MED437
KING SAUD UNIVERSITY

Immunology team - 437

غيداء ال مصمع
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Revised by

Rheumatic Heart Diseases

Objectives :

- To understand basis of rheumatic fever as an immunologically mediated late complication of Streptococcal infection
- To know that autoimmunity results from production of cross reacting antibodies against Streptococcal antigens
- To describe rheumatic heart disease as one of the several manifestations of rheumatic fever
- To know the signs, symptoms, pathogenesis, treatment and prophylaxis of rheumatic heart disease

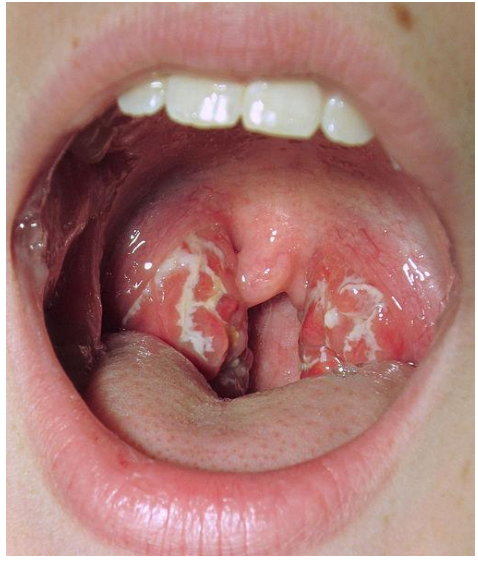
Rheumatic Fever:

Definition: an inflammatory disease which may develop after a Group A Streptococcal infection[1].
such as: "Strep. throat infection"[2] or "scarlet fever"[3].

1. Can involve[4]: the heart, joints, skin, and brain.
2. It commonly appears in children ages 5 through 15.

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:

1. Low standard of living.
2. Crowding.
3. Individual (HLA)[5] susceptibility is also important.
4. Antigen-presenting cells bearing the HLA-DR7 molecule from RHD patients preferentially recognize heart-tissue protein.
5. Other views in the literature exist, due to:
   A- The various HLA-typing methods.
   B- Ways of grouping the cases.

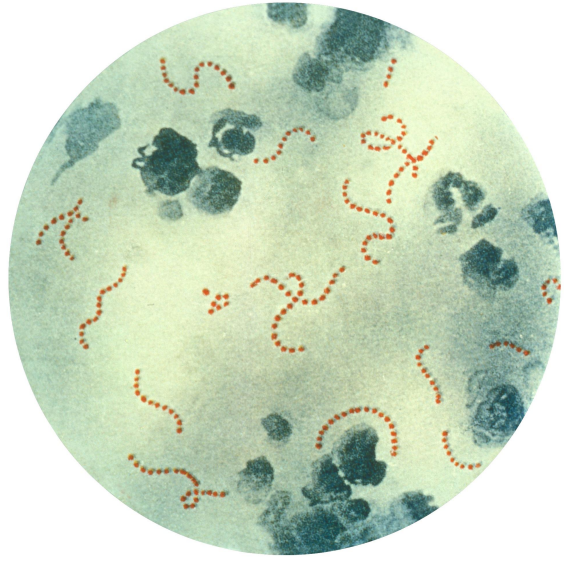
1: It doesn't frame the disease.
2: Pharyngitis or tonsillitis.
3: Scarlet fever, also known as scarlatina, is an infection that can develop in people who have strep throat. It's characterized by a bright red rash on the body, usually accompanied by a high fever and sore throat. The same bacteria that causes strep throat also causes scarlet fever.
4: as complication.
5: Human Leukocyte Antigen.

Organism:

Caused by Group A beta-haemolytic streptococcus.

