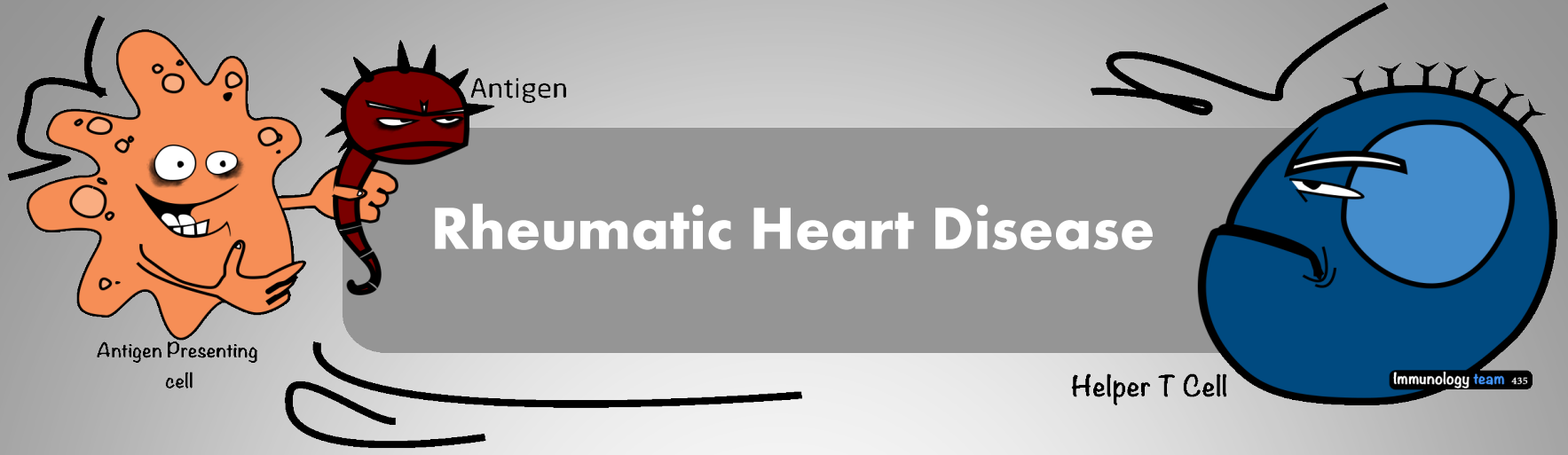


Rheumatic Heart Disease

Objectives:

- To understand the 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

Red: important
Grey: Extra explanation

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

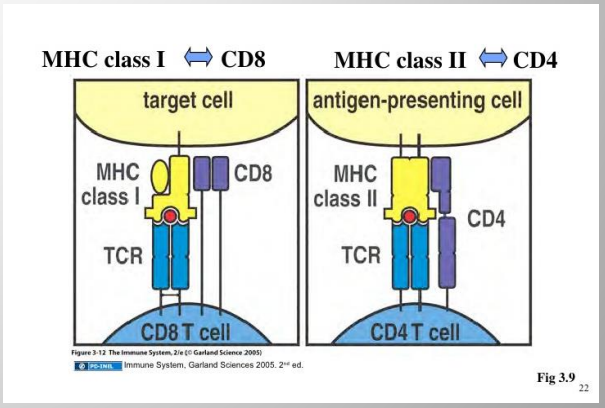
Risk factors:
1)Crowding in developing countries
2)Low standard of living due to immunodeficiency
3)Individual (HLA) susceptibility

- An inflammatory disease that can involve the heart, joints, skin, and brain.
- All cases associated with recent infection by Group A β-haemolytic streptococcus.

e.g. Strep. throat infection (Pharyngitis) or scarlet fever.

