Cardiovascular Block

Immunology

Lecture 1

Rheumatic Fever and

Rheumatic Heart Disease.

In this document you will find some main points gathered from the 1st lecture..This document is NOT a replacement for the lecture..If you need additional information go back to the lecture or use a book as a reference so you understand everything correctly.

Hopefully all the information is correct and Hope you find them Useful.

Good Luck to everyone.

430 Immunology Team Members

Hadeel F. AlSajjan
Hanan AlSalman
Lujain AlYousef
Nora AlMfgaie
Alaa AlHumaid

Abdelelah AlFreem AlEnazi
Mohammed ALAnazi
Abdulrhman ALAnazi

Immunology

Rheumatic Fever and

Rheumatic Heart Disease.

Some main points you can go through and revise from:

Definition:

Rheumatic fever → is an inflammatory disease which may develop after a Group A Streptococcal infection such as a 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

Epidemiology

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

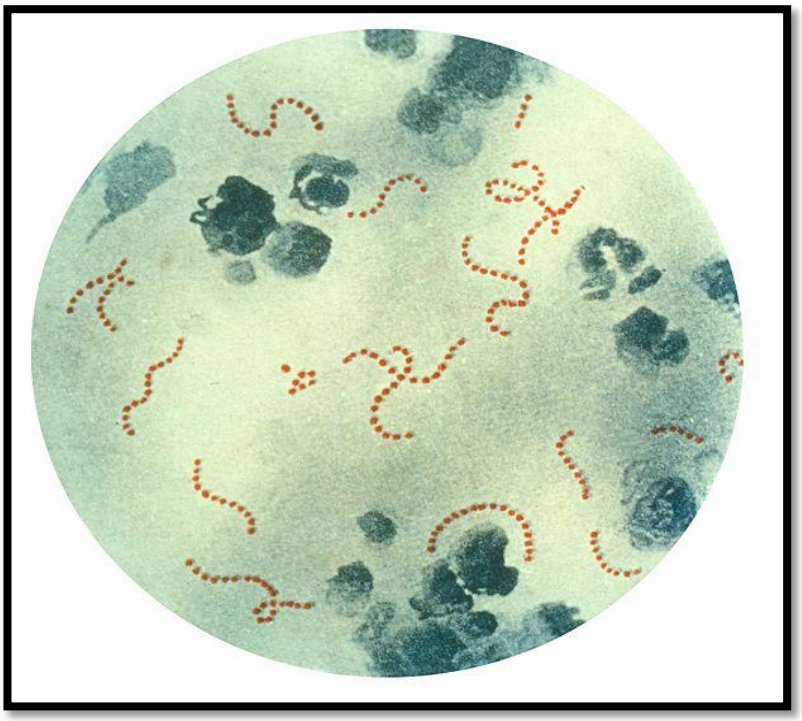
Risk factors

- Low standard of living
- Crowding

*Individual (HLA)-Human Leukocyte Antigen- susceptibility is also important
*Antigen-presenting cells bearing the HLA-DR7 molecule from RHD patients preferentially recognize heart-tissue protein

Organism

- Caused by group A streptococcus (β-hemolytic streptococci)
- 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.
- All cases associated with recent infection (e.g. pharyngitis) .
- Antibodies and the cellular immune response cross-react with human connective tissue.



