

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 polyarthritides), 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).

A. **Definition.** Rheumatic fever is a *delayed, nonsuppurative, autoimmune complication occurring 2–4 weeks after an upper respiratory infection with group A β -hemolytic streptococcus (GABHS) (*Streptococcus pyogenes*)*. It is characterized by inflammation of the heart, blood vessels, joints, CNS, and skin.

B. Epidemiology

1. Rheumatic fever is now **rare in the United States** and Western Europe but was a worldwide problem during the 1960s. It remains a primary cause of cardiac death in the developing world in patients younger than 50 years.
 2. It is **most common in children 5–15 years of age**, reflecting the age group most susceptible to streptococcal throat infections.
 3. There is no gender predilection.
 4. The major risk factor is **pharyngitis** caused by certain strains of **GABHS**. *The streptococcal strains that cause streptococcal skin infection (i.e., impetigo) do not cause rheumatic fever.*
- C. **Etiology.** The **cause of rheumatic fever is unknown**, but the disease appears to be autoimmune in nature and may represent “molecular mimicry,” in which streptococcal antigens resemble autoantigens and trigger an autoimmune response.

Risk factors

- 1- Onset between 5-15 year (rare before 5 years).
- 2- Low socioeconomic status..
- 3- Genetic predisposition (Associated with certain HLA).
- 4- Group A β -hemolytic strept pharyngitis (with M serotypes 1, 3, 5, 6,18, 24)

Pathogenesis

- ✧ Latent period of 1-3 weeks usually lapse between pharyngitis & acute rheumatic fever
- ✧ Theories of etiology:
 - 1- Cross reactivity theory :Following strept infection antibodies formed against strept cross react against host connective tissue antigens.
 - 2- Antigenic similarity theory: group A strept antigens is similar to cardiac valve antigens.
- ✧ Inflammation is either:
 - Exudative (as in joints) → resolve without residual damage
 - Proliferative → with Aschoff nodules (as in the heart) → heal by fibrosis.

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.:

A. Major criteria of Rheumatic fever

I- Arthritis (75%)

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- Usually affect big joints (e.g. knee, ankles, wrist, elbow).
- Polyarticular, either simultaneous or successive.
- Migratory (fleeting) from one joint to another.
- Affected joint is :
 - red - hot – swollen
 - with absolute limitation of movement (severely tender)
- Dramatic response to salicylates.
- Resolve without residuals, even without treatment, over days to few weeks.

II- Carditis (50%)

Endocarditis:

- Valvulitis affecting commonly mitral valve with or without aortic valve:
 - 1- Mitral valve:
 - Leaflets oedema → transient mitral stenosis (Carey Combs murmur)
 - Leaflets destruction → mitral regurge.
 - 2- Aortic valve → aortic regurge.

Myocarditis:

- 1- Tachycardia out of proportion to age & fever (rarely bradycardia due to heart block)
- 2- Heart failure (with cardiomegaly , gallop rhythm, & muffled heart sounds) indicates severe carditis

Pericarditis:

- 1- Dry pericarditis:
 - Stitching chest pain.
 - Pericardial rub (on the bare area , unrelated to respiration).
- 2- Pericardial effusion:
 - Uncommon.
 - Dull aching pain.
 - Dullness outside the apex.
 - Distant heart sounds.
 - Low voltage ECG.

N.B: Carditis may be silent or late onset (appear after 6 week – 6 months of onset)

III- Rheumatic chorea “Sydenham chorea” (10%)

- Incidence
 - more in girls 8-12 years (school age).
 - occur weeks or months after strept pharyngitis so, other criteria are usually lacking.
- A/E: Dysfunction of the basal ganglia due to antineuronal antibodies.

- **Manifestations:**

- 1- Emotional lability and personality changes.

- 2- Involuntary movements:

- Spontaneous purposeless movements of limbs and facial grimace.
- increase with emotional stress and decrease by sleep.
- Last for months.

- 3- Hypotonia.