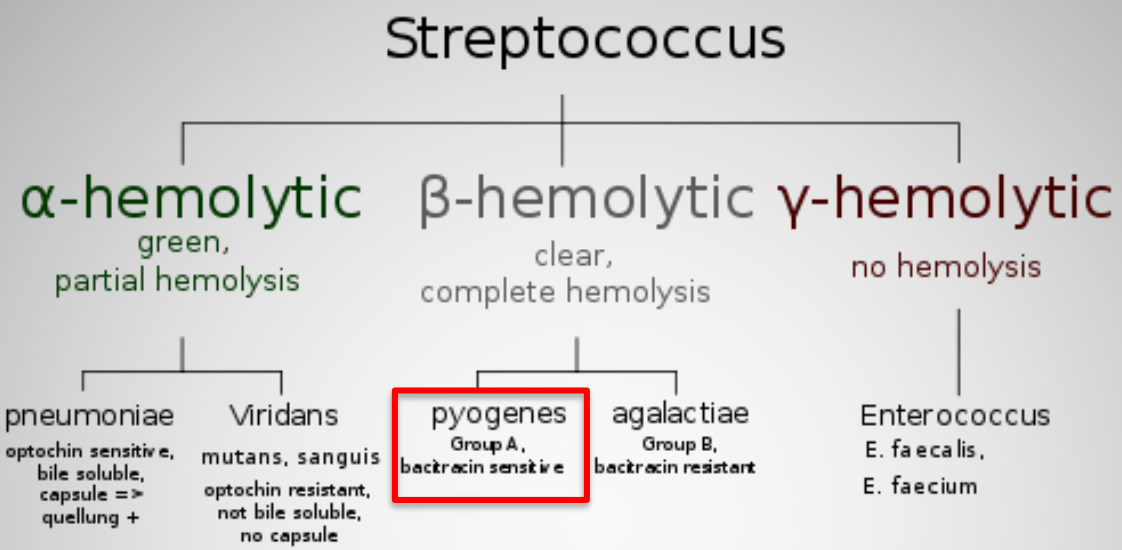
- Commonly appears in children ages 5-15, However it can arise in adulthood
- The onset of the clinical features is delayed about 3-4 weeks after the infection (Latent period)

MHC class II allele DR7 is associated with RHD, and its combination with certain DQ alleles is seemingly associated with the development of valvular lesions (genetic factors). *So APC's bearing the DR7 molecule recognize heart tissue protein!*



The associated alleles probably encode molecules that facilitate the presentation of some streptococcal peptides to T cells that later trigger autoimmune reactions mediated by molecular mimicry.

Group A β-haemolytic streptococcus



- The antibodies generated by the immune system generates against the M proteins may **cross-react** with
  - Connective tissue (peri-areteriolar connective tissue)
  - Cardiac myofiber protein myosin
  - Smooth muscle cells of arteries

Type II hypersensitivity reaction (molecular mimicry) :
The antibodies bind to antigen on the patient's own cell surface

- This organism can also cause "Post streptococcal glomerulonephritis". It is auto-immune disease affects kidney (Type III hypersensitivity reaction)

Virulence Factors :

Molecule	Function
M proteins " Most important molecule in group A strept. , without it we won't have RF! "	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 and platelets.

Pathogenesis :

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) IgE antibodies , Also it activates cross-reactive T-cells which release TNF , IFN-y , IL-2 and other cytokines

4. Antibodies may cross react with Myocardium , valvular tissue and joints producing the symptoms of Rheumtic fever. This inflammation occurs through direct attachment of complement and Fc receptor-mediated recruitment of neutrophils and macrophages.

