CME

Diagnosis, management, and prevention of acute rheumatic fever in the United States

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ABSTRACT

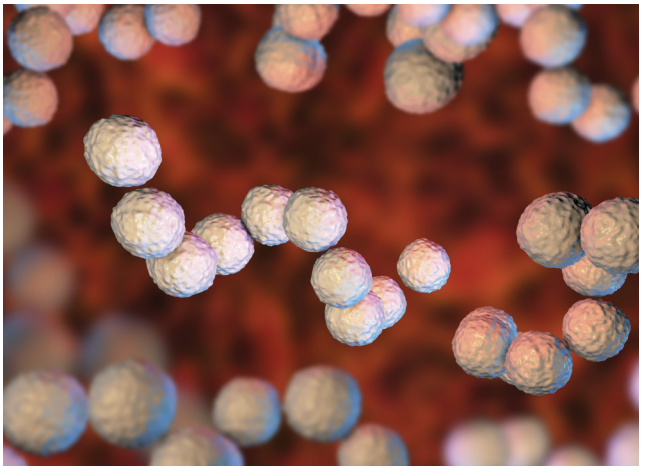
Acute rheumatic fever is a multisystem autoimmune disease caused by infection with group A streptococcus. The condition most commonly affects children ages 5 to 14 years who are from low-income populations. The diagnosis is clinical; however, the 2015 Jones Criteria can help support it. Acute rheumatic fever poses a significant health risk secondary to rheumatic heart disease. Although acute rheumatic fever is rare in the United States, outbreaks still occur, and certain populations continue to be at increased risk. This article describes how to identify acute rheumatic fever and provides prompt management and prevention strategies to reduce patient risk for lifelong complications.

Keywords: acute rheumatic fever, rheumatic heart disease, group A *Streptococcus*, migratory polyarthritis, carditis, Sydenham chorea, erythema marginatum

Learning objectives

- Describe the epidemiology and pathophysiology of acute rheumatic fever.
- Identify the major and minor criteria used to diagnose acute rheumatic fever based on the 2015 Jones Criteria.
- Discuss the main treatment strategies for the major criteria.
- Define primordial, primary, and secondary prevention as it relates to acute rheumatic fever.

Acute rheumatic fever is a multisystem autoimmune response to group A streptococcal infections that mainly affects children and young adults.[1] Although rates of acute rheumatic fever in the United States are low, affecting 0.61 per 100,000 children between 2000 and 2012, outbreaks and individual cases still occur.[2] If misdiagnosed or inadequately managed, acute rheumatic fever may lead to lifelong complications that can result in increased morbidity and mortality.[1] Clinicians who know when to suspect acute rheumatic fever can start appropriate treatment and prevention strategies, reducing their patients' risk for rheumatic heart disease. Proper prevention strategies can help patients avoid significant complications of acute rheumatic fever such as heart failure, valve stenosis, atrial fibrillation, pregnancy difficulties, infective endocarditis, stroke, and premature death.[1,3,4]



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PATHOPHYSIOLOGY

Inadequately treated group A streptococcal infections can trigger acute rheumatic fever in 0.3% to 3% of people, with the fever occurring 2 to 3 weeks after initial infection.[1,3] This risk depends on the patient's immunity, living environment, and the particular strain of group A streptococcus.[5]

Although acute rheumatic fever is not fully understood, it is thought to be caused by antibodies produced against a specific streptococcal protein, protein M, which mimics several different types of proteins in the body.[6] As a result, the body produces an abnormal immune response that leads to inflammation in the brain, heart, joints, and skin.[7] In certain rheumatogenic strains, group A streptococcus contains subtypes of protein M that are more virulent and more likely to result in an autoimmune response.[1,8] Although the process is not fully understood, certain people may be more genetically susceptible to these types of protein M and thus more likely to develop acute rheumatic fever.[1]

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Key points

- Acute rheumatic fever is an inflammatory, autoimmune response to group A streptococcal infections, especially pharyngitis, and is most common in children ages 5 to 14 years.
- Although the disease is rare in the United States, outbreaks still occur and some populations are affected more than others.
- Diagnosis is made using the 2015 Jones Criteria, with the major manifestations being carditis, arthritis, Sydenham chorea, subcutaneous nodules, and erythema marginatum.
- Mainstay of prevention includes improvement of the patient's socioeconomic environment, prompt treatment of the current group A streptococcal infection, and continuous antibiotic therapy for prevention of rheumatic heart disease.

