

Acute Rheumatic Fever

Lecture In Internal Medicine

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Definition

- **Acute Rheumatic Fever (ARF) is an illness caused by an immunological reaction to infection with the bacterium group A streptococcus (GAS). It causes an acute, generalised inflammatory response, and is an illness that affects only certain parts of the body, mainly the heart, joints, brain and skin.**

RHDAustralia (ARF/RHD writing group), National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand.

Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (2nd edition). 2012

Classification (WHO Expert Consultation: rheumatic fever and rheumatic heart disease, 2004)

- **Primary episode of ARF:** a patient without a prior episode of rheumatic fever and without evidence of established rheumatic heart disease presents with a clinical illness that meets the requirements of the Jones criteria for diagnosis of ARF
- **Recurrent episode of ARF:** a patient who has had documented rheumatic fever in the past, but without evidence of established rheumatic heart disease, who presents with a new clinical illness that meets the requirements of the Jones criteria for diagnosis of ARF
- **Recurrent episode of ARF in patients with rheumatic heart disease:** a patient who has evidence of established rheumatic heart disease, who presents with a new clinical illness that meets the requirements of the Jones criteria for diagnosis of ARF

Epidemiology

Primary episodes of acute rheumatic fever

- occur mainly in **5-15 yrs**
- rare **<3 yrs and > 30 yrs old**
- girls>boys
- Environmental factors-- ***over crowding, poor sanitation, poverty***
- ***Incidence more during fall ,winter & early spring***

Global prevalence of rheumatic heart disease in children aged 5 to 14 years.

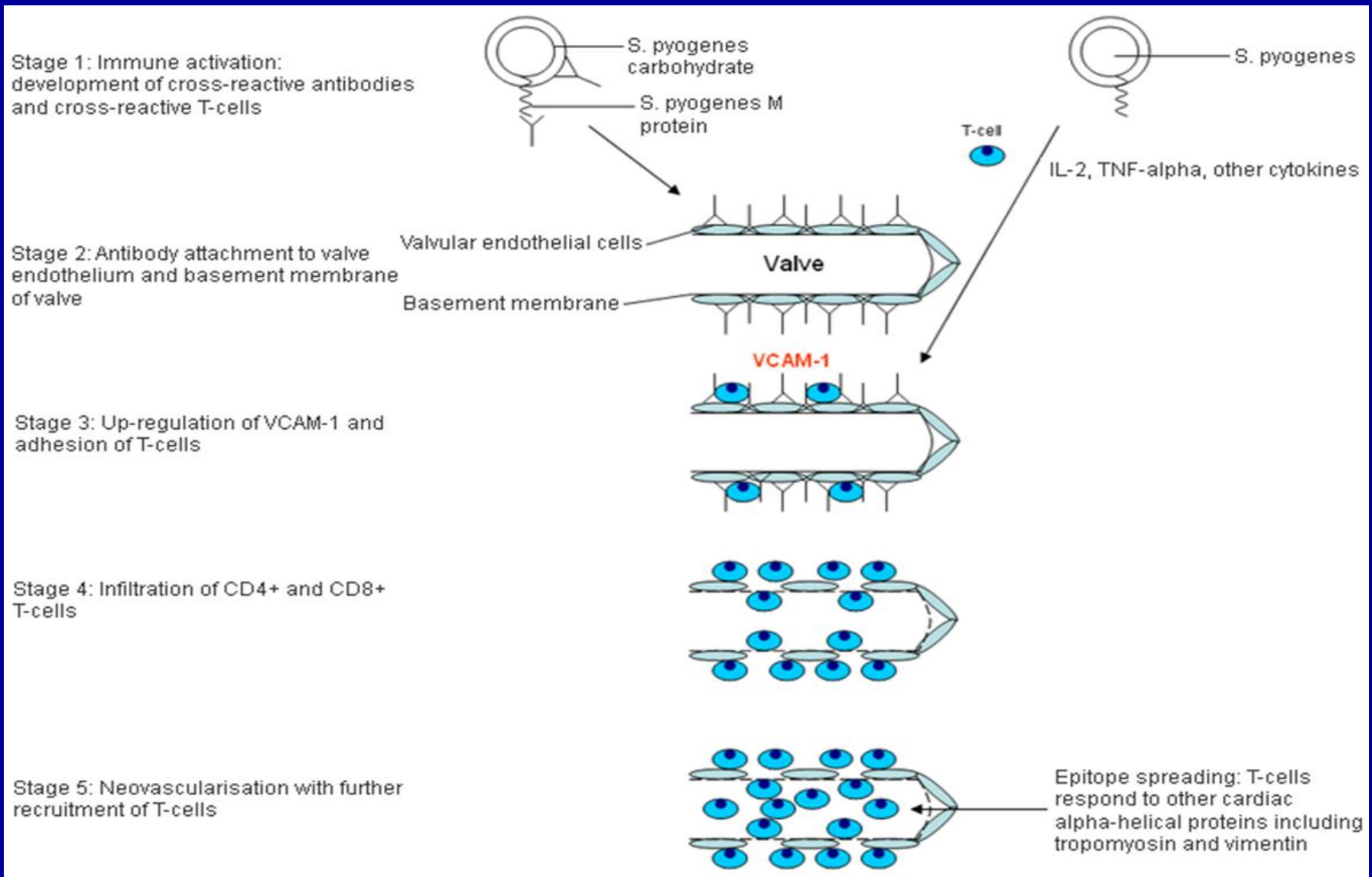
The greatest burden of acute rheumatic fever and rheumatic heart disease is in people in developing countries and in populations of indigenous people living in poverty in industrialised countries



Etiopathogenesis

- **Acute rheumatic fever** is a hypersensitivity reaction induced by group A streptococci.
- Antibodies against M proteins of certain strains of streptococci cross react with antigens in heart, joints and other tissues.
- Genetic susceptibility is suggested
- Autoimmune response to self antigens also suggested.
- **Chronic sequelae** are a result of progressive fibrosis (healing process) and blood turbulence in valvular areas

Proposed pathological mechanism of valvular inflammation in ARF



Group A Beta Hemolytic Streptococcus

- Strains that produces rheumatic fever -
M types 1, 3, 5, 6, 18 & 24
- Pharyngitis- produced by GABHS can lead to- acute rheumatic fever ,
rheumatic heart disease &
post strept. Glomerulonephritis
- Skin infection- produced by GABHS leads to post streptococcal glomerulonephritis only. It will not result in Rh.Fever or carditis as skin lipid cholesterol inhibit antigenicity

Pathologic Lesions

- Fibrinoid degeneration of connective tissue, inflammatory edema, inflammatory cell infiltration & proliferation of specific cells resulting in formation of **Ashcoff nodules**, resulting in-
 - Pancarditis** *in the heart*
 - Arthritis** *in the joints*
 - Ashcoff nodules** *in the subcutaneous tissue*
 - Basal gangliar lesions** *resulting in chorea*

Key diagnostic factors of ARF

Fever

- Common
- Occurs in nearly all cases at the onset of the illness.
- Historically, most cases will have fever above 39°C (102.2°F), but many experts suggest that 38°C (100.4°F) measured orally, rectally, or tympanic is significant.