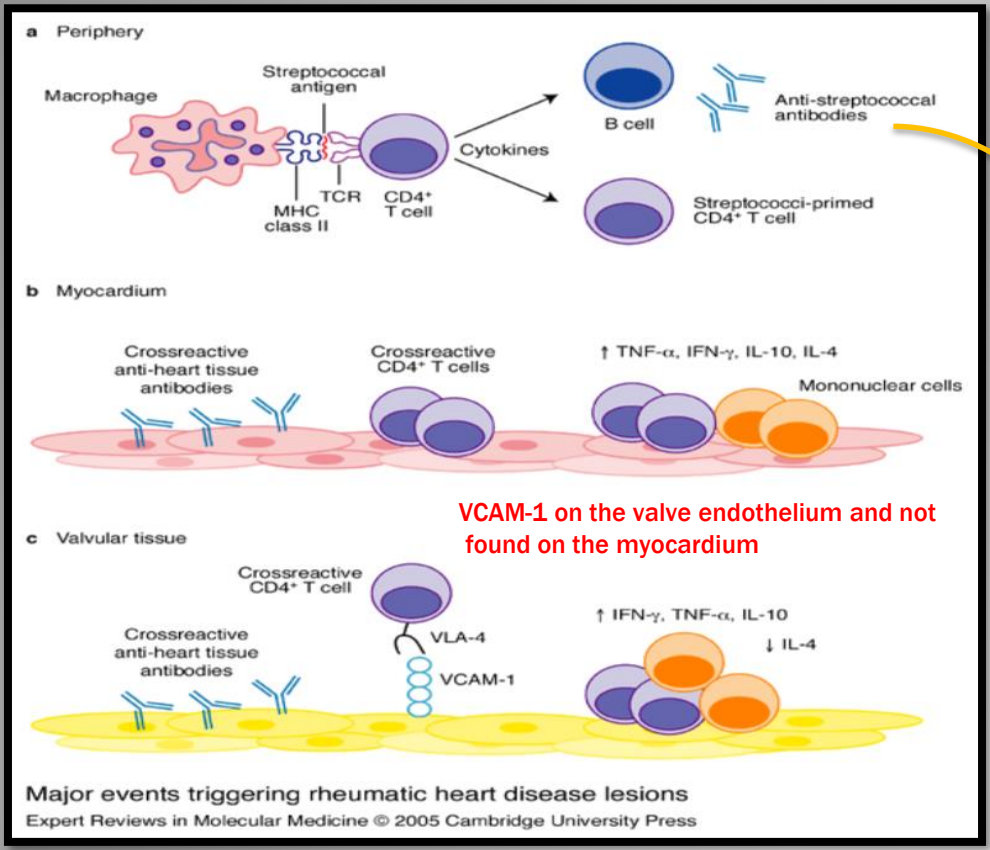
5. Up-regulates the vascular cell adhesion molecule-1 (VCAM-1) on the valve and T-cells adhere to the VCAM-1 on the valve endothelium and extravasate into the valve

6. Tissue destruction (endothelium) making the inner structure exposed "laminar basment membrane"

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

The inflammatory hypersensitivity reaction type II response causes :