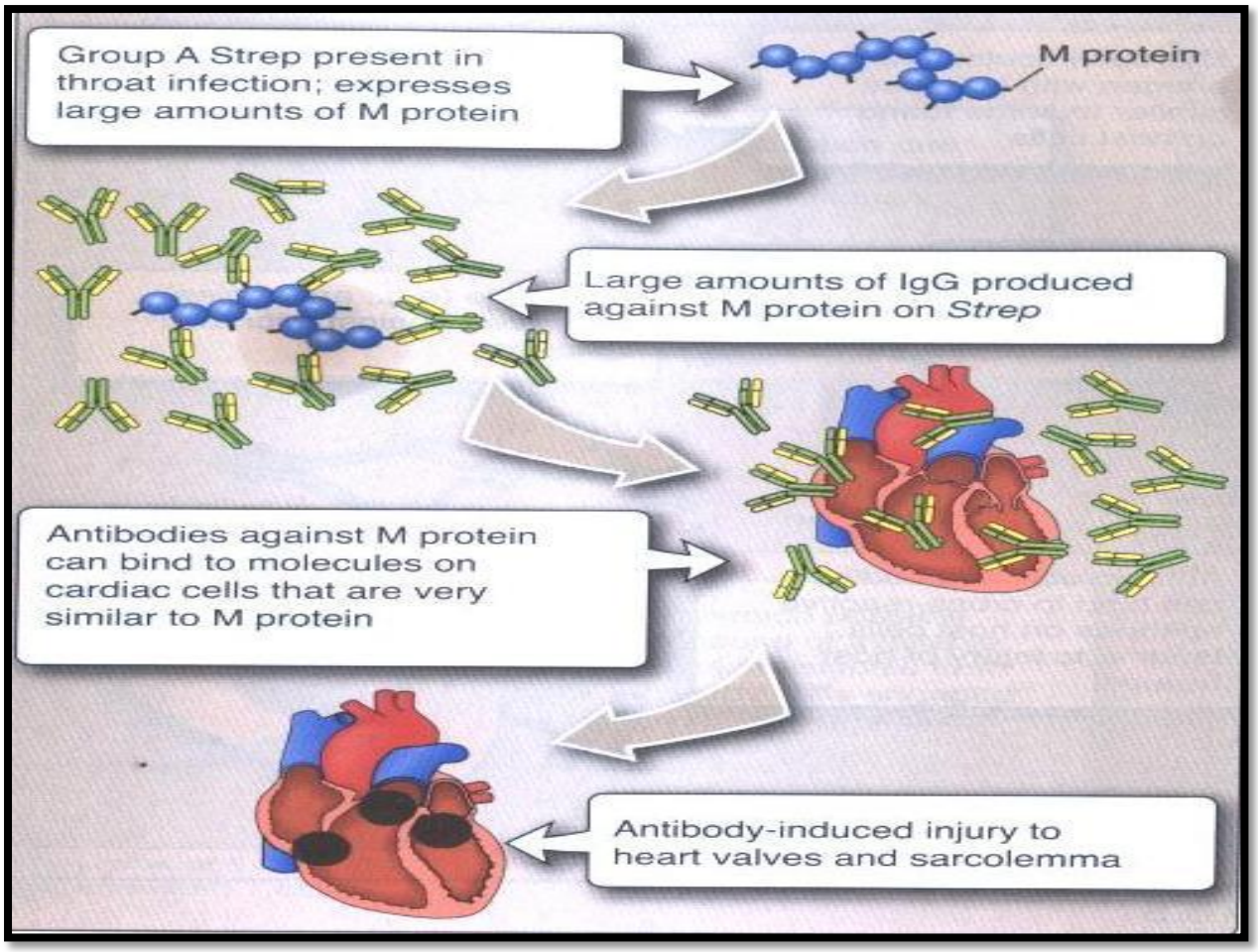
Enzymes:

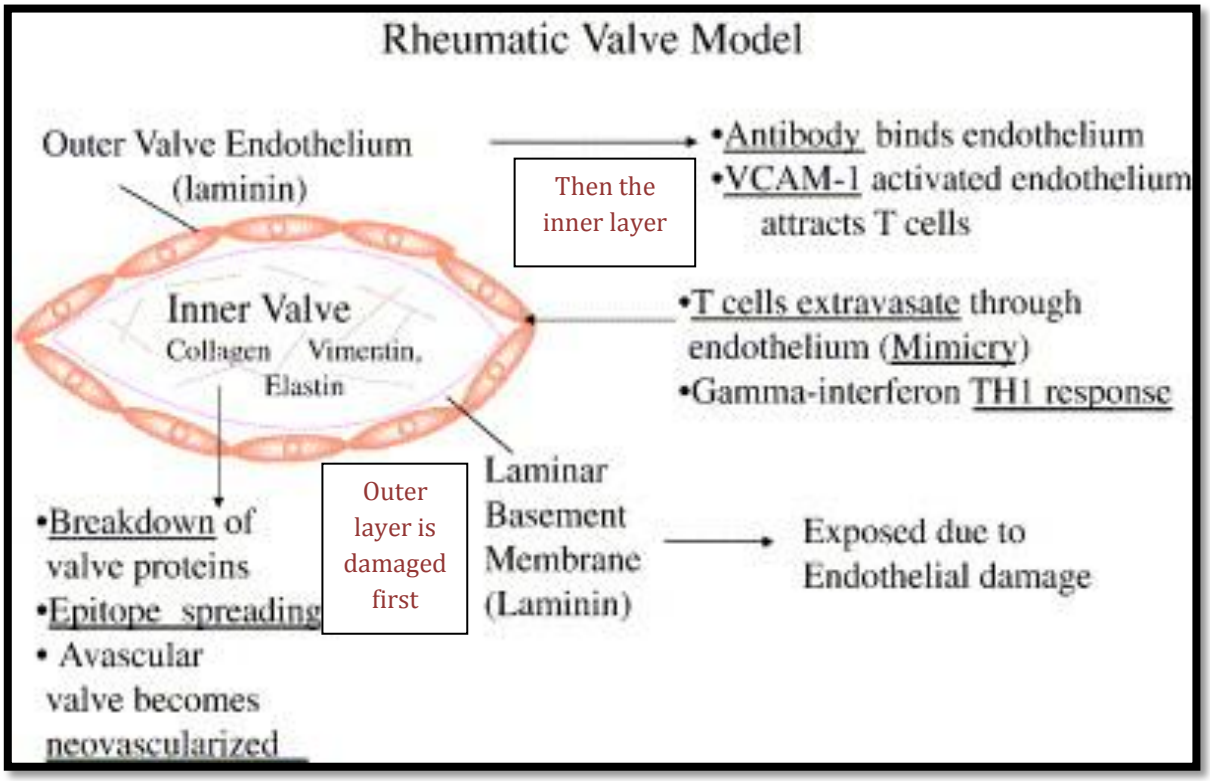
M proteins	• **Attachment & interferes with host immune response.**
Hyaluronic acid	• **Capsule Camouflages the bacterium.** *(Hides the Bacteria from our immune systems)
Streptokinases	• **Dissolves blood clots.** *(So the bacteria can spread easily)
Peptidases	• **Degrades proteins involved in immune response.**
Pyrogenic toxins	• **Stimulate fever, rash & shock.**
Streptolysins	• **Lyses erythrocytes, leukocytes & platelets.**

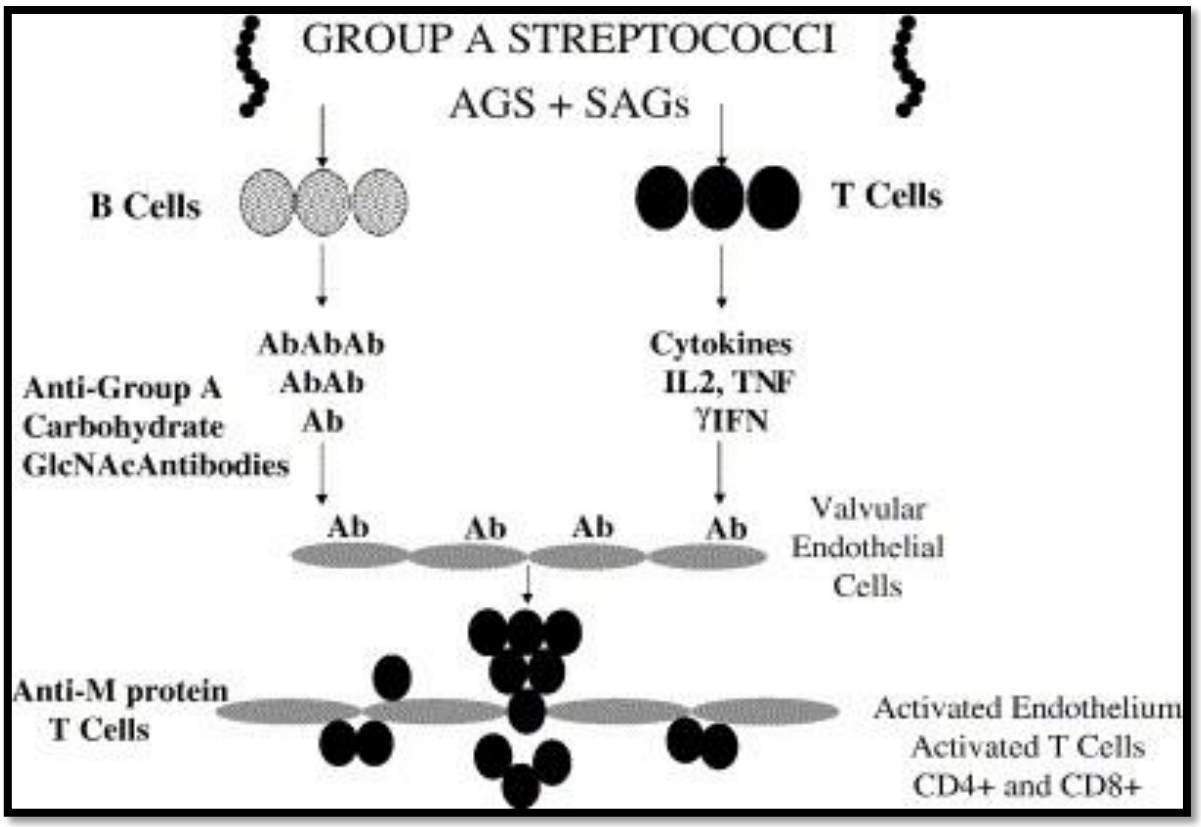
Note:
Post streptococcal glomerulonephritis is caused by streptococcal antigen-antibody immune complexes (Type III hypersensitivity reaction) .