Recent sore throat or scarlet fever

- common
- may suggest recent group A streptococcal infection

Arthritis

- The most common manifestation, present in 60-80% of patients
- In addition to arthralgia, the joints are red, warm and swollen.
- Arthritis is characteristically asymmetrical, migratory, and very painful, although some patients may present mild joint complaints.
- It usually resolves spontaneously in 2- 3 weeks.
- Commonly involved joints: knee, ankle, elbow & wrist
- **An excellent response to salicylates.**
- *Arthritis do not progress to chronic disease*

Arthritis



- asymmetrical, red, warm and swollen.

Arthritis

- If the patient has monoarthritis and is suspected to have ARF, but does not meet the criteria for diagnosis, the patient should withhold from treatment with NSAIDs so that the appearance of migratory polyarthritis (a major manifestation) is not masked.
- The arthritis of ARF is very sensitive to salicylates such as aspirin (as well as other NSAIDs), and if joint symptoms do not respond within 1 to 2 days of treatment with these anti-inflammatory drugs, the diagnosis should be reconsidered.

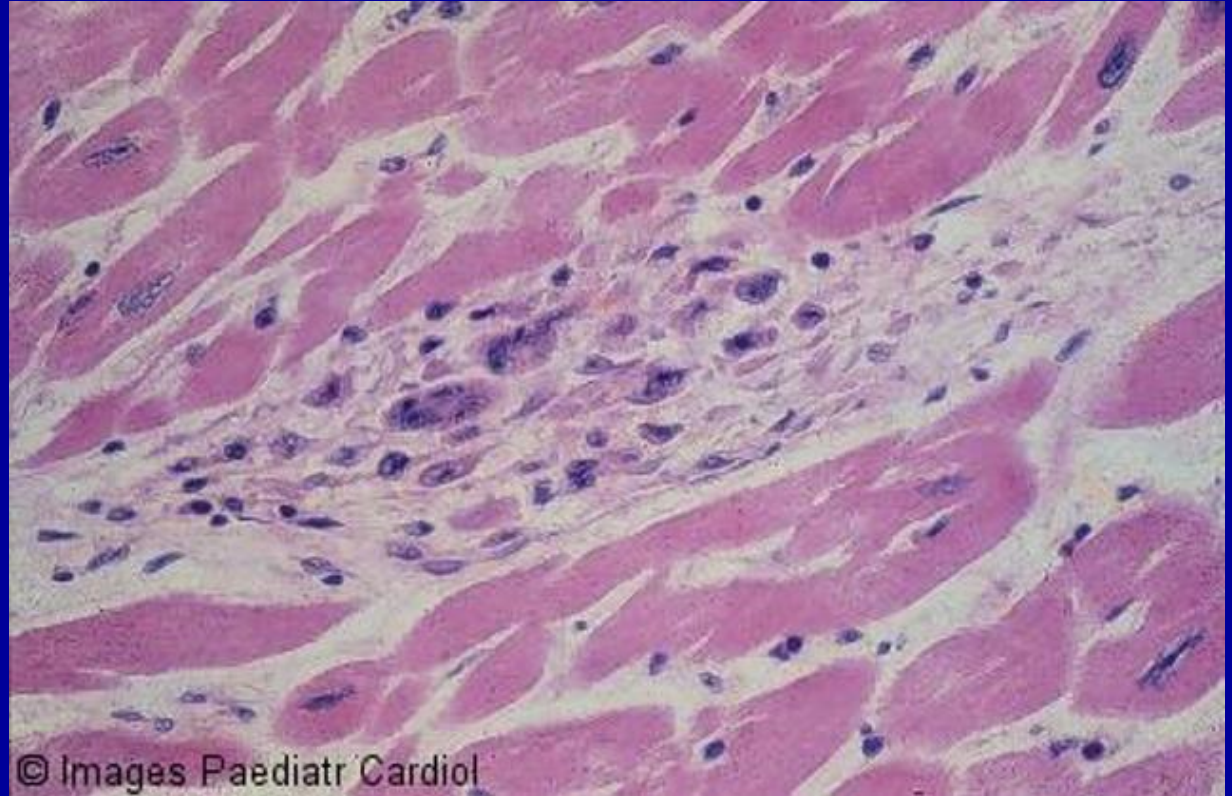
Carditis

Rheumatic inflammation in the heart may affect

- the pericardium (often asymptomatic),
- the myocardium (rarely contributes to cardiac failure),
- **or the endocardium** (the most common and the most important [i.e., the valvular tissue]).
- granulomatous inflammation manifests in the myocardium as Aschoff bodies

Carditis: Aschoff bodies

Aschoff bodies consist of fibrinoid change in connective tissue, lymphocytes, occasional plasma cells, and abnormal characteristic histiocytes.



