Immunology Team

Cardiovascular Block

Lecture 1

Rheumatic Fever and Rheumatic Heart Disease

➔ Note or explanation.

Red ➔ Important point.

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Definition:

Rheumatic fever is an inflammatory disease which may develop after a **Group A Streptococcal infection** such as Strep. throat infection or scarlet fever .

Rheumatic fever:

- Can involve the **heart, joints, skin, and brain**
- It commonly appears in children ages **5 through 15**

RF is secondary to pharyngitis

Epidemiology of Rheumatic Fever (RF):

- ~3% of persons with untreated group A streptococcal **pharyngitis** develop rheumatic fever
- 15-20 million new cases a year in developing countries

Risk factors

- Low standard of living
- Crowding

Ppl who have HLA DR7 (have to know that it is from class 2) are the most prone to develop RF even if the person got treated for their throat infect.

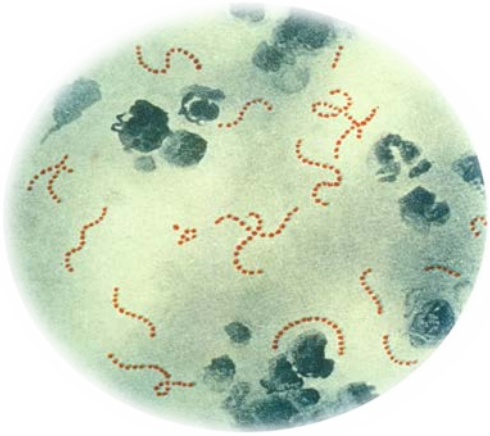
Individual (HLA) susceptibility is also important.

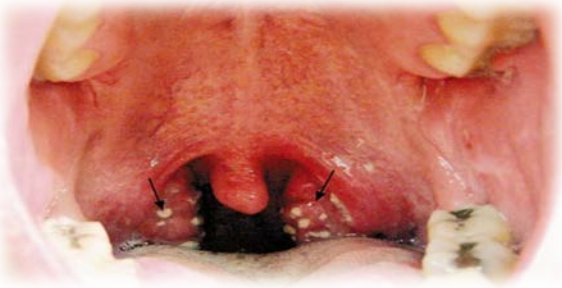
Antigen-presenting cells bearing the **HLA-DR7** molecule from RHD patients preferentially recognize heart-tissue protein.

Organism

group A streptococcus arrange in chain

- Caused by **group A streptococcus**
- There is a latent period of **~3 weeks (1–5 weeks)** between the group A streptococcal infection and the appearance of the clinical features of RF.





white patches (pus) in the tonsillitis

Group A b-haemolytic streptococcus

- All cases associated with **recent infection** (e.g. pharyngitis)
- **Antibody and cellular immune response** cross-reacts with human connective tissue

M proteins	**Attachment & interferes with host immune response** (* antigenic protein that is found in cell wall which protect the cell from phagoctic)
Hyaluronic acid capsule	**Camouflages the bacterium**
Streptokinases	**Dissolves blood clots** (*that will lead to spread the infection very quickly)
Peptidases	**Degrades proteins involved in immune response**
Pyrogenic toxins	**Stimulate fever, rash & shock**
Streptolysins	**Lyse erythrocytes, leukocytes & platelets** (* when we do ASO test we check the Streptolysins if it's high so the person have RF)

Post streptococcal glomerulonephritis is caused by streptococcal antigen-antibody immune complexes **(Type III hypersensitivity reaction)**