- **Tests for chorea:**

- Milk maid's grip: irregular contraction & relaxations while squeezing examiner fingers
- Extension of arm → spooning & pronation of hands. (*choreic hand*).
- Wormian movements of tongue upon protrusion.
- Evaluate hand writing.

iv- Erythema marginatum (< 5%)

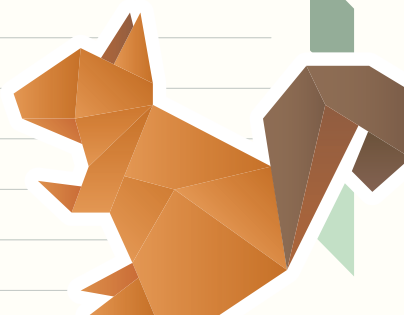
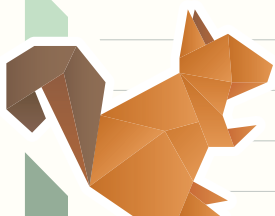
- Site → on the trunk & proximal parts of the limbs.
- Criteria → large erythematous macules.
→ with pale centers & serpiginous borders.
→ evanescent.
→ not pruritic



v- Subcutaneous nodules (< 1%)

- Site → over the extensor surfaces of tendons near bony prominences.
- Criteria → size about 1 cm.
→ firm, mobile, painless.
→ usually associated with severe carditis.

SIGN	COMMENTS
1. Polyarthrititis	Common; swelling, limited motion, tender, erythema Migratory; involves large joints but rarely small or unusual joints, such as vertebrae
2. Carditis	Common; pancarditis, valves, pericardium, myocardium Tachycardia greater than explained by fever; new murmur of mitral or aortic insufficiency; Carey-Coombs mid-diastolic murmur; heart failure
3. Chorea (Sydenham disease)	Uncommon; presents long after infection has resolved; more common in females; antineuronal antibody positive
4. Erythema marginatum (10%)	Uncommon; pink macules on trunk and proximal extremities, evolving to serpiginous border with central clearing; evanescent, elicited by application of local heat; nonpruritic
5. Subcutaneous nodules	Uncommon; associated with repeated episodes and severe carditis; present over extensor surface of elbows, knees, knuckles, and ankles or scalp and spine; firm, nontender



B. Minor criteria of Rheumatic fever

i. Clinical

1. Fever → usually between 38.4 – 40 °C
2. Arthralgia (can't be used as minor manifestation in presence of arthritis)

ii. Laboratory

3. Prolonged P-R interval (can't be used as minor manifestation in presence of carditis)
4. Elevated acute phase reactants (↑ ESR, ↑ C-reactive protein, leucocytosis)

Modified Jones criteria for rheumatic fever diagnosis (1993)

A. Two major criteria or One major & Two minor criteria Plus

B. Evidence of recent antecedent streptococcal infection ;

- Positive throat swab or
- ↑ ASO titer or
- ↑ Anti Deoxyribonuclease (DNase) β titre.

Exceptions to Jones criteria:

- 1- Rheumatic chorea
- 2- Late onset carditis

Each can diagnose acute rheumatic fever alone in absence of other criteria and evidence of recent strept infection but after active exclusion of other causes for both.

- 3- Occasionally, patients with rheumatic fever recurrences (rheumatic activity) may not fulfill Jones criteria so in patients with documented chronic rheumatic heart disease diagnosis of rheumatic activity can be made in absence of major criteria i.e minor criteria plus evidence of recent strept infection is enough to make the diagnosis.

To Sum up:

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1. Major features

- a. **Cardiac involvement** is the **hallmark** and **most important complication** of rheumatic fever. The inflammatory process may involve all layers of the heart (pancarditis), including the epicardium, endocardium, myocardium, and pericardium.
 1. **Valvulitis** is frequent and typically causes insufficiency of the **left-sided valves** (mitral and aortic). *Mitral regurgitation* is the most common early valvular manifestation. It rarely affects the pulmonic or tricuspid valves.
 2. **Myocarditis** is usually manifested by **tachycardia out of proportion to the extent of the fever**. Other severe manifestations include cardiac dilatation and heart failure.
 3. Pericarditis and pericardial effusions are less common.
- b. **Arthritis** is classically **migratory, asymmetric, and exquisitely painful** and often the earliest manifestation of acute rheumatic fever. It occurs in 70% of patients and most commonly involves the elbows, knees, ankles, and wrists. **It does not result in chronic joint disease and responds quickly to NSAIDs and aspirin.**
- c. **Sydenham chorea** occurs later than the other rheumatic fever manifestations, often beginning subtly, months after GABHS pharyngitis. It reflects involvement of the basal ganglia and caudate nuclei. Chorea may start as hand clumsiness and progress to choreoathetoid movements with emotional lability.
- d. **Skin involvement**
 1. **Erythema marginatum** is an evanescent, nonpruritic rash that starts as pink to red macules, which may coalesce and spread centrifugally with central clearing over the trunk and proximal limbs.
 2. **Subcutaneous nodules**, although rarely seen, are associated with severe cardiac involvement. These small, mobile, and painless nodules occur on the bony prominences of the extensor surfaces of the extremities.