Streptococcus pharyngitis is the most common cause of this response.[1] Skin infections also may trigger acute rheumatic fever, but are not as common.[1] Group C and group B streptococcal infections are not thought to cause acute rheumatic fever.[9] Patients who are asymptomatic carriers of group A streptococcus are not considered at particular risk of developing acute rheumatic fever.[9]

EPIDEMIOLOGY

Children ages 5 to 14 years comprise the population most commonly affected by acute rheumatic fever because of their increased likelihood of developing strep pharyngitis.[1,9] Therefore, rheumatic fever remains the leading cause of heart disease in children and young adults, due to the development of rheumatic heart disease.[10] Acute rheumatic fever rarely affects children younger than age 3 years and adults older than age 30 years.[1,6] The disease can recur often until patients are age 40 years.[1] Incidence is equal among men and women, though women are more likely to develop rheumatic heart disease.[1]

In 2015, an estimated 33 million patients worldwide were affected by acute rheumatic fever, with an additional 320,000 dying each year from rheumatic heart disease.[10] The highest incidence rates of acute rheumatic fever occur in low-income regions, including sub-Saharan Africa, South Asia, American Samoa, and the Pacific Islands.[1,5] In addition, rates of acute rheumatic fever are as high as 17.2 to 194 per 100,000 children in the aboriginal populations of Australia and New Zealand.[1] The rates are estimated to be higher in Africa, but much of the incidence data in Africa are unknown.[10]

Since the 1950s, efforts to reduce poverty and household overcrowding have led to a reduction in cases of acute rheumatic fever in the United States.[11] In addition, proper identification and treatment of streptococcal infections has led to reduced spread of group A streptococcus, reducing the cases of acute rheumatic fever.[9] In the United States, the number of deaths from rheumatic heart disease has been reduced by nearly 50% from 1990 to 2015.[10] However, each year more than 10,000 patients in the United States die from rheumatic heart disease.[12] The actual prevalence may be higher because the United States no longer considers acute rheumatic fever a reportable disease.[2]

Although the overall incidence rate in the United States remains low, outbreaks of acute rheumatic fever still occur, with some populations more endemic than others.[2] In particular, Utah is affected by group A streptococcus at higher rates, about 14 per 100,000 children in 2010, due to higher rates of overcrowding and greater numbers of households with children compared with the rest of the United States.[13] High incidence rates are also seen in Hawaii, Alaska, Mississippi, Alabama, and Kentucky; especially in those of Asian and Pacific Islander descent.[2,12] Increases in immigration also raise the possibility that US clinicians will see more patients with acute rheumatic fever.[10,14]

TABLE 1. Initial testing recommendations for acute rheumatic fever[3,4,6,8,9,15]

Blood tests
- ESR and CRP—acute phase reactants likely will be elevated
- CBC count—may show leukocytosis or anemia
- Creatinine—recommended to monitor kidney function with NSAID treatment
- Pregnancy test—increased demands on the heart during pregnancy increase the risk for rheumatic heart disease

Cardiac evaluation
- ECG—evaluate for prolonged PR interval. Repeat at 2 weeks and 2 months if prolongation is seen.
- Echocardiogram—should be done within 12 weeks of presentation to determine presence of valve disease.
- Chest radiograph—useful in patients with carditis. May see pulmonary infiltrates and cardiac enlargement.

Streptococcal testing
- Rapid strep antigen test or throat culture—indicates a current streptococcal infection
- Anti-streptolysin O (ASO) titer or anti-deoxyribonuclease (DNase) B titer—indicates a past streptococcal infection. Repeat 2 to 4 weeks after initial test. ASO titer rises 1 week after the start of infection and reaches peak elevation at 3 to 6 weeks. Anti-DNase B rises 1 to 2 weeks after the start of infection and reaches peak elevation at 6 to 8 weeks.