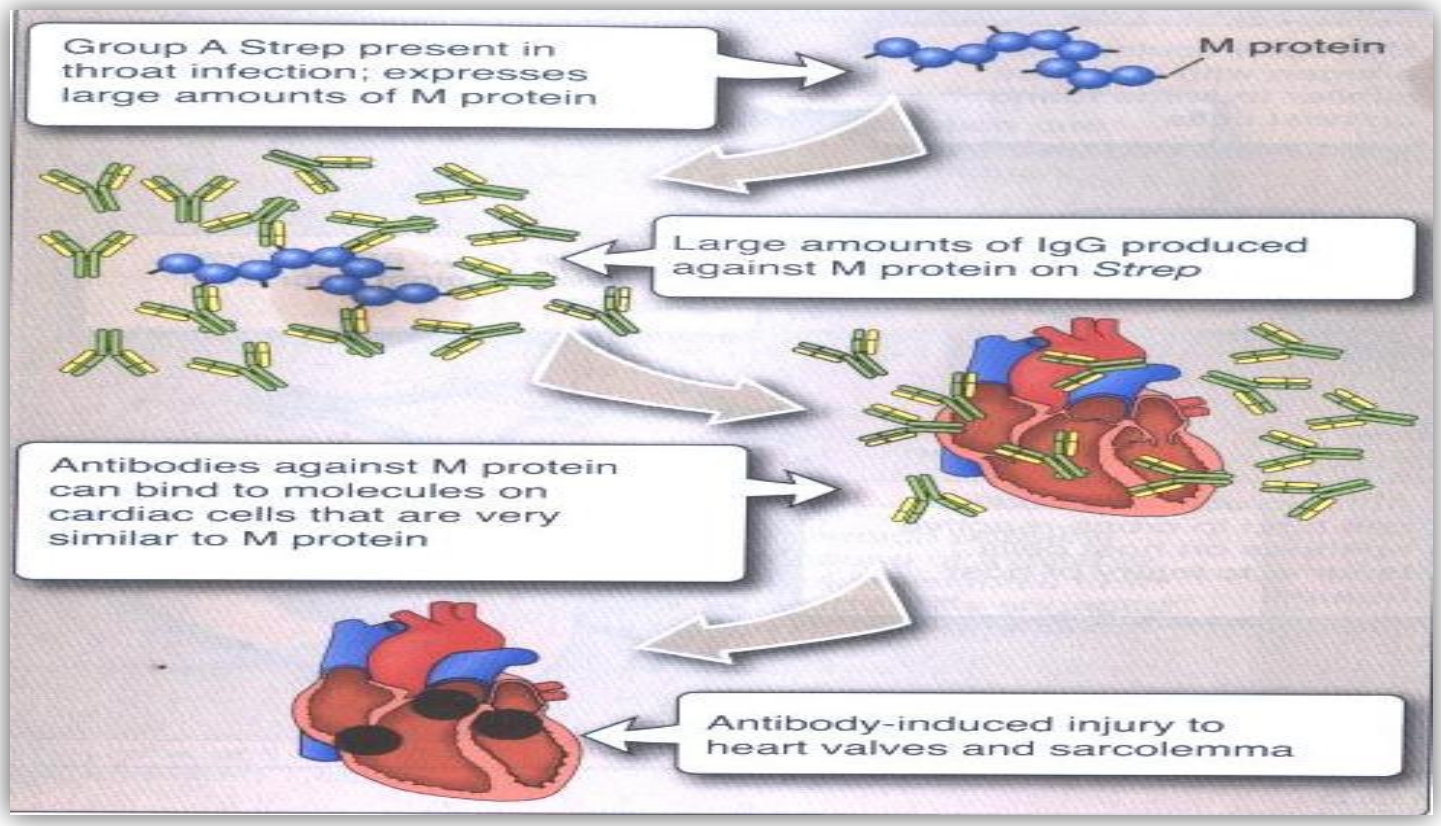
PATHOGENESIS

means around the arteries.

- Rheumatic fever affect the **peri-arteriolar** connective tissue
- It is believed to be caused by **antibody cross-reactivity**
- This cross-reactivity is a **Type II hypersensitivity** reaction and is termed ***molecular mimicry***

body cell Ag are similar to pathogenic organism Ag

- Group A streptococcus pyogenes has a cell wall composed of branched polymers which sometimes contain **"*M proteins* "** that are highly antigenic
- The **antibodies** which the immune system generates against the **"*M proteins*"** may cross react with **cardiac myofiber protein myosin and smooth muscle cells of arteries, inducing cytokine release and tissue destruction**
- This inflammation occurs through direct attachment of **complement** and **Fc receptor-mediated recruitment of neutrophils and macrophages**