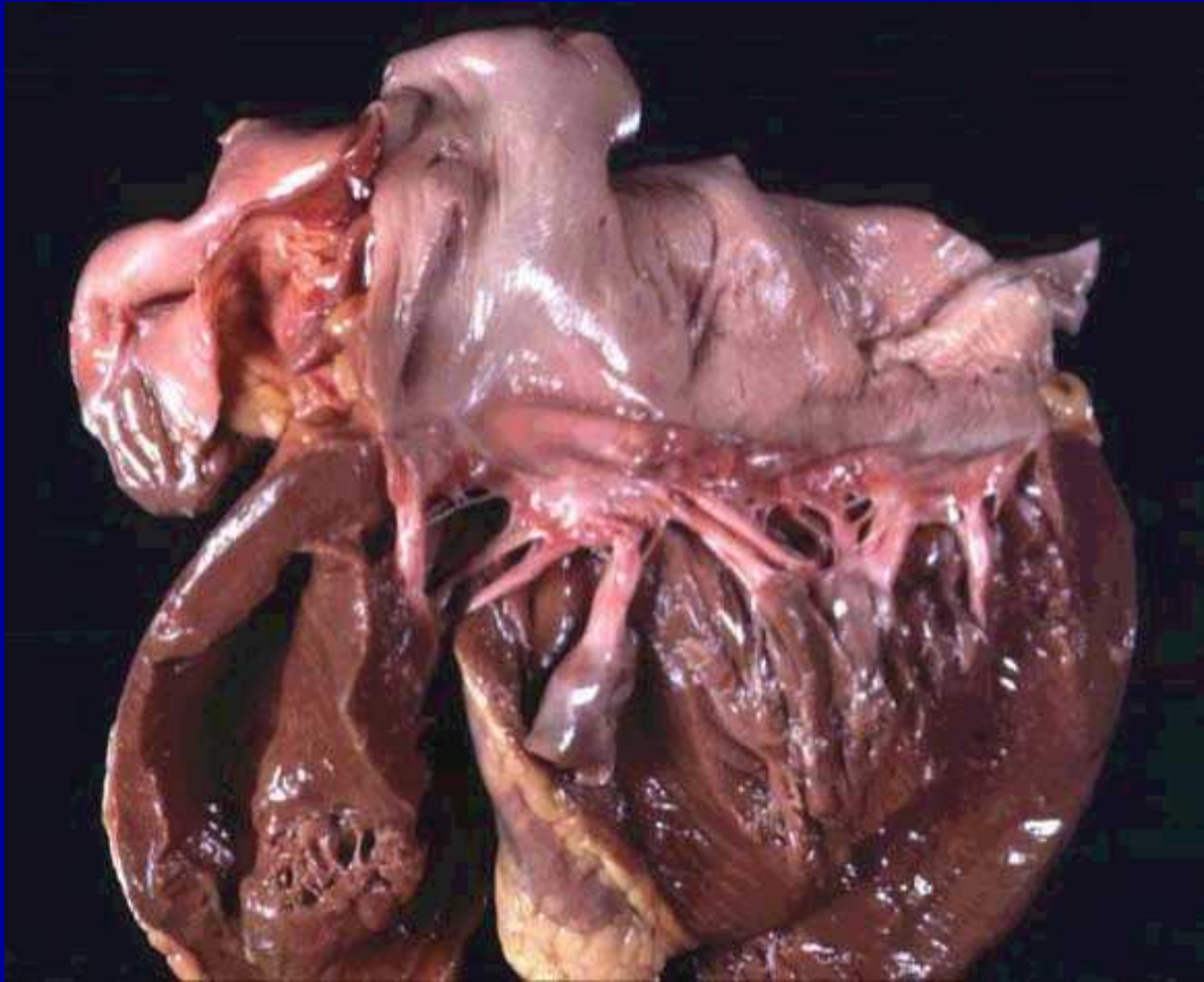
These may disrupt the electrical conduction pathways leading to prolongation of the PR interval on electrocardiogram

Clinical Features: Carditis

- Manifest as **pancarditis**(endocarditis, myocarditis and pericarditis), occur in 40-50% of cases
- Carditis is the only manifestation of rheumatic fever that leaves a sequelae & permanent damage to the organ
- Valvulitis occur in acute phase
- Chronic phase- fibrosis, calcification & stenosis of heart valves(**fishmouth valves**)

Carditis

- **Mitral valve** is most often affected with rheumatic heart disease, followed by **mitral and aortic together**, then **aortic alone**, then **mitral, aortic, and tricuspid together**.
- **Mitral stenosis (99% cases)** as a result of calcification.



Rheumatic
heart
disease.

Abnormal
mitral
valve.
Thick,
fused
chordae

Mitral valve in chronic rheumatic heart disease

- Mitral valve as seen from above in the left atrium.
- Typical "fish mouth" shape with chronic rheumatic scarring. Also buttonhole stenosis may occur



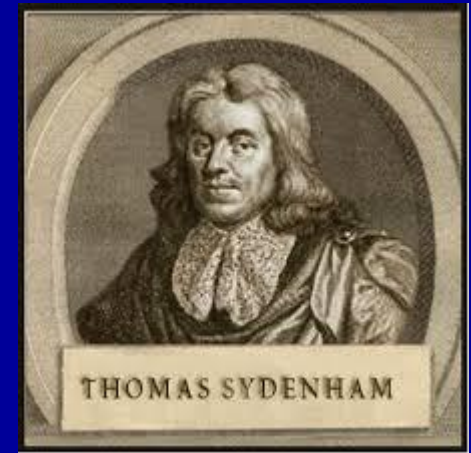
Stenotic mitral valve seen from left atrium. Both commissures are fused; the cusps are severely thickened. The left atrium is huge. The valve is both incompetent and stenotic



Carditis

- The clinical picture includes high pulse rate, congestive heart failure, arrhythmias and pericardial friction rubs.
- On the first attack, valvulitis is suspected in the presence of a new apical systolic murmur of mitral regurgitation (associated or not with an apical mid-diastolic murmur) and/or a basal diastolic murmur of aortic regurgitation.
- Cardiomegaly is noted on X-Ray and on echocardiogram.
- Myocarditis and/or pericarditis in the absence of valvular involvement is unlikely due to acute RF. It is contentious if myocardial dysfunction in acute RF is valvular or myocardial in origin.
- In a subset of patients, the initial presentation may be quite severe, with overt heart failure, fever and toxaemia, making the differential diagnosis with infective endocarditis very difficult, in particular in patients with recurrent rheumatic heart disease

Sydenham Chorea



- Occurs in 5-10% of cases
- Mainly in girls of 1-15 yrs age
- It is often the sole manifestation of ARF: web.stanford.edu
- It is usually a delayed manifestation: typically affects pts after a latency period of up to 6 months after group A streptococcal infection
- Involuntary movements, specially of the face and limbs, muscle weakness, disturbances of speech and gait.
- Chorea always disappears with sleep, and is made more pronounced by purposeful movements
- Children usually exhibit concomitant psychologic dysfunction, especially obsessive-compulsive disorder, increased emotional lability, hyperactivity, irritability and age-regressed behavior.