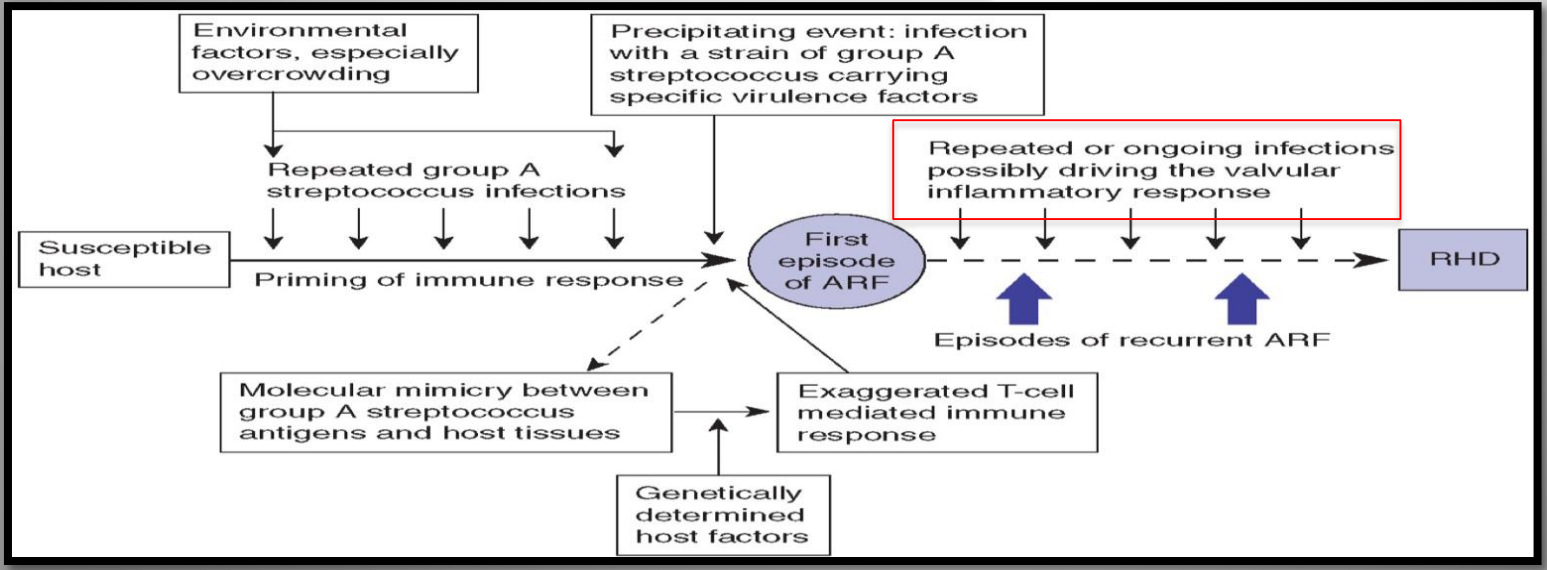
1. Breakdown of valve proteins
2. Epitope spreading (T-cells respond to other valve proteins such as Vimentin and collagen)
3. **A**vascular valve become neovascularized "the healthy valves which don't have blood supply are now having blood going through them"



Anti-streptococcal antibodies cause :

1- Antigen-antibody complex (Type III hypersensitivity reaction)

2- Antibody attached to tissues (Type II hypersensitivity reaction)



Clinical presentation

JONES criteria

1. Joints (Arthritis)

- Usually polyarthritis
- Sometimes flitting from joint to joint **(migratory)**
- Affecting the **larger joints** more than the smaller ones.

Findings:

- Swelling, Redness & Tenderness (**common**)
- Joint effusions (**occasionally**)

2. Heart

-Up to 60% of patients with RF progress to **Rheumatic Heart Disease**

- The endocardium (including valves and chordae tendineae) , pericardium (fibrinous or serofibrinous deposition between visceral and parietal pericardium) and myocrdium (can cause sudden death) may be affected **(pandcarditis)**

-**Valvular damage** is the hallmark of rheumatic carditis (mitral valve is almost affected)