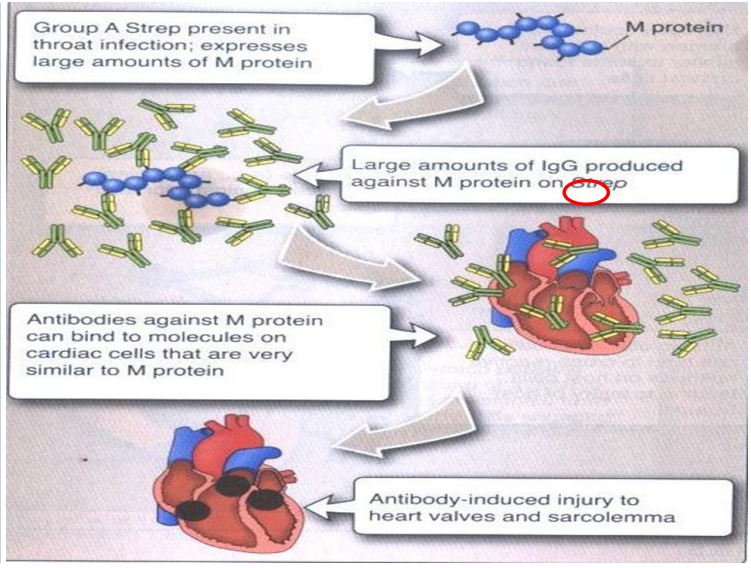
- There is a latent period of ~3 weeks (1–5 weeks) between the group A streptococcal infection and the appearance of the clinical features of Rheumatic Fever.
- All cases associated with recent infection (e.g. pharyngitis).
- Antibody and cellular immune response cross-reacts with human connective tissue.

Substance	Function
M proteins	Adherence of Streptococcus pyogenes to host cells & inhibiting the host immune response. **"Highly antigenic"**
Hyaluronic acid capsule	Camouflages the bacterium " it means that your body won't recognize it as a foreign body"
Streptokinases	Dissolve blood clots
Peptidases	Degrades proteins involved in immune response
Pyrogenic toxins	Stimulate fever, rash & shock
Streptolysins	Lyse erythrocytes, leukocytes & platelets



PATHOGENESIS

- 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**
    - 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**



The inflammatory hypersensitivity reaction type II response causes:
1. Breakdown of valve proteins
2. Epitope spreading (T-cells respond to other valve proteins such as Vimentin and collagen)
3. Avascular valve become neovascularized "the healthy valves which don't have blood supply are now having blood going through them"

Recall:
Type I = IgE
Type II = Antibody
Type III = immune complex
Type IV = cell mediated
the Fc region is the region where antibody attach to its antigen

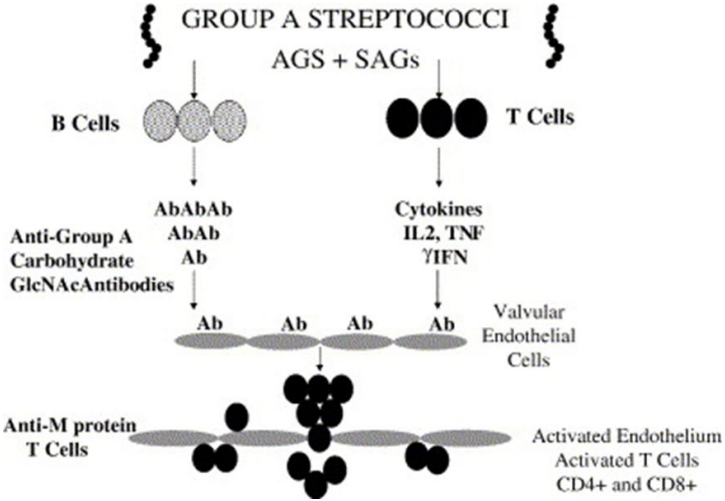


Diagram illustrating **The two hit theory** of rheumatic heart disease. Group A streptococcal infection leads to the production of anti-group A carbohydrate antibody which cross-reacts with the valve endothelium as well as with the myocardium and up-regulates vascular cell adhesion molecule-1 (VCAM-1)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