Sydenham Chorea

- Restlessness
- Clumsiness
- Emotional lability and personality changes
- Jerky, uncoordinated choreiform movements
- Inability to maintain protrusion of the tongue (chorea affecting the tongue). May resemble a 'bag of worms' when protruded.
- Milkmaid's grip. Rhythmic squeezing when the patient grasps the examiner's hands,
- Spooning sign . Flexion of the wrists and extension of the fingers when the hands are extended, seen with chorea.
- Pronator sign. Turning outwards of the arms and palms when held above the head, seen with chorea.

Sydenham Chorea



- involuntary movements, especially of the face and limbs,
- muscle weakness,

Erythema Marginatum

- Occurs in <5%.
- Evanescent, erythematous, non-pruritic rash with pale centers and rounded or serpiginous margins of 1-2 inches in size.
- Occur mainly on the trunk and proximal extremities and may be induced by application of heat.
- *Often associated with chronic carditis*

Erythema Marginatum



<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3232519/figure/F12/>

Erythema Marginatum

- The rash may appear and then disappear before the examiner's eyes, leading to the descriptive term of patients having '**smoke rings**' beneath the skin.
- Usually appears during the acute phase of rheumatic fever but may recur for weeks or even months after the acute phase has subsided.
- May be difficult to detect in dark-skinned people.

Subcutaneous nodules

- Rare, occurring in <5% of cases
- *Always associated with severe carditis*
- Painless, pea-sized, palpable firm, movable, measuring around 0.5 to 2 cm nodules
- Mainly over extensor surfaces of joints (particularly knees, wrists and elbows), or bony protuberances (spine, scapulae & scalp)
- Associated with strong seropositivity
- Often appear after the onset of acute rheumatic fever and last from a few days to 3 weeks.

Subcutaneous nodules

Painless, pea-sized, palpable nodule
over extensor surface of the elbow

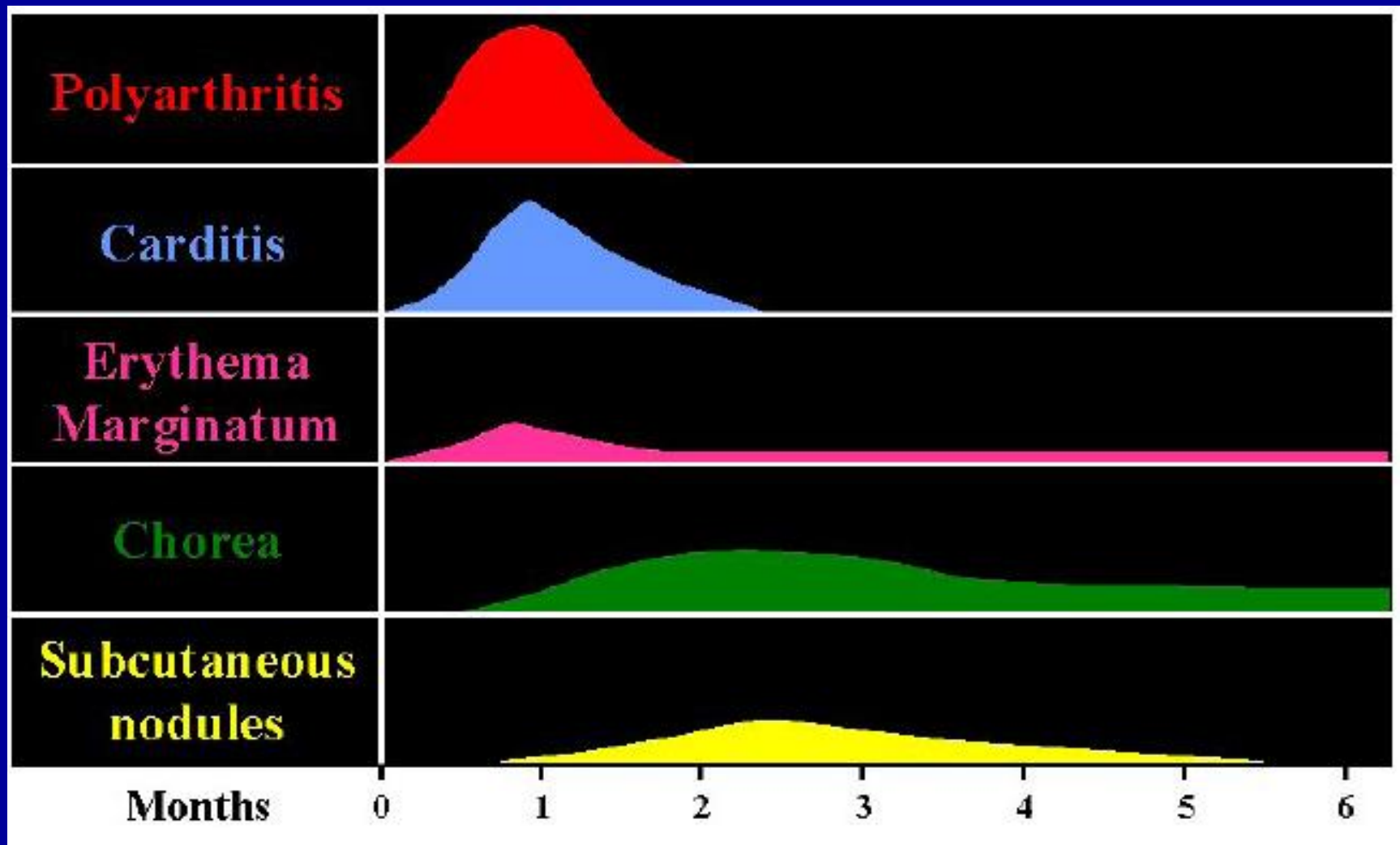


Subcutaneous nodule on the extensor surface of elbow of a patient with acute RF



© Images Paediatr Cardiol

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3232519/figure/F11/>



With the exception of Sydenham's chorea, which has a latency period of several months, the clinical manifestations of acute RF present after about 3 weeks following the streptococcal throat infection

Laboratory Findings

- High ESR
- Anemia, leucocytosis (rare!)
- Elevated C-reactive protein
- Elevated ASO titer (The test specificity has been shown to be 93% with ASO titers above 960 IU/ml)
 - Peak value attained at 3 weeks, then comes down to normal by 6 weeks
- Anti-DNAse B test
- Throat culture-GABH streptococci (prior to antibiotic therapy to culture for group A Streptococcus. Less than 10% are positive, reflecting the post-infectious nature of the disease)