3. Subcutaneous Nodules

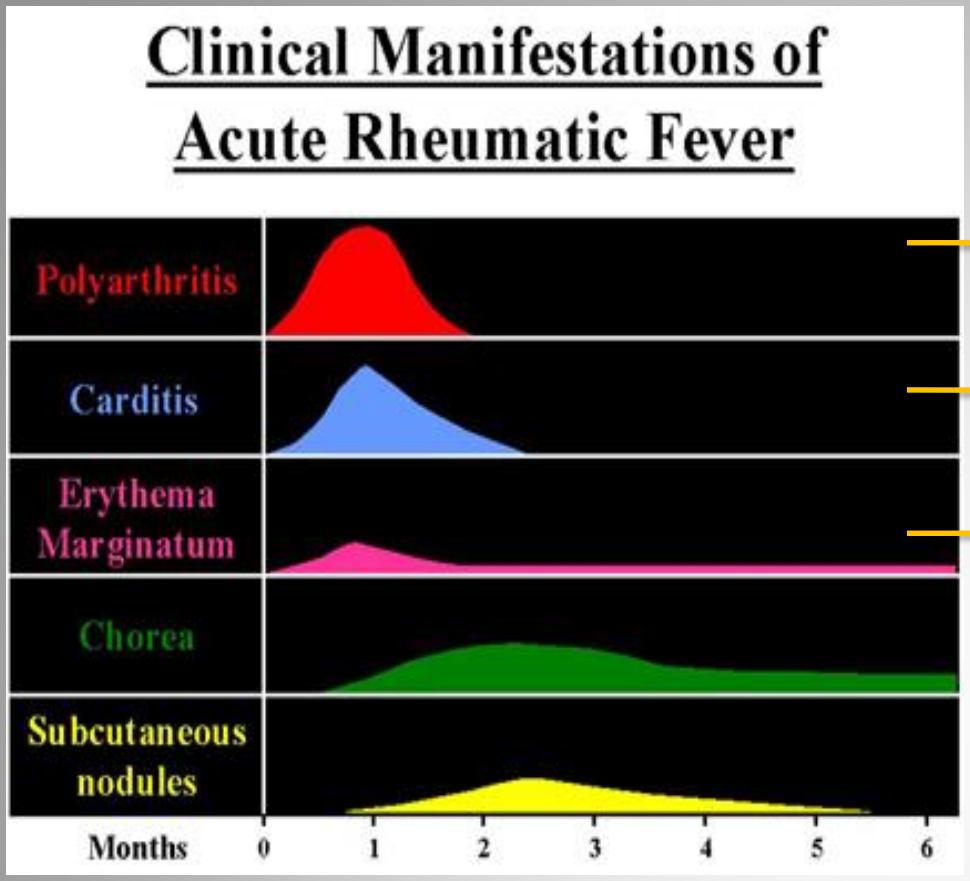
- These are painless, round, firm lumps overlaid by normal looking skin.
- They range from a few millimeters to 1.5 cm in diameter, and are localized **over bony prominences** like the elbow, shin and spine.
- They sometimes last **longer than a month.**

4. Skin (Erythema Marginatum)

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

5. Central nervous system (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**



Occurs at the beginning, Severe and Reversible

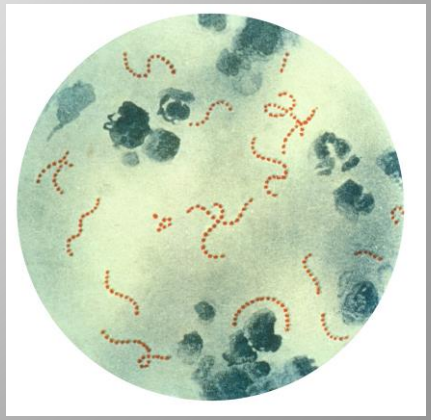
Occurs at the beginning, Severe and Irreversible

Occurs at the beginning and Reversible

Occurs after the development of Rheumatic fever , Reversible and Long

Investigation of RF

1. **Anti-streptolysinO (ASO) titer**: blood test to measure antibodies against streptolysinO (produced by the bacteria)
- 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 and Anti-hyaluronidase test:** to determine previous infection
4. **Throat culture for group A streptococci** (obtain 2 or 3 cultures)



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. Because of damaged valves

Rheumatic Fever is divided into :

1.Acute 2.Recurring 3. Chronic

- Symptoms prone to recur with subsequent Strep. Infections

- Repeated attacks of Streptococcal throat infection over the years damage heart valves resulting in either stenotic or incompetent heart valves.

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

Treatment of Rheumatic Fever

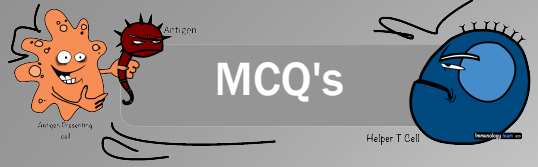
- Treat first strep throat infection with **penicillin**

(patients with rheumatic fever long term administration of penicillin is recommended for prevention of future infections by group A Streptococcus)

- Treat other manifestations **symptomatically**

- **Prophylactic** long term anti-strep therapy given to anyone who has had rheumatic fever

- Treatment involves **surgical** replacement of the damaged heart valves



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- Yeast.