Pathogenesis

- Rheumatic fever affects the peri-arteriolar connective tissue.
- This cross-reactivity is a Type II hypersensitivity (molecular mimicry) *Molecular mimicry → is when the pathogens antigens resemble our own antigens
- The cell wall of streptococcus group A contain high amount of M protein *which helps with the bacterium's attachment
- Antibodies which are generated against M protein may cross react with the cardiac myofiber protein myosin and smooth muscle cells of arteries → inducing cytokine release and tissue destruction.
- This inflammation occurs through direct attachment of complements and Fc receptor-mediated recruitment of neutrophils and macrophages.


Group A Strep present in throat infection; expresses large amounts of M protein
M protein
Large amounts of IgG produced against M protein on Strep
Antibodies against M protein can bind to molecules on cardiac cells that are very similar to M protein
Antibody-induced injury to heart valves and sarcolemma


Rheumatic Valve Model
Outer Valve Endothelium (laminin)
•Antibody binds endothelium
•VCAM-1 activated endothelium attracts T cells
Then the inner layer
Inner Valve
Collagen Vimentin, Elastin
•T cells extravasate through endothelium (Mimicry)
•Gamma-interferon TH1 response
Laminar Basement Membrane (Laminin)
Exposed due to Endothelial damage
Outer layer is damaged first
•Breakdown of valve proteins
•Epitope spreading
• Avascular valve becomes neovascularized



Pathophysiology

- During a Strep. Infection activated antigen presenting cells → activated Helper T cells → T cells subsequently activate self reactive B cells.
- However the antibodies may also react against the myocardium and joints, producing the symptoms of rheumatic fever.