Laboratory Findings (Contd)

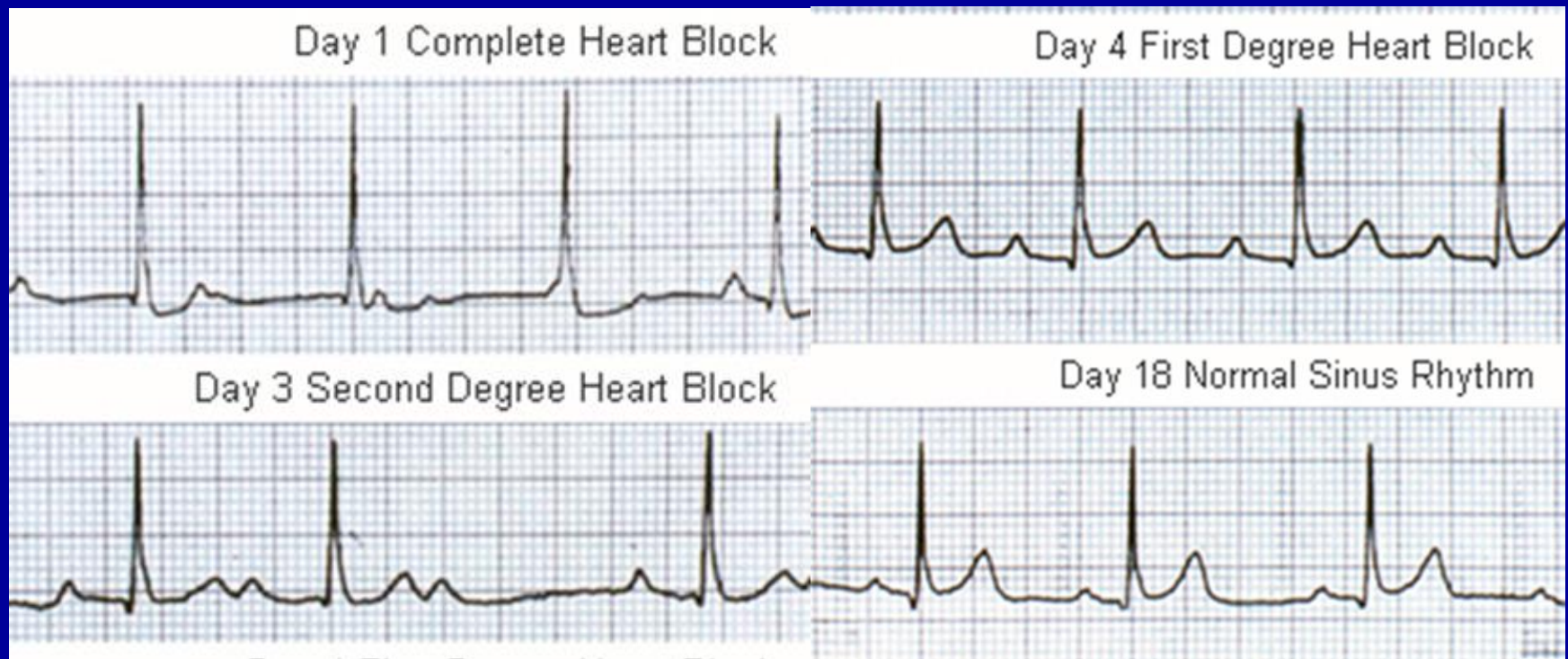
- Chest X-ray
- ECG- prolonged PR interval, 2nd or 3rd degree blocks, ST depression, T inversion
- 2D Echo cardiography- valve edema, mitral regurgitation, LA & LV dilatation, pericardial effusion, decreased contractility

Chest radiograph of an 8 year old patient with acute carditis before treatment b: Same patient after 4 weeks