DIAGNOSIS

Acute rheumatic fever is a clinical diagnosis; it cannot be definitively detected by laboratory tests alone.[1] However, comprehensive initial testing can be beneficial for all patients when the diagnosis is not clear (**Table 1**).[8] Depending on the patient's symptoms and laboratory results, the Jones Criteria may assist with the diagnosis (**Table 2**).[15] The Jones Criteria have evolved with time, with the most recent modification in 2015 adding specific recommendations for both low-risk and moderate- to high-risk populations.[15]

TABLE 2. Stepwise approach to the diagnosis of acute rheumatic fever[4,15,22]

Step 1. Check for group A streptococcal infection	
Any one of the following: Positive rapid antigen test with appropriate clinical presentation OR Positive throat culture OR Increased or rising ASO or anti-DNase B titers Yes—go to Step 2 No—consider alternate diagnosis	
Step 2. Determine population risk.* Identify number of major and minor manifestations based on appropriate population risk. Go to Step 3.	
Low-risk population *Major criteria* • Carditis** • Polyarthritis*** • Sydenham chorea • Erythema marginatum • Subcutaneous nodules *Minor criteria* • Prolonged PR interval** • Polyarthralgia*** • Fever (38.5° C or greater) • ESR of 60 mm/h or greater and/or CRP of 3 mg/dL or greater	**Moderate- to high-risk population** *Major criteria* • Carditis** • Monoarthritis, polyarthritis, or polyarthralgia*** • Sydenham chorea • Erythema marginatum • Subcutaneous nodules *Minor criteria* • Prolonged PR interval** • Monoarthralgia*** • Fever (38° C or greater) • ESR of 30 mm/h or greater and/or CRP of 3 mg/dL or greater
Number of major criteria met_____ Number of minor criteria met_____	
Step 3. Determine if patient has a history of acute rheumatic fever. Determine if patient meets the needed criteria based on appropriate episode of acute rheumatic fever.	
First episode 2 major OR 1 major and 2 minor criteria	**Second episode** 2 major OR 1 major and 2 minor criteria OR 3 minor criteria****
Yes—acute rheumatic fever confirmed No—consider alternate diagnosis	

*Low-risk population means two or fewer cases of acute rheumatic fever per 100,000 people (or 1 or fewer cases of rheumatic heart disease per 1,000 people).
**Carditis and prolonged PR interval cannot be used in the same patient.
***Arthritis and arthralgia cannot be used in the same patient.
****Only use if all other possible diagnoses can be excluded.

The United States is considered a low-risk population, as its incidence of acute rheumatic fever remains below 2 cases per 100,000 people.[5,15] However, if the patient is from a moderate- or high-risk population, the patient's individual risk should be based on state of residence or country of origin.[2,14]

Major criteria The initial presentation of acute rheumatic fever can vary greatly from patient to patient.[15] What does not vary is that all patients must have at least one major manifestation in order to be diagnosed with acute rheumatic fever.[15] Carditis and arthritis are the most common, followed by Sydenham chorea, subcutaneous nodules, and erythema marginatum.[15] With the exception of chorea, the other manifestations typically appear within a few weeks of a streptococcal infection.[15]

• *Carditis* remains the most common and most serious feature of acute rheumatic fever, affecting 50% to 90% of patients.[1,15] It affects the endocardium, myocardium, and pericardium and can lead to mitral and aortic valve regurgitation, cardiomyopathy, and heart failure.[4,15] In many patients, carditis causes no symptoms and can only be found by an auscultated murmur or by echocardiography.[16] Symptoms become apparent only as the carditis worsens and as more areas of the heart are affected.[16] As carditis progresses, usually over a period of months to years, the valves begin to stenose, and the patient develops rheumatic heart disease.[3]

• *Arthritis* is the second most common symptom of acute rheumatic fever, affecting 35% to 75% of patients.[1,15] The classic presentation is migratory asymmetrical polyarthritis in the large joints, especially in the hips, knees,

elbows, and wrists.[3,6,15] Patients rarely have symptoms in the axial skeleton or small joints.[1] Typically, this arthritis self-resolves in about 4 weeks and does not cause long-term damage.[15]