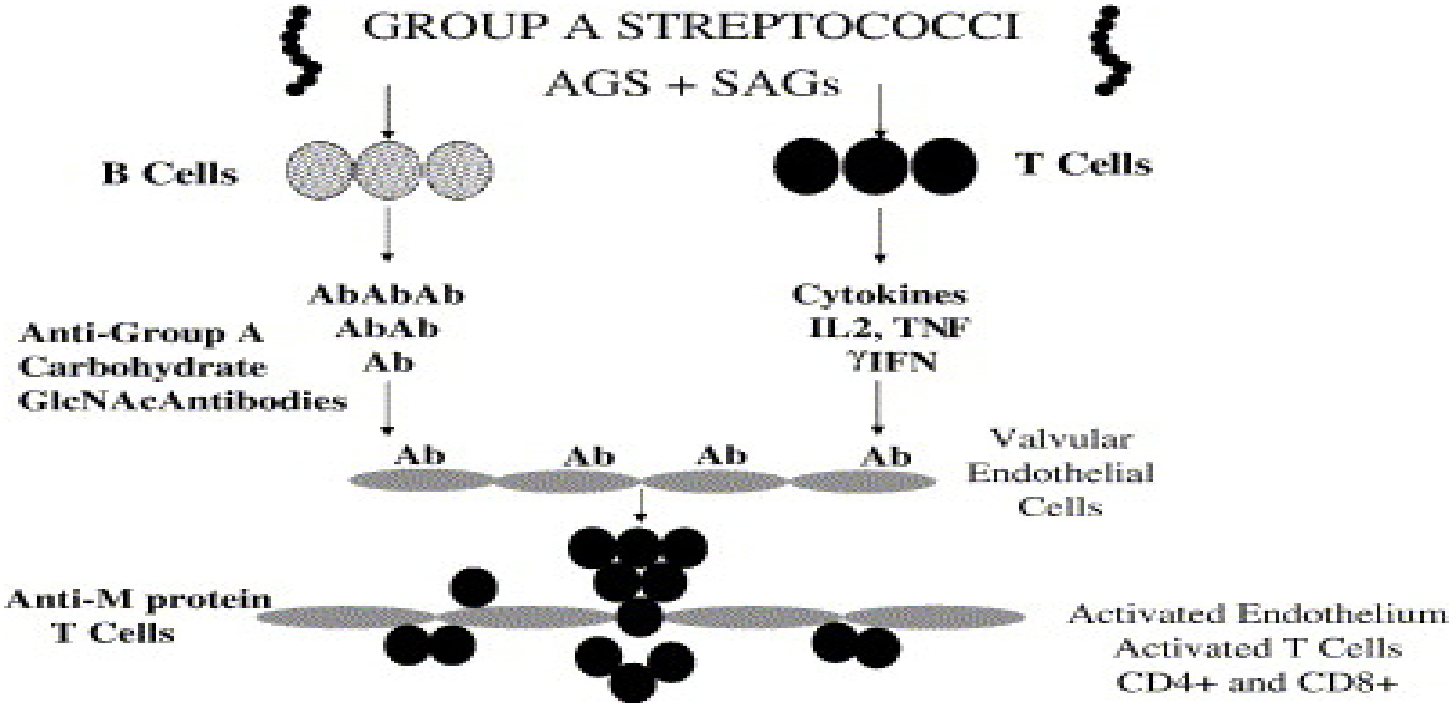
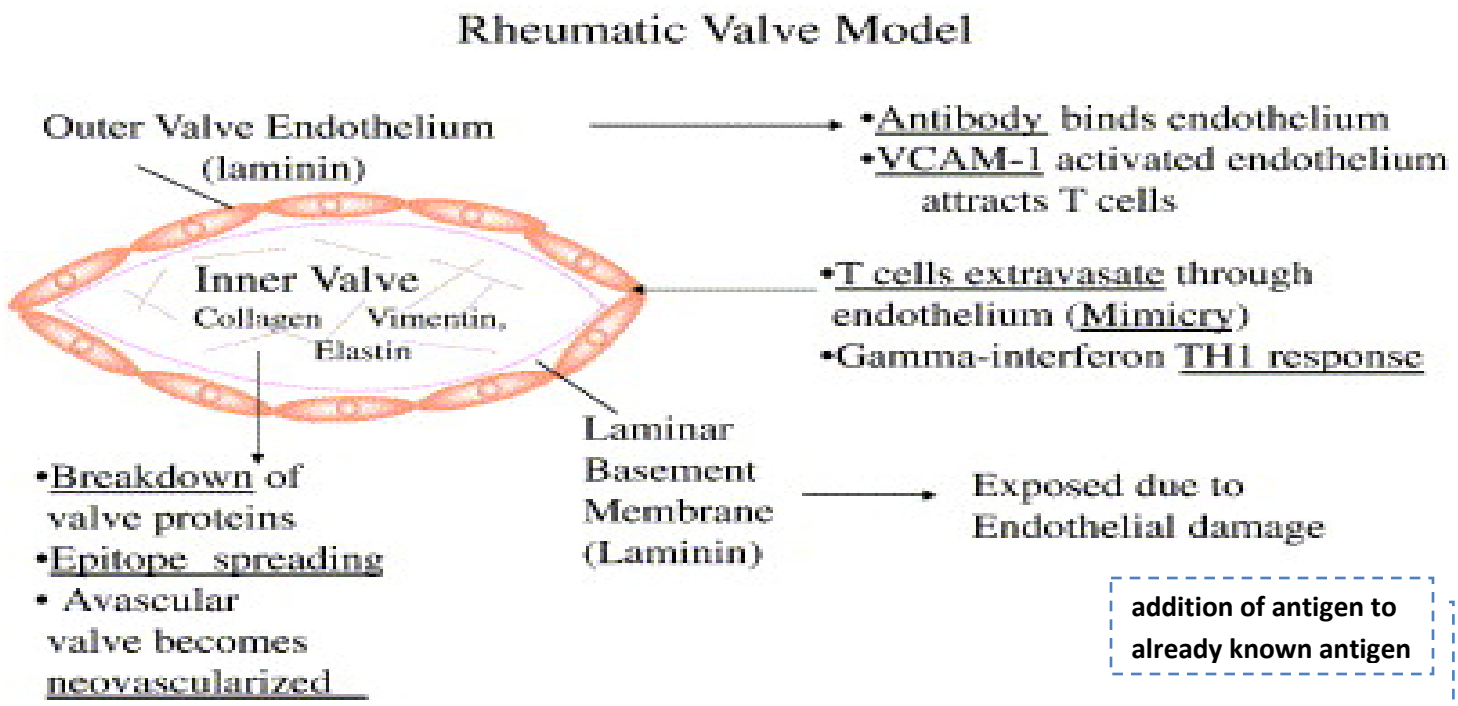


Diagram illustrating the two hit theory of rheumatic heart disease. Group A streptococcal infection leads to the production of anti-group A carbohydrate antibody which cross-reacts with the valve endothelium as well as with the myocardium and **up-regulates vascular cell adhesion molecule-1 (VCAM-1)** on the valve endothelium. T cells adhere to the VCAM-1 on valve endothelium and extravasate into the valve.



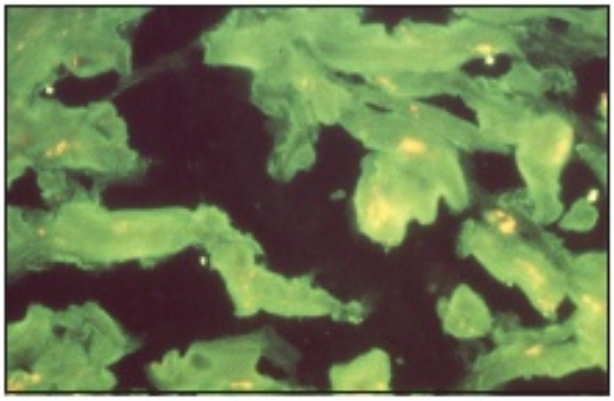
addition of antigen to already known antigen

Diagram illustrating the process of initial mimicry which leads to **granuloma formation, gamma interferon production and scarring in the valve.** After the initial process has developed inflammation in the valve, other proteins in the valve may then be recognized by the immune system leading potentially to **epitope spreading** and responses against other valve proteins such as **vimentin and collagen**.