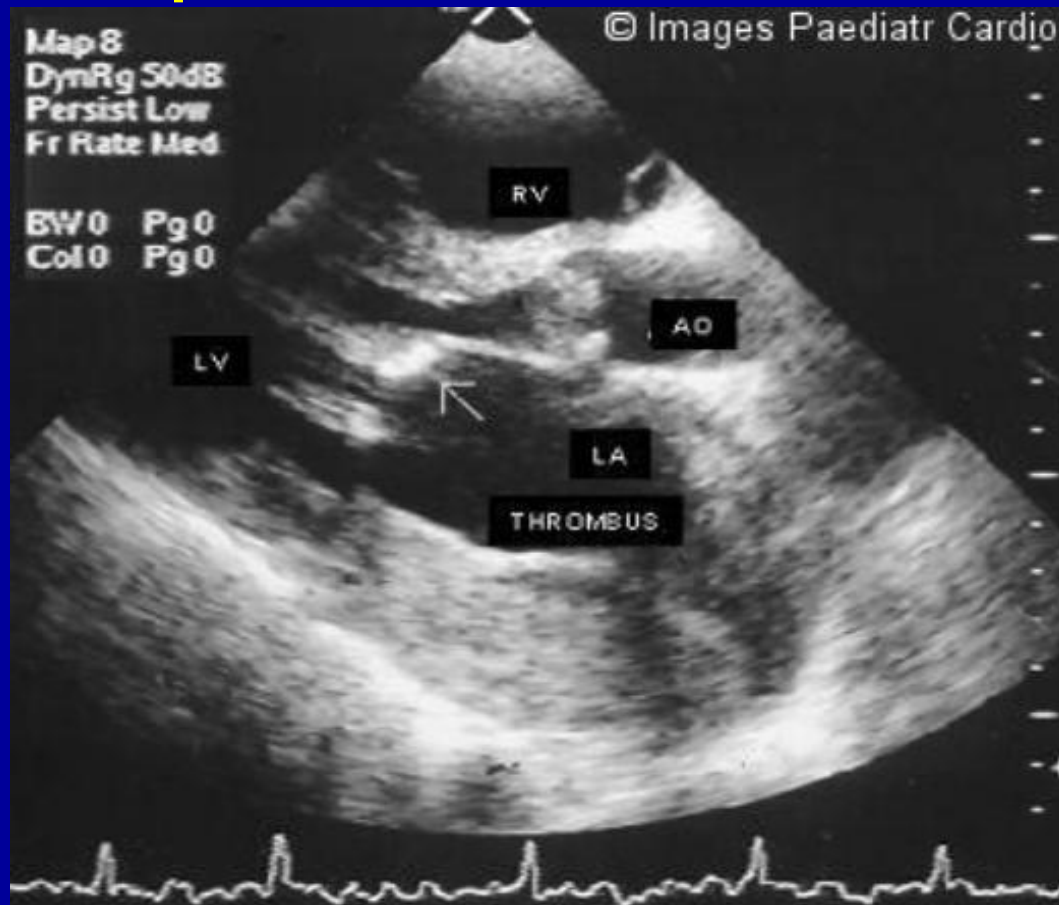


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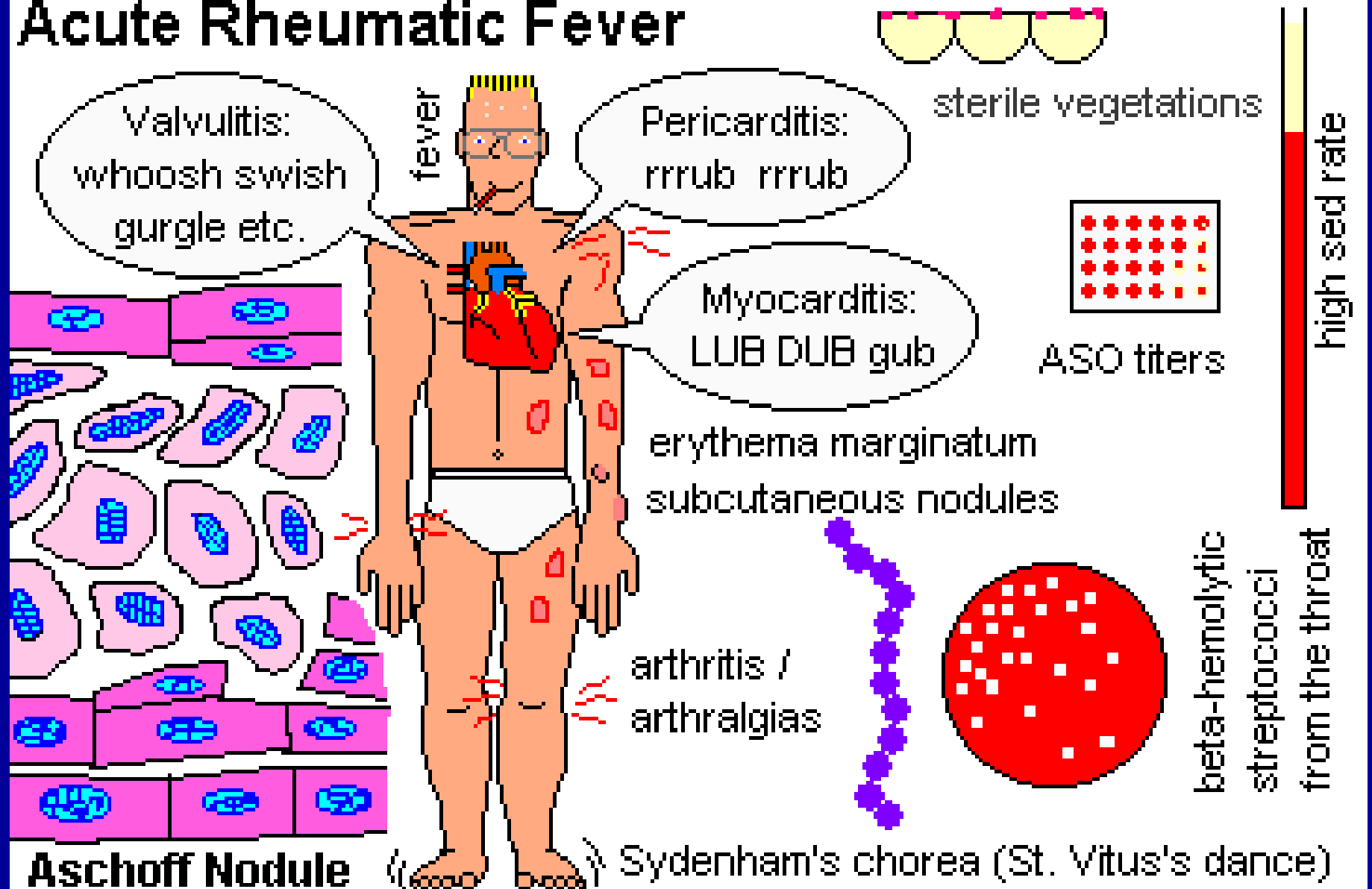
ECG showing heart block in ARF



Two-dimensional parasternal long-axis view of a patient with mitral stenosis, showing thickened valve cusps (arrow), with poor leaflet separation in diastole. Left atrium is enlarged, with a thrombus in the posterior aspect of it. Aortic valve is also stenotic



Acute Rheumatic Fever



Diagnosis

- Rheumatic fever is mainly a clinical diagnosis
- *No single diagnostic sign or specific laboratory test available for diagnosis*
- Diagnosis based on **MODIFIED JONES CRITERIA**, the latest revision of the Jones criteria were published in 2015

Revised Jones criteria, 2015

1. Two separate sets of criteria:

- low-risk settings (i.e., those with a rheumatic fever incidence ≤ 2 per 100,000 school-aged children or all-age rheumatic heart disease prevalence ≤ 1 per 1000 population per year)
- moderate- to high-risk populations

2. The diagnosis of possible rheumatic fever.

This category of diagnosis allows for the situation when a given clinical presentation may not fulfil the revised Jones criteria but the clinician may still have good reason to suspect the diagnosis.

The diagnosis of a primary episode of ARF

Any of the following criteria are met.

- Evidence of a **recent group A streptococcal** infection with at least **2 major** manifestations or **1 major plus 2 minor** manifestations present.
- **Rheumatic chorea**: can be diagnosed without the presence of other features and without evidence of preceding streptococcal infection. It can occur up to 6 months after the initial infection.
- **Chronic rheumatic heart disease**: established mitral valve disease or mixed mitral/aortic valve disease, presenting for the first time (in the absence of any symptoms suggestive of acute rheumatic fever).

Evidence of antecedent group A streptococcal infection

1 of the following:

- Elevated or rising streptococcal antibody titre
- Positive throat culture
- Positive rapid antigen test for group A streptococci
- Recent scarlet fever.

