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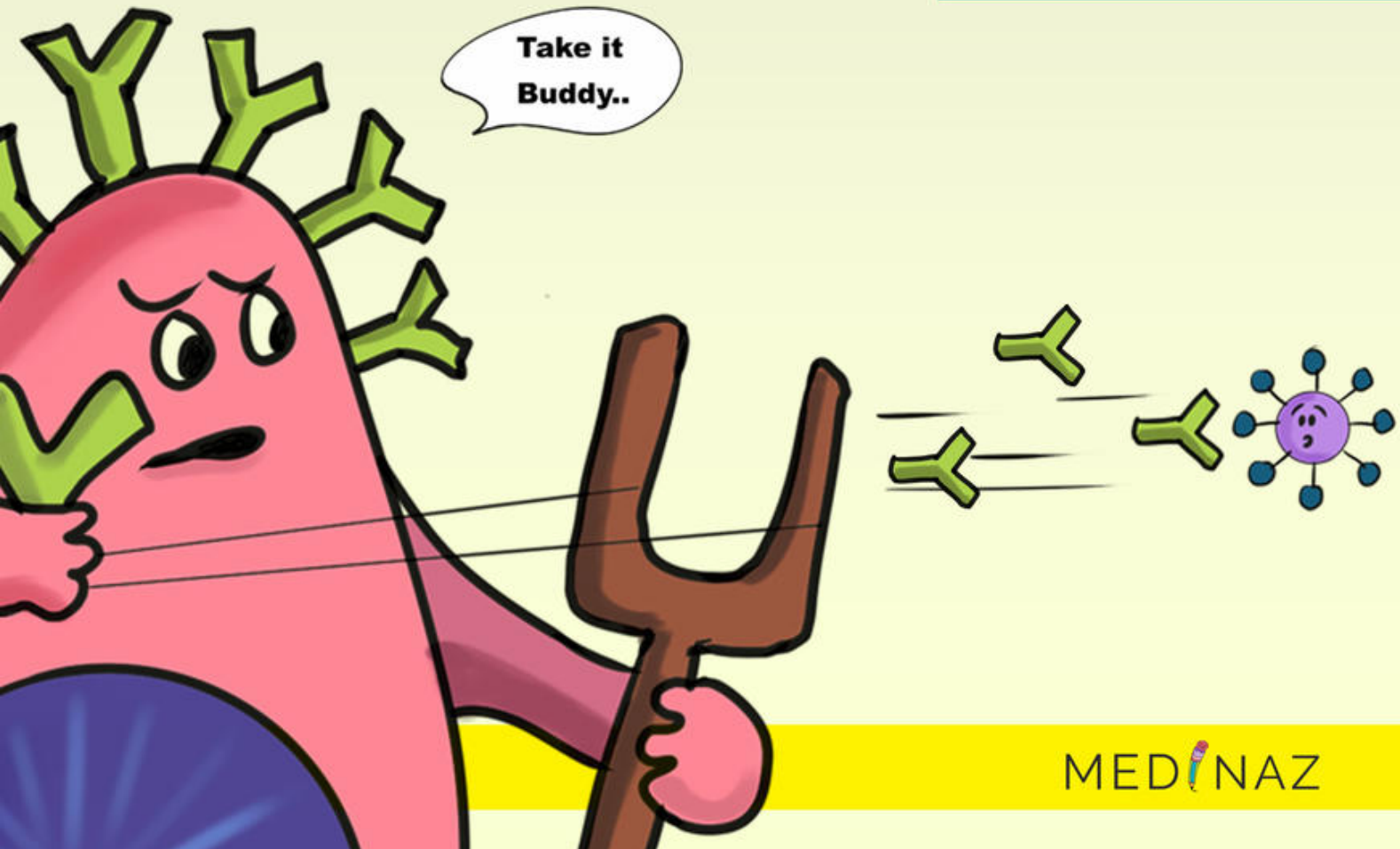
FIRST EDITION

HIGH YIELD VISUAL IMMUNOLOGY

FOR USMLE, NBDE, FMGE, NEET

- **200+** Practice Questions & Answers
- **100** Conceptual MCQs with deatailed explanation
- **1500+** Frequently tested facts
- **100+** Diagrams & Mnemonics

DR.NAZMUL ALAM



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From the publisher's Desk

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The Immune organ system

Primary organs:-

Bone Marrow - B cell maturation, immune cell production

Thymus - T cell maturation

Bone marrow = B cell

Thymus = T cell

Secondary organs :-

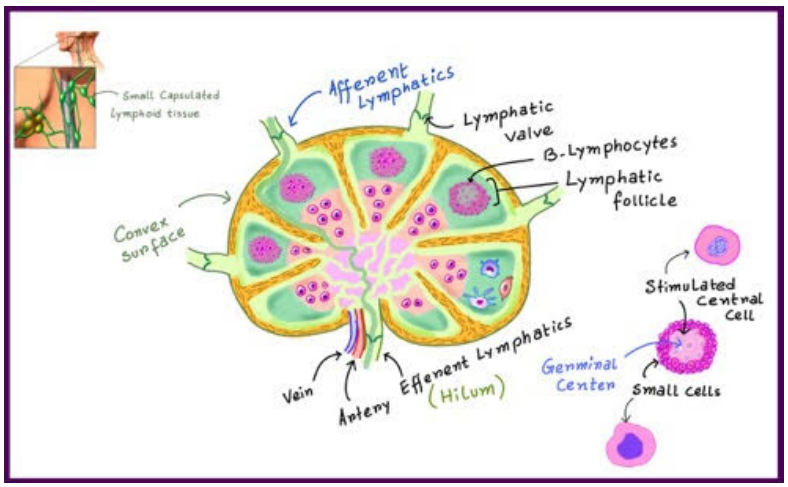
Spleen, lymph nodes, tonsils, Peyer patches

Allow immune cells to interact with antigen

Secondary organ = Spleen

Lymph node

- **Follicles** present in outer cortex of lymph node
- **1^0 follicles** are dense and dormant.
- **2^0 follicles** have **pale** central germinal centers and are active.



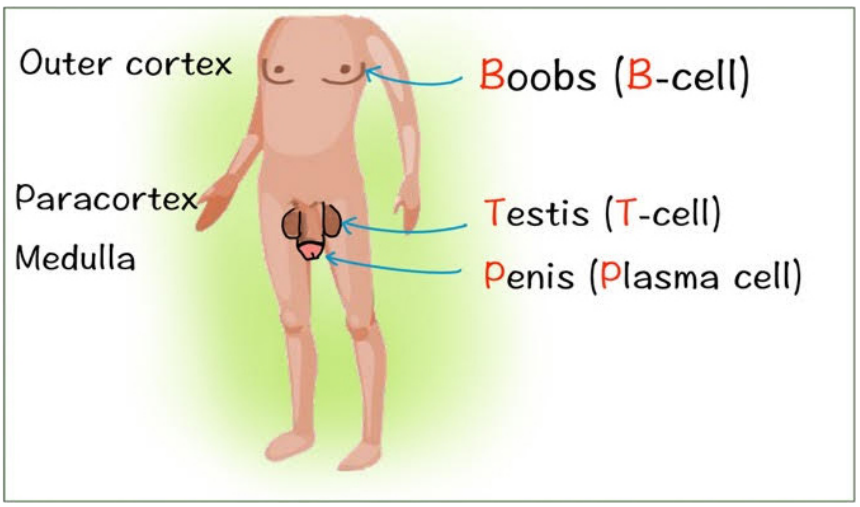
• **T cells** present in Paracortex of lymph node

• It is **underdeveloped** in patients with DiGeorge syndrome.

• Paracortex **enlarges** in an extreme cellular immune response (eg. Viral infection).

• **Plasma cells** are present in Medulla

• **Outer cortex** contain Follicular dendritic cells & **Paracortex** contain Dendritic cells.



Thymus :-

• **Thymus** is an Encapsulated gland.

• Thymus is derived from the Third pharyngeal pouch.

• **Cortex** is dense with immature T cells

• **Medulla** is pale with mature T cells and Hassall corpuscles containing epithelial reticular cells.

•Normal **neonatal** thymus "sail-shaped" on **CXR**, involves with age

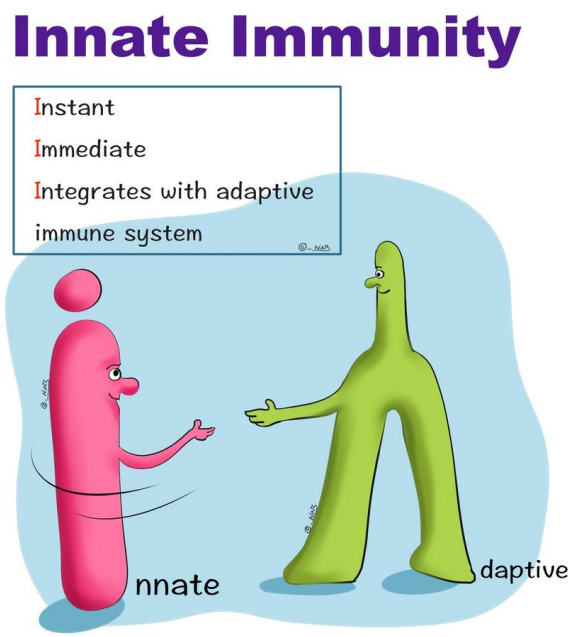
Thymus = Third p. pouch

Innate Immunity

Provides the body's first line of defense against infectious agents.

Components:-

Neutrophils, macrophages, monocytes, dendritic cells, natural killer (NK) cells (lymphoid origin), complement, physical epithelial barriers, secreted enzymes.



•Complement system is a part of innate immunity

•Resistance persists through generations; does not change within an organism's lifetime

•Are present intrinsically with or without previous stimulation

•**Secreted proteins -** Lysozyme, complement, C-reactive protein (CRP), defensins

•Have limited specificity for shared microbe and cellular structures (patho- gen-associated molecular patterns [PAMPs] and damage associated molecular patterns[DAMPs])

•Have limited diversity as reflected by a limited number of pattern recognition receptors

Are not enhanced in activity upon subsequent exposure—no memory

Inflammasome:-

The inflammasome is an important part of the innate immune system. It is expressed in myeloid cells as a signalling system for detection of pathogens and stressors.

Activation of the inflammasome results in the production of IL-1β and IL-18, which are potent inflammatory cytokines.