Explanation (gist)of Page 5 (slide 13 – 14)

(as pointed out before: organism has M protein which the body forms AB against. But these AB will also target both the endocardium around the valves and the myocardium itself leading to formation of inflame. Binding of the AB to the Ag on the heart similar to the M protein will activate the endothilum to release adhesion molecules (VCAM-1). These molecules will lead to further accumulation of other cells which will (hypersensitivity type 2) eventually lead to penetration of the 1st layer (gramuloma formation with fibrosis (hypersensitivity type 4)) and then release of sequestered Ag and another prob. Begins (autoimmunity). Release of large amounts of these hidden Ag is called epitope spreading.

Immunofluorescent staining of heart muscle with serum obtained from an **acute rheumatic fever patients**



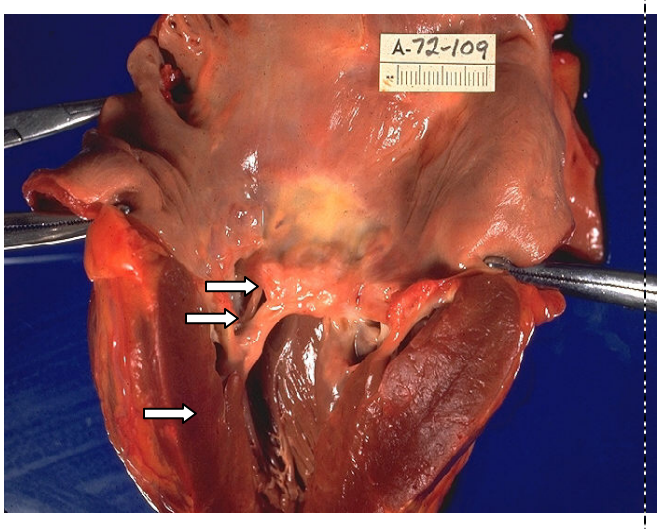
Pathophysiology

- During a Strep. infection activated antigen presenting cells such as macrophages present the bacterial antigen to helper T cells
- Helper **T cells subsequently activate self reactive B cells** and induce the production of antibodies against the cell wall of Streptococcus
- **However the antibodies may also react against the myocardium and joints, producing the symptoms of rheumatic fever**

Clinical Presentation

Heart

- Up to 60% of patients with ARF progress to Rheumatic Heart Disease (RHD)
- The endocardium, pericardium, or myocardium may be affected **(pancarditis)**
- Valvular damage is the hallmark of rheumatic carditis. The **mitral valve** is almost always affected



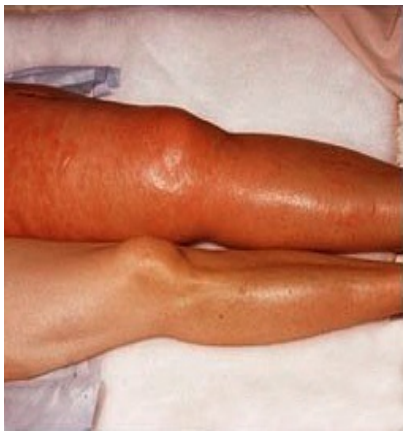
Mitral valve is the most commonly effected. When the valve is affected it becomes either stenoisis (narrow) or incompetent (won't close). Mitral incompetency is associated with hypertrophy.