• *Sydenham chorea* is defined as an abrupt onset of involuntary, uncoordinated, jerky movements in the face, tongue, trunk, and extremities.[4,6,15,17] It affects 10% to 30% of patients, and is more common in girls and women.[1,18] Symptoms do not occur while sleeping.[6] Chorea often is seen with facial grimacing, fidgeting, weakness, gait instability, and emotional outbursts.[3,6,15,17] In serious cases, it can lead to falls, difficulty with work or school, and an inability of patients to groom or feed themselves.[3,18]

Unlike the other clinical manifestations of acute rheumatic fever, Sydenham chorea can appear 1 to 8 months after a streptococcal infection.[1,6,17] With the extended length of time between the appearance of symptoms and the streptococcal infection, laboratory testing may have negative results.[1,3] If the likelihood of acute rheumatic fever is high, and probability of an alternative diagnosis is low, then Sydenham chorea can be considered the only manifestation necessary for the diagnosis of acute rheumatic fever.[1,4] Sydenham chorea is associated with carditis in as many as 90% of patients.[1,4] In most patients, the chorea will gradually resolve within 6 weeks to 6 months, but sometimes can last for 2 to 3 years.[4,6,17]

• *Subcutaneous nodules* are painless, firm, and mobile tissue growths, typically lasting about 2 weeks.[1,3] They are 0.5 to 2 cm in diameter and occur over the extensor surfaces in the joints of the upper and lower extremities, along the spinous processes, and on the occiput.[1,4,15] Although subcutaneous nodules occur in fewer than 10% of patients, they are highly specific for acute rheumatic fever.[1] As with Sydenham chorea, subcutaneous nodules almost always are paired with carditis.[4,15]

• *Erythema marginatum* is a serpiginous, maculopapular pink rash that can last weeks to months.[4,15] The rash is nonpruritic and nonpainful, but its appearance can worsen with heat exposure.[6,15] As with subcutaneous nodules, erythema marginatum also is specific to acute rheumatic fever, but occurs in fewer than 6% of patients.[15]

Minor criteria Unlike the major manifestations in acute rheumatic fever, the minor criteria typically do not show as much variation between cases.[15] Patients may have multiple minor manifestations or none at all.[15] These criteria include fever, elevated acute phase reactants, a prolonged PR interval, and arthralgia.[15]

• *Fever* is the most common presentation, affecting about 90% of patients.[1] Fever is typically low-grade and can be transient.[4,15] In low-risk groups, the fever must be documented during evaluation.[4] In moderate- to high-risk groups, a temperature taken at home and reported can be considered if it is reliable information.[4]

• *Elevated acute phase reactants* such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) occur secondary to inflammation in the heart and joints.[3] ESR usually will be elevated for several weeks after the infection and then will normalize months later; CRP increases and returns to normal more quickly.[3] Although the specificity of ESR and CRP testing is low, the sensitivity of these tests in patients with acute rheumatic fever is high because these patients almost never have normal levels.[3,15]

• *Prolonged PR interval* in patients with acute rheumatic fever can be an indication of acute carditis.[19] Most commonly, patients present with a first-degree heart block; however, this may vary, as some may have a second-degree heart block, complete heart block, or accelerated junctional rhythm.[4] Considering that some healthy people can normally have a prolonged PR interval, repeat ECGs are important because the PR prolongation should resolve over the course of days to weeks in those with acute rheumatic fever.[4]

• *Polyarthralgia* is considered a minor criterion in low-risk areas such as the United States.[15] Clinicians must differentiate between arthritis and arthralgia because symptoms can vary over the course of a flare of acute rheumatic fever.[3] But, like polyarthritis, polyarthralgia is migratory and affects the larger joints.[4]

TABLE 3. Treatment options for major manifestations of acute rheumatic fever[1,4,8,9,15-18]

Severity	Treatment
Carditis	
Mild	Rest and reduced activity for days to weeks.
Moderate to severe	• Cardiology consultation • Bed rest for several weeks • Gradual return to regular activity • Treat advanced disease with appropriate medications, therapy modalities, or surgery*
Arthritis	
Before diagnosis	Acetaminophen
Mild to severe	High-dose aspirin or naproxen. Stop when symptom-free for 1 to 2 weeks.
Sydenham chorea	
Mild	Rest, avoiding overstimulation, and keeping the environment calm.
Moderate to severe	Valproic acid and/or carbamazepine. When symptom-free for 1 month, gradually taper.
Very severe or refractory	• Neurology or psychiatry consultation • Prednisone, IVIG, and plasmapheresis

