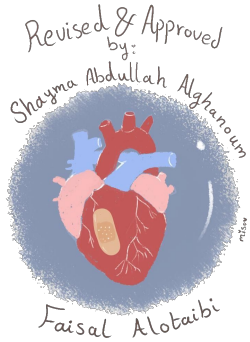


Rheumatic Heart Disease (RHD)

Color index

Important

Extra information

Notes

Slide reference

IMMUNOLOGY

TEAM 439

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 (mimicry) 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.

Editing File

Click here!

Please check frequently

Introduction: Rheumatic Fever (RF)

Rheumatic Fever

An acute, multisystemic, **autoimmune inflammatory disease** that develops **after** a Group A Streptococcal infection.Manifestation can involve the **heart**, joints, skin, and brain.

RHD

A heart disease caused by rheumatic fever.

How is **Rheumatic heart disease** developed?

Streptococcal Pharyngitis

↓

Rheumatic Fever

↓

Rheumatic Heart Disease (RHD)
Title of lecture

Watch before (osmosis)

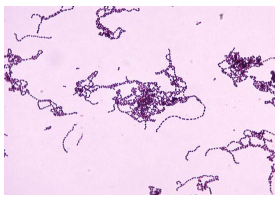
Epidemiology of RF

- ~3% of persons with **untreated** GAS pharyngitis (or any other strep. infection) develop rheumatic fever
- Commonly appears in children 5-15 (immunity is less mature in children)
- 15-20 million new cases a year in developing countries
- **Risk factor (Environmental):** Crowding, Low standard of living
- **Risk factor (Genetic):** Individual HLA susceptibility (APC's bearing HLA-DR7 preferentially recognize heart tissue proteins)

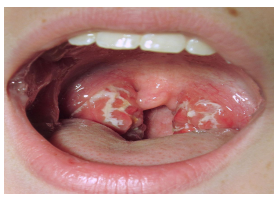
HLA-DR7 (human leukocyte antigen HLA). This protein is a MHC class II molecule which has a role of **increasing** the possibility of developing rheumatic fever.

Causative organism: Rheumatic Fever (RF)

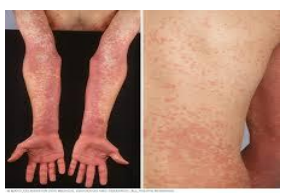
- **All cases** of RF are associated with recent infection caused by Group A β-haemolytic streptococcus (ex. Streptococcus Pyogenes)
- Streptococcal infections could cause pharyngitis or scarlet fever.
- Latent period: Clinical manifestations of RF appear **~3 weeks** (1–5 weeks) after streptococcal infection.
- Antibody and cellular immune response cross-reacts with human connective tissue. (Explained later)



S. Pyogenes



GAS Pharyngitis



Scarlet fever

Virulence factors of Streptococcal Group A β-hemolytic (ex. S. Pyogenes)	
M proteins (On cell wall, highly antigenic)	Adherence of Streptococcus pyogenes to host cells & inhibiting the host immune response
Hyaluronic acid capsule	Camouflages the bacterium
Streptokinases	Dissolve blood clots
Peptidases	Degrades proteins involved in immune response
Pyrogenic toxins	Stimulate fever, rash & shock
Streptolysin (enzyme)	**Lysis** of erythrocytes (β-hemolytic), leukocytes & platelets

Pathogenesis: Rheumatic Fever

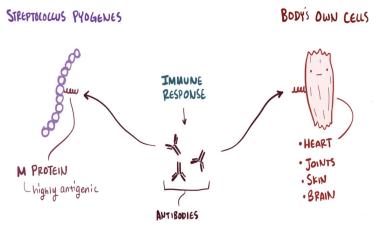
1. During a Strep. infection activated APC's such as macrophages present the bacterial antigen (**M proteins** located on the cell wall of GAS) to helper T cells.