Major manifestations of ARF:

1. Carditis: includes carditis demonstrated only by echocardiogram (i.e., subclinical carditis).
2. Arthritis: polyarthritis (low-risk populations) or monoarthritis or polyarthritis or polyarthralgia (moderate- to high-risk populations).
3. Chorea.
4. Erythema marginatum:
5. Subcutaneous nodules.

Minor manifestations of ARF

1. Fever: $\geq 38.5^{\circ}\text{C}$ ($\geq 101.3^{\circ}\text{F}$; low-risk populations) or $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$; moderate- to high-risk populations)
2. Arthralgia: polyarthralgia (low-risk populations) or monoarthralgia (moderate- to high-risk populations)
3. Elevated inflammatory markers: ESR ≥ 60 mm/hour and/or CRP ≥ 28.57 nanomols/L (≥ 3.0 mg/dL) (low-risk populations) or ESR ≥ 30 mm/hour and/or CRP ≥ 28.57 nanomols/L (≥ 3.0 mg/dL) (moderate- to high-risk populations)
4. Prolonged PR interval on ECG: a prolonged PR interval that resolves over 2 to 3 weeks may be a useful diagnostic feature in cases when clinical features are not definitive. First-degree heart block sometimes leads to a junctional rhythm. Second-degree and even complete block are less common but can occur

Major and minor manifestations of ARF

- in a patient in whom arthritis is considered a major manifestation, arthralgia cannot be counted as a minor manifestation
- in a patient in whom carditis is considered as a major manifestation, a prolonged PR interval cannot be counted as a minor manifestation

Diagnosing recurrent rheumatic fever

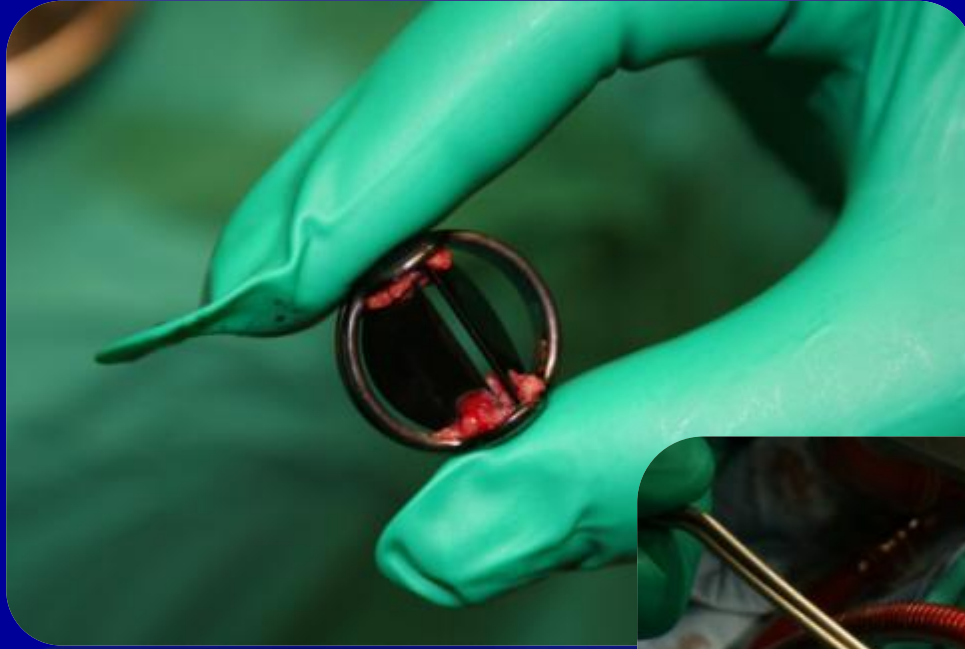
Recurrence of rheumatic fever, with or without evidence of established rheumatic heart disease, requires

- the same criteria as a primary episode. (i.e., 2 major manifestations, or 1 major plus 2 minor manifestations) *or*
- the presence of 3 minor manifestations.

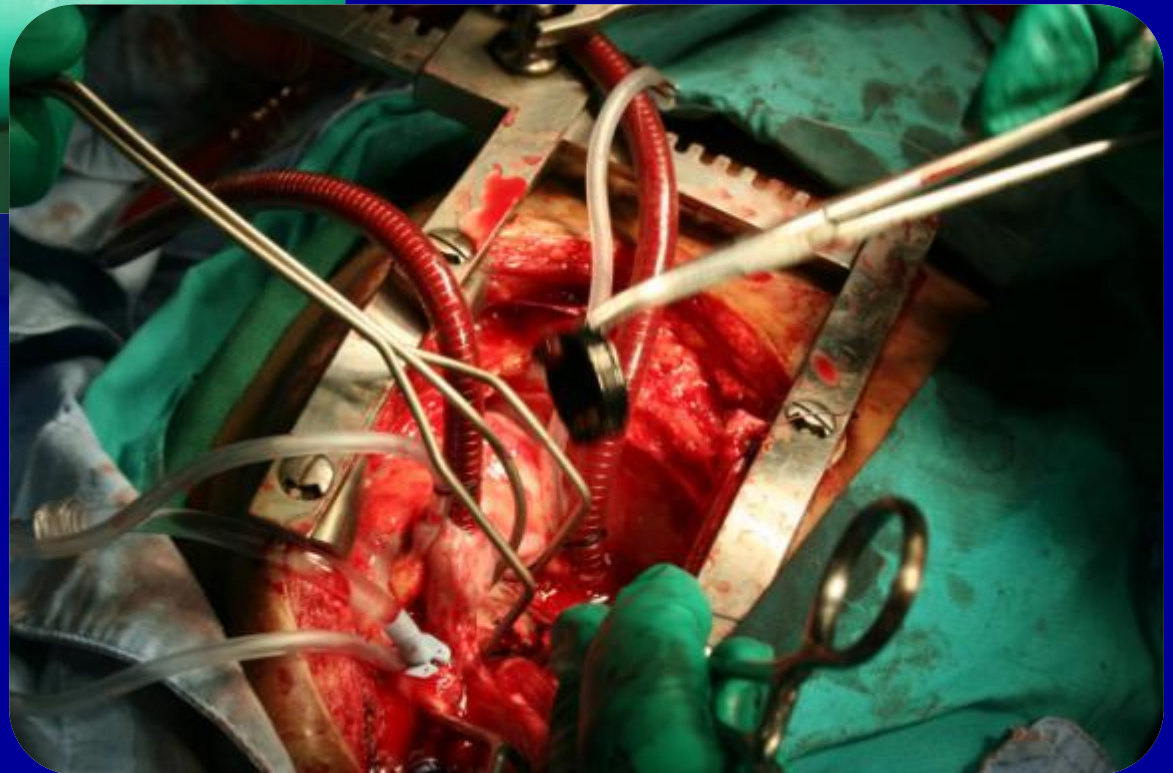
Diagnosis of recurrence requires evidence of a recent group A streptococcal infection