*Heart failure, mitral regurgitation or stenosis, atrial fibrillation, infective endocarditis

TREATMENT

The main goal of treatment is symptom reduction. (**Table 3**).[17] Carditis, arthritis, and Sydenham chorea can

cause mild symptoms that require minimal treatment, or severe symptoms that can greatly affect patient well-being.[3] Unlike the other manifestations, subcutaneous nodules and erythema marginatum pose no problems to patient health and rarely require treatment.[4] Although treatment does not reduce the progression of symptoms, it can make the symptoms more tolerable.[1]

Carditis Most patients have mild to moderate carditis with acute rheumatic fever, but as many as a third will have severe mitral regurgitation, and 10% will have heart failure.[1] Obtain a cardiology consult in patients with moderate to severe carditis or heart failure.[4] Bed rest is recommended for several weeks with a gradual return to regular activity.[3] Medications such as diuretics or vasodilators may be used depending on the severity of the patient's symptoms.[3] Corticosteroids and aspirin sometimes are used to reduce inflammation in the heart, but evidence shows limited benefit and lack of improved patient outcomes.[16] Ultimately, patients may need valve repair, which is preferred to replacement because repair has better long-term results and eliminates the need for long-term anticoagulation.[3]

Arthritis The primary treatment for arthritis related to acute rheumatic fever is high-dose aspirin (80 to 100 mg/kg/day divided into three or four doses).[1] Aspirin has been better researched, but naproxen is an alternative because it can be taken just twice daily (15 to 20 mg/kg/day) and has a reduced adverse reaction profile.[1] Start the patient on aspirin or naproxen as soon as possible after the diagnosis is confirmed.[6] Acetaminophen is recommended before the diagnosis is confirmed so as not to mask the symptoms.[4] Pain resolution is almost immediate with nonsteroidal anti-inflammatory drugs (NSAIDs), but continuing treatment for 1 to 4 weeks may be necessary.[1,3,15] Continue NSAID therapy until the patient has been symptom-free for 1 to 2 weeks.[8] If aspirin or naproxen fail to improve symptoms within 72 hours, consider an alternate diagnosis.[15] Corticosteroids are not recommended for treatment of arthritis because they provide minimal benefit, have increased risk of rebound, and cause adverse reactions.[1]

Sydenham chorea Some patients may need treatment for the symptoms of Sydenham chorea, depending on its severity.[17] For patients with mild cases, supportive measures are recommended, including rest, avoidance of overstimulation, and keeping the environment calm.[4] First-line medications include valproic acid (20 mg/kg/day) and carbamazepine (15 mg/kg/day).[18] Other medications that may be considered include risperidone, olanzapine, haloperidol, and pimozide.[18] In patients with severe or refractory cases of chorea, prednisone, IV immunoglobulin (IVIG) therapy, and plasmapheresis have been suggested.[17,18] If the patient is symptom-free after 1 month, the medications can be gradually tapered.[17] Remember that these treatments remain experimental because there have been few trials of their efficacy and recommendations are based largely on anecdotal evidence.[18]

TABLE 4. Antibiotic recommendations for secondary prevention of acute rheumatic fever[1,7,8,20]

Medication	Adult dose	Child dose
First-line therapies		
Penicillin G benzathine	1.2 million units IM every 21 to 28 days*	• ≤27 kg (59.5 lb)—600,000 units IM every 21 to 28 days • >27 kg—same as adult dose
Penicillin V	250 mg oral twice daily	Same as adult dose
Option for patients allergic to penicillin		
Sulfadiazine	1,000 mg oral once daily	≤27 kg—500 mg oral once daily >27 kg—same as adult dose
Options for patients allergic to penicillin and sulfadiazine		
Erythromycin	250 mg oral twice daily	10 mg/kg oral twice daily (maximum 500 mg daily)
Azithromycin	250 mg oral once daily	6 mg/kg oral once daily (maximum 250 mg daily)