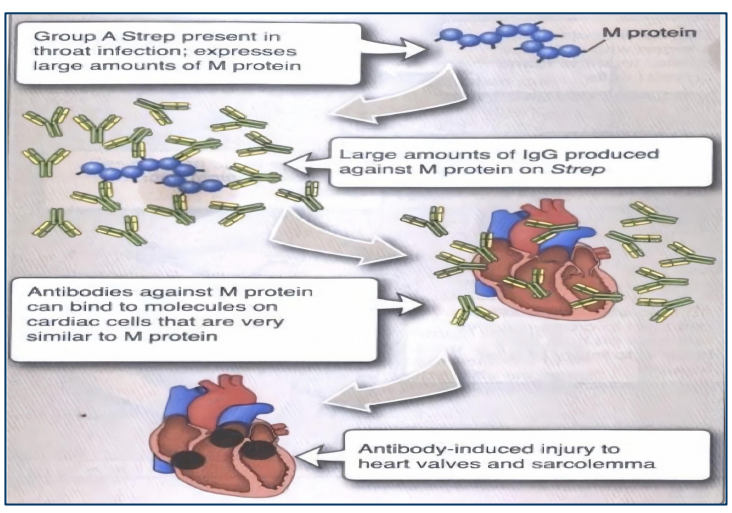
2. Helper T cells (CD4+, **Th2**) subsequently activate self reactive B cells and **induce the production of antibodies** against the cell wall of Streptococcus .

3. The antibodies generated by the immune system against the M proteins antigens may cross-react with any of the following:
   a. Connective tissue (peri-areteriolar connective tissue)
   b. Cardiac myofiber protein myosin
   c. Smooth muscle cells of arteries
   d. Brain ganglioside (if CNS is affected)

It is believed (not yet completely understood) to be caused by antigen-antibody cross reactivity, also known as Molecular Mimicry (Type II hypersensitivity reaction).

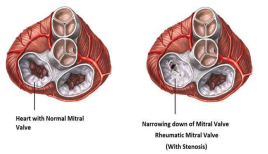
4. When they cross-react, it will **induce an inflammatory reaction** (which includes cytokine release and tissue destruction) through activating the complement system, classical pathway, (why classical pathway? Induced by anitgen-anitbody complex or immune complex) and Fc receptor-mediated (attachment of antibody-antigen) recruitment of neutrophils and macrophages. This will stimulate macrophages which will stimulate T helper to create inflammation. (Both humoral and cell mediated immunity)



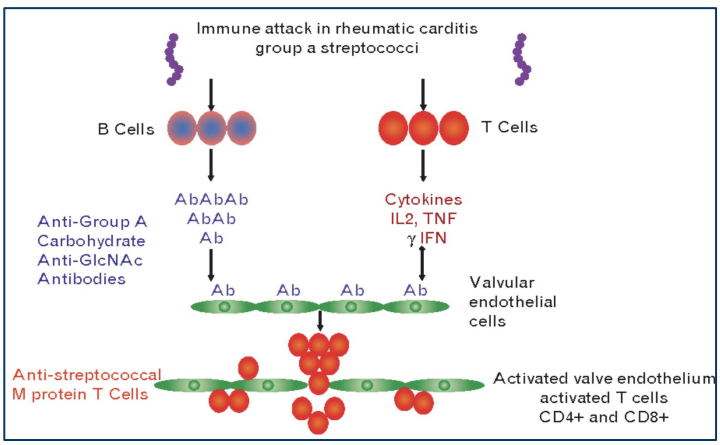


MSK: Molecular mimicry (cross-reaction): when foreign antigens shares sequence or structure similarities with self-antigen. Cross reaction occurs when **antibodies or T cells cross react** with normal antigens. T cell will fight the normal antigens rather than foreign antigens and then destroy them.
Foundation: This will cause type II hypersensitivity as the body is making antibodies to fight normal tissue leading to tissue destruction.