Q3:Which of the following is not effected by Rheumatic fever ?

A- heart. B-Skin. C- Brain. D- Liver.

Q4: Rheumatic fever commonly appears in children that are 5 to 15 years old ?

A- True. B- False.

Q5: All cases are associated with recent infection like Laryngitis ?

A- True. B- False.

Q6: Which proteins help in the Adherence of Streptococcus pyogenes to host cells and inhibit the host's immune response ?

A- M proteins. B- IgE. C- IgM. D- Monoclonal antibodies.

Q7: The function of Streptokinases is to ?

A- Degrades proteins. B- Camouflage the bacterium. C- Dissolve blood clots.

Q8: The cross-reactivity is a Type …….. hypersensitivity reaction.

A- Molecular Mimicry. B- Type I hypersensitivity. C- type III hypersensitivity .

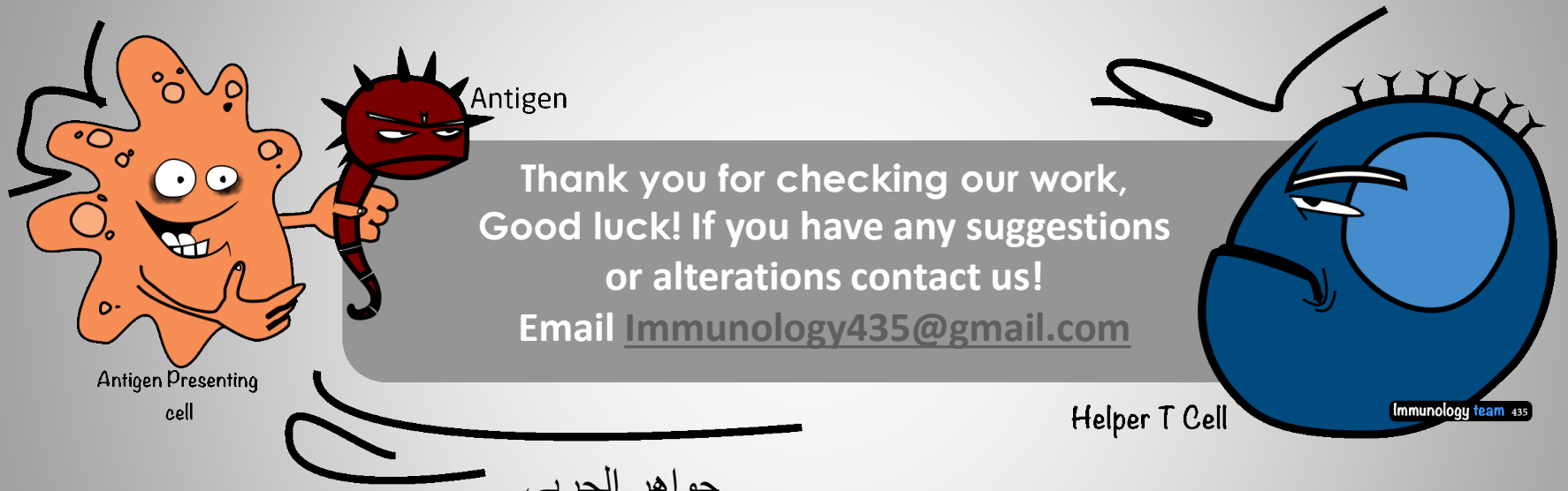
Q9: During a Strep. infection activated antigen presenting cells such as macrophages present the bacterial antigen to helper T cells ?

A- True. B- False.

Q10: Up to 20% of patients with ARF progress to Rheumatic Heart Disease ?

A- True. B- False.

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



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Good luck! If you have any suggestions or alterations contact us!
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