Left ventricle has been cut open to display characteristic severe thickening of mitral valve, thickened chordae tendineae, and hypertrophied left ventricular

Joints (arthritis)

- This is usually **polyarthritis**, sometimes **flitting from joint to joint (migratory)**, affecting the larger joints more than the smaller ones.
- Swelling, redness and tenderness are the common findings and occasionally joint

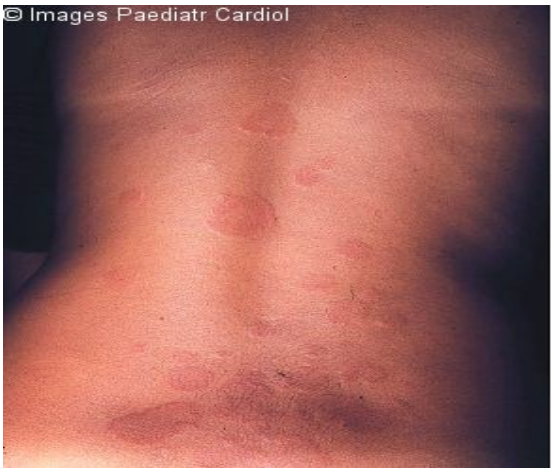
- Inflamed **Keen Joint**



Skin (erythema marginatum)

Abnormal redness of skin due to capillary congestion as in infflamation

- **Skin lesions:** The classical **erythema marginatum**—large erythematous lesions with prominent margins slightly raised.

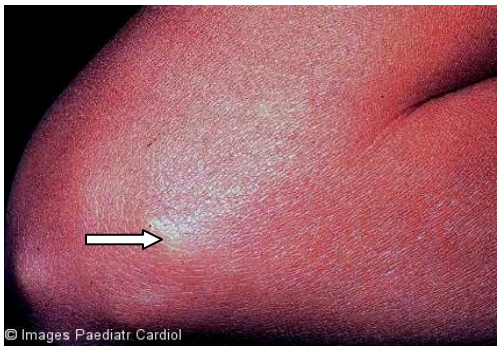


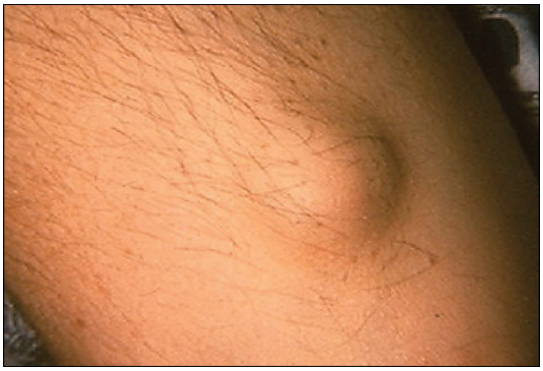
Central nervous system (chorea)

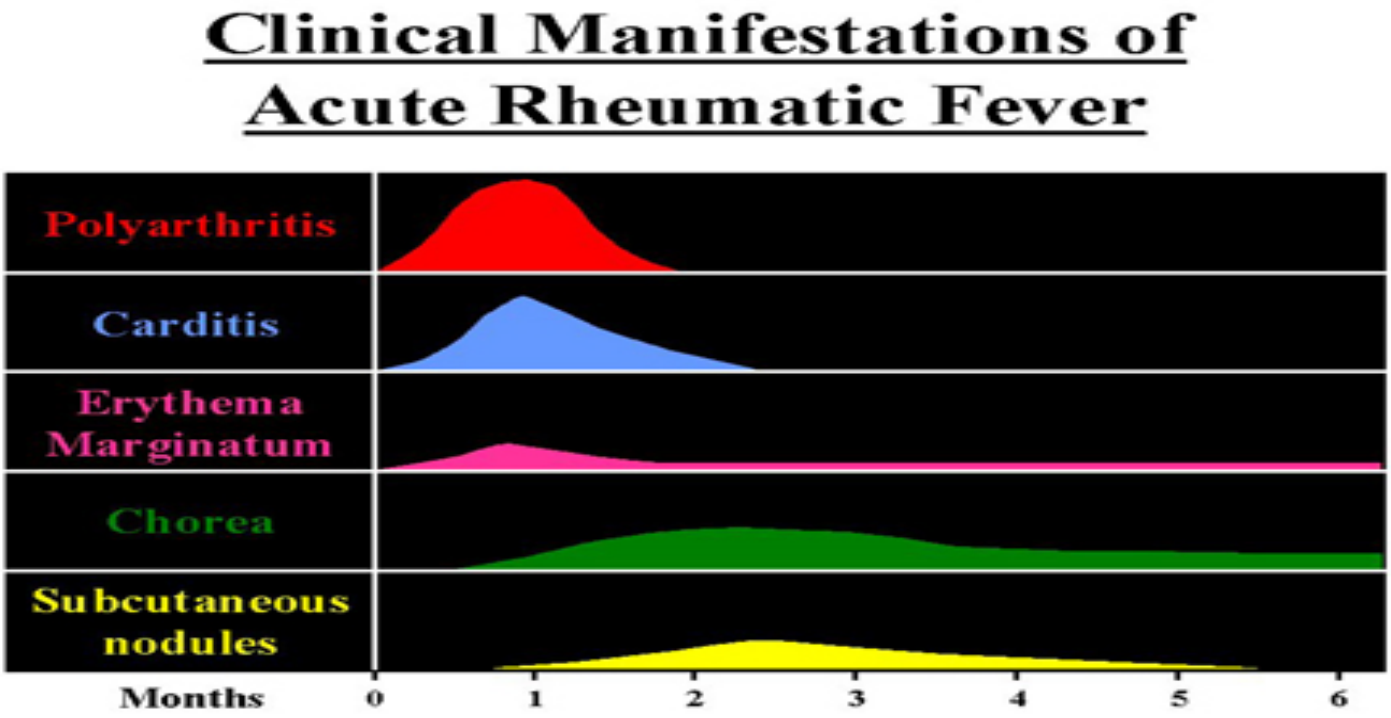
- **Sydenham's chorea**
- **The choreiform movements affect particularly the head and the upper limbs**
- **They may be generalized or restricted to one side of the body (hemi-chorea)**
- **Chorea eventually resolves completely, usually within 6 weeks**