Pathogenesis: Rheumatic Heart Disease

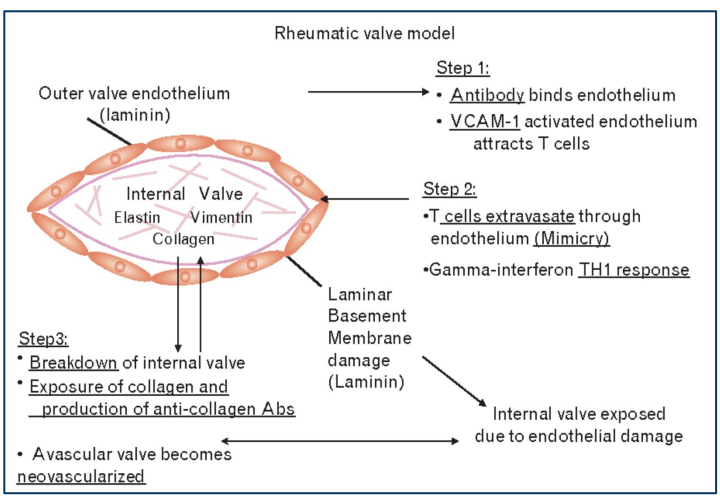


Hallmark of RHD is valvular damage, which is explained in detail:



Two hit theory of RHD expressing both humoral (b cells on left) and cell mediated (t cells on right) immunities.

- The cross reaction of the Anti-Group A carbohydrate antibodies with the valve endothelium will up-regulate VCAM-1 (Vascular Cell Adhesion Molecule) on the valve endothelium as well as the myocardium.
- T cells adhere to VCAM-1 on the valvular endothelium and penetrate **into** the valve (inner valve), causing damage through **Th1 response (Inflammation).** The response is done through release of TNF, IFN-γ, IL-2 and other cytokines



Please read this diagram

Step1&2: initial mimicry which leads to IFN-γ production, granuloma formation, and scarring in the valve.

Step3: After initial process has developed inflammation in valve, other proteins in valve may then be recognized by the immune system leading potentially to **epitope spreading(1)** and responses against other valve proteins such as vimentin and collagen.

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 and form antibodies against their antigens)

3

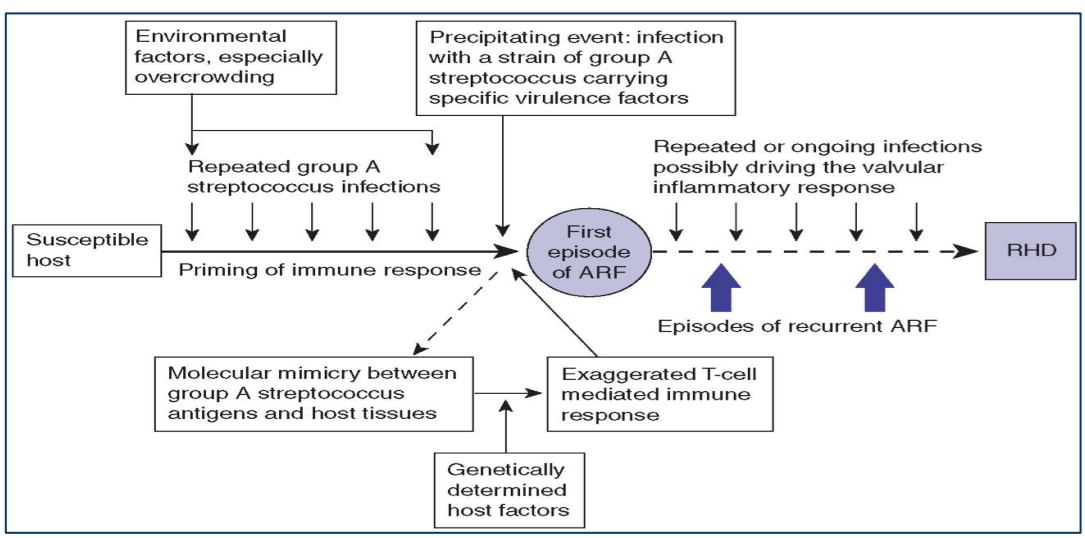
Avascular valve become neovascularized
(healthy valves which were avascular valves become vascular which brings blood with components that have a role in inflammation and fibrosis)

Epitope spreading(1): The antibodies start attacking the outer valve and work their way through to the inner valve and its structures (valve proteins), where the immune system will continue to destruct the region. If we were to expose a normal inner valve to the body, it will not fight it and there will be *no epitope spreading*. (Different concept than sequestered antigens explained in MSK)

Pathogenesis: Rheumatic Heart Disease Summary

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 cell wall of streptococcus (anti-group A carbohydrate antibody) IgG antibodies. Also it activates **cross-reactive T cells** which release TNF, IFN-γ, IL-2 and other cytokines
4. **Antibodies may 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

-Team435



What leads to the first episode of RF?

