

Rheumatic Fever:

Summary

Acute rheumatic fever (ARF) is an inflammatory sequela involving the heart, joints, skin, and central nervous system (CNS) that occurs two to four weeks after an untreated infection with group A Streptococcus (GAS). The pathogenic mechanisms that cause rheumatic fever are not completely understood, but molecular mimicry between streptococcal M protein and human cardiac myosin proteins is thought to play a role. Because of the structural similarities between the two proteins, antibodies and T cells activated to respond to streptococcal proteins also react with the human proteins, causing tissue injury and inflammation. In addition to nonspecific symptoms (e.g., fever, malaise, and fatigue), patients present with symptoms involving the heart (carditis or valvulitis), joints (migratory polyarthritis), skin (subcutaneous nodules, erythema marginatum), and/or CNS (Sydenham chorea). The diagnosis of ARF is primarily clinical and based on the Jones criteria. Diagnostic evaluation in ARF typically shows elevated inflammatory markers, positive antistreptococcal antibodies, and valvular damage on echocardiogram. The first-line treatment is penicillin combined with symptomatic anti-inflammatory treatment, typically with salicylates or glucocorticoids (if salicylates are not effective). ARF may be complicated by progressive, permanent damage to the heart valves (especially the mitral valve), resulting in chronic rheumatic heart disease. Preventing the cardiac complications of ARF is the main goal of both primary prophylaxis (i.e., antibiotic therapy for GAS pharyngitis) and secondary prophylaxis (antibiotic administration following an episode of ARF).

Definition

- Delayed inflammatory complication of group A β -hemolytic streptococcal pharyngitis that usually occurs within 2–4 weeks of acute infection^[1]
- One of the nonsuppurative complications of GAS pharyngitis
- **Rheumatic heart disease** refers to two clinical entities:
 - Acute pancarditis as a sequela of GAS infection
 - Chronic cardiac valvular changes as a complication of acute rheumatic fever

FEEDBACK

ETIOLOGY AND EPIDEMIOLOGY

- most common in children 6 - 15 years old.
- It is due to an immunologic reaction that is a delayed sequela of group A beta-hemolytic streptococcal infections of the pharynx
- A family history of rheumatic fever and lower socioeconomic status are additional factors.

Beta-hemolysis (complete blood hemolysis), gram positive cocci :

- **Streptococcus pyogenes (Group A Streptococcus, GAS)** : cause
 1. strep throat : tonsillitis , pharyngitis
 2. skin and soft tissue infections as impetigo , cellulitis , perinanal streptococcal dermatitis
 3. immunological inflammation : rheumatic fever , poststreptococcal glomerulonephritis
- **Streptococcus agalactiae (Group B Streptococcus, GBS)** : a common cause of severe infection in newborns

both sensitive for Penicillin & cephalosporins

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Pathophysiology

- The exact pathogenesis is not yet entirely understood.
- Most commonly accepted mechanism involves the following: acute tonsillitis/pharyngitis caused by GAS without antibiotic treatment → development of antibodies against streptococcal **M protein** → cross-reaction of antibodies with nerve and myocardial proteins (most commonly myosins) due to molecular mimicry → **type II hypersensitivity reaction** → acute inflammatory sequela [2][4]

FEEDBACK

Pathology

- **Myocardial findings** [5][6]
 - **Aschoff bodies** 
 - Granuloma of rheumatic inflammation
 - Central area of fibrinoid necrosis
 - Surrounded by characteristic multinucleated giant cells (Aschoff cells) and other inflammatory cells (mononuclear cells, plasma cells, and T lymphocytes) due to a type IV hypersensitivity reaction. 
 - **Anitschkow cells**
 - Cardiac histiocytes (mononuclear cells) appearing in Aschoff bodies
 - Large and elongated cells
 - Longitudinal section: ovoid nucleus containing wavy, caterpillar-like bar of chromatin (caterpillar cell)
 - Transverse section: owl-eye appearance 