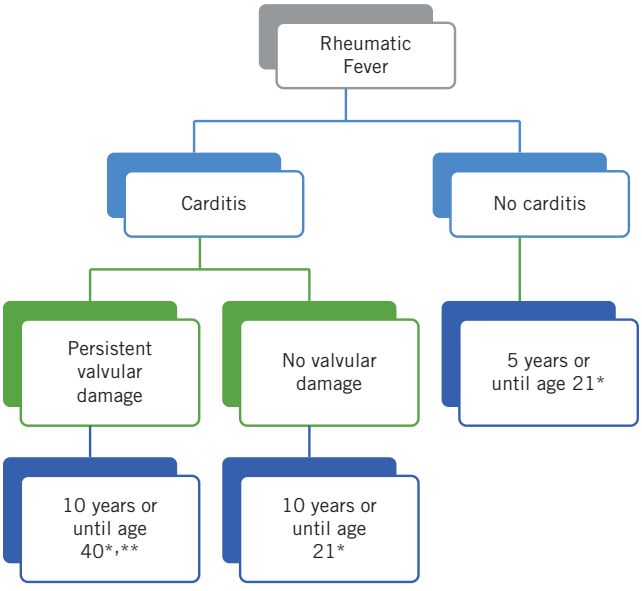
*Give every 21 days in high-risk areas and in patients with a history of rheumatic heart disease and multiple recurrences of acute rheumatic fever.

PREVENTION

The reduction of the overall incidence of acute rheumatic fever and rheumatic heart disease in the United States is directly the result of prevention.[1] Prevention of acute rheumatic fever is categorized as *primordial, primary,* and *secondary*.[4]

Primordial prevention The goal of this type of prevention is to reduce the spread of group A streptococcal infections.[8] Interventions include improving the patient's socioeconomic environment, including reduced overcrowding, improved access to care, and improved overall hygiene.[4] This is the main reason why acute rheumatic fever numbers have dropped in the developed world since the mid-20th century.[15]

Primary prevention The next preventive step is to identify and treat group A streptococcal infections as soon as possible to avoid the development of acute rheumatic fever.[20] Appropriate antibiotic therapy should start within 9 days of the onset of group A streptococcal pharyngitis.[5] Penicillin is considered first-line treatment; it should be given either once IM or orally for 10 days.[6,8] Amoxicillin is an alternative for patients who are not allergic to but who cannot otherwise tolerate penicillin.[9] If penicillin allergy is a concern, other options include narrow-



*Select whichever is longer.
**Consider lifelong treatment for severe valvular disease or after valve surgery.

FIGURE 1. Antibiotic duration for secondary prevention of acute rheumatic fever[9]

spectrum cephalosporins, clindamycin, azithromycin, or clarithromycin.[6] Streptococcal carriers do not require treatment because they are considered at low risk of being carriers for a rheumatogenic strain.[9]

Secondary prevention The principal goal for secondary prevention is to reduce recurrence of acute rheumatic fever and patient risk for developing rheumatic heart disease.[20] Between 60% and 65% of patients develop rheumatic heart disease within 5 years of their initial episode of acute rheumatic fever, and each recurrence of fever increases that risk because of continued heart damage.[20]

Prevention involves continuous scheduled dosing of antibiotics (**Table 4**).[9] Again, penicillin is the treatment of choice, but alternatives are available for patients who are intolerant or allergic.[9] Even 50% adherence to antibiotic treatment reduces the risk of acute rheumatic fever recurrence by 85%.[21] Further, for every 10% increase in adherence to antibiotic treatment, there is a 12% reduction in risk of death.[21]

Duration of prophylaxis typically is 5 to 10 years depending on the patient's echocardiography findings (**Figure 1**).[9] Patients with a history of acute rheumatic fever are at risk of recurrence if they develop another group A streptococcal infection whether symptomatic or not, so long-term prophylaxis is important and indicated for all patients diagnosed with acute rheumatic fever.[9]

CONCLUSION

Acute rheumatic fever is the main cause of rheumatic heart disease, which leads to increased morbidity and mortality throughout the world. In the acute phase, rheumatic fever can be quite disabling, and when left untreated, can lead to an increased risk of lifelong complications and death. The 2015 Jones Criteria have helped identify more patients with acute rheumatic fever, but clinicians must know when to suspect acute rheumatic fever and how to manage and prevent it.[15] **JAAPA**

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