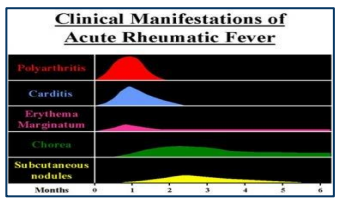
- Environmental factors that help repeated exposure to gas Infection, usually untreated
- Genetic factors like HLA-DR7, molecular mimicry, exaggerated T cell immune mediated response
- Precipitating event, "last straw" to start this condition: infection with a strain of gas that **has M proteins** and other virulence factors

Continuity/ repeated exposure of the conditions listed above will lead to the development of RHD.

1 2 3

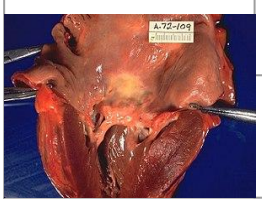
Clinical Manifestation of Acute Rheumatic Fever (ARF)

Clinical manifestations (signs & symptoms) of rheumatic fever are seen in various organs as it is multisystemic. After a certain period of time it could affect any of the following organs: (& others which is less common)



1. **Heart** — Only manifestation with significant potential to cause long-term disability and/or death.
2. **Joints (arthritis)**
3. **CNS**
4. **Skin**
5. **Subcutaneous**

Heart



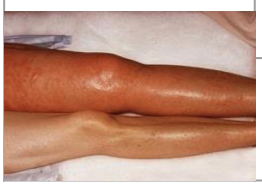
- Up to 60% of patients with RF progress to Rheumatic Heart Disease (most common of all 5 manifestations).
- Patient presents with pancarditis (inflammation of entire heart, **all 3 layers**)
- Valvular damage is the hallmark of rheumatic carditis (**mitral** valve is almost affected)
- Findings:
  - Severe thickening of mitral valve, thickened chordae tendineae, and hypertrophied left ventricle

Subsequent attacks:

- Carditis worsens with each attack .
- Heart valves are frequently deformed (mitral).
- Heart failure develops after decades.

- Clinical manifestation appear highest after the first month and lasts for 2 months. **(One of the first manifestations)**

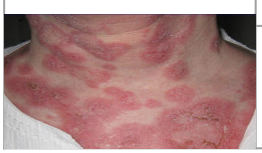
Joints (Arthritis)



- Migratory polyarthritis (Affecting the larger joints ex wrist, elbow, knee, ankle) (spreads from joint to joint).
- Findings:
  - Swelling, Redness & Tenderness (common)
  - Joint effusions (occasionally)

- Clinical manifestation appear highest after the first month and lasts for 2 and a half months. **(One of the first manifestations)**

Skin



- Also known as (Erythema Marginatum). Erythema: redness of skin. Marginatum: Lesions with prominent margins slightly raised

- Clinical manifestation appear highest during the first month and lasts for 6+ months. **(One of the first manifestations)**

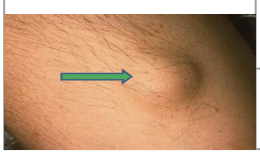
Clinical Manifestation of Acute Rheumatic Fever (ARF)

CNS (Sydenham's chorea)

- Occurs in children rare in adults
- Likely due to molecular mimicry with autoantibodies reacting with **brain ganglioside** (antibodies-M protein attack this region)
- Chorea eventually **resolves completely**, usually within 6 weeks. (Heart manifestations are the only ones with long-term disabilities. This is in the cns and resolves completely).
- 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)

- Clinical manifestation appear highest after 1-4 months and lasts for 6+ months.