2. **Minor features** include fever, arthralgias, leukocytosis, increased ESR, and prolonged PR interval on electrocardiogram.

Approach [11][12]

- Patients should be evaluated for evidence of a preceding GAS infection via throat culture, antigen, or antibody test.
- ARF is diagnosed using the revised Jones criteria.
- All patients with suspected or confirmed ARF require a cardiac workup.

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 large joints) • Carditis (pancarditis, including valvulitis) • Sydenham chorea (CNS involvement) • Subcutaneous nodules • Erythema marginatum	• Arthritis (monoarthritis or migratory polyarthritis) • Polyarthralgia • Carditis (pancarditis, including valvulitis) • Sydenham chorea (CNS involvement) • Subcutaneous nodules • Erythema marginatum
Minor criteria	• Polyarthralgia • High fever ($\geq 38.5^{\circ}\text{C}$) • $\uparrow$ Acute phase reactants (ESR ≥ 60 mm/hour and/or CRP ≥ 30 mg/L) • ECG showing prolonged PR interval	• Monoarthralgia • High fever ($\geq 38.5^{\circ}\text{C}$) • $\uparrow$ Acute phase reactants (ESR ≥ 30 mm/hour and/or CRP ≥ 30 mg/L) • ECG showing prolonged PR interval

Routine laboratory studies [11]

Initial laboratory findings typically show nonspecific signs of infection.

- **Complete blood cell count**
 - Typically shows leukocytosis
 - May show normochromic, normocytic anemia of chronic inflammation
- **Acute phase reactants**
 - 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



Assessment for neurological involvement [17][18]

- The diagnosis of Sydenham chorea is based on clinical and laboratory findings.
- Neuroimaging (MRI or CT brain)
 - Not routinely indicated but may be performed to exclude other forms of chorea
 - Findings are nonspecific and variable. 
- Lumbar puncture: not routinely indicated; may be performed to exclude other disorders
- Echocardiography should be obtained in all patients with Sydenham chorea because concurrent cardiac involvement is common. [14]

To sum up:

E. **Diagnosis.** The Jones criteria for rheumatic fever are shown in Table 16-6. Diagnosis requires evidence of recent streptococcal infection and either two major criteria or one major plus two minor criteria.

F. Laboratory findings

- Nonspecific inflammatory markers
 - Elevated ESR and CRP
 - Elevated WBC count
- Serologic markers
 - Antistreptolysin-O** titers are abnormally elevated in 70–80% of patients with rheumatic fever and are evidence of a recent GABHS infection.
 - Anti-DNase** antibodies may also be used to document GABHS infection.
- Echocardiography typically shows evidence of carditis, such as decreased ventricular function, valvular insufficiency, or pericardial effusion.

Major criteria
Migratory polyarthritits
Carditis
Sydenham chorea
Erythema marginatum
Subcutaneous nodules
Minor criteria
Fever
Arthralgia
Previous rheumatic fever
Leukocytosis
Elevated erythrocyte sedimentation rate
Elevated C-reactive protein
Prolonged PR interval on electrocardiogram

Differential diagnosis

1. Other causes of arthritis

- Rheumatoid arthritis: - Chronic arthritis ;last at least for 6 weeks.
- Can involve small peripheral joints.
- Non migratory
- No evidence of recent strept. infection.
- No response to salicylates within 48 hours.
- Deformities are common.
- Infections : viral, bacterial, tuberculous
- Hematologic e.g. Acute leukemia , hemophilia.
- Immunologic e.g. Systemic lupus erythematosus& Henoch Schonlein purpura

2. Other causes of carditis e.g.:

- Viral carditis.
- Infective endocarditis.
- Drug induced.

3. Other causes of chorea e.g.:

- Wilson disease.
- Huntington chorea
- Cerebral palsy.

Complications of rheumatic fever

1. Congestive heart failure:

1. Acute : due to myocarditis
2. Chronic : with episodes of acute failure precipitated by:
 - Rheumatic activity
 - Infective endocarditis
 - Chest infections

2. Cardiomegaly:

- ✧ Due to: carditis or heart failure or multivalvular lesions
- ✧ Detected by:
 - Clinically : Precordial bulge, precordial and epigastric pulsations.
 - Chest x ray.

3. Chronic valve lesions :

- ✧ Carditis ,especially in recurrences, can cause permanent organic valve lesions e.g. MS, MR , AS , AR or combined valve lesions.
- ✧ Organic valve lesions can be complicated with pulmonary hypertension, arrhythmia, infective endocarditis, thromboembolism & shortened life span.

