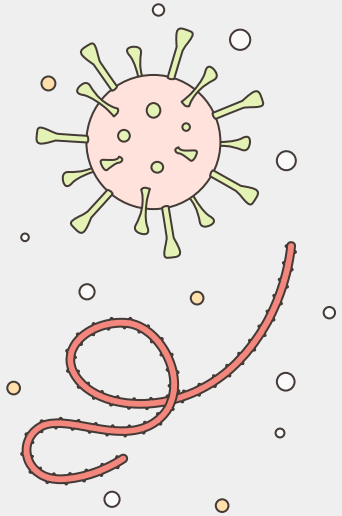


Rheumatic Heart Disease

Color Index:
-Main Text
-Important
-Notes
-Male Slides
-Female Slides
-Extra

Editing File

Objectives

Helpful video

01

To understand basis of rheumatic fever as an immunologically mediated late complication of Streptococcal infection

02

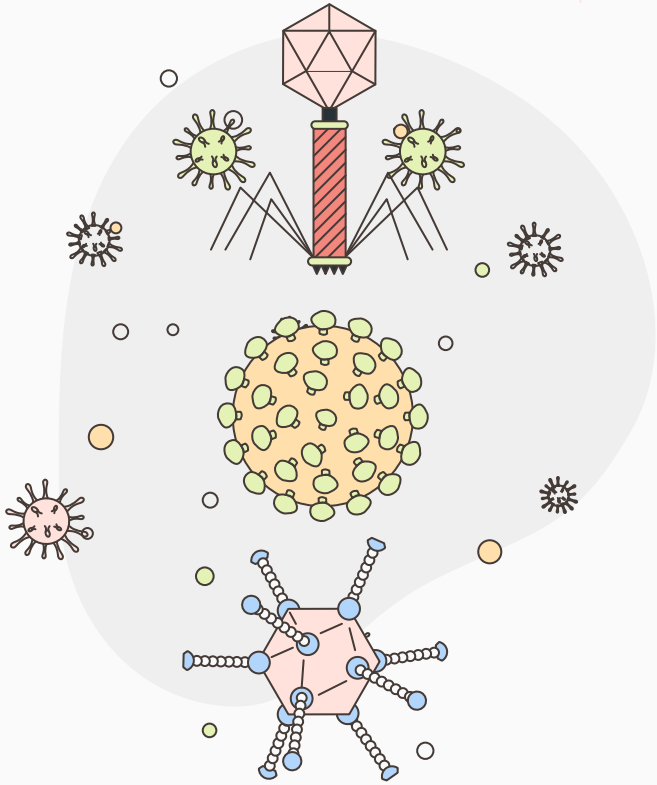
To know that autoimmunity results from production of cross reacting antibodies against Streptococcal antigens.

03

To describe rheumatic heart disease as one of the several manifestations of rheumatic fever.

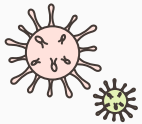
04

To know the signs, symptoms, pathogenesis, treatment and prophylaxis of rheumatic heart disease.



IMPORTANT!

Rheumatic fever



Definition

- Rheumatic fever is an inflammatory disease which may develop after a group A streptococcal infection such as : 1-Strep. throat infection 2-Scarlet fever.

Sites

- Can involve the heart, joints, skin and brain.

Epidemiology

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

It commonly appears in children ages 5-15 years.

Risk factors

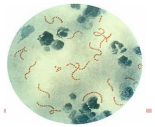
- Low standard of living
- .crowding.
- Individual (HLA) susceptibility is also important .
- Antigen-presenting cells bearing the HLA-DR7 molecule from RHD patient preferentially recognize heart-tissue proteins.

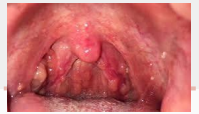
other views in the literature exist, due to :

-The various HLA-Typing methods.

-Ways of grouping the cases.

Organism:

Organism	
Causative organism	Group A (beta haemolytic) streptococcus 
Type of immune response	Antibody and cellular immune response cross reacts with human connective tissue.
Latent period	3 weeks (1-5 weeks) between the group A streptococcal infection and the appearance of clinical features of Rheumatic fever (RF).

All cases associated with recent infection (e.g. pharyngitis) 

Virulence factors of group A streptococcus

M-protein

- Adherence of streptococcus pyogenes to host cells.
- Inhibiting the host immune response.

hyaluronic acid capsule

IMPORTANT!

Camouflages the bacterium.

streptokinases

Dissolve blood clots.

peptidases

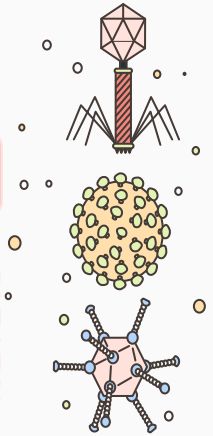
Degrades proteins involved in immune response

pyrogenic toxins

Stimulates fever, rash & shock

streptolysins

Lyse erythrocytes, leukocytes & platelets.



Pathogenesis

What does Rheumatic fever affect?

It affects the **peri-arteriolar connective tissue**

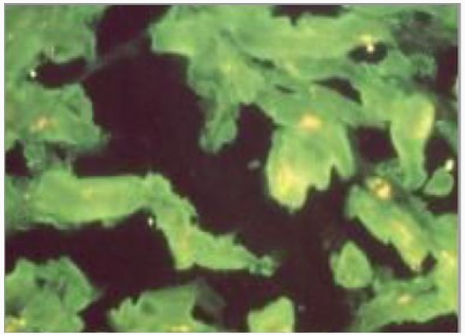
(adjust to Arteriole)

What's the type of immune response associated with it?

It is believed to be caused by **antibody cross-reactivity.**

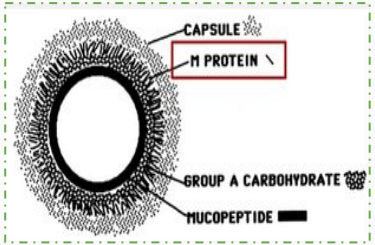
This cross-reactivity is a **type II hypersensitivity reaction and is termed molecular mimicry.**

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

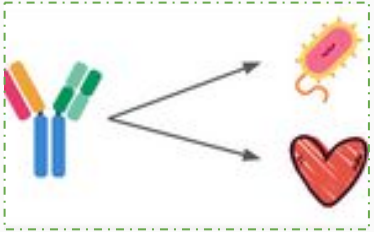


Pathogenesis

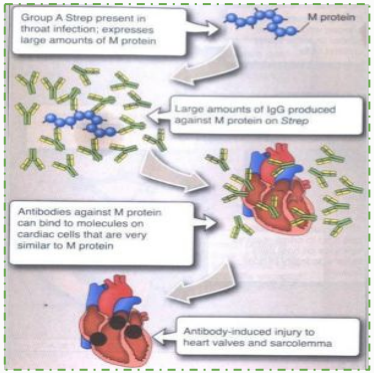
1 group A streptococcus pyogenes has a cell wall composed of branched polymers which sometimes contain M proteins that are highly antigenic.

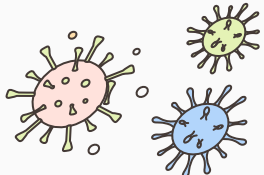


2 The antibodies which the immune system generates against the -M protein- may cross react with cardiac myofiber protein myosin and smooth muscle cells of arteries, inducing cytokine release and tissue destruction.



3 This inflammation occurs through direct attachment of complement and Fc receptor-mediated recruitment of neutrophils and macrophages.





Pathogenesis steps:

Male's slides

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.

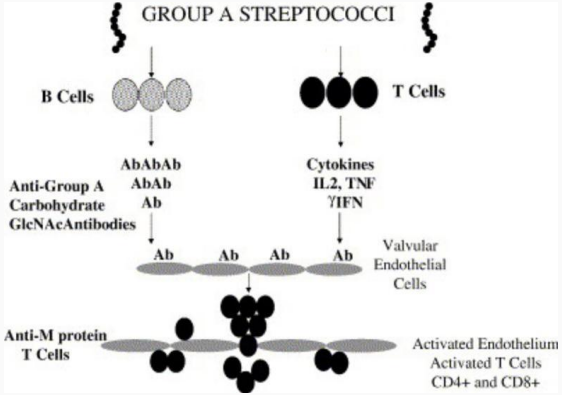
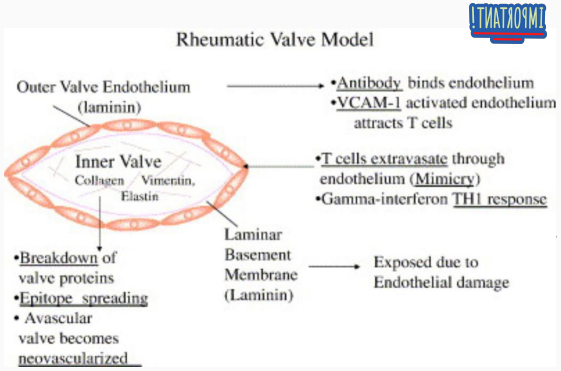
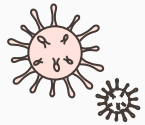


Diagram illustrating the process of initial mimicry which leads to granuloma formation, gamma interferon production and scarring in the valve. After the initial process has developed inflammation in the valve, other proteins in the valve may then be recognized by immune system leading potentially to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



Pathogenesis steps Extra



1- Group A Streptococcus cell wall composed of M proteins that are highly antigenic.

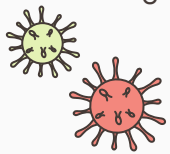
2- Activated antigen presenting cells present the bacterial antigen to helper T cells .

3- Helper T cells activate self reactive B cells and produce antibodies against the cells wall of streptococcus (anti-group A carbohydrate antibody) IgG antibodies.
Also it activates cross-reactive Tcells which release TNF, IFN-Y, IL-2 and other cytokines.

4- Antibodies mat cross react with myocardium, valvular tissue and joints producing the symptoms of RF. this inflammation occurs through direct attachment of complement and Fc receptor-mediated recruitment of neutrophils and macrophages.

5- Up-regulates the vascular cell adhesion molecule-1 (VCAM-1) on the valve and T-cells adhere to the VCAM-1 on the valve endothelium and extravasate into the valve.

6- Tissue destruction (endothelium) making the inner structure of the valve exposed (Laminar basement membrane).



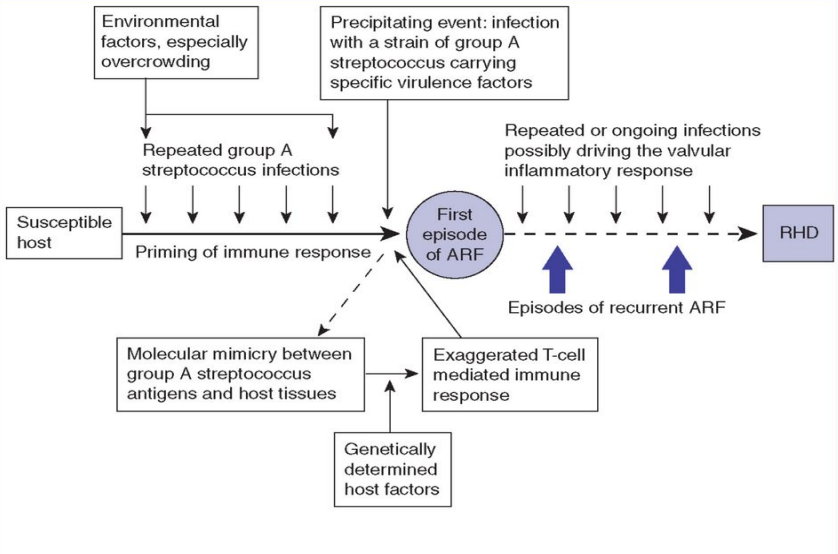
7-Granuloma formation, gamma interferon production and scarring in the valve.

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)

• only manifestation of ARF with significant potential to cause long-term disability and/or death

• The endocardium, pericardium, or myocardium may be affected (pancarditis) —> all layers are affected

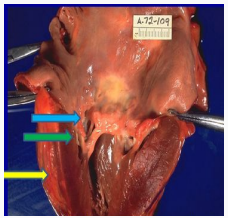
• Valvular damage is the hallmark of rheumatic carditis. The mitral valve is almost affected .

Joints (arthritis)

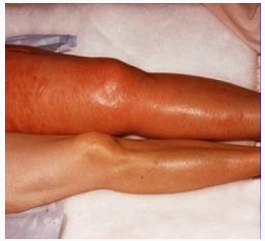
• This is usually polyarthritis, sometimes flitting from joint to joint (migratory), affecting the larger joints more than the smaller ones.

• Swelling, redness and tenderness are the common findings and occasionally joint effusions.

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



Inflamed Knee Joint



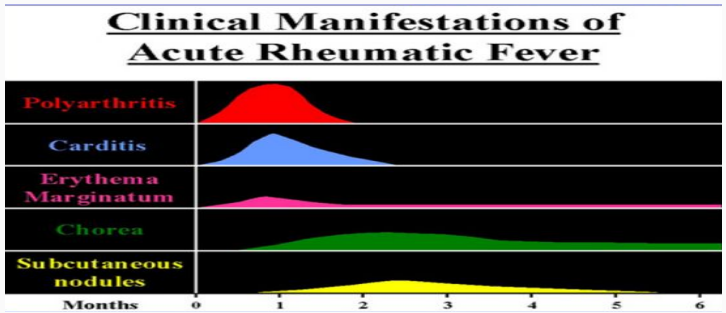
Clinical presentation

Central Nervous System (chorea)

Sydenham's chorea

Dr: dance-like movement named "Saint Vitus Dance"

- 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.

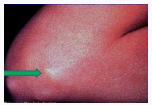


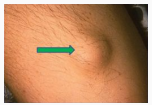
Subcutaneous nodules

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.

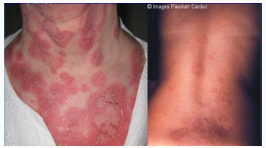
They sometimes last longer than a month.





Skin (Erythema Marginatum)

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



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)
- Heart failure devolps after decades

Acute, recurring, chronic

- Symptoms prone to recur with subsequent Strep. infections
- **Chronic disease leads to fibrosis** (chordae of heart valves + valve cusps) which makes the valves stiff and unable to move the blood in a proper way

Stenotic mitral valve seen from left atrium

Opened stenotic mitral valve

Investigation & Treatment

Investigation of Rheumatic Fever

1- **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)

2- **Anti-DNAse B** Another Antibody, more reliable because it lasts longer

3- **Anti-hyaluronidase test**

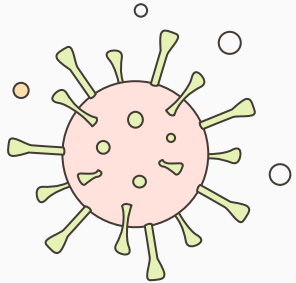
4- **Throat culture** for group A streptococci (obtain 2 or 3 cultures).

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



Extra slide

- Rheumatic fever is an inflammatory disease which may develop **after a Group A streptococcal infection.**
- It can involve the **heart, joint, skin, and brain.**
- antibodies and cellular immune response cross reacts with human connective tissue.
- M protein -> 1- Helps adherence of streptococcus pyogenes to host cells. 2-inhibiting the host immune response.
- **M proteins are highly antigenic and strongly associated with rheumatic heart disease.**
- Rheumatic fever affect the peri-arteriolar connective tissue.
- Rheumatic fever believed to be caused by **antibody cross-reactivity** , this cross-reactivity is a type **II hypersensitivity reaction** and is termed **molecular mimicry.**

Extra slide

- Subsequent attack :

reactivation of disease---> same symptoms with each attack --->carditis ---->mitral heart valves deformed ---> heart failure (after decades).

- Chronic disease leads to fibrosis (chordae of heart valves + valve cusps).

- **How can we investigate Rheumatic fever ?**

by :

1-Antistreptolysin O (ASO) titer.

2-Anti-DNAse B

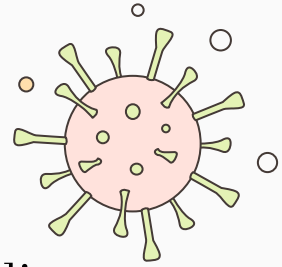
3-Anti-hyalurondase test.

4-Throat culture for group A streptococcal (obtain 2-3 cultures).

What's the treatment of Rheumatic fever ?

Pencillin	**For first strep throat infection**
Symptomatically	For Other manifestations
Prophylactic long term anti-strep therapy	For anyone who has had rheumatic fever

Take home messages



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.

MCQs

01

1. Which symptom presented is NOT a sign of rheumatic fever?

A) Erythema marginatum lesions
B) joint tenderness
C) Painless, round, firm lumps
D) Truncal rash

02

2. Rheumatic fever is caused by which of the following bacteria?

A) Group B streptococcus
B) Staphylococcus aureus
C) Group A streptococcus
D) Staphylococcus pyogenes

03

3. The commonest valvular abnormality in rheumatic heart disease is

A) Mitral regulation
B) Mitral stenosis
C) Aortic stenosis
D) Aortic regurgitation

1. D

2. C

3. B

MCQs

04 The most important laboratory test for the diagnosis of rheumatic fever is

A) Full blood count B) Anti stretolysin O titre C) Blood elecrolytes D) Blood culture

05 In rheumatic fever, the antibodies are directed against

A) Hyaluronic acid capsules B) Pyrogenic toxins C) M protein D) Staphylococcus pyogenes

06 **In rheumatic fever, the duration from streptococcal infection to the onset of symptoms is**

A) 2-3 months B) 3 Days C) 3 weeks D) 4-6 Days

4. B

5. C

6. C

Meet our team

Leaders

Bandar Alzaaidi

Shaden Alshammari

Members

Faris Alturaiki

Lamyaa Alrasheed

Immunology.444ksu@gmail.com