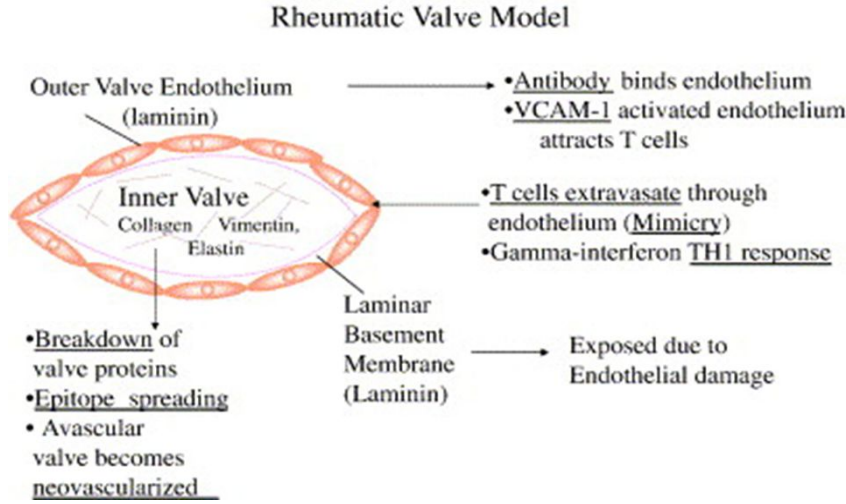
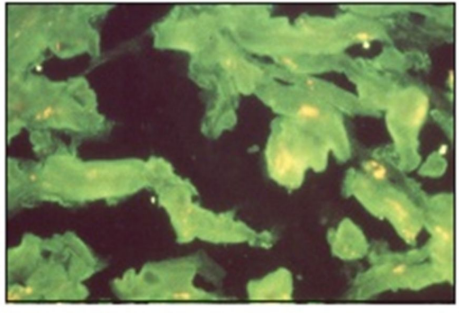


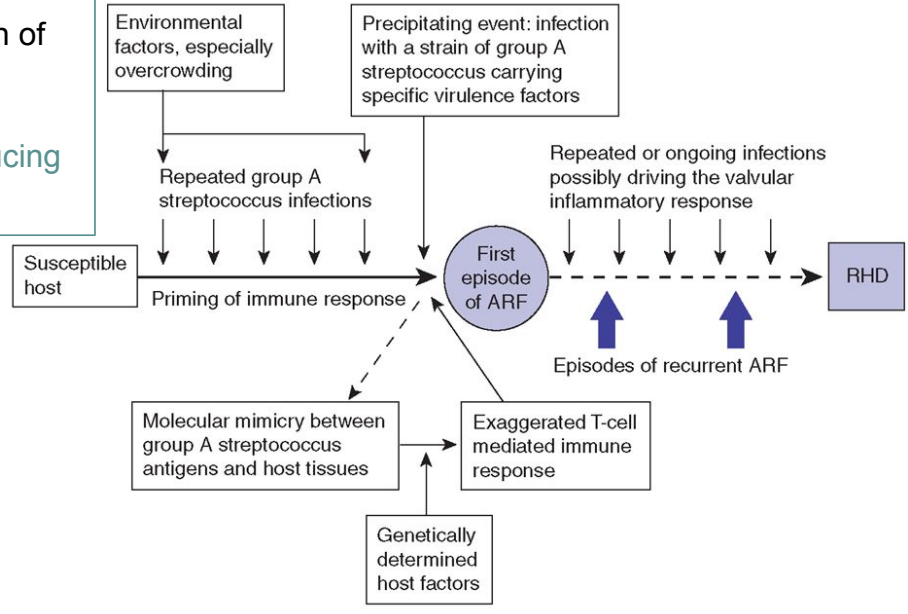
Diagram illustrating the process of **initial mimicry** which leads to granuloma formation, gamma interferon production and scarring in the valve. **After the initial process** has developed inflammation in the valve, other proteins in the valve may then be recognized by the immune system leading potentially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