Subcutaneous nodule



- Subcutaneous nodules (painless, round, firm lumps overlaid by normal skin)
- Range from a few millimeters to 1.5 cm in diameter
- localized over bony prominences (elbow, shin and spine)

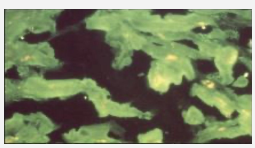
- Clinical manifestation appear highest after 2-3 months and lasts for 5 months

Subsequent attack of RF

- Increased vulnerability to reactivation of disease with subsequent streptococcal infections.
- Same symptoms with each attack.
- Can be acute, recurrent, or chronic.
  - In rheumatic heart disease, chronic disease leads to **fibrosis** of cusps and chordae. (Avascular valves become vascular which brings blood with fibrin and collagen which are responsible for causing fibrosis. Fibrosis makes the valve stiff and unable to move the blood in the proper way).

RF- Investigation

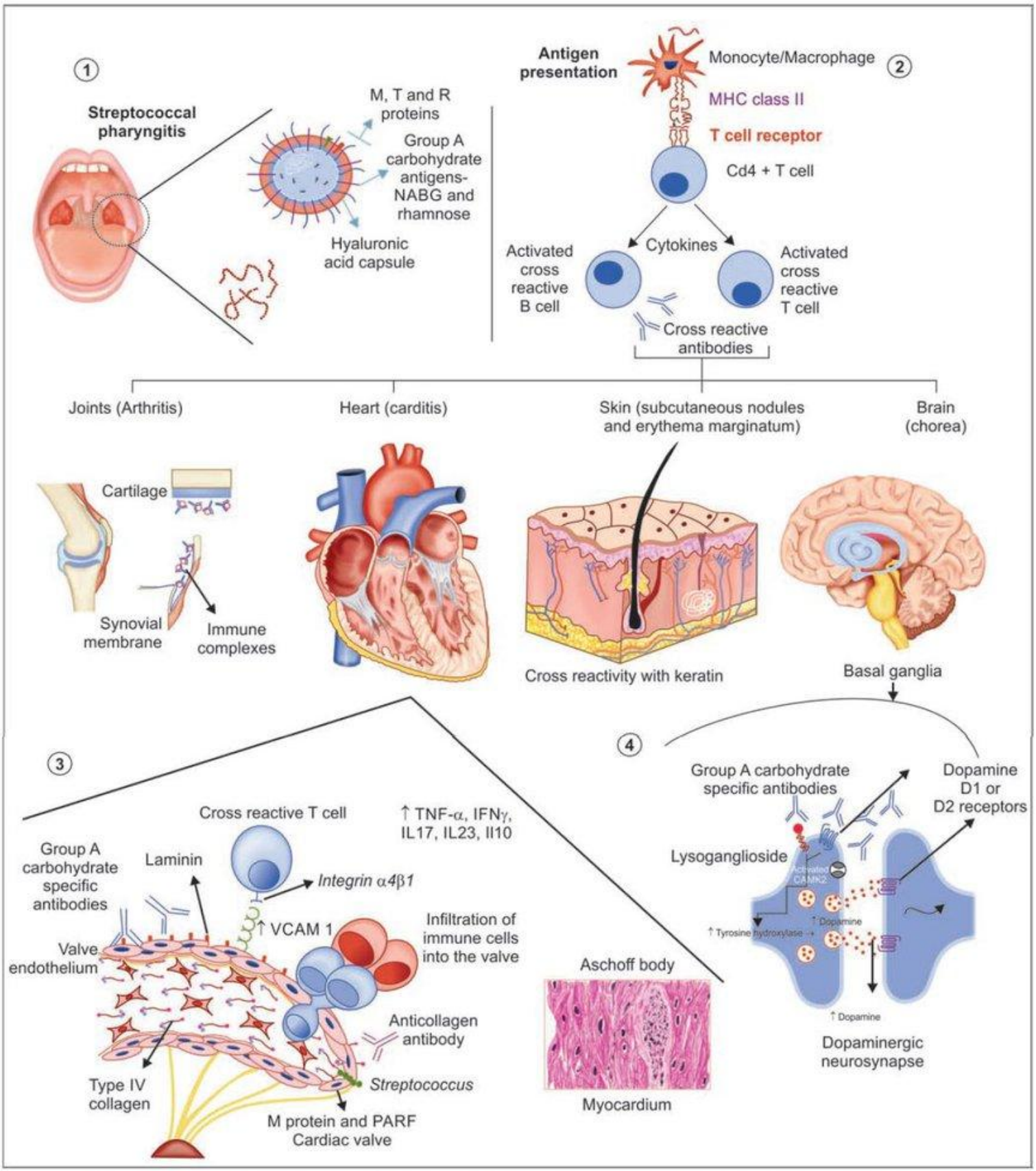
- Throat culture (2-3 cultures), gold standard
- **Anti-Streptolysin O** titer (at least 80% have elevated ASO titer)
- Anti-hyaluronidase test
- Anti-DNAse B
- In order to know whether the heart has antibodies, we use **immunofluorescent stain**