Clinical points

- Mutation in signaling molecules effecting **TLR**s cause Recurrent, severe bacterial infections (pneumonia)
- **Gain of function** mutations in inflammasome cause **gout, atherosclerosis, type II diabetes**
- **NOD-2** mutations cause **IBD**
- **IL-12** receptor and **IFN-γ** receptor deficiency cause Recurrent infections with intracellular bacteria (Mycobacterium)

Toll Like Receptors (TLR):-

They are the principle host cell receptors of innate immunity

They are so named because they are similar to Toll receptors present in the fruit fly (Drosophila)

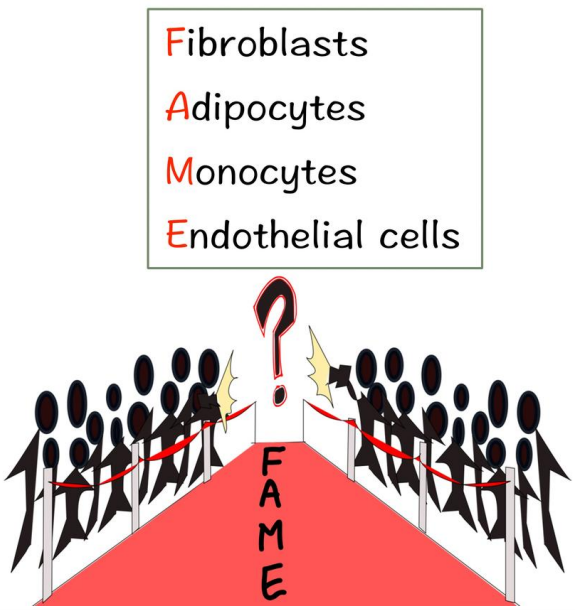
TLR – 2	binds to bacterial peptidoglycan
TLR – 3	binds to dsRNA of viruses
TLR – 4	binds to LPS of gram-ve bacteria
TLR – 5	binds to flagella of bacteria
TLR – 7&8	binds to ssRNA of viruses
TLR – 9	binds to bacterial DNA

Acute Phase Reactant (APR) proteins:-

Protein in nature and synthesized by liver at steady concentration

Also **synthesize by -** Endothelial cells, fibroblasts, monocytes & adipocytes

Antimicrobial & **anti-inflammatory**



Positive ARPs – level increase during acute inflammation:-

- Serum amyloid A
- C- reactive protein
- Complement protenis: C1-C9, factor B, D, and properdin
- Coagulation proteins (fibrinogen, von Willebrand factors)
- Alpha 1 antitripsin
- Alpha 1 acid glycoprotein
- Mannose binding protein
- Haptoglobin
- Metal binding proteins : ceruloplasmin

Negative ARPs - level decrease during acute inflammation

E.g. – Albumin, Transferrin & Antithrombin

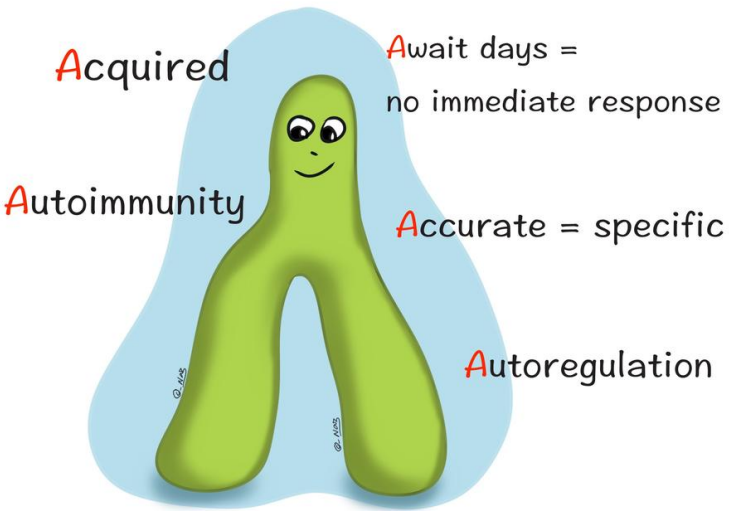
C- reactive protein (CRP):-

- Acute Phase Reactant (APR) proteins that increases during acute inflammation
- CRP is so named because it precipitates with C-carbohydrate (polysaccharide) antigen of pneumococcus
- Commonest marker of acute inflammation and most widely used
- Normal level - <0.2 mg/dl
- Detection limit of latex agglutination test – 0.6 mg/dl

Adaptive Immunity

Components - B and T lymphocytes and their effector cells.

- Each B and T lymphocyte is specific for a particular antigen
- **Secreted proteins -** Immunoglobulins
- Have immunologic memory
- Are capable of distinguishing self from non-self
- Are self-limiting, highly specific, refined over time



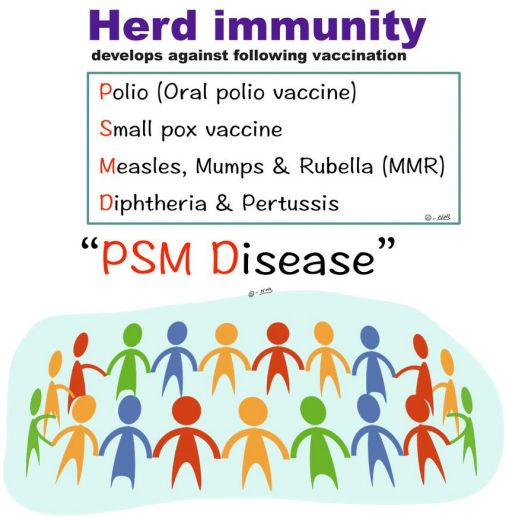
Local (or mucosal) immunity

- Immune response that is active at the mucosal surface
- Mediated by secretory IgA
- Induced by natural infection or by live vaccine

Active immunity	Passive immunity
Produced actively by host immune system	Immunoglobulins received passively
Induced by: Infection (natural) Vaccination (artificial)	Acquired by : Mother to fetus IgG transfer (natural) Readymade antibody transfer (artificial)
Long lasting	Lasts for short time
Lag period present	No lag period
Memory present	No memory
Booster doses are useful	Subsequent doses are less effective
Negative phase may occur	No negative phase
Not useful in immunodeficiency	Useful in immunodeficiency

Herd Immunity :-

- Overall immunity of a community (or herd) towards a pathogen
- Good herd immunity – epidemics are less likely to occur
- Herd immunity develops following vaccination against
- Polio (Oral polio vaccine)
- Small pox vaccine
- Measles, Mumps & Rubella (MMR)
- Diphtheria & Pertussis



Adoptive Immunity :-

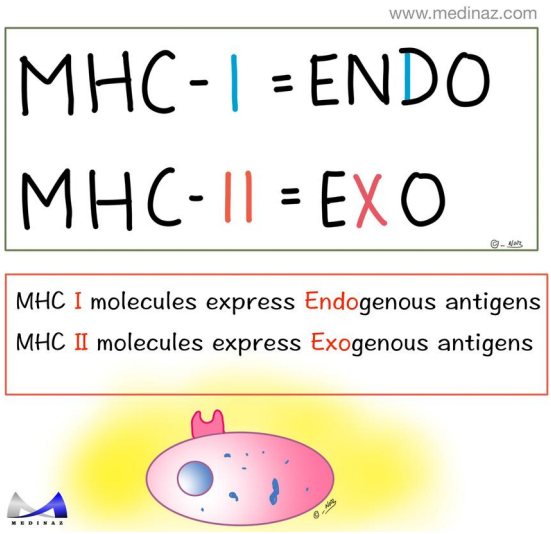
- It is the process of transfer of CMI from one individual to other
- It occurs following injection of immunologically competent T-lymphocytes known as transfer factor
- It is useful for treatment when the CMI is low. E.g. – in lepromatous leprosy

Key points

- Toll like receptor acts by **cytokine release**
- **Transfer factor** is an example of Adoptive immunity
- Innate immunity is stimulated by **carbohydrate sequence** in the **cell wall** of bacteria
- Active immunity can be induced by **toxoids, sub-clinical infection & antigen exposure**

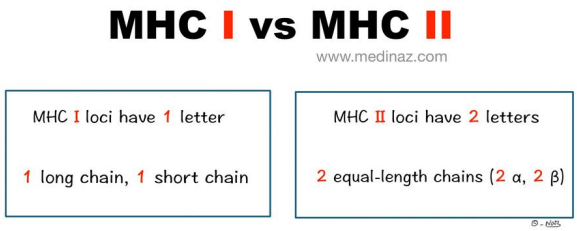
Major Histocompatibility Complex :-

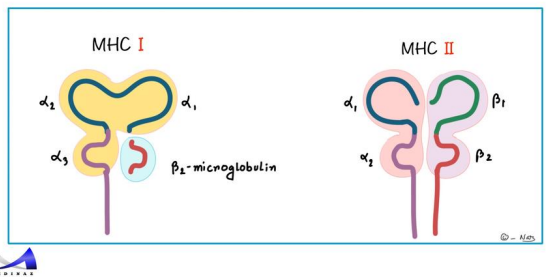
MHC I



- Present on all nucleated cells (except sperms) & platelets
- Different loci - HLA-A, HLA-B, HLA-C
- It binds with TCR (T-cell receptor) & CD8 molecule
- It contains 1 long chain, 1 short chain
- It expressed on all nucleated cells, APCs, platelets Not on RBCs
- Present endogenously synthesized antigens (eg, viral or cytosolic proteins) to CD8+ cytotoxic T cells
- Associated protein - β2-microglobulin

MHC II





- Present on all APCs
- Different loci - HLA-DP, HLA-DQ, HLA-DR
- It contains 2 equal-length chains (2 α, 2 β)
- It binds with TCR (T-cell receptor) & CD4 molecule
- It expressed on APCs
- Present exogenously synthesized antigens (eg, bacterial proteins) to CD4+ helper T cells

MHC III

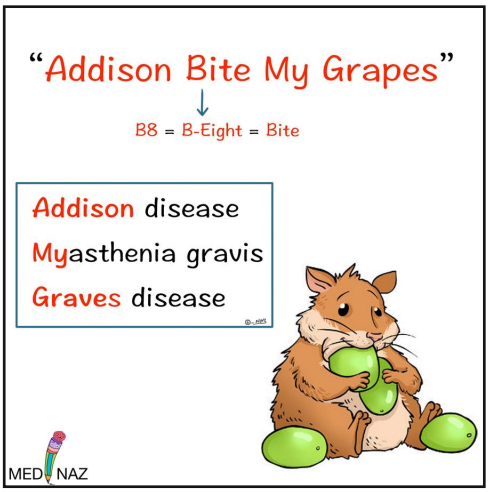
MHC class III contains genes for :

- Complement components C2 & C4 of classical pathway
- Properdin factor B of alternate pathway
- TNF alfa and beta
- Heat shock protein 70
- Enzyme Tyrosine hydroxylase
- Genes for MHC are located on short arm of chrosome 6

HLA Sub types associated with diseases

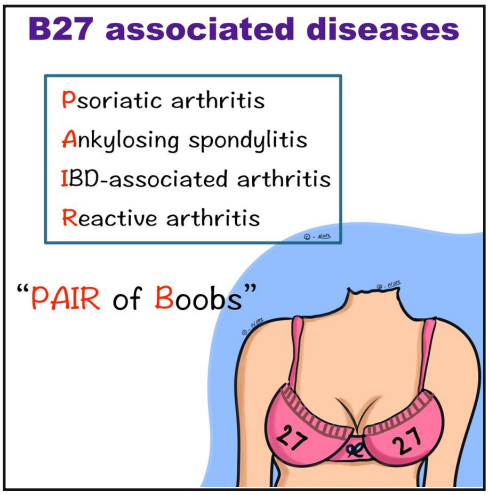
A3 - Hemochromatosis

B8 - Addison disease, myasthenia gravis, Graves disease

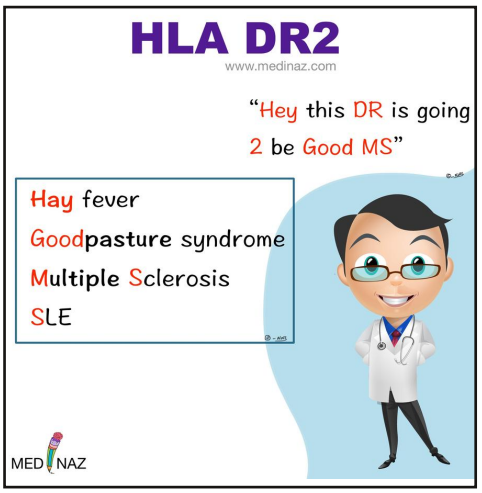


B27 - Psoriatic arthritis, Ankylosing spondylitis, IBD-associated arthritis, Reactive arthritis

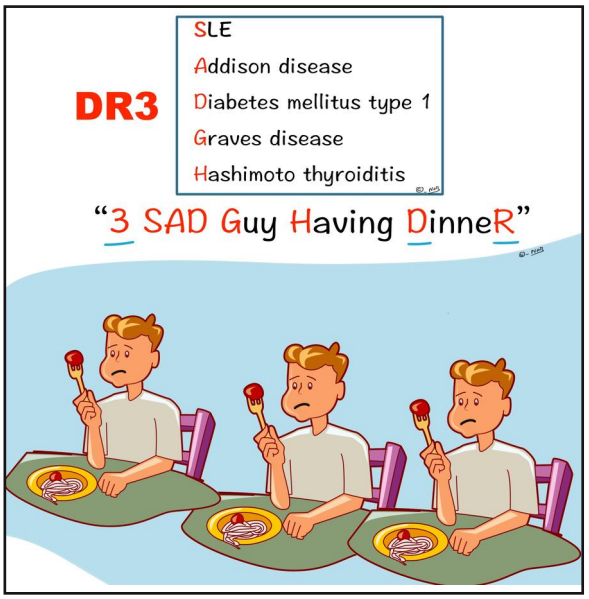
DQ2/DQ8 - Celiac disease



DR2 - Multiple sclerosis, hay fever, SLE, Goodpasture syndrome



DR3 - Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis, Addison disease



DR4 - Rheumatoid arthritis, diabetes mellitus type 1, Addison disease

DR5 - Hashimoto thyroiditis

T & B - Lymphocytes

T - Lymphocytes :-

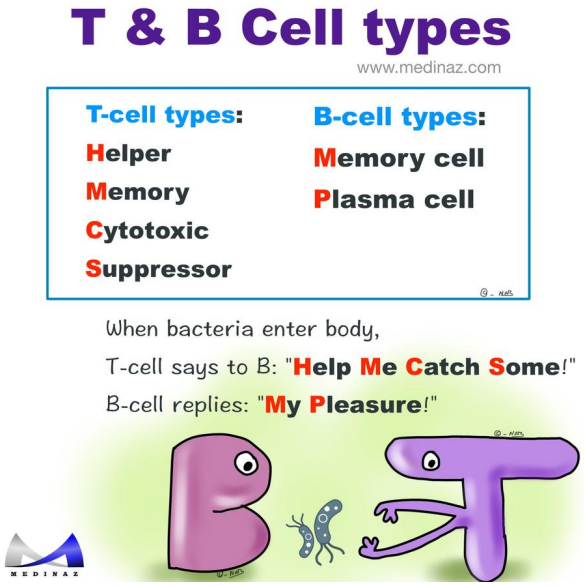
Origin - bone-marrow

Maturation - in Thymus

Peripheral blood - 70-80% of total lymphocytes

CD markers - CD-3,4,8

Cell-mediated immunity



CD4+ T cells help B cells make antibodies and produce cytokines to recruit phagocytes and activate other leukocytes

CD8+ T cells directly kill virus-infected cells

Regulatory T-cells (TREG) cells process surface markers such as CD4, CD25, and Foxp3

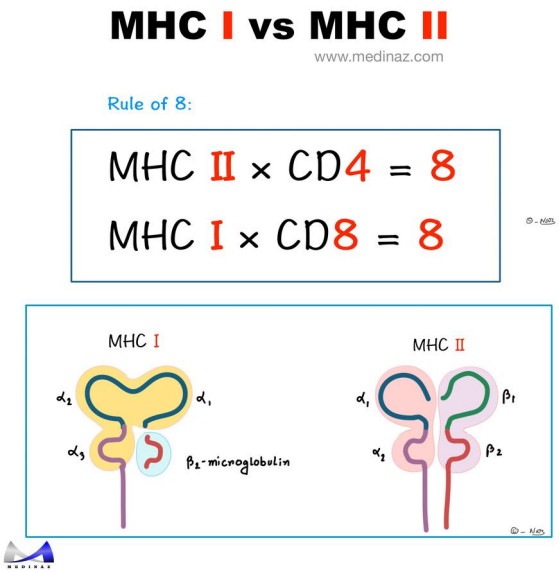
Key points

Deficiency of **Foxp3** receptors leads to a severe form of autoimmune disease known as Immune dysregulation Polyendocrinopathy, Enteropathy X-linked (**IPEX**) syndrome (Characterized by enteropathy,endocrinopathy, nail dystrophy, dermatitis,and/or other autoimmune dermatologic conditions. Associated with diabetes in male infants)

Cytotoxic T-cells :-

Kill virus-infected, neoplastic, and donor graft cells by inducing apoptosis. Release cytotoxic granules containing preformed proteins (eg, perforin, granzyme B). Cytotoxic T cells have CD8, which binds to MHC I on virus-infected cells.

- **γ - δ** T-cells lack both CD4 & CD8 molecules
- Delayed cell-mediated hypersensitivity (type IV)
- Acute and chronic cellular organ rejection



B-lymphocytes

Origin - bone-marrow

Maturation - bone-marrow

Peripheral blood - 10-15% of total lymphocytes

CD markers - CD19, 21,24

Humoral immunity

Recognize antigen - undergo somatic hypermutation to optimize antigen specificity

Produce antibody - differentiate into plasma cells to secrete specific immunoglobulins

Maintain immunologic memory - memory B cells persist and accelerate future response to antigen.

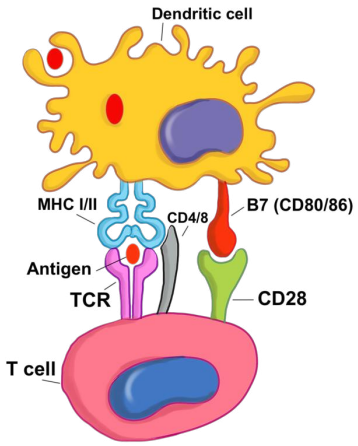
T & B Cell Activation

T-cell activation

Dendritic cell (specialized APC) samples antigen, processes antigen, and migrates to the draining lymph node.

T-cell activation (signal 1): antigen is presented on MHC II and recognized by TCR on Th (CD4+) cell. Endogenous or cross-presented antigen is presented on MHC I to Tc (CD8+) cell

Proliferation and survival (signal 2): costimulatory signal via interaction of B7 protein (CD80/86) on dendritic cell and CD28 on naïve T cell

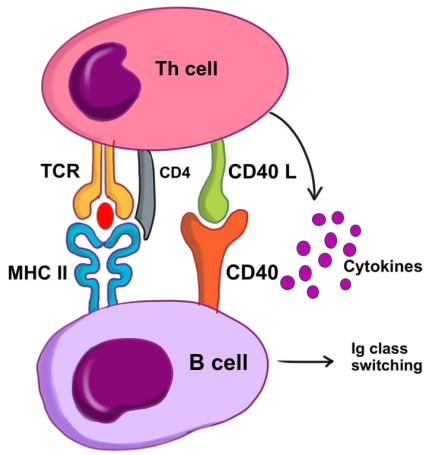


Th cell activates and produces cytokines. Tc cell activates and is able to recognize and kill virus-infected cell

B-cell activation and class switching

Th-cell activation as above.

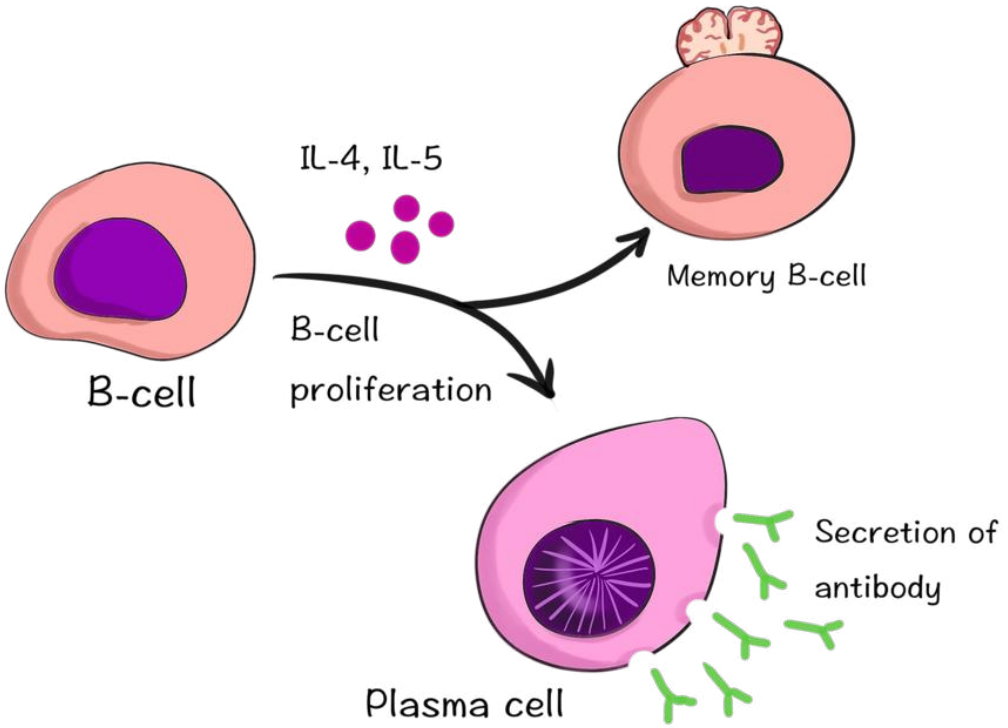
B-cell receptor–mediated endocytosis; foreign antigen is presented on MHC II and recognized by TCR on Th cell



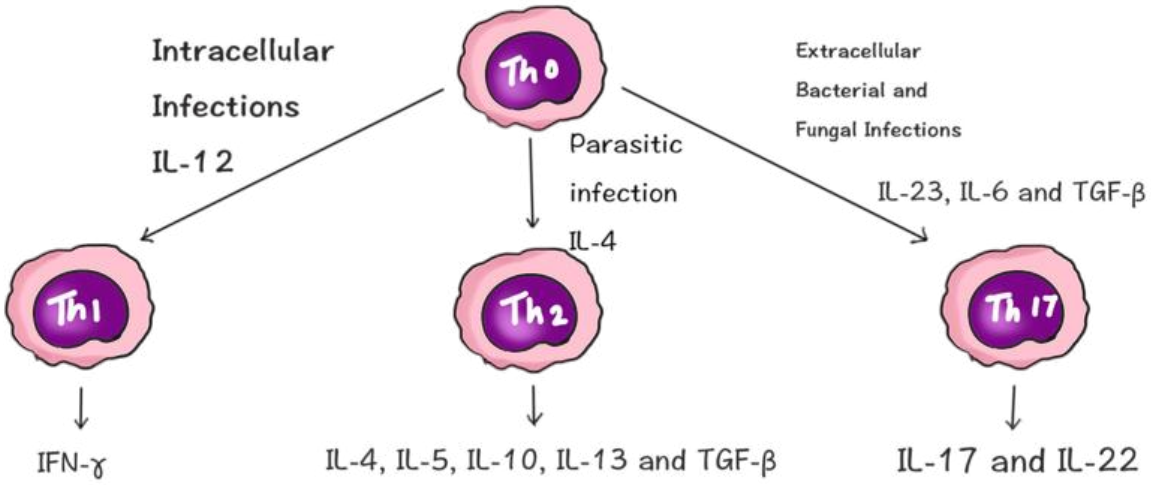
CD40 receptor on B cell binds CD40 ligand (CD40L) on Th-cell

Th-cell secretes cytokines that determine Ig class switching of B cell. B cell activates and undergoes class switching, affinity maturation, and antibody production

Plasma Cell and Memory Cell Formation



Subsets of Helper T Cells



- Amplifies Th1 response
- Inhibits Th2 response
- Activates classic macrophage
- Drives isotype switching to IgG

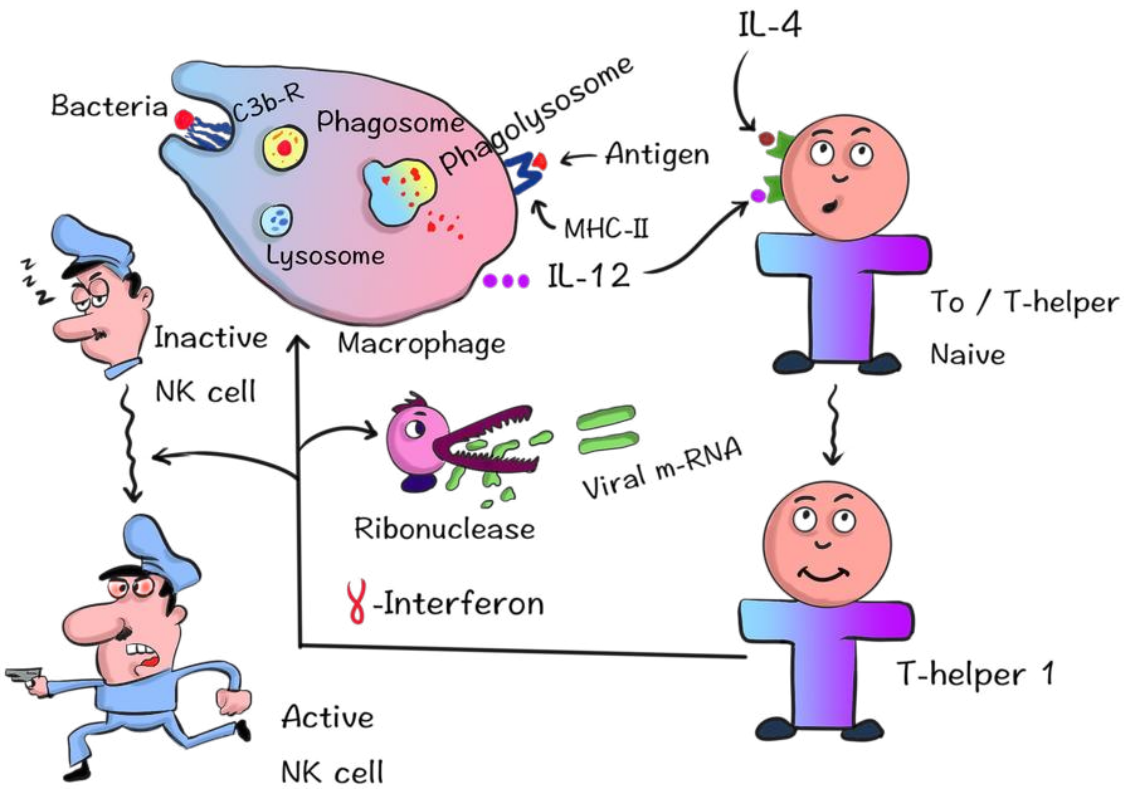
- IL-4 amplifies Th2 response
- IL-4 and IL-10 inhibit Th1 response
- IL-5 drives eosinophil maturation
- Activates alternate macrophage
- IL-4 and IL-13 drive isotype switching to IgE and alternative macrophage activation
- IL-5 and TGF-β drive isotype switching to IgA

- IL-17 activates tissue cells and leukocytes to secrete inflammatory cytokines leading to recruitment of neutrophils
- IL-17 and IL-22 act on epithelial cells to secrete anti-microbials and improve barrier function

Null Cells / NK cells

Constitute 5-10% of circulating lymphocytes
These are large granular lymphocytes that is developed inside of bone marrow.

They contain azurophilic granules
They do not have any T cell receptors (TCR)
They present CD16 & CD56
Examples (Subsets) are –
Antigen dependent cytotoxic cells (ADCC)
Lymphokine activated killer cells (LAK cells) are NK cells activated with IL-2, used for the treatment of RCC
Activation of NK cells is regulated by INF gamma. Proliferation of NK cells is done by IL-2 and IL-15 (?)



Function

Part of innate immune response
1st line defense against virus infected cells & cancer cells – osmotic lysis or trigger apoptosis. Lyse the cell without prior sensitization (Cytotoxicity is not MHC restricted)

No prior sensitization is required for NK cells to act
No immunological memory (Non immune mediated)
No antibody induced action

Phagocytic cells

Macrophages

Microphages
- Neutrophils
- Eosinophils
- Basophils

Dendritic cells (DCs)

- Found in all tissues
- Antigen processing and presentation
- Long cytoplasmic arms CD14 positive
- Two major functions: initiate inflammatory response and stimulate adaptive immune response

Mast cells

- Skin, mucosa

- 2 pathways for activation: innate TLRs and antibody-dependent (IgE)

Antigen presenting cells

Types:
• Professional APC
• Non-Professional APC

Professional APC :-
• Express MHC II molecules
• Capture and present antigen routinely

Examples:•
Dendritic cells (Including Langerhans cell)
B-cell
Macrophage

Non-Professional APC :-
• Express MHC I molecules
• Can be induced to present antigen by cytokines like INF-gama

Examples:-
Endothelial cell
Fibroblast
Pancreatic cells
Glial cell
Thymic epithelial cell

Antibody structure and function

All antibodies are immunoglobulins (Ig)

All immunoglobulins are glycoproteins consisting of **2 light** chains and **2 heavy** chains.

Fab (containing the variable/hypervariable regions) consisting of light (L) and heavy (H) chains recognizes antigens.

Fc region of IgM and IgG fixes complement.

Heavy chain contributes to Fc and Fab regions. Light chain contributes only to Fab region.

Fab - Fragment, antigen binding (ab = antigen binding)

Determines idiotype: unique antigen-binding pocket; only 1 antigenic specificity expressed per B cell

Fc

Constant

Carboxyl terminal

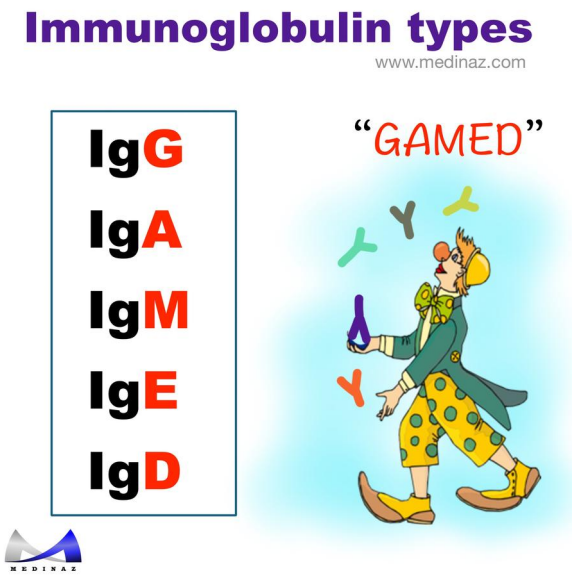
Complement binding

Carbohydrate side Chain

Crystallization when treated with papin

Cross placenta

Catch mast Cell



All isotypes can exist as monomers. Mature, naive B cells prior to activation express IgM and IgD on their surfaces. They may differentiate in germinal centers of lymph nodes by isotype switching (gene rearrangement; induced by cytokines and CD40L) into plasma cells that secrete IgA, IgE, or IgG.

Isotype switching - Gene rearrangement process whereby the **μ** and **∂ C_H** gene segments are sliced out and replaced with either

Anamnestic reaction - It is augmented antibody production on subsequent exposure. It is seen in person who have had past typhoid/enteric fever or who have had immunization against typhoid.

Enzymatic digestion

Papain digestion - Papain cleaves the Ig molecule at a point **above** the hinge region, resulting in three fragments: 2 Fab fragments and 1 Fc fragments

Pepsin digestion - Pepsin cleaves the Ig molecule at a point **below** the hinge region resulting in formation of One F (ab)2 fragments and many smaller fragments

Mercaptoethanol digestion - generates 4 fragments (2H & 2L chains) as it cleaves only disulphide bonds sparing the peptide bonds

IgG

Most abundant isotype in serum

Main antibody in **2° response** to an antigen

Complement fixation and **opsonization** of bacteria

Most potent in opsonizing

Neutralizes bacterial toxins and viruses

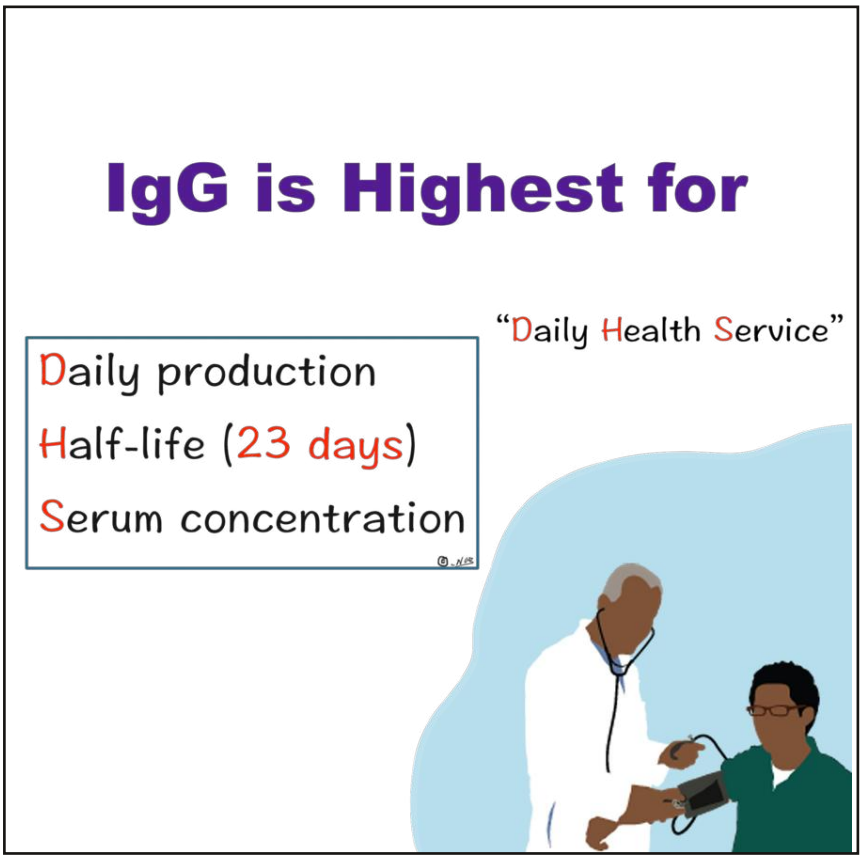
Only isotype that **crosses the placenta** (provides infants with passive immunity).

IgG is highest for -

Daily production

Half-life (23 days)

Serum concentration

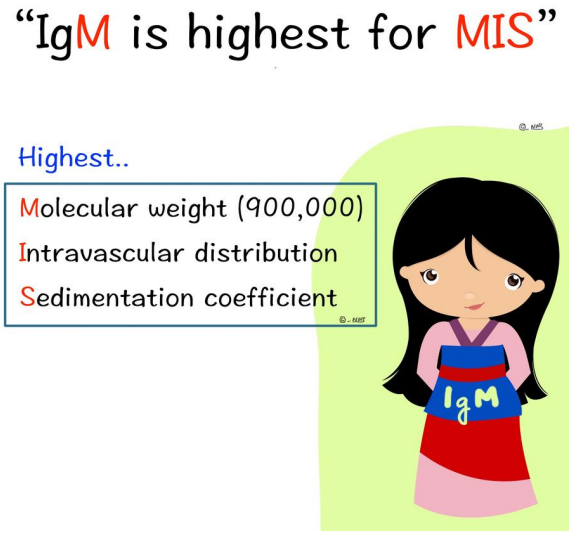


IgA

- Predominant immunoglobulin in **saliva** - IgA
- Released into **secretions** (tears, saliva, mucus) and **breast milk**
- **Monomer** when present in circulation and **dimer** when secreted
- Crosses epithelial cells by **transcytosis**
- Produced in **GI tract** (eg, by Peyer patches) and protects against gut infections (eg, Giardia).
- **Most produced** antibody overall, but has **lower serum concentrations**
- Picks up secretory component from **epithelial cells**, which protects the Fc portion from **luminal proteases**
- **Most common** immunoglobulin deficiency is IgA

IgM

- Produced in the **immediate response** to an antigen
- **Monomer** on B cell, **pentamer** with J chain when secreted
- Help in **complement fixation**
- Act as an **antigen receptor** on B cell surface
- Unable to cross placenta
- Gives strong **agglutination** reaction

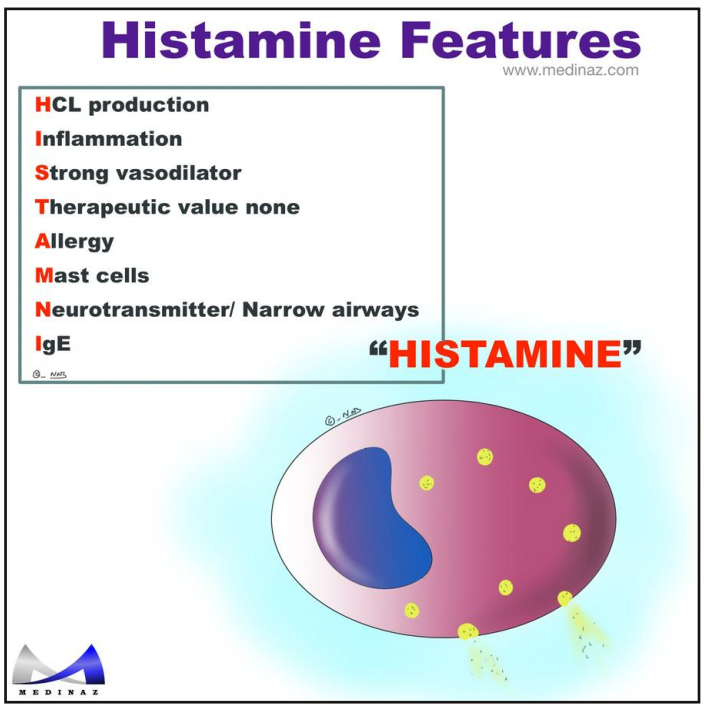


IgD

- Unclear function. Found on surface of many **B cells** and in **serum**.
- Process highest **carbohydrate** content

IgE

- **Lowest** concentration in serum
- Binds mast cells and basophils and helps in degranulation
- Mediate immediate type of hypersensitivity reaction (type I) through release of inflammatory mediators (eg, histamine)
- Activates eosinophils and contributes immunity to parasites.



Abnormal Immunoglobulin

Bence Jones proteins

• They are produced in multiple myeloma (light chain disease)

• The **cancerous plasma cells** produce excess of **light chains** which are accumulated in patient's serum and excreted in urine.

• It has unique property of getting coagulated at 50^0C and redissolving again at 70^0C

Waldenstrom's Macroglobulinemia

• It is a lymphoma affecting B-cells producing excess IgM

• It has been seen in **Multiple Myeloma**

Heavy Chain Disease

• It is characterized by an excessive production of heavy chains that are short and truncated

• Based on H chain involved 4 types have been recognized

• **Alpha** (Seligmann's disease)

• **Gamma** (Franklin's disease)

• **Mu** chain disease

• **Delta** chain disease

Cryoglobulinemia

• It is a condition where blood contains cryoglobulins, a type of Ig that becomes **insoluble** (precipitate) at low temperature but redissolves again if the blood is heated

• Usually consist of IgM directed against the Fc region of IgG

• They have been associated with multiple myeloma and hepatitis C infection

Antigen Type and Memory

Thymus-independent antigens - Antigens lacking a **peptide** component (eg, lipopolysaccharides from gram-ve bacteria); cannot be presented by MHC to T cells. Weakly immunogenic; vaccines often require boosters and adjuvants (eg, pneumococcal polysaccharide vaccine).

Thymus-dependent antigens - Antigens containing a **protein** component (eg, diphtheria vaccine). Class switching and immunologic memory occur as a result of direct contact of B cells with Th cells.

Haptens

Small molecules that are **antigenic** but not **immunogenic**
Haptens have immunological reactivity but no immunogenicity
They are able to react with preformed antibodies but are unable to stimulate their production independently
They require carrier for it to become immunogenic (production of antibody)
Eg. Quinine, Penicillin, Hydralazine, Halothane
Complex haptens - contains 2 or more epitopes
Simple haptens - contains only one epitope

Antibody affinity – Tendency of an antibody to bind a specific epitope

Forssmann antigen – Heterogenetic or heterophile glycolipid protein found in different biological species & classes (E.g Dogs, horse, cats, sheep, guinea pig kidney cells and enteric organisms, pneumococci etc, Cold agglutination test in mycoplasma)

Epitope (Antigenic determinant)

Part of antigen that is recognized by the immune system specifically by antibodies, B-cells or T-cells
Epitope is the smallest unit of **antigenicity**

Paratope is the combining area of antibody corresponding to epitope
Idiotopes are the specific antigenic determinants present on paratope
2 types: **Linear/sequential** type (T-cells related), **Confirmational** type (B-cell related)

Antigen-antibody reaction curve

Prozone phenomenon is due to – Antibody excess
Equivalence zone is due to – Antigen-antibody complex precipitation
Post-zone phenomenon is due to – Antigen excess

Reagin antibody

Also called homocytotropic antibody or prausnitz-kustner antibody
Type of antibody found in the serum and skin of allergically hypersensitive persons and in smaller amounts in the serum of normally sensitive persons.
Easily destroyed by heating and cannot pass the placental barrier
In **syphilis** is – IgG
In **atopy** is – IgE
In false +ve **VDRL** is – IgM

Heterophile antigens

Heterophile antigens share epitopes with each other
Antibody produced against antigen of one species can react with the other and vice versa

Applications

Weil-Felix reaction – Used to diagnose typhoid fever. Antibodies against rickettsial antigens are detected by using cross-reacting proteus antigens

Paul-Bunnell test – Used for Infectious mononucleosis (caused by EBV). Here sheep blood cell (RBC) antigens are used to detect cross-reacting antibodies in patient's sera.

Superantigen

• A class of antigens (protein molecules) which does not require antigenic processing & not specific for a T-cell receptor

• Generate massive immune response by activating upto 20% of T-cells & massive release of cytokines like TNF alpha, IL-1(conventional antigens activate only 0.001% T-cells)

• There is no processing of the toxin by APCs

•They bind to invariant region (alpha chain of MHC II) with beta chain of T-cell receptor

• **Examples:**
Staphylococcal enterotoxins (F) in Kawasaki disease
Pyrogenic exotoxin C
Toxic Shock Syndrome toxin (TSST-1) produced by Staph. aureus
Group A streptococcal pyro/erythrogenic exotoxin A

COMPLEMENT

System of hepatically synthesized plasma proteins that play a role in **innate immunity** and **inflammation**
Complement proteins also produced by Macrophage & Endothelial cells
Membrane attack complex (MAC) defends against gram -ve bacteria

Activation pathways

Classical pathway is IgG and IgM mediated

Alternative - microbe surface molecules.

Lectin - mannose or other sugars on microbe surface.

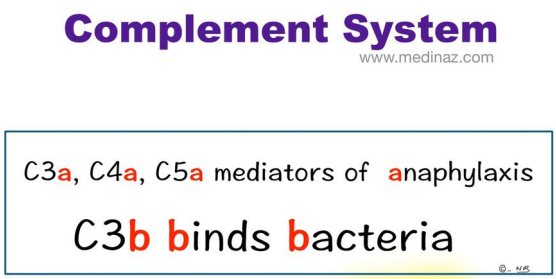
Functions

C3b - Opsonization

C3a, C4a, C5a - anaphylaxis.

C5a - neutrophil chemotaxis

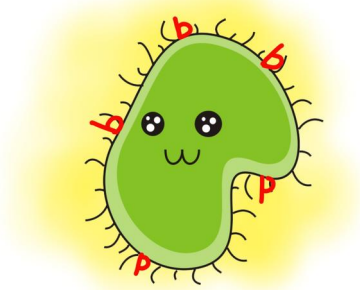
C5b-9 - cytolysis by MAC



C3b and **IgG** are the two 1° opsonins in bacterial defense; enhance phagocytosis.

C3b helps to clear immune complexes.

Decay-accelerating factor (DAF, aka CD55) and C1 esterase inhibitor help prevent complement activation on self cells (eg, RBCs).



Disorders
C1 – C4 deficiency - Increased risk of severe, recurrent pyogenic sinus and respiratory tract infections. Increased risk of SLE

C5-C9 - Increased susceptibility to recurrent Neisseria bacteremia.

C1 esterase inhibitor deficiency - Causes hereditary angioedema due to unregulated activation of kallikrein – Increase bradykinin. Characterized by C4 levels.

ACE inhibitors are contraindicated.

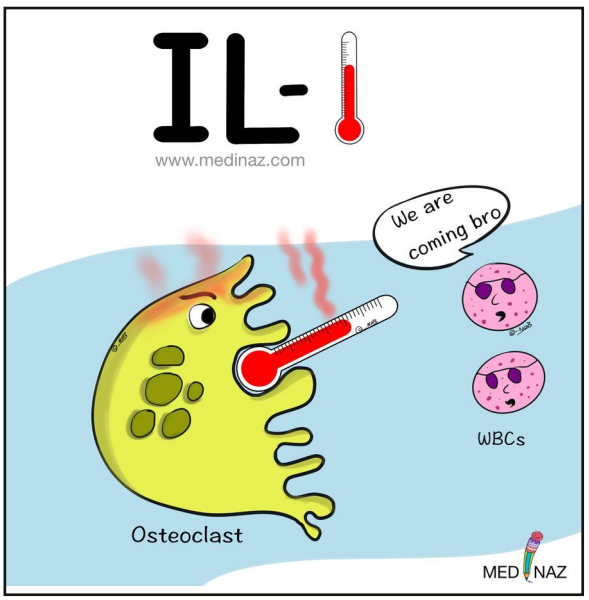
Paroxysmal Nocturnal Hemoglobinuria (PNH) - A defect in the PIGA gene preventing the formation of anchors for complement inhibitors, such as decay-acclerating factor (DAF/CD55) and membrane inhibitor of reactive lysis (MIRL/CD59). Causes complement-mediated lysis of RBCs.

CYTOKINES

Secreted by **macrophages -** IL-1, IL-6, IL-8, IL-12, TNF-alpha,
Secreted by all **T cells -** IL-2, IL-3,
From **Th1 cells -** Interferon gamma
From **Th2 cells -** IL-4, IL-5, IL-10

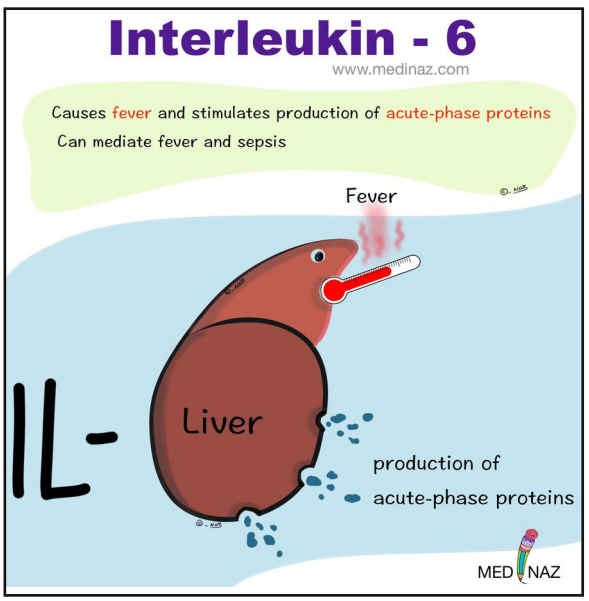
Interleukin-1

- Also known as osteoclast-activating factor
- Causes **fever**, **acute** inflammation
- Activates endothelium to express **adhesion molecules**.
- Induces **chemokine** secretion to recruit WBCs

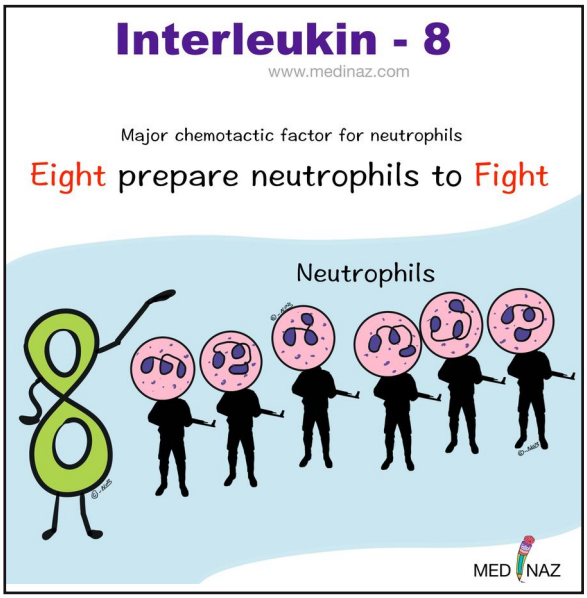


Interleukin-6

- Causes fever and stimulates production of acute- phase proteins.
- Can mediate fever and sepsis



Interleukin-8
Major **chemotactic** factor for neutrophils.



Interleukin-12
Induces differentiation of T cells into Th1 cells. Activates NK cells.

TNF-alpha
- Activates endothelium. Causes WBC recruitment, vascular leak.
- Causes **cachexia** in malignancy
- Maintains **granulomas** in TB
- Can mediate fever and sepsis

Interleukin-2
- Stimulates growth of helper, cytotoxic, and regulatory T cells, and NK cells.

Interleukin-3
- Supports growth and differentiation of bone marrow stem cells. Functions like GM-CSF

Interferon gamma
- Secreted by **NK cells** and **T cells** in response to antigen or IL-12 from macrophages; stimulates macrophages to kill phagocytosed pathogens.

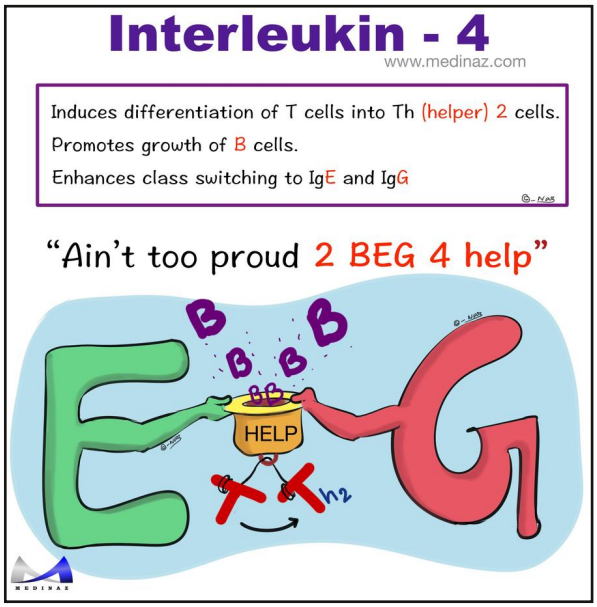
- Inhibits differentiation of **Th2** cells.

- Activates **NK cells** to kill virus-infected cells.

- Increases MHC expression and antigen presentation by all cells.

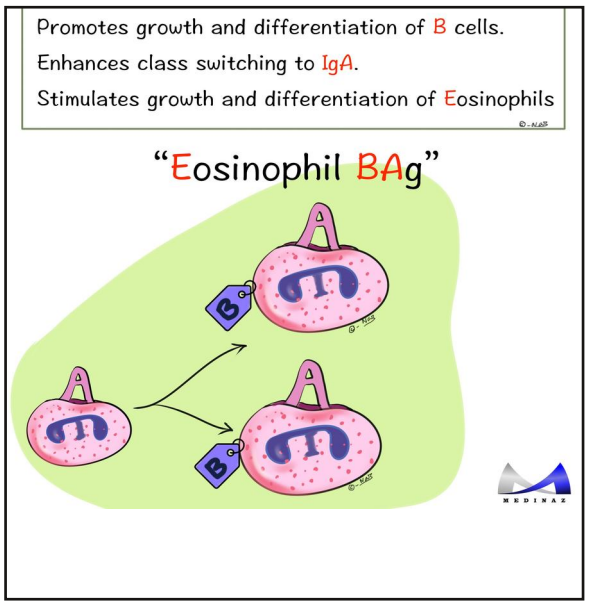
Interleukin-4

- Induces differentiation of **T cells** into **Th (helper) 2 cells**.
- Promotes growth of **B cells**.
- Enhances class switching to IgE and IgG



Interleukin-5

- Promotes growth and differentiation of **B cells**.
- Enhances class switching to IgA.
- Stimulates growth and differentiation of eosinophils.



Interleukin-10

- Attenuates inflammatory response.
- Decreases expression of MHC class II and Th1 cytokines.
- Inhibits activated **macrophages** and **dendritic cells**.
- Also secreted by **regulatory T cells**.

Hypersensitivity

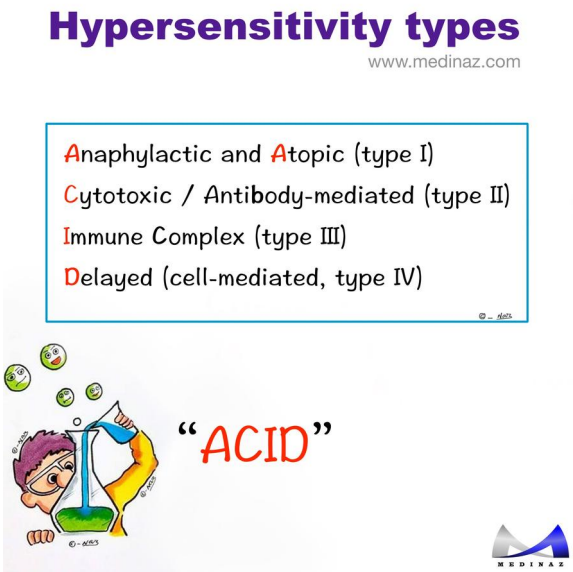
Types: Four types :

Anaphylactic and Atopic (type I),

Cytotoxic / AntiBody-mediated (type II),

Immune Complex (type III),

Delayed (cell-mediated, type IV).



Type I Hypersensitivity

Anaphylactic and **atopic**—two phases: Immediate (minutes) & Late (hours)

Immediate (minutes): antigen crosslinks preformed IgE on presensitized mast cells - immediate degranulation - release of histamine (a vasoactive amine) and tryptase (a marker of mast cell activation).

Late (hours): chemokines (attract inflammatory cells, eg, eosinophils) and cytokines (eg, leukotrienes) from mast cells - inflammation and tissue damage.

(Mn. First (type) and Fast (anaphylaxis).

Mediators

Primary mediators and their functions

Histamin, Heparin & Serotonin – Increase vascular permeability and Increase smooth muscle contraction
Eosinophil chemotactic factor (ECF-A) – Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A) – Neutrophil chemotaxis
Proteases – Bronchial muscle secretion; degradation of blood vessel basement membrane

Secondary mediators

Platelet activating factors (PAF) – Platelet aggregation and degranulation; contraction of pulmonary smooth muscle
Leukotrines – Increase vascular permeability; contraction of pulmonary smooth muscle
Bradykinin – Increase vascular permeability; smooth muscle contraction
Prostaglandins – Increase vasodilation; contraction of pulmonary smooth muscle; platelet aggregation
Cytokines (IL-1 & TNF alpha) – Systemic anaphylaxis; increase expression of cell adhesion molecules (CAMs) on venular endothelial cells

Key points

Histamin is responsible for early clinical features because it is **preformed** mediator
PAF is the major mediator of the **late phase** reaction
IgE is the most important antibody to cause type I hypersensitivity reaction
IL-4 is responsible for the secretion of **IgE** from the **B-cells**
IL-5 is the most potent Eosinophil-activating cytokine known

Test: skin test or blood test (ELISA) for allergen-specific IgE.
Example: Anaphylaxis (eg, food, drug, or bee sting allergies)

Type II Hypersensitivity

Antibodies bind to **cell-surface antigens** - cellular destruction, inflammation, and cellular dysfunction.

Direct Coombs test — detects antibodies attached **directly** to the RBC surface.

Indirect Coombs test — detects presence of unbound antibodies in the serum

Cellular destruction — cell is opsonized (coated) by antibodies, leading to either:

Phagocytosis and/or activation of complement system.

NK cell killing (antibody-dependent cellular cytotoxicity).

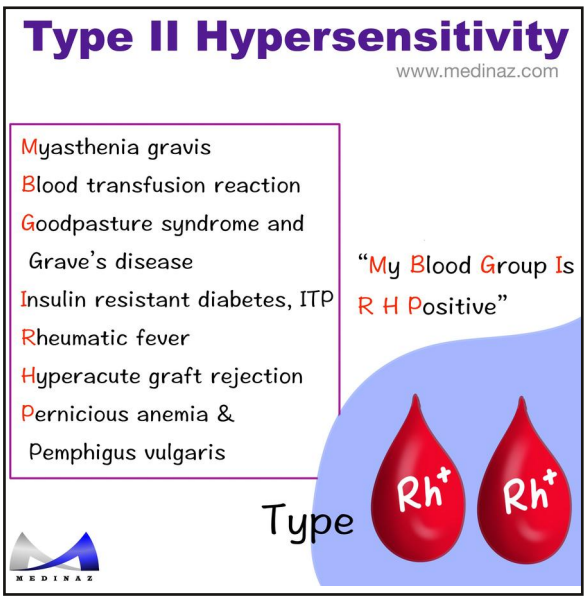
Examples:
Autoimmune-hemolytic anemia
Immune thrombocytopenia
Transfusion reactions
Hemolytic disease of the newborn

Inflammation - binding of antibodies to cell surfaces - activation of complement system and Fc receptor-mediated inflammation.

Examples:
Goodpasture syndrome
Rheumatic fever
Hyperacute transplant rejection

Cellular dysfunction - antibodies bind to cell surface receptors - abnormal blockade or activation of downstream process.

Examples:
Myasthenia gravis
Graves disease
Pemphigus vulgaris
Blood transfusion reaction
Goodpasture syndrome and Grave's disease
Insulin resistant diabetes, ITP
Rheumatic fever
Hyperacute graft rejection
Pernicious anemia & Pemphigus vulgaris



Type III Hypersensitivity

Immune complex — antigen-antibody (mostly IgG) complexes activate complement, which attracts neutrophils; neutrophils release lysosomal enzymes.

Can be associated with vasculitis and systemic manifestations.

In type **III** reaction, imagine an immune complex as 3 things stuck together: antigen- antibody-complement.

Examples:
SLE
Polyarteritis nodosa
Poststreptococcal glomerulonephritis

Serum sickness - the prototype immune complex disease. Antibodies to foreign proteins are produced and 1–2 weeks later, antibody- antigen complexes form and deposit in tissues - complement activation - inflammation and tissue damage.

Fever, urticaria, arthralgia, proteinuria, lymphadenopathy occur 1–2 weeks after antigen exposure. Serum sickness-like reactions are associated with some drugs (may act as haptens, eg, penicillin) and infections (eg, hepatitis B).

Arthus reaction - a local subacute immune complex-mediated hypersensitivity reaction. Intradermal injection of antigen into a presensitized (has circulating IgG) individual leads to immune complex formation in the skin. Characterized by edema, necrosis, and activation of complement.

Examples -

Serum sickness, shick test, SLE

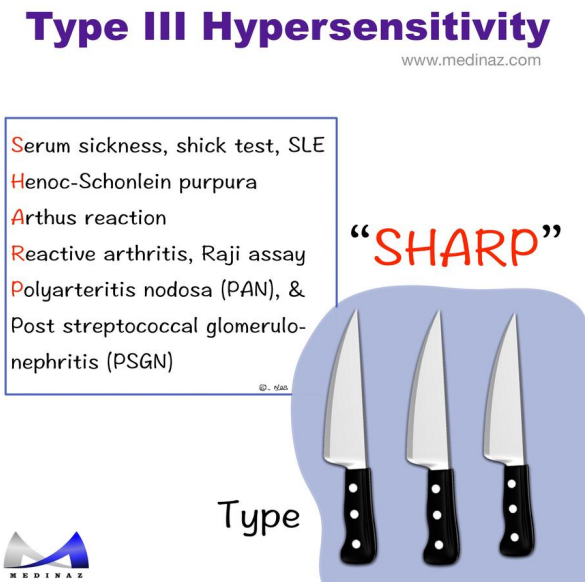
Henoc-Schonlein purpura

Arthus reaction

Reactive arthritis, Raji assay

Polyarteritis nodosa (PAN), &

Post streptococcal glomerulo-nephritis (PSGN)



Type IV Hypersensitivity

Two mechanisms, each involving T cells:

1. **Direct cell cytotoxicity:** CD8+ cytotoxic T cells kill targeted cells.
2. **Inflammatory reaction:** effector CD4+

T cells recognize antigen and release in ammation-inducing cytokines

Response does not involve antibodies (vs types I, II, and III).

Examples:

contact dermatitis (eg, poison ivy, nickel allergy) and graft-versus-host disease. Tests (purpose): PPD (tuberculosis infection); patch test (cause of contact dermatitis); Candida extract (T cell immune function).

4**T**'s:

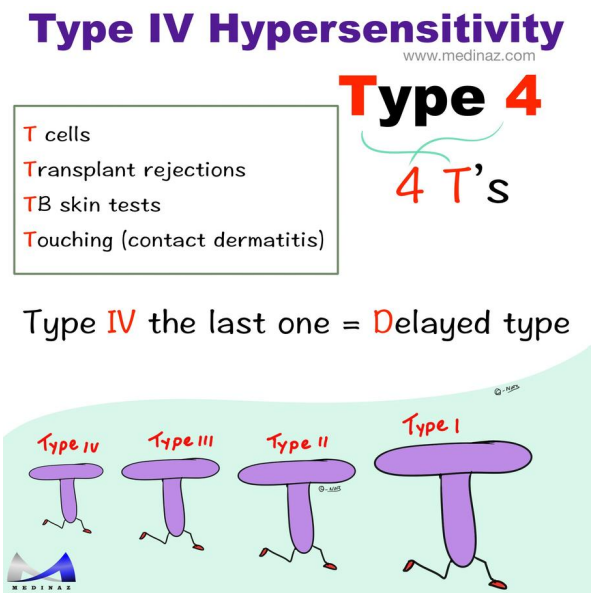
T cells,

Transplant rejections,

TB skin tests,

Touching (contact dermatitis).

Fourth (type) and **last** (delayed).



Blood transfusion reactions

Allergic/anaphylactic reaction

Pathogenesis - Type I hypersensitivity reaction against plasma proteins in transfused blood. IgA- deficient individuals must receive blood products without IgA.

Clinical presentation - Urticaria, pruritus, fever, wheezing, hypotension, respiratory arrest, shock.

Timing - Within minutes to 2–3 hours

Febrile non-hemolytic transfusion reaction

Pathogenesis - Two known mechanisms: type II hypersensitivity reaction with host antibodies against donor HLA and WBCs; and induced by cytokines that are created and accumulate during the storage of blood products.

Clinical presentation - Fever, headaches, chills, flushing.

Timing - Within 1–6 hours

Acute hemolytic transfusion reaction

Pathogenesis - Type II hypersensitivity reaction. Intravascular hemolysis (ABO blood group incompatibility) or extravascular hemolysis (host antibody reaction against foreign antigen on donor RBCs).

Clinical presentation - Fever, hypotension, tachypnea, tachycardia, flank pain, hemoglobinuria (intravascular hemolysis), jaundice (extravascular).

Timing - Within 1 hour

Transfusion-related acute lung injury

Pathogenesis - Donor anti-leukocyte antibodies against recipient neutrophils and pulmonary endothelial cells.

Clinical presentation - Respiratory distress and noncardiogenic pulmonary edema.

Timing - Within 6 hours

Autoantibody related disorders

Anti-ACh receptor - Myasthenia gravis

Anti-presynaptic voltage-gated calcium channel - Lambert-Eaton myasthenic syndrome

Anti-β2 glycoprotein - Antiphospholipid syndrome

Antinuclear (ANA) - Nonspecific screening antibody, often associated with SLE

Anticardiolipin, lupus anticoagulant - SLE, antiphospholipid syndrome

Anti-dsDNA, anti-Smith - SLE

Anti-histone - Drug-induced lupus

Anti-U1 RNP (ribonucleoprotein) - Mixed connective tissue disease

Rheumatoid factor (IgM antibody against IgG Fc region), anti-CCP (more specific) - Rheumatoid arthritis

Anti-Ro/SSA, anti-La/SSB - Sjögren syndrome

Anti-Scl-70 (anti-DNA topoisomerase I) - Scleroderma (diffuse)

Anticentromere - Limited scleroderma (CREST syndrome)

Antisynthetase (eg, anti-Jo-1), anti-SRP, anti - helicase (anti-Mi-2) - Polymyositis, dermatomyositis

Antimitochondrial 1° biliary cirrhosis - 1° biliary cholangitis

Anti-smooth muscle - Autoimmune hepatitis type 1

MPO-ANCA/p-ANCA - Microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg- Strauss syndrome), ulcerative colitis

PR3-ANCA/c-ANCA - Granulomatosis with polyangiitis (Wegener)

Anti-phospholipase A2 receptor - 1° membranous nephropathy

Anti-hemidesmosome - Bullous pemphigoid

Anti-desmoglein (anti-desmosome) - Pemphigus vulgaris

Antimicrosomal, antithyroglobulin, antithyroid peroxidase - Hashimoto thyroiditis

Anti-TSH receptor - Graves disease

IgA anti-endomysial, IgA anti-tissue transglutaminase, IgA and IgG deamidated gliadin peptide - Celiac disease

Anti-glutamic acid decarboxylase, islet cell cytoplasmic antibodies - Type 1 diabetes mellitus

Antiparietal cell, anti-intrinsic factor - Pernicious anemia

Anti-glomerular basement membrane - Goodpasture syndrome

Immunodeficiencies

B-cell disorders

X-linked (Bruton) agamaglobulinemia

Selective IgA deficiency

Common variable immunodeficiency

T-cell disorders

Thymic aplasia (DiGeorge syndrome)

IL-12 receptor deficiency

Autosomal dominant hyper-IgE syndrome (Job syndrome)

Chronic mucocutaneous candidiasis

B & T – cell disorders

Severe combined immunodeficiency

Ataxia-telangiectasia

Hyper-IgM syndrome

Wiskott-Aldrich syndrome

Phagocyte dysfunctions

Leukocyte adhesion deficiency (type 1)

Chédiak-Higashi syndrome

Chronic granulomatous disease

Autoimmunity

Autoimmunity is a condition in which the body's own immunologically competent T-cells or antibodies act against its self-antigens resulting in structural or functional damage

Immunological tolerance -

Immunological tolerance is a state in which an individual is incapable of developing an immune response against his own tissue antigens.

Types

•Central tolerance

•Peripheral tolerance

Central tolerance

In thymus: Removes the self-reacting T-cells by negative selection

In bone marrow: Removes the self-reacting B-cells by negative selection and receptor editing

Peripheral tolerance (mechanism)

•Ignorance
•Anergy (CTLA-4 mediated)
•Phenotypic skewing
•Apoptosis of self-reactive T-cells
•Regulatory T-cells mediated
•Dendritic cells (immature DC and tolerogenic) mediated
•Sequestration of self-antigen

Mechanism of autoimmunity

•Breakdown of CTLA-4 mediated T-cell anergy: seen in multiple sclerosis, rheumatoid arthritis and psoriasis

•Failure of Activation induced cell death (AICD): seen in SLE

•Loss of Treg cells

•Providing T-cell help to stimulate self-reacting B-cells

•Release of Sequestrated antigens (spermatozoa and ocular antigens) due to injury to organs

•Molecular mimicry in post streptococcal acute rheumatic fever and glomerulonephritis

•Polyclonal lymphocyte activation: mediated by superantigens, EBV and HIV

•Exposure of cryptic self-epitopes

•Epitope spreading

•Bystander activation

Acquired Immunodeficiency Syndrome (AIDS)

AIDS is the **commonest** secondary immunodeficiency disorder caused by retrovirus {Diploid genome (2 molecules of RNA)}

Most common mode of spread of infection – Sexual contact (least efficacious)

Male to male transmission is more common than male to female transmission

The risk of transmission of HIV is 0.3% with **needle stick** injury whereas the risk of **hepatitis B** is 30%

Vertical transmission is the **commonest** cause for AIDS in the pediatric population

Commonest cause of AIIDS in India is HIV-1 group M sub-type C

The 3 structural genes (protein coded for):

env (gp120 and gp41) :
Formed from cleavage of gp160 to form envelope glycoproteins

gp120 : attachment to host CD4+ T cell

gp41 : fusion and entry.

gag (p24 and p17) : capsid and matrix proteins, respectively.

pol : reverse transcriptase, aspartate protease, integrase

Virus binds CD4 as well as a coreceptor, either CCR5 on **macrophages** (early infection) or CXCR4 on **T cells** (late infection).

Defective CCR5 receptors lead to protective effect of providing resistance to the development of AIDS

Acute retroviral syndrome is seen for 3-12 weeks and characterized by high level of plasma viremia, and wide spread seeding of the lymphoid tissue

Key points

Acute stage – Macrophage affected

Chronic stage – TH1 cells affected

HIV cytotoxic to CD4+ T cells leading to loss of cell-mediated immunity

AIDS is also known as "Slim's disease" because of severe weight loss

Follicular dendritic cells act as a **reservoir** for HIV in AIDS

Pneumocystis jiroveci is the most common **fungal infection** in AIDS in World

M. tuberculosis is the most common infection with HIV in India

Candidiasis is the most common fungal infection in AIDS in India

Kaposi's sarcoma is the most common **cancer** in AIDS patients

CNS is the most common extranodal site for development of lymphoma in AIDS patients

Toxoplasma gondii is responsible for 50% of all mass lesions in the CNS

AIDS dementia complex is the most common **neurological** manifestation in AIDS patients

Microglia is responsible for **neurological** manifestation in AIDS patients

Inflammatory myopathy is the commonest **skeletal muscle** disorder in AIDS patients

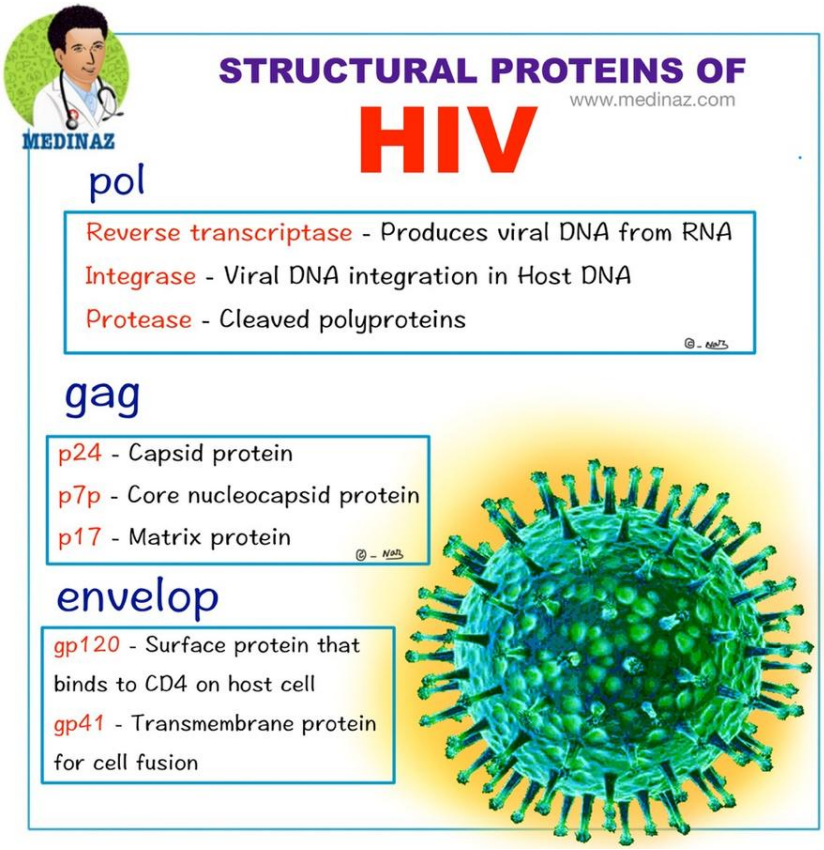
Window period – the term is used for initial 2-4 weeks when the patient is infectious and the screening test is negative during which the investigation of HIV is made by using PCR for the detection of viral nucleic acids

ELISA is the most sensitive and best screening test used for the detection of antibodies against viral proteins

Western blot is the most specific or the confirmatory test for HIV

Direct detection of the viral infection is with p24 antigen capture assay, RT-PCR, DNA-PCR, and culture of the virus from the monocytes and CD4+ T cells

Immune reconstruction inflammatory syndrome - some patients with advanced disease in HIV paradoxically deteriorate on initiating the antiviral therapy.



Systemic Lupus Erythematosus

Systemic, remitting, and relapsing autoimmune disease

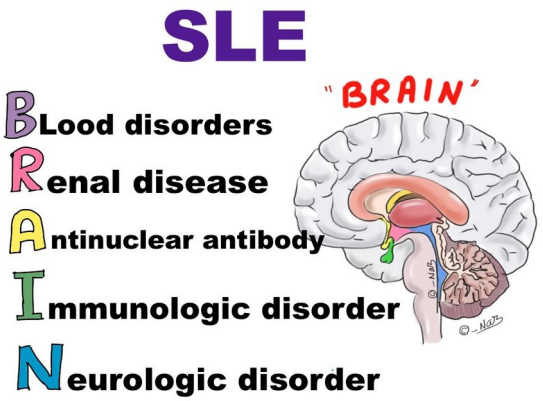
The deficiency of early complement proteins (C1, C2, and C4) has been postulated to be associated with increased incidence of SLE

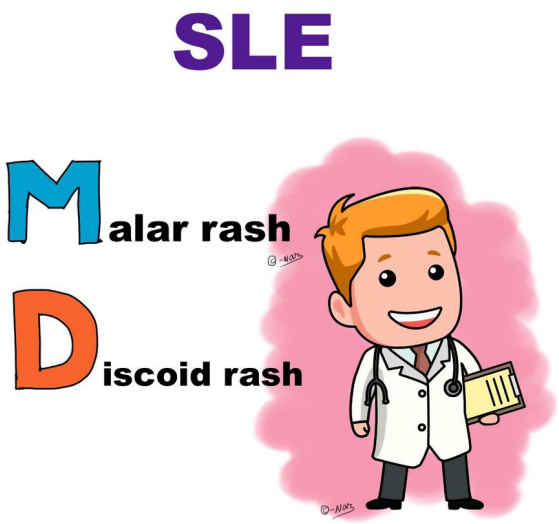
Decrease clearance of immune complexes is seen

Organ damage primarily due to a type III hypersensitivity reaction and, to a lesser degree, a type II hypersensitivity reaction

Classic presentation:

rash, joint pain, and fever in a female of reproductive age
s
(especially of African-American or Hispanic descent).



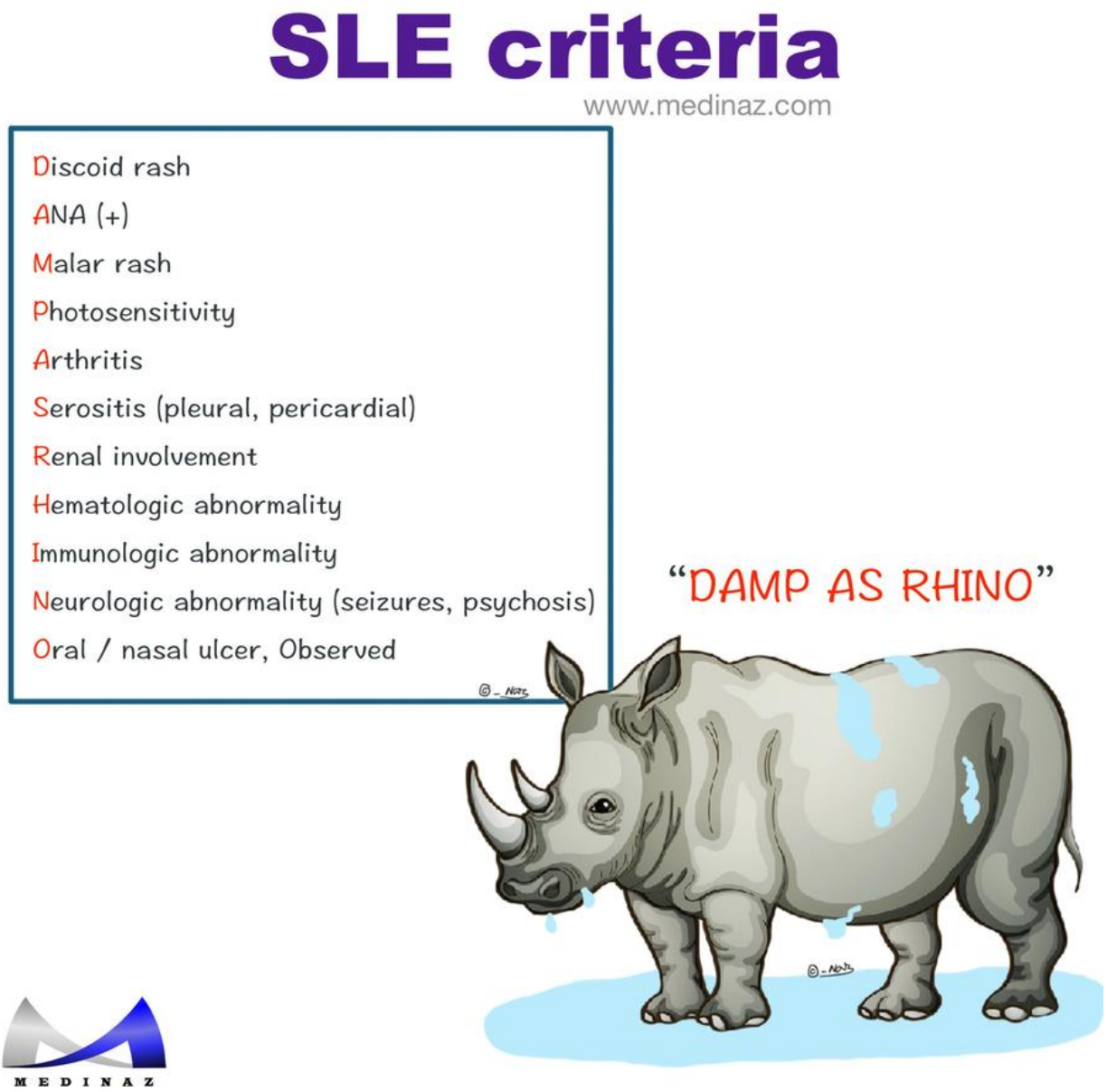


Golden Points

Diffuse proliferative or type IV glomerulonephritis (glomerular deposition of DNA-anti-DNA immune complexes) is the **most common** and **most serious** renal lesion

SLE nephropathy has the findings called as "**Full house phenomenon**"

Libman-Sacks Endocarditis—nonbacterial, verrucous thrombi usually on mitral or aortic valve and can be present on either surface of the valve (but usually on undersurface).



The presence of sub-endothelial deposits give rise to "Wire loop" lesions on light microscopy in SLE

Anti dsDNA antibody and the antibody against smith (Sm) antigen "Highly specific" for SLE

Anti-nuclear antibody (ANA) "Highly sensitive" for SLE

Anti Ro antibody – Neonatal lupus, subacute cutaneous lupus

Anti-P antibody – Associated with lupus psychosis

Anti SS-A & Anti SS-B antibody – associated with Congenital heart block & Cutaneous lupus

Anticardiolipin antibodies may produce a false positive VDRL test for syphilis

SLE is an example of both type I and type II hypersensitivity reaction

Rat liver is used for detection of antinuclear antibodies

Rheumatoid arthritis

Pathogenesis - Autoimmune - inflammation induces formation of pannus (proliferative granulation tissue), which erodes articular cartilage and bone

Predisposing factors - Female, HLA-DR4 , smoking. rheumatoid factor (IgM antibody that targets IgG Fc region; in 80%), anti-cyclic citrullinated peptide antibody (more specific)

Main features -
Arthritis (chronic inflammation of the joints, begins at synovium; most common joints involved are small joints of the hand feet and cervical spine)

Pain, swelling, and morning stiffness lasting > 1 hour, improving with use

Symmetric joint involvement. Systemic symptoms (fever, fatigue, weight loss)

Extraarticular manifestations include rheumatoid nodules (fibrinoid necrosis with palisading histiocytes) in subcutaneous tissue and lung (+ pneumoconiosis - Caplan syndrome), interstitial lung disease, pleuritis, pericarditis, anemia of chronic disease, neutropenia + splenomegaly (Felty syndrome), AA amyloidosis, Sjögren syndrome, scleritis, carpal tunnel syndrome.

Joint findings - Erosions, juxta-articular osteopenia, soft tissue swelling, subchondral cysts, joint space narrowing.

Deformities: cervical subluxation, ulnar finger deviation, swan neck, boutonniere. Involves MCP, PIP, wrist; not DIP or 1st CMC. Synovial fluid inflammatory

Treatment - NSAIDs, glucocorticoids, disease-modifying agents (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide), biologic agents (eg, TNF-α inhibitors).

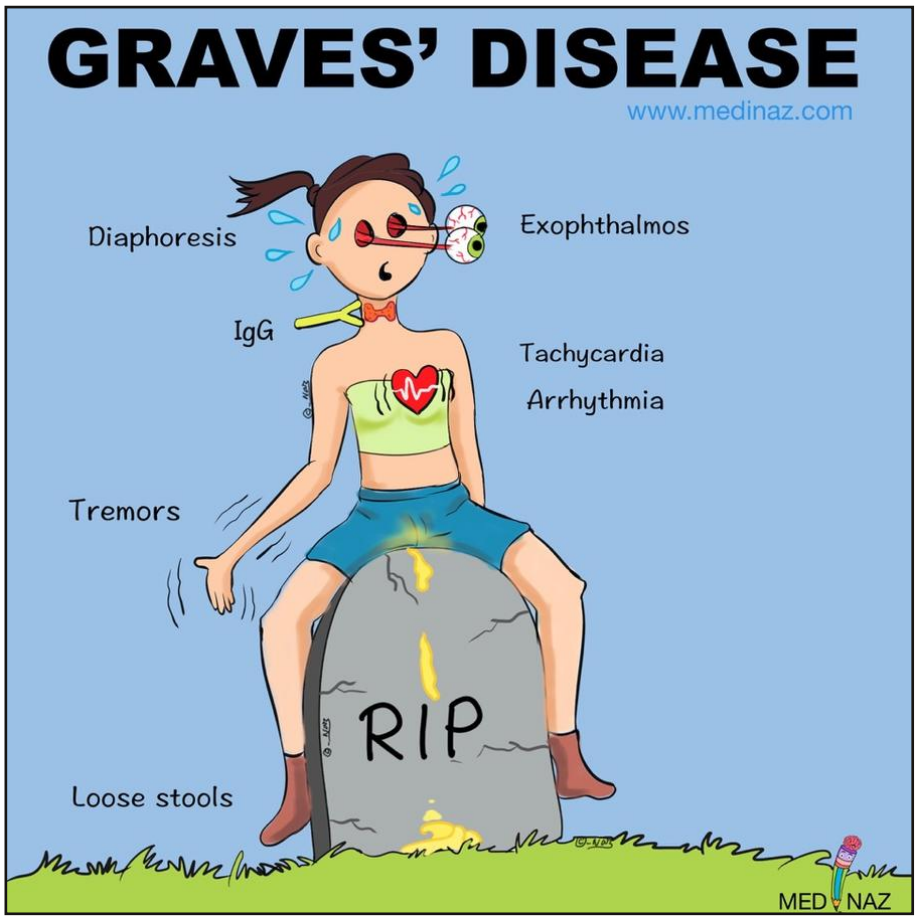
Grave's Disease

Most common cause of **hyperthyroidism**

Infiltration of retroorbital space by activated T-cells - increase cytokines (eg, TNF-α, IFN-γ) – increase fibroblast secretion of hydrophilic GAGs – increase osmotic muscle swelling, muscle inflammation, and adipocyte count - exophthalmos

Autoimmune hyperