TEHRAN UNIVERSITY OF MEDICAL SCIENCES

Department of Cardiology– Tehran University of Medical Science

Rheumatic Fever

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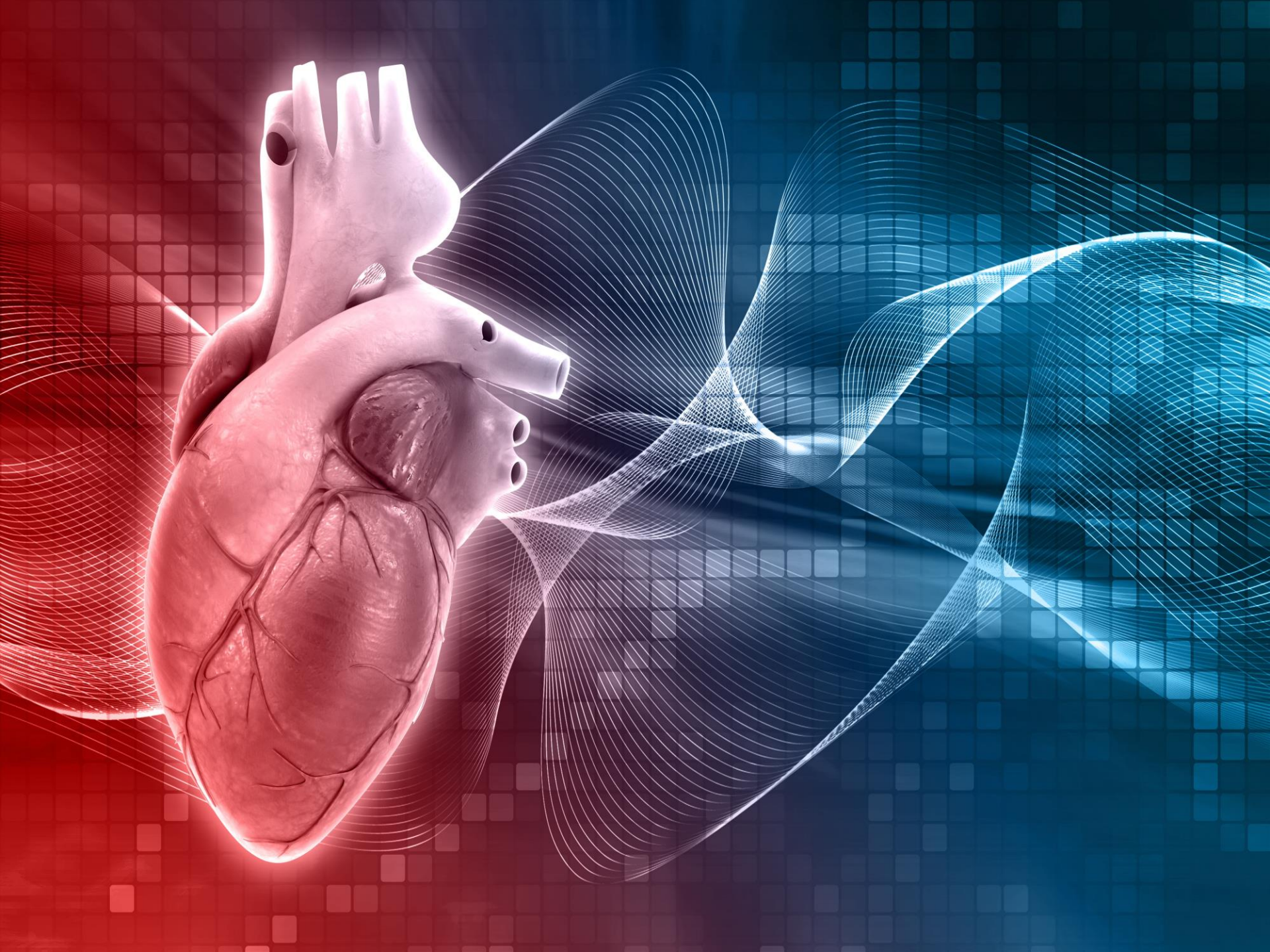


EPIDEMIOLOGY

Rheumatic fever (RF) is a leading cause of acquired heart disease in children and young adults worldwide. It is an illness preceded by a pharyngeal infection with group A beta-hemolytic streptococci (GAS), occurring most often between 5 and 15 years.
The burden of RF and RHD is most salient within marginalized communities in developed nations as well as in low-and middle-income regions.
The condition is more prevalent among young people, particularly between the ages of 5 to 30, and although its occurrence is similar between women and men, the inherent biological factors, the risk of illness during pregnancy, exposure to GAS through child rearing, and poor accessibility to resources make women approximately 1.8 times more susceptible to developing RHD

PATHOGENESIS

RF is a multifactorial disease that follows GAS pharyngitis in a susceptible individual who lives under deprived social Conditions.
The theory of molecular mimicry holds that GAS pharyngitis triggers an autoimmune response in susceptible individuals by cross-reacting with similar epitopes in the heart, brain, joints, and skin, and that repeated episodes of RF lead to RHD.
In situations of untreated epidemic GAS pharyngitis, up to 3% of patients develop the disease.
The risk of RF is substantially reduced by effective antibiotic therapy

CLINICAL FEATURES

The typical attack of RF follows an episode of GAS infection—usually symptoms of GAS pharyngitis—after a latent period of 2 to 3 weeks, during which there are no clinical or laboratory evidence of active inflammation. However, as many as one-third of patients who develop RF do so after asymptomatic GAS. Preceding symptomatic pharyngitis is recognized in only about two-thirds of patients with ARF in high-income countries, and even less in endemic regions.

A first episode of ARF can occur at any age but occurs most often between 4 and 15years, ages that are also the peak years for streptococcal pharyngitis. However, in developing countries there are reports of RHD occurring at age 3 to 5 years. ARF typically involves some combination of the joints, heart, skin, and CNS. The most common major sign is polyarthritis, which occurs in two-thirds to three-quarters of patients, followed by carditis and chorea. The illness usually begins with high fever, but in some patients the fever may be low-grade or absent

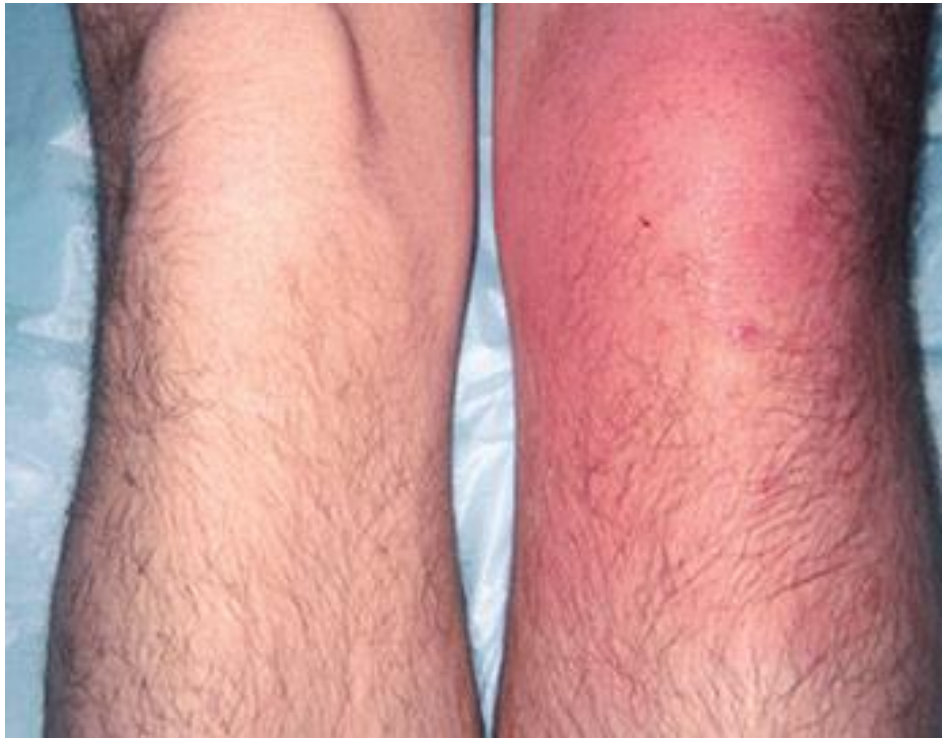
Arthritis

Joint involvement is more common and more severe in young adults (100%) than in teenagers (82%) and children (66%). At the onset of the illness usually affects the lower limbs initially before spreading to the upper limbs. *Migratory polyarthritis* is the most common manifestation of ARF, occurring in about 35% to 66% of children, often accompanied by fever. In some cases the joint involvement may be additive rather than migratory.

The affected joint may be inflamed for only a few days to 1 week before inflammation subsides. The polyarthritis is severe for approximately 1 week in two-thirds of the patients and may last for another 1 or 2 weeks in the remainder, before it resolves completely. If the joint swelling persists after 4 weeks, it becomes necessary to consider other conditions, such as JIA or systemic lupus erythematosus (SLE).

Monarthritis occurs in high-risk indigenous populations, as has been reported in 17% to 25% of patients. Joints become extremely painful and tender.
The large joints such as ankles, knees, elbows, and wrists are usually involved. Shoulders, hips, and small joints of the hands and feet may also be involved, but almost never alone. If vertebral joints are affected, another disorder should be suspected. Joint pain and fever usually subside within 2 weeks and seldom last more than 1 month.

The synovial fluid has characteristics of sterile inflammation. There may be reduction in complement components C1q, C3, and C4, suggesting their consumption by immune complexes. Radiographs may show features of a join effusion, but no other abnormality is noted.



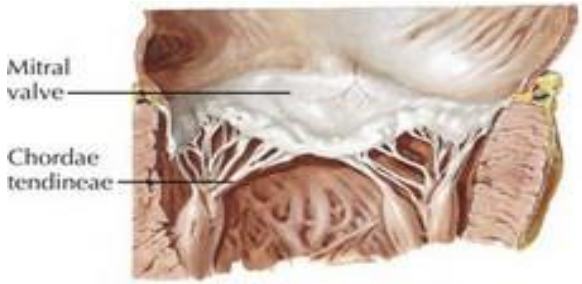
Jaccoud arthritis or arthropathy (or chronic post-RF arthropathy) is a rare manifestation of RF characterized by deformities of the fingers and toes. The condition may occur after repeated attacks of RF and results from recurrent inflammation of the fibrous articular capsule. There is ulnar deviation of the fingers.

The hand is usually painless, and there are no signs of inflammation. The deformities usually correctible but may become fixed in the later stages. There are no true erosions on radiography, and the rheumatoid factor is usually negative. A similar form of arthropathy is seen in patients with SLE.

FIGURE 81.3 Post-rheumatic fever Jaccoud arthropathy. **A,** Swan neck deformity in Jaccoud arthropathy, with ulnar deviation and metacarpophalangeal subluxation. **B**, Plain radiograph of the left hand showing deformities but not

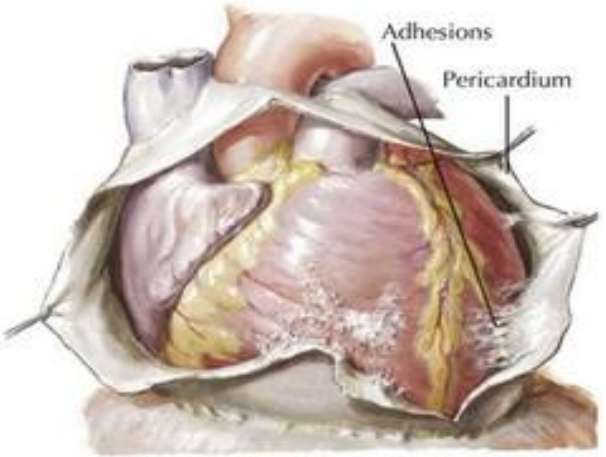
Carditis

The incidence of carditis during the initial attack of RF varies from 40% to 91%. Carditis is the most serious manifestation of RF because it may lead to chronic RHD. It may be asymptomatic and detected during clinical examination of patients with arthritis or chorea. Heart failure results from a combination of carditis and valvular dysfunction and occurs in 5% to 10% of the initial episodes, more frequently during recurrences of RF. Patients may have high fever, chest pain, or both; tachycardia is common, especially during sleep



Mitral valve.
Some fusion of chordae tendineae and thickening of cusps at contact areas; blood vessel growing into the cusps

Aortic valve.
Fusion of right cusp and posterior cusp, resulting in a bicuspid valve that is still competent



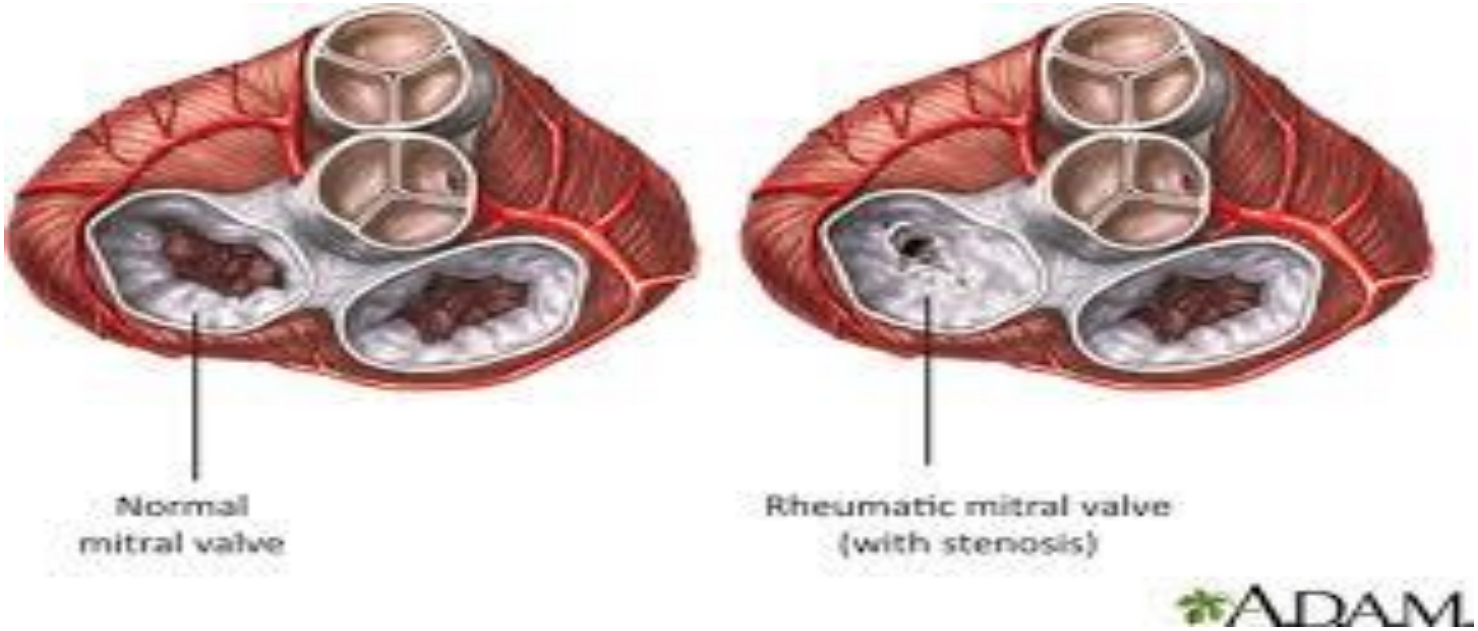
Adhesive pericarditis with focal calcification

Photomicrograph of interstitial nodule of myocardium.
Representing a healed Aschoff body (arrows)

Valvulitis

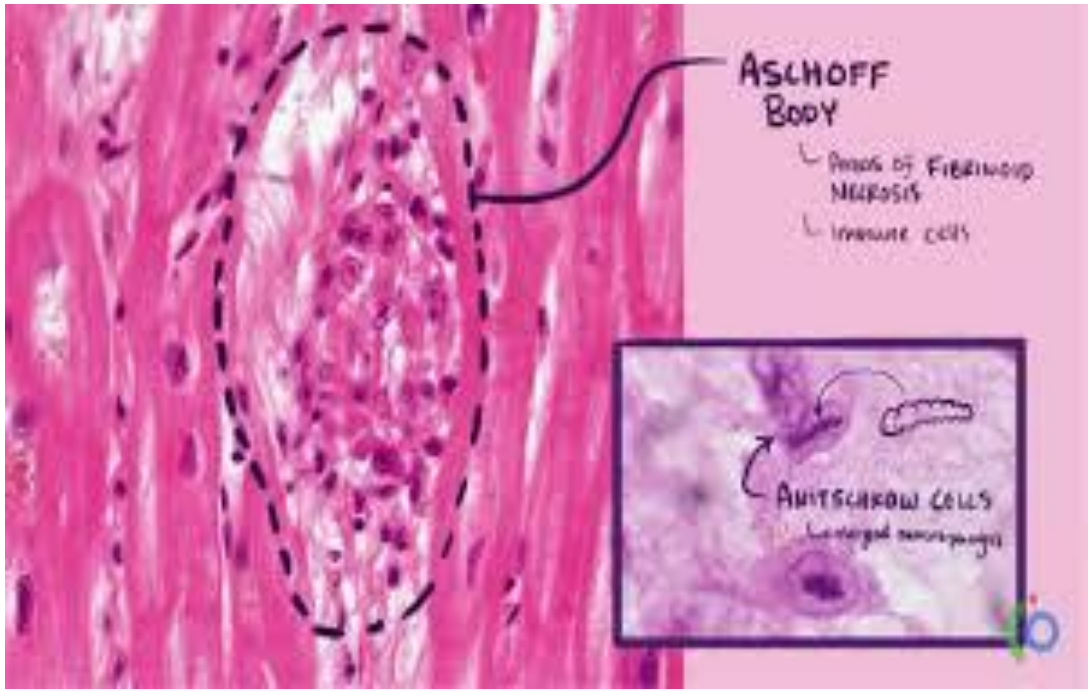
The clinical diagnosis of valvulitis has classically been made by auscultation of murmurs, but subclinical cases detected by echocardiography may occur in up to 18% of cases of ARF.

The most common valvular lesion is mitral regurgitation; aortic regurgitation is less common. Stenotic lesions are uncommon in the early stages of RF, but a transient apical mid-diastolic murmur (Carey-Coombs) may occur in association with the murmur of mitral regurgitation. In the presence of history of previous RHD, a change in the character of the murmurs or the appearance of a new murmur is indicative of acute rheumatic carditis.



Myocarditis

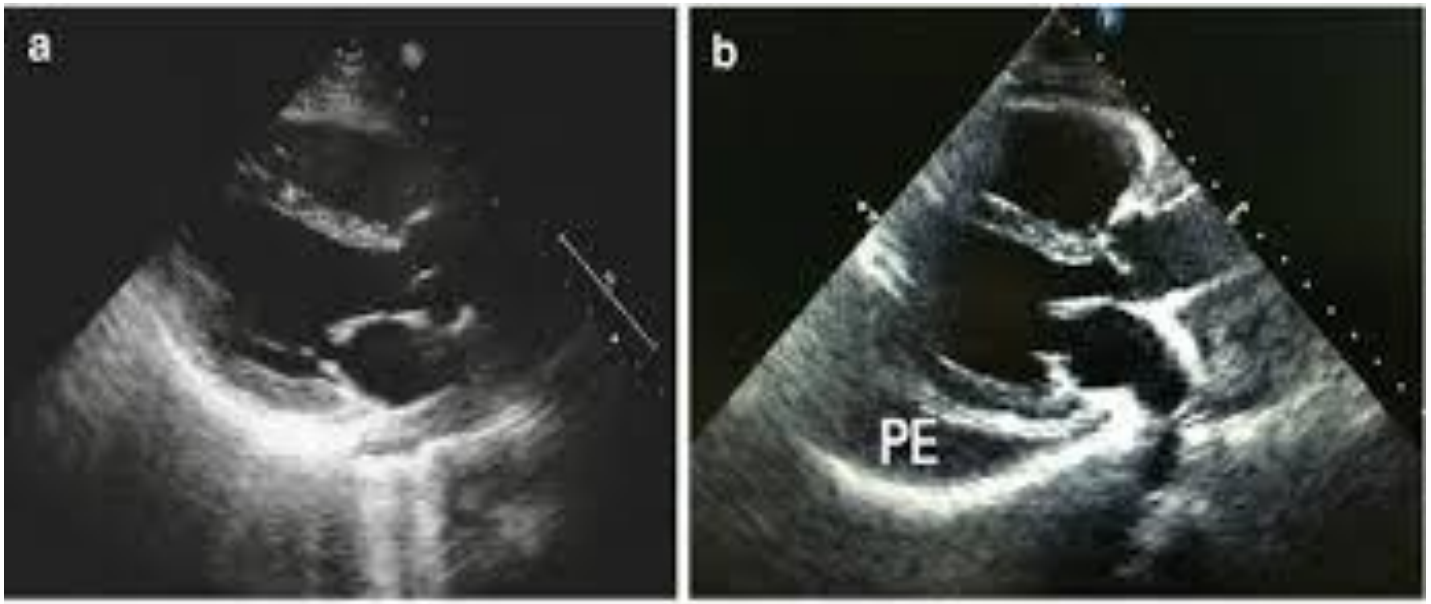
Inflammation of the myocardium is unlikely to be rheumatic in origin in the absence of valvulitis. Patients with myocarditis develop cardiomegaly or congestive heart failure, which may be severe and life threatening. Electrocardiographic abnormalities include varying degrees of heart block.



Pericarditis

Pericarditis occurs in approximately 10% of patients and may be manifested by anterior chest pain and a pericardial friction rub. The pericardial effusion may sometimes be large, but cardiac tamponade is rare and constrictive pericarditis does not occur.

Echocardiography is recommended for all patients with suspected or definite ARF, as it is more sensitive and specific than cardiac auscultation for detection of acute rheumatic carditis



"Dry pericarditis" "Wet pericarditis"

Sydenham Chorea

The CNS is affected in up to 40% of children with RF, predominating in females after puberty. The latent period between GAS pharyngitis and chorea is longer (6 to 8 weeks) than for arthritis and carditis; its onset is typically insidious and may be preceded by inappropriate laughing or crying. It can last for up to 2 years (usually 8 to 15 weeks); if it occurs in isolation, all inflammatory markers may be normal and the diagnosis may be overlooked as an indicator of ARF. It does not occur simultaneously with arthritis but may coexist with carditis.

Characteristic findings include fluctuating grip strength (milkmaid's grip), tongue fasciculations or tongue, facial grimacing, and explosive speech with or without tongue clucking.


Video 1

subcutaneous nodules

Rarely, subcutaneous nodules and erythema marginatum develop in patients already having carditis, arthritis, or chorea; they almost never occur alone. The subcutaneous nodules of RF occur most frequently on the extensor surfaces of large joints. They may be detected over the occiput, elbows, knees, ankles, and Achilles tendons.

Ordinarily, the nodules are firm, painless, and freely movable over the subcutaneous tissue; they vary in size from 0.5 to 2 cm and tend to occur in crops that may be related to the severity of the carditis. They are transitory (seldom more than 1 month) and respond to treatment of joint or heart inflammation. Fewer than 10% of children with ARF have nodules

GURE 81.4 Subcutaneous nodules of rheumatic fever over the bony pr

Erythema Marginatum

Erythema marginatum occurs as a serpiginous, flat, nonscarring, and painless rash in fewer than 6% of children. The rash usually appears on the trunk and proximal extremities but not the face and is evanescent, pink, and nonpruritic. It extends centrifugally while the skin at the center returns to normal, always with an irregular serpiginous border.

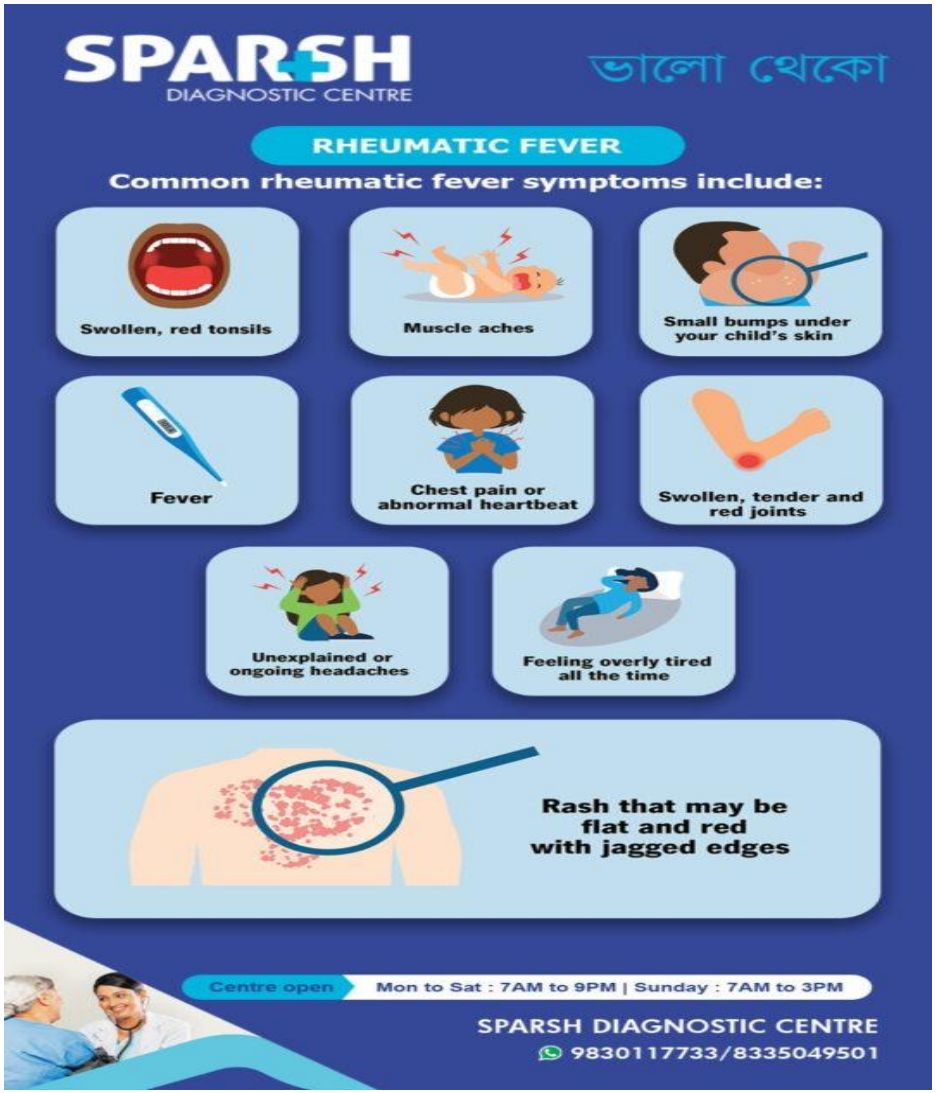
It sometimes lasts less than 1 day and may become more prominent after a shower. Its appearance is often delayed after the inciting streptococcal infection, with or after the other manifestations of rheumatic inflammation.

FIGURE 81.5 Erythema marginatum in acute rheumatic fever. The pen mark shows the location of the rash approximately 60 minutes previously. (From Cohen J, Powderly WG. Infectious Diseases. 2nd ed. St Louis: Mosby; 2004.)

Other Manifestations

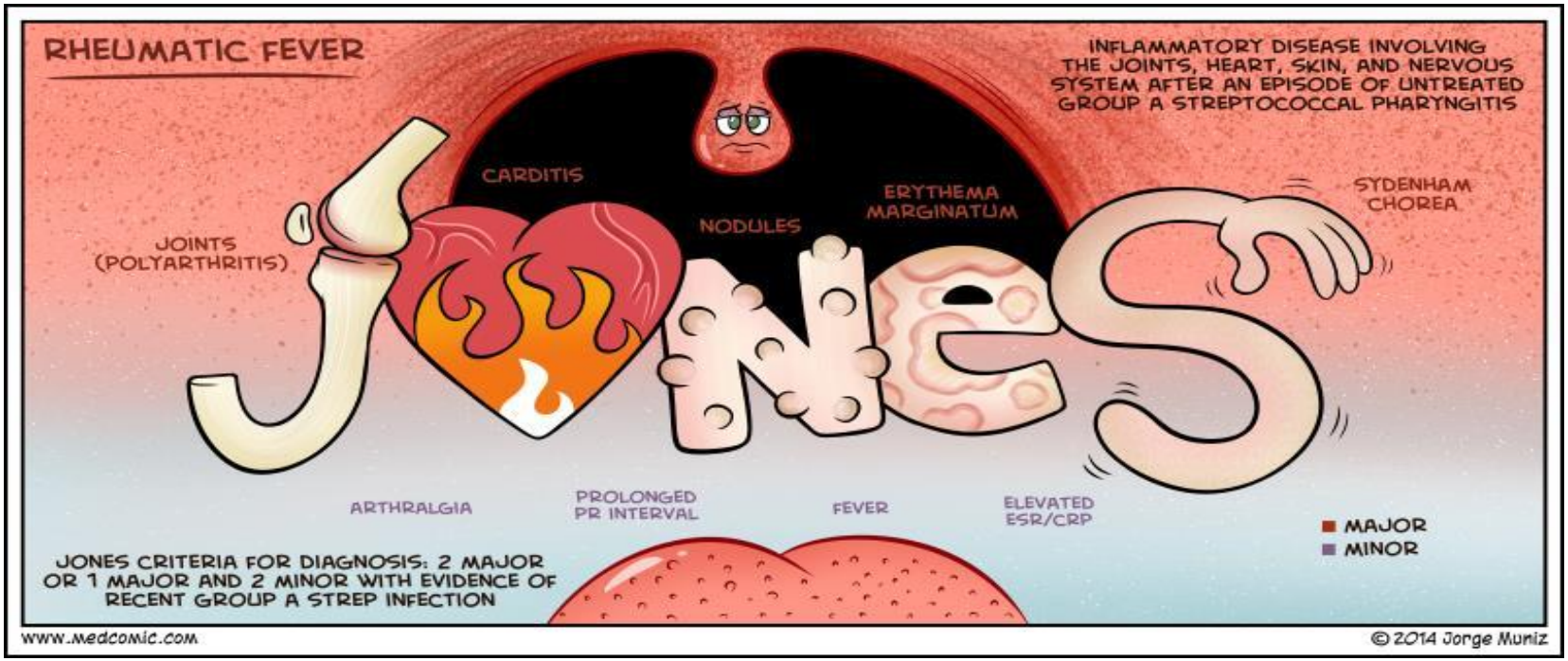
Fever (≥38.5°C), tachycardia during sleep, tachycardia out of proportion to fever, anorexia, and malaise can be prominent but are not specific.

The temperature usually decreases within 1 week, rarely lasting more than 4 weeks. Abdominal pain and anorexia can occur because of the hepatic involvement in heart failure or because of concomitant mesenteric adenitis; rarely, the situation may resemble acute appendicitis.



DIAGNOSIS

Diagnosis of a first episode of ARF is based on two major criteria, or one major and two minor criteria, each along with evidence of preceding GAS infection. Sydenham chorea alone (i.e., without minor criteria) fulfills diagnostic criteria if other causes of movement disorder are ruled out. Recent scarlet fever is highly suggestive.



Evidence of Preceding GAS Infection

Recent GAS infection is suggested by a recent history of pharyngitis and confirmed by one or more of the following:

1) throat swab culture (positive in about 11% of patients with diagnosis of RF),
2) an increased or preferably rising antistreptolysin O (ASO) titer
3) a positive rapid antigen detection test (RADT) in a child with clinical manifestations suggestive of streptococcal pharyngitis.

	History	Examination	Photographs	Bacteriological tests	Serological tests
Throat	Checklist of symptoms	CDR + Tonsillar Hypertrophy Grading Scale	Pharynx 	RADT, Molecular POCT, Culture 	ASO 
Skin sores	Checklist of symptoms	Total body sore score	Sores 	Culture 	ASO 

At present, serologic testing of antistreptolysin and anti- Dnase B antibody titers in two blood samples taken 2 to 4 weeks apart with seroconversion is thought to distinguish true GAS pharyngitis from pharyngeal GAS carriers. Throat cultures and RADT tests are often negative by the time ARF manifests, whereas ASO titers and anti- Dnase B typically peak 3 to 6 weeks after GAS pharyngitis;
about 80% of children with ARF have a significantly elevated ASO titer.
Polymerase chain reaction (PCR) based tests have been used with more than 90% specificity

TABLE 81.2 2015 American Heart Association Revised Jones Criteria for Diagnosis of Acute Rheumatic Fever

A. FOR ALL PATIENT POPULATIONS WITH EVIDENCE OF PRECEDING GAS INFECTION	
Diagnosis: Initial ARF	Two major manifestations or one major plus two minor manifestations
Diagnosis: Recurrent ARF	Two major, or one major and two minor, or three minor manifestations
B. MAJOR CRITERIA	
Low-Risk Populations*	**Moderate and High-Risk Populations**
Carditis†	Carditis†
• Clinical and/or subclinical	• Clinical and/or subclinical
Arthritis	Arthritis
• Polyarthritis only	• Monoarthritis or polyarthritis
	• Polyarthralgia‡
Chorea	Chorea
Erythema marginatum	Erythema marginatum
Subcutaneous nodules	Subcutaneous nodules
C. MINOR CRITERIA	
Low-Risk Populations*	**Moderate and High-Risk Populations**
Polyarthralgia	Monoarthralgia
Fever ≥ 38.5°C	Fever ≥ 38°C
ESR ≥60 mm in the first hour and/or CRP ≥ mg/dL§	ESR ≥30 mm/hr and/or CRP ≥3.0 mg/dL§
Prolonged PR interval after accounting for age variability (unless carditis is a major criterion)	Prolonged PR interval after accounting for age variability (unless carditis is a major criterion)

From Dougherty S, et al. Acute Rheumatic Fever and Rheumatic Heart Disease. 1st

MANAGEMENT

The primary goals of the treatment of a proven attack of ARF are to suppress the inflammatory response and minimize its effects on the heart and joints, to eradicate GAS from the pharynx, to provide relief of acute symptoms, and to initiate prophylaxis to prevent recurrent heart disease

General Management

Patients should limit their activities if they have symptoms of arthritis, chorea, or heart failure. Strenuous exertion should be avoided, especially in patients with carditis. In asymptomatic carditis, strict bed rest has no proven value, despite its traditional usage. Bed rest appears to be appropriate to lessen joint pain, and its duration should be individually determined. Ambulation can usually be started once fever has subsided and acute-phase reactants are returning to normal.

Antibiotic Treatment

Although poststreptococcal inflammation is well developed by the time ARF is detected, and throat swabs are rarely positive for GAS, a 10-day course of oral penicillin or amoxicillin, or a single injection of intramuscular benzathine penicillin (or erythromycin if allergic to penicillin) is used to eradicate any lingering organisms; however, this conventional strategy is untested. Thereafter, secondary prophylaxis should be commenced as described later.