Note: *Important*

*The antibodies react and T cells are activated

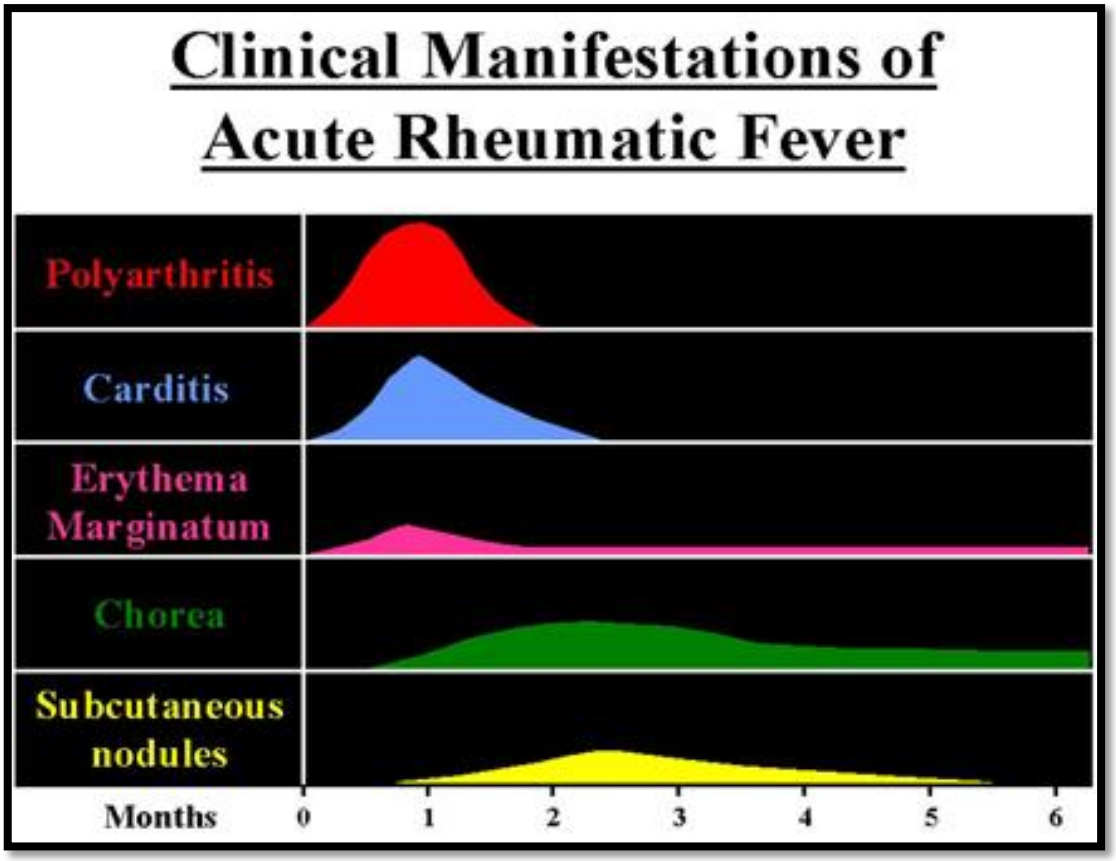
Histopathology

- Aschoff bodies. *composed of swollen eosinophilic collagen surrounded by lymphocytes and macrophages
- Anitschkoff cell. *an unusual spindly macrophage
- Aschoff giant cells. *Form from large Macrophages

Clinical Presentation

Heart *(very common)	• The endocardium, pericardium, or myocardium may Be affected (pancarditis). • Valvular damage is the hallmark of rheumatic carditis. • The mitral valve is almost always affected.
Joints (arthritis)	• This is usually polyarthritis, sometimes flitting (spreading) from joint • to joint(migratory), affecting the larger joints more than the Smaller ones.
Skin (erythema marginatum)	• Skin lesions: The classical erythema marginatum (large erythematous lesions with prominent margins slightly raised)
Central nervous system (Sydenham's chorea chorea)	• The choreiform movements affect particularly the head and the upper limbs , can affect whole side of the body (hemi-chorea)
Subcutaneous nodules	• These are painless, roundish, firm lumps overlaid by normal Looking skin.

From top to bottom → *The manifestations are in order, beginning from the one which appears first*



Note:

A combination of both major and minor criteria appears in patients, for example 2 of major criteria & 3 of the minor ones.

Revised Jones criteria for diagnosis of acute rheumatic fever

Major criteria	Minor criteria
Carditis (inflammation of the heart)	Arthralgia (aching joints without apparent swelling)
Polyarthritis (arthritis successively in several of the large joints)	Fever
Sydenham's chorea (see text)	Increased acute-phase response as judged by a raised erythrocyte sedimentation rate (ESR) or raised levels of C-reactive protein (CRP)
Erythema marginatum (rash)	Prolonged PR interval (delay in conduction of contraction signals in heart, which can be discerned in an electrocardiogram)
Subcutaneous nodules	

Investigation of Rheumatic Fever

- 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 *if it rises above 200 ml there is a risk to develop RF

Other tests :

- 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)

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