Treatment

- Step I** - primary prevention
(eradication of streptococci)
- Step II** - anti inflammatory treatment
(aspirin,steroids)
- Step III**- supportive management &
management of complications
- Step IV**- secondary prevention
(prevention of recurrent attacks)



**THIS IS TOO
LATE**



STEP I: Primary Prevention of ARF (Treatment of Streptococcal Tonsillopharyngitis)

Primary options

- phenoxymethylpenicillin potassium: children ≤ 27 kg: 250 mg orally two to three times daily for 10 days; children > 27 kg and adults: 500 mg orally two to three times daily for 10 days
- benzathine benzylpenicillin: children ≤ 27 kg: 600,000 units intramuscularly as a single dose; children > 27 kg and adults: 1.2 million units intramuscularly as a single dose
- amoxicillin: children: 50 mg/kg/day orally given in 2 divided doses for 10 days, maximum 1000 mg/day; adults: 875 mg orally twice daily for 10 days

STEP I: Primary Prevention of ARF (Treatment of Streptococcal Tonsillopharyngitis)

Secondary options

- azithromycin: adults: 500 mg orally once daily for 5 days
- clarithromycin: adults: 250 mg orally twice daily for 10 days
- erythromycin base: adults: 250-500 mg orally four times daily for 10 days
- cephalexin: adults: 500 mg orally twice daily for 10 days
- cefadroxil: adults: 1000 mg/day orally given in 1-2 divided doses for 10 days
- clindamycin: adults: 300-600 mg orally every 8 hours for 10 days

Step II: Anti inflammatory treatment

NSAIDs – if arthritis is present

Primary options

- aspirin: adults: 4000 mg/day orally given in divided doses every 4-6 hours

Secondary options

- naproxen: adults: 250-500 mg orally twice daily, maximum 1250 mg/day
- ibuprofen: adults 400-800 mg orally three times daily, maximum 2400 mg/day

Step II: Anti inflammatory treatment

Glucocorticoids (GCSs)

- Most patients with mild or moderate carditis without cardiac failure do not require any therapy.
- A subset of patients with **carditis who have cardiac** failure do require treatment. The side effects of GCSs include gastrointestinal bleeding and fluid retention, both of which can worsen heart failure.
- Concurrent administration of ranitidine (or PPI) should be considered to reduce the risk of gastrointestinal bleeding.

Step II: Anti inflammatory treatment

Glucocorticoids (GCSs)

- GCSa will usually also control joint pain and fever, and so aspirin can be discontinued while the patient is being treated with GCSs; aspirin may need to be restarted after the patient completes the course of glucocorticoid treatment, particularly if this course is short.
- If more than 1 week of treatment is required, taper by 20% to 25% each week.

Step II: Anti inflammatory treatment

Glucocorticoids (GCSs)

Primary options

- prednisolone: children and adults: 1-2 mg/kg/day orally for 7 days, maximum 80 mg/day
- methylprednisolone: children and adults: 24 mg orally once daily for 7 days

Step III: Supportive management & management of complications

- Bed rest
- Treatment of congestive cardiac failure
- Treatment of chorea
- Rest to joints & supportive splinting

STEP IV : Secondary Prevention of Rheumatic Fever

The WHO defines secondary prophylaxis for rheumatic fever as "the continuous administration of specific antibiotics to patients with a previous attack of rheumatic fever, or well-documented rheumatic heart disease. The purpose is to prevent colonisation or infection of the upper respiratory tract with group A streptococci and the development of recurrent attacks of rheumatic fever"

Duration of secondary prophylaxis

Suggested duration of secondary prophylaxis*

Category of patient	Duration of prophylaxis
Patient without proven carditis	For 5 years after the last attack or 18 years of age (whichever is longer)
Patient with carditis (mild mitral regurgitation or healed carditis)	For 10 years after the last attack, or 25 years of age (whichever is longer)
More severe valvular disease	Lifelong
Valvular surgery	Lifelong

*These are only recommendations and must be modified by individual circumstances as warranted.

Antibiotics used in secondary prophylaxis of RF (from WHO Technical Report on RF and RHD 2004)

Antibiotic	Mode of administration	Dose
Benzathine benzylpenicillin	Single IM injection every 3-4 weeks	$\geq 30\text{kg}$: 1.2 million units $< 30\text{kg}$: 600,000 units
Penicillin V	Oral	250 mg twice daily
Sulfonamide (e.g. sulfadiazine, sulfasoxazole)	Oral	$\geq 30\text{kg}$: 1 gram daily $< 30\text{kg}$: 500mg daily
Erythromycin	Oral	250mg twice daily

WHO Expert Consultation on Rheumatic Fever and Rheumatic Heart Disease.
Rheumatic fever and rheumatic heart disease: report of a WHO Expert Consultation,
29 October - 1 November 2001. Geneva; 2004

Prognosis

- Rheumatic fever can recur whenever the individual experience new GABH streptococcal infection,if not on prophylactic medicines
- Good prognosis for older age group & if no carditis during the initial attack
- Bad prognosis for younger children & those with carditis with valvar lesions

Summary

- ARF continues to cause a large burden of mortality and morbidity in developing countries. It is less common in developed countries but continues to be seen in indigenous communities and during outbreaks.
- It is caused by an autoimmune process following infection with group A streptococci.
- No single test can diagnose acute rheumatic fever. Diagnosis is clinical and relies on the Jones criteria.
- The 5 major manifestations of acute rheumatic fever are carditis, arthritis, chorea, erythema marginatum, and subcutaneous nodules, of which the most common are carditis and arthritis.

Summary (cont'd)

- The Jones criteria were revised in 2015 to include separate criteria for low-risk and moderate- to high-risk populations.
- While all other manifestations of acute rheumatic fever resolve without sequelae, carditis can lead to chronic rheumatic heart disease.
- No treatment has been shown to alter the progression of acute rheumatic fever to chronic rheumatic heart disease.
- Secondary prophylaxis can improve the prognosis of established rheumatic valvular disease.