CLINICAL MANIFESTATIONS

- Acute rheumatic fever is diagnosed using the **revised Jones criteria**, which consist of clinical and laboratory findings.
 - ♥ The presence of either two **major criteria** or one major and two **minor criteria**, along with evidence of an antecedent **streptococcal infection** confirm the diagnosis e.g.:
 1. scarlet fever
 2. positive throat culture
 3. elevated antistreptolysin O or other antistreptococcal antibodies
- The infection often precedes the presentation of rheumatic fever by 2 to 6 weeks.
- Streptococcal antibody tests, such as the antistreptolysin O titer, are the most reliable laboratory evidence of prior infection.
- **Arthritis** is the **most common major manifestation**. It involves the large joints and is migratory.
- ♥ Arthralgia cannot be used as a minor manifestation if arthritis is used as a major manifestation.
- **Carditis** occurs in 50% of pts.
 1. Tachycardia
 2. new murmur (mitral or aortic regurgitation)
 3. pericarditis
 4. cardiomegaly
 5. **Signs of CHF**
- **Erythema marginatum**, a serpiginous, nonpruritic, and evanescent rash, uncommon, occurs on the trunk, and is brought out by warmth.
- **Subcutaneous nodules**: predominantly with chronic or recurrent dz. firm, painless, non-pruritic, mobile nodules, on the extensor surfaces of large and small joints, scalp & spine.
- **Chorea** (Sydenham chorea or St. Vitus dance) consists of neurologic and psychiatric signs. It also is uncommon and often presents long after the infection.



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Revised Jones criteria [12][11]

- Diagnostic criteria for patients with laboratory findings of a preceding GAS infection 
 - Initial episode of ARF: two major criteria or one major plus two minor criteria
 - Recurrent ARF: either the same as for an initial episode of ARF or the presence of three minor criteria

Revised Jones criteria for the diagnosis of ARF

	Low-risk populations 	Moderate- to high-risk populations
Major criteria	• Migratory polyarthritis (primarily involving the <u>large joints</u>)  • Carditis (pancarditis, including <u>valvulitis</u>)  • Sydenham chorea (CNS involvement) • Subcutaneous nodules • Erythema marginatum	• Arthritis (monoarthritis or migratory polyarthritis) • Polyarthralgia  • Carditis (pancarditis, including <u>valvulitis</u>)  • Sydenham chorea (CNS involvement) • Subcutaneous nodules • Erythema marginatum
Minor criteria	• Polyarthralgia • High fever ($\geq 38.5^{\circ}\text{C}$) • $\uparrow$ <u>Acute phase reactants</u> (ESR ≥ 60 mm/hour and/or CRP ≥ 30 mg/L) • <u>ECG</u> showing prolonged PR interval 	• Monoarthralgia • High fever ($\geq 38.5^{\circ}\text{C}$) • $\uparrow$ <u>Acute phase reactants</u> (ESR ≥ 30 mm/hour and/or CRP ≥ 30 mg/L) • <u>ECG</u> showing prolonged PR interval 

Routine laboratory studies [11]

Initial laboratory findings typically show nonspecific signs of infection.

- **Complete blood cell count** [11][13]
 - Typically shows leukocytosis
 - May show normochromic, normocytic anemia of chronic inflammation
- **Acute phase reactants** [11]
 - CRP: elevated, typically ≥ 30 mg/L
 - ESR: elevated, typically ≥ 60 mm/hour

Confirmation of GAS infection [11]

- Used to rule out differential diagnoses
- Any of the following test results can confirm recent GAS infection:
 - Tests showing elevated or rising antibodies
 - $\uparrow$ **Antistreptolysin O titer (ASO)**
 - $\uparrow$ **Antistreptococcal DNase B titer (ADB)**
 - Positive throat culture
 - Positive rapid GAS carbohydrate antigen detection test
- False positives are possible due to colonization of GAS in the upper respiratory tract.
- For more information on the diagnosis of GAS pharyngitis, see "Acute tonsillitis."

Assessment for cardiac involvement [11][14][15]

- All patients with confirmed or suspected rheumatic fever require an ECG and echocardiography.

Cardiac workup for ARF	
Modality	Characteristic findings [14][13][15]
ECG	• Most common: prolonged PR interval (first-degree AV block) • Potential additional findings include: ◦ Second-degree AV block ◦ Complete heart block ◦ Sinus tachycardia ◦ Accelerated junctional rhythm ◦ ECG features of pericarditis
Echocardiography	• Acute infection: features of rheumatic valvulitis, e.g., mitral regurgitation, aortic regurgitation • Chronic disease: mitral stenosis [16]
Chest x-ray	• Enlarged left atrium • Enlarged left ventricle • X-ray findings of pulmonary edema

TREATMENT AND PREVENTION

- Management of acute rheumatic fever consists of :
 1. **benzathine penicillin** to eradicate the betahemolytic streptococcus,
 2. anti-inflammatory therapy with **salicylates** after the diagnosis is established
 3. **bed rest**.
- **Long-term penicillin prophylaxis**, preferably with IM benzathine penicillin G, 1.2 million U every 28 days, is required. Oral regimens for prophylaxis are not as effective.

PROGNOSIS

- acute rheumatic fever depends on the degree of permanent cardiac damage.
- Cardiac involvement may resolve completely, especially if it is the first episode and the prophylactic regimen is followed.
- The severity of cardiac involvement worsens with each recurrence of rheumatic fever.