Subcutaneous nodules

- **Subcutaneous nodules : These are painless, round, firm lumps overlaid by normal looking skin**
- **They range from a few millimeters to 1.5 cm in diameter, and are localized over bony prominences like the elbow, shin and spine. They sometimes last longer than a month**







The first three conditions usually seen in patient with acute RF

Investigation of Rheumatic Fever

MeansAmount

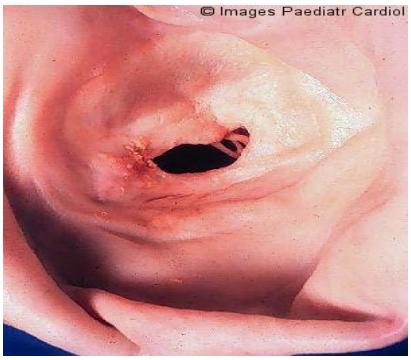
- Anti-streptolysin O (ASO) titer
    - At least 80% of patients with ARF have an elevated **anti-streptolysin O** titer at presentation
        - Rising titer is more convincing
    - **Anti-DNAse B**
    - **Anti-hyaluronidase test**
- **Throat culture** for group A streptococci (obtain 2 or 3 cultures)

Rheumatic Fever – Clinical Course

- **Subsequent attacks**
    - Increased vulnerability to **reactivation of disease** with subsequent strep infections
    - **Same symptoms** with each attack
    - **Carditis** worsens with each attack
    - **Heart valves** are frequently deformed (mitral)
    - **Hear failure** develops after decades

Acute, recurring, chronic:

- Symptoms prone to recur with subsequent Strep. infections
- Chronic disease leads to fibrosis (chordae of heart valves + valve cusps)



Stenotic mitral valve seen from left

Narrowing or constriction of diameter

Opened stenotic mitral valve

Treatment of Rheumatic Fever

- Treat first strep throat infection with **penicillin**
- Treat other manifestations **symptomatically**
- **Prophylactic** long term anti-strep therapy given to anyone who has had rheumatic fever

Prevention

Take home message

- Rheumatic heart disease results from **cross reacting antibodies** binding the heart valves
- Repeated attacks of Streptococcal throat infection over the years damage heart valves resulting in either **stenotic or incompetent** heart valves
- Treatment involves **surgical** replacement of the damaged heart valves
- In patients with rheumatic fever long term administration of **penicillin** is recommended for prevention of future infections by group A Streptococcus

Unable to function