4. Rheumatic activity (Recurrences):

- ✧ Suggested by:
 - Fever with arthritis or arthralgia.
 - Change in character of already existing murmur
 - Appearance of new murmurs.
 - Carditis with heart failure.
 - Pericardial involvement.
- ✧ Clinical value: it can diagnose rheumatic fever attack in presence of evidence of recent antecedent streptococcal infection

5. Pulmonary hypertension:

- ✧ Due to long standing mitral valve lesions
- ✧ Symptoms: dyspnea, fatigue, may be syncope
- ✧ Signs:
 - Pulmonary pulsations(diastolic shock)
 - Dull pulmonary area
 - Accentuated P2
 - Soft ejection systolic murmur over pulmonary area.
- ✧ Chest x ray: Dense hilar shadows& RVH.

Treatment of acute Rheumatic fever:

1- Prophylactic:

1st prevention:

- Hygienic housing.
- Treat streptococcal pharyngitis: penicillin or erythromycin for 10 days.

2nd prevention:

- Prevent recurrence of Rheumatic fever by:
 - * Long acting penicillin (Benzathine penicillin)
 - Dose : 1.2 million unit single injection, I.M every 3 - 4 weeks.
 - For at least 5 years after last episode for cases without carditis
 - For at least 10 years after last episode for cases with carditis without residuals
 - For life or till age of 40 for cases with carditis with residuals
 - * Alternatives: daily oral penicillin V or erythromycin (250 mg twice daily)

2- Treatment of acute attack:

1. Bed rest: needed mainly for cases with carditis & heart failure till heart failure is controlled & ESR is normalized
2. Diet: light, low salt in cases with heart failure.
3. Eradicate strept. infection by: A 10 days course of oral penicillin V or single injection of Benzathine penicillin or Erythromycin (for penicillin sensitive).
4. Anti inflammatory drugs.
 - a- Salicylates
 - ⊕ Indications: - Rheumatic arthritis
 - Mild rheumatic carditis without heart failure.
 - During steroid withdrawal
 - ⊕ Dose: 100 mg/kg/day (max = 6 gram /day); in four divided doses.
 - For 3-5 days **then** 75 mg/kg/d for 4 weeks, then
 - Gradual withdrawal monitored by decline in ESR & CRP
 - ⊕ Side effect: - Toxicity (early symptoms are tinnitus, hyperventilation)
 - Others :Gastritis , Reye's syndrome
 - b- Corticosteroids (Prednisone)
 - * Indications: - Moderate to severe carditis
 - Heart failure.
 - * Dose: 2 mg/kg/d (max = 60 mg/day); in divided doses for 2-3 weeks , then
 - Taper the dose by reducing 5 mg (one tablet) every 2-3 days.
 - With tapering , aspirin is started with dose 75 mg/kg/d for 6 weeks.
5. Treatment of rheumatic chorea:
 - * Avoid emotional stress.
 - * Control abnormal movements:
 - Phenobarbitone 15-30 mg / 8 hours oral.
 - Alternative: Haloperidole (Safinase tablet) 0.01-0.03 mg/kg.
 - * Long acting penicillin prophylaxis.
6. Treatment of: - heart failure (diuretics-vasodilators–Digoxin used cautiously).
 - Infective endocarditis.

Prognosis

- 1- Arthritis sub side within days to weeks even without treatment.
- 2- Chorea subside within few months without residuals.

To sum up all:

ACUTE RHEUMATIC FEVER

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Acute rheumatic fever		
Epidemiology	• Peak incidence: age 5-15 • Twice as common in girls	
Clinical features	Major	• Joints (migratory arthritis) • ♥ (Carditis) • Nodules (subcutaneous) • Erythema marginatum • Sydenham chorea
	Minor	• Fever • Arthralgias • Elevated ESR/CRP • Prolonged PR interval
Late sequelae	Mitral regurgitation/stenosis	
Prevention	Penicillin for group A streptococcal (<i>Streptococcus pyogenes</i>) pharyngitis	

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

1. It can present with carditis:
 - a. Friction rub
 - b. Prolonged PR interval
 - c. Diffuse ST elevations
2. Also look for continuous hand wringing (rapid, irregular jerks) → chorea
 - a. Sydenham chorea has the longest latency period
 - i. 1-8 months
3. Diagnosis is based on clinical or laboratory evidence of a preceding event of group A streptococcus infection along with one of the following:
 - a. 2 major Jones criteria
 - b. 1 major and 2 minor criteria
4. Erythema marginatum (annular pink rash with sharp, raised edges and central clearing)
5. ↑acute phase reactants