TABLE 81.3 Management Protocol for Acute Rheumatic Fever

Diagnosis
• Admission to hospital
• Investigation to confirm ARF and to exclude other pathologies
• Blood tests including acute-phase reactants and serology for the streptococcal organism
• Electrocardiogram
• Echocardiographic evaluation
Eradication of GAS
• Oral penicillin V* for 10 days OR single dose of intramuscular benzathine penicillin G
• Treatment of coexisting streptococcal impetigo
Arthritis/Arthralgia and Symptomatic Treatment
• Paracetamol until the diagnosis has been confirmed
• NSAIDs (naproxen is preferably used)
• Corticosteroids in cases where NSAIDs cannot be used
Carditis/Heart Failure
• Bed rest, fluid restriction, heart failure medications (furosemide, spironolactone, ACEI)
• Corticosteroids for severe heart failure if surgery is not indicated or unavailable
• Surgery for intractable heart failure associated with severe mitral or aortic regurgitation; preferable to defer surgery until acute rheumatic activity has resolved
Chorea
• Penicillin V* orally or intramuscular benzathine penicillin G
• Haloperidol or carbamazepine can be considered if the abnormal movements interfere with daily activities
• Valproic acid reserved for refractory cases
• Multidisciplinary input as required for significant motor or neuropsychiatric manifestations
Discharge Procedure
• Discharge once there is clinical improvement and reduction in ESR or CRP
• Notification to health authorities
• Patient and family education
• Secondary prophylaxis
• Outpatient follow-up

PREVENTION

Primordial Prevention

Improvement of social conditions and increasing access to primary health care have been associated with dramatic fall in the incidence of RF even before the advent of antibiotics. Therefore, primordial prevention requires improving the broad determinants of health in people at high risk, including environmental, economic, social, behavioral, and cultural.

Primary Prevention

Antibiotic treatment of proven or presumed GAS pharyngitis with intramuscular (IM) penicillin appears to reduce the attack rate by as much as 80%. Eradication of GAS from the upper respiratory tract can usually be achieved with a single IM injection of benzathine penicillin or by a 10-day course of oral penicillin

TABLE 81.4 Drug Regimens for Primary and Secondary Prevention of Rheumatic Fever

ANTIBIOTICS FOR GROUP A STREPTOCOCCAL PHARYNGITIS				
AGENT	**DOSE**	**ROUTE**	**DURATION**	**RATING**
Penicillins				
Penicillin V (phenoxymethyl penicillin)	**Children** (≤27 kg [≤60 lb]) 250 mg 2-3 times daily **Children** (>27 kg [>60 lb]) **Adolescents and adults:** 500 mg 2-3 times daily	Oral	10 days	IB
Amoxicillin	50 mg/kg once daily (maximum 1 g)	Oral	10 days	IB
Benzathine penicillin G	600,000 U for patients ≤27 kg (≤60 lb), 1,200,000 U for patients >27 kg (>60 lb)	Intramuscular	Once	IB
For Individuals Allergic to Penicillin				
Narrow-spectrum cephalosporin* (cephalexin, cefadroxil)	Variable	Oral	10 days	IB
Clindamycin	20 mg/kg per day divided in three doses (maximum 1.8 g/day)	Oral	10 days	IIaB
Azithromycin	12 mg/kg once daily (maximum 500 mg)	Oral	5 days	IIaB
Clarithromycin	15 mg/kg per day divided bid (maximum 250 mg bid)	Oral	10 days	IIaB

Recommendations for Secondary Prevention of Acute Rheumatic Fever

- Secondary prophylaxis of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) comprises long-term antibiotic therapy for an individual's diagnosis with ARF or RHD to prevent ARF recurrences triggered by recurrent group A streptococcal (GAS) infection and therefore prevent the development of RHD or worsening of existing RHD.
- International guidelines differ slightly on recommendations of antibiotic choice, duration, and patient groups in whom it is indicated.
- Key standard recommendations usually include use of parental (intramuscular) benzathine penicillin G (BPG) every 4 weeks in individuals diagnosed with ARF and/or RHD for minimum 5- to 10-year period after diagnosis of the most recent ARF episode, or to the age of 21, whichever comes later. In some countries, duration for severe cases is lifelong.

*To be avoided in those with immediate (type I) hypersensitivity to penicillin.

Secondary Prevention

RCTs strongly support the superiority of IM compared with oral penicillin for prevention of RF recurrences. Shorter intervals between injections are more effective. Evidence strongly supports injections every 2 weeks (with an almost 50% reduction in the risk of RF recurrence compared with injections every 4 weeks), while it is less strong for injections taken every 3 weeks.

The duration should be individualized, taking into account the socioeconomic conditions, the risk of exposure to GAS, and the previous history of carditis with or without valve involvement.

Children without carditis should receive prophylaxis for 5 years or until age 21, whichever is longer; those with carditis with mild mitral regurgitation or healed carditis should receive prophylaxis for 10 years or until age 25 (whichever is longer).

Children with carditis and evidence of residual heart damage, or those who had valve surgery, should receive prophylaxis indefinitely or, alternatively, until age 40.

Finally, prophylaxis should be lifelong in all patients with severe valvular disease who have close contact with young children because these have a high rate of GAS carriage

Thank you
for your attention