culturing may be the preferred strategy.

Antigen Detection Tests

Most of these tests have a high degree of specificity, but their sensitivity in clinical practice can be unacceptably low. Treatment is indicated for the patient with acute pharyngitis who has a positive RADT (AHA 2009 statement, I-B). However, as with the throat culture, a positive test may reflect chronic colonization instead of active infection. A negative test does not exclude the presence of GAS, and a throat culture should be performed (AHA 2009 statement, I-B).

Newer tests with improved sensitivity are developed. Physicians who use newer tests without culture backup in children and adolescents should compare the results of that specific RADT with those of blood agar plate cultures to confirm adequate sensitivity in their practice (AHA 2009 statement, IIa-C). Because of the low incidence of GAS infections and extremely low risk of acute rheumatic fever in adults, diagnosis of GAS pharyngitis on the basis of an antigen detection test alone, without confirmation of negative RADT results by a negative throat culture, is reasonable and an acceptable alternative to diagnosis on the basis of throat culture results (AHA 2009 statement, IIa-C).

Streptococcal Antibody Tests

Antistreptococcal antibody titers reflect past and not present immunologic events and therefore cannot be used to determine whether an individual with pharyngitis and GAS in the pharynx is truly infected or merely a streptococcal carrier.

Therapy

The 2009 AHA recommendations are presented in Tables 5-7.¹ Although resistance of GAS strains to penicillin has not been reported, tolerance is well recognised, but its clinical significance is unknown.² Steroids have not proven effective in reducing progression to rheumatic heart disease. Streptococcal infections that occur in family members of patients with current or previous rheumatic fever should also be treated promptly (AHA 2009 statement, I-B).

Prophylaxis

An individual with a previous attack of rheumatic fever in whom GAS pharyngitis develops is at high risk for a recurrent attack of rheumatic fever. A recurrent attack can be associated with worsening of the severity of rheumatic heart disease that developed after a first attack, or less frequently with the new onset of rheumatic heart disease in individuals who did not develop cardiac manifestations during the first attack.¹⁻³ Continuous prophylaxis had been recommended for patients with well-documented histories of rheumatic fever (including cases manifested solely by Sydenham chorea) and those with definite evidence of rheumatic heart disease (ACC/AHA 2020 GL on VHD, I-C-EO), and especially mitral stenosis.^{1,14} The evidence, however, is rather weak, and a short duration of antibiotic prophylaxis (10 years, or up to age 40 years after the index acute rheumatic fever or rheumatic heart disease diagnosis, whichever is later) might also be appropriate. The ACC/AHA 2020 recommendations on antibiotics and duration of prophylaxis are presented in Tables 8 and 9. Such prophylaxis should be initiated as soon as acute rheumatic fever or rheumatic heart disease is diagnosed. A full therapeutic course of penicillin first should be given to patients with acute rheumatic fever to eradicate residual GAS, even if a throat culture is negative at that time. Secondary prevention of rheumatic heart disease has been shown to be cost-effective. However, in the first year after an acute episode, the incidence of progression to rheumatic heart disease is 10 times higher than that of acute rheumatic fever recurrence.⁶ Children with moderate to severe latent rheumatic heart disease have poor outcomes. Although long-term outcome remains unclear, the initial change in latent rheumatic heart disease may be evident during the first 1 to 2 years following diagnosis.¹⁵ In the GOAL randomized trial, secondary antibiotic prophylaxis reduced the risk of progression of latent rheumatic heart disease at 2 years in children and adolescents 5 to 17 years of age.¹⁶

It should be noted that the evidence that community-based programs that focus on the early treatment of GAS pharyngitis are effective in reducing the risk of ARF is limited. The disappearance of ARF in developed countries is most likely the result of changes in streptococcal M-protein types leading to reduced rheumatogenicity.¹⁷

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