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



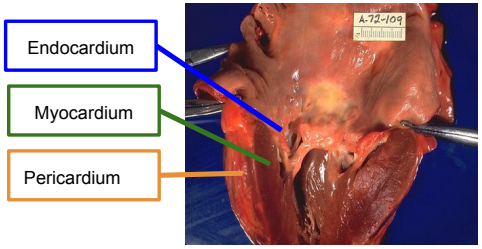
Immunofluorescent staining of heart muscle with serum obtained from an acute rheumatic fever patients



Clinical presentation

Heart

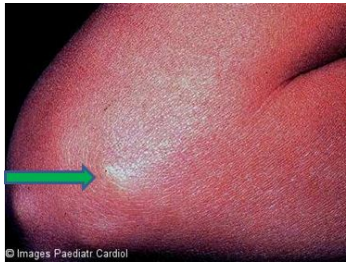
- Up to 60% of patients with ARF progress to Rheumatic Heart Disease (RHD)
- Only manifestation of ARF with significant potential to cause long-term disability and/or death
- The endocardium, pericardium, or myocardium may be affected (pancarditis)
- Valvular damage is the hallmark of rheumatic carditis. The mitral valve is almost always affected

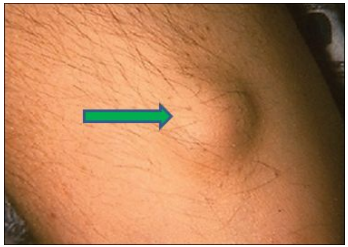


Left ventricle has been cut open to display characteristic severe thickening of mitral valve, thickened chordae tendineae, and hypertrophied left ventricular

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





CNS (chorea)

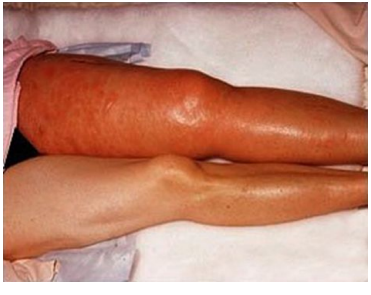
- Sydenham's chorea
- Occurs in children, rare in adults
- The choreiform movements affect particularly the head and the upper limbs
- They may be generalized or restricted to one side of the body (hemi-chorea)
- Chorea eventually resolves completely, usually within 6 weeks
- Likely due to molecular mimicry, with autoantibodies reacting with brain ganglioside

Generalized Chorea and Restricted Chorea (Hemichorea)

Clinical presentation

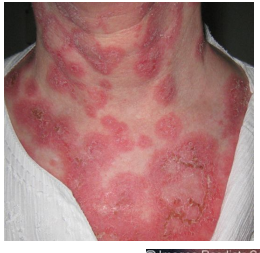
Joints (Arthritis)

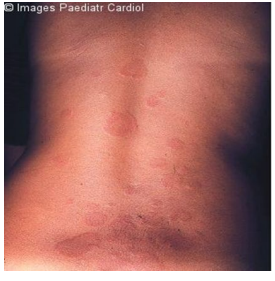
- This is usually polyarthritis, sometimes flitting from joint to joint (migratory), affecting the larger joints more than the smaller ones.
- Swelling, redness and tenderness are the common findings and occasionally joint effusions.
- Inflamed Knee Joint



Skin
(Erythema Marginatum)

- The classical erythema marginatum lesions with prominent margins slightly raised