This picture shows a slide of heart muscle with serum taken from a patient with rheumatic fever and is dyed with immunofluorescent staining. This is how it looks like under specialized immunofluorescence microscope.

RF- Treatment

- Treat the streptococcal throat **infection** with **penicillin.**
- Other manifestations are to be treated according to the symptoms.
- Treat with surgery/valve replacement in case of chronic (fibrotic) cases.
- For patients who previously had rheumatic fever, they should receive long-term prophylactic anti-streptococcal therapy.



Pathogenesis of rheumatic fever. **1.** GAS pharyngitis leads to antigenic presentation of pathogenic peptides to T-cells. **2.** In immunologically susceptible individuals, the innate and adaptive (both humoral and cellular) immune responses gets activated leading to the development of cross-reactive antibodies and cross-reactive T-cells which incites immune response in the joints, heart, skin, and brain leading to different manifestations of ARF. **3.** In the heart, valve damage is initiated by 'endothelial activation' by cross-reactive antibodies which trigger increased expression of vascular cell adhesion molecule-1 (VCAM-1). This facilitates T-cell infiltration leading to cytokine-mediated immune damage. Exposure of Type-IV collagen can lead to production of collagen-specific antibodies which can cause further damage. **4.** In the brain, autoantibodies can target dopamine receptors and lysoganglioside leading to increased release of dopamine by the neurons thereby causing rheumatic chorea

Abbreviations: ARF, acute rheumatic fever; GAS, group A *Streptococcus*; IL, interleukin; IFN, interferon; NABG, N-acetyl-β-d-glucosamine; PARF, peptide associated with rheumatic fever; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule-1

Source : Essentials of Postgraduate Cardiology 2018

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

Extra

Rheumatic fever + heart disease (osmosis)

Rheumatic fever (ninja nerd)

QUIZ

Q1) What is the Antigen-presenting molecule from RHD patients that recognizes heart-tissue proteins ?

A	CYT p450	B	HLA-DR7	C	CD40L	D	CD28

Q2) Rheumatic fever is an inflammatory disease which may develop after a ..... infection?

A	Staphylococcus Aureus	B	Group A streptococcal	C	Group B streptococcal	D	Staphylococcus epidermidis

Q3) Which of the following is not affected by Rheumatic fever ?

A	Heart	B	Brain	C	Skin	D	Liver

Q4) Which proteins help in the Adherence of Streptococcus pyogenes to host cells and inhibit the host's immune response ?

A	M protein	B	Hyaluronic acid capsule	C	Pyrogenic toxins	D	IgG

Q5) The pathogenesis of rheumatic heart diseases is?

A	Allergy	B	Molecular mimicry + type II hypersensitivity	C	Viral infection	D	Bacterial infection

Q6) Which of the following is the target for the antibodies in rheumatic fever?

A	Streptolysin O	B	Bacterial nucleic acid	C	M protein	D	Hyaluronic acid capsule

Q7) After five days of GAS infection, which of the following RF clinical manifestation should be observed?

A	Pancarditis	B	Migratory polyarthritis	C	Sydenham's chorea	D	None of the above

Q8) Which valve is most commonly affected in RHD?

A	Tricuspid	B	Mitral	C	Aortic	D	Pulmonary

Q9) Which of the following is the most severe clinical presentation of RF?

A	Pancarditis	B	Migratory polyarthritis	C	Sydenham's chorea	D	Erythema marginatum

Q10) Which of the following happens after T cells extravasate into the valve?

A	Antibodies bind to the endothelium	B	Epitope spreading	C	VCAM-1 attracts B cells	D	None of the above

Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
B	B	D	A	B	C	D	B	A	B

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