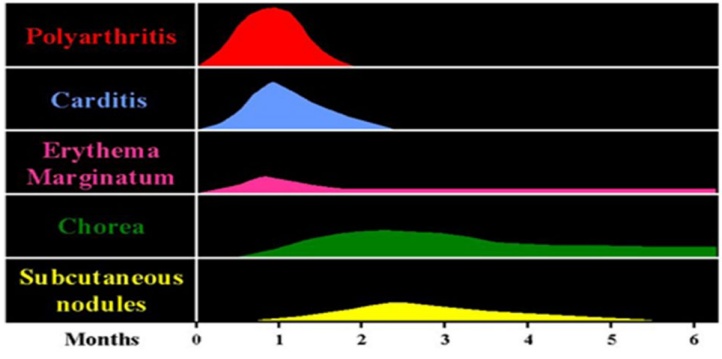




For easy memorization

J♥NES (major criteria):
Joint (migratory polyarthritis)
♥ (carditis)
Nodules in skin (subcutaneous)
Erythema marginatum
Sydenham chorea

Clinical Manifestations of Acute Rheumatic Fever



- Notice that Polyarthritis and carditis peak at the first month and end around the second
- Erythema marginatum peaks at 1 month and continue until the end
- Chorea starts at the end of first month and proceeded until the End
- Subcutaneous nodules starts at the end of first month peaks at the middle of the second and ends after the fifth month

Rheumatic Fever – Clinical Course

Investigation of Rheumatic Fever

- Anti-streptolysin O (ASO) titer

At least 80% of patients with ARF (acute rheumatic fever) have an elevated anti-streptolysin O titer at presentation

- Anti-DNAse B
- Anti-hyaluronidase test
- Throat culture for group A streptococci (obtain 2 or 3 cultures)

Treatment of Rheumatic Fever

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

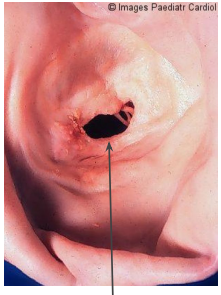
Acute, recurring, chronic:

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

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)
- Heart failure develops after decades

Opened stenotic mitral valve



Stenotic mitral valve seen from left atrium

Take home messages today,
Take hospital messages tomorrow.

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

Quiz: Test Yourself!

1- Which one of the following is a risk factor for Rheumatic Fever?
A- High economic status
B- Crowding
C- Over consumption of lipids
D- Excess uric acid in the bloodstream

2- What is the function of streptolysin?
A- Dissolves blood clots
B- Lyses erythrocytes, leukocytes & platelets
C- Degrades proteins involved in immune response
D- Stimulates fever, rash & shock

3- Rheumatic Fever follows which type of hypersensitivity?
A- Type I hypersensitivity
B- Type II hypersensitivity
C- Type III hypersensitivity
D- Type IV hypersensitivity

4- What is the hallmark of rheumatic carditis?
A- Lesions with prominent margins slightly raised
B- Choreiform movements particularly affecting the head and the upper limbs
C- Swelling, redness and tenderness mainly affecting large joints
D- Valvular damage

5- What is the most common causative organism of Rheumatic fever?
A- *M. tuberculosis*
B- *S. aureus*
C- Group A strep.
D- *H. influenza*

6- Which investigation should be done to confirm presence of Rheumatic fever?
A- Anti-streptolysin O (ASO) titer
B- Tympanocentesis
C- Throat culture
D- A&C

7- After acquiring rheumatic fever, when would heart failure develop?
A- With each attack
B- After 2-3 hours
C- After decades
D- None of the above

8- We should initially treat a strep throat infection with penicillin.
A- True
B- False

9- The antibodies which the immune system generates against the ..... may cross react with cardiac myofiber protein myosin and smooth muscle cells of arteries.
A- Peptidase
B- M protein
C- Streptokinase
D- Streptolysin

10- Which one of the "proposed mechanism of autoimmunity" does Rheumatic fever lie under?
A- Sequestered antigens mechanism
B- Molecular mimicry
C- Inappropriate class II MHC expression on non-APC
D- Polyclonal B cell activation

1-B 2-B 3-B 4-D 5-C 6-D 7-C 8-A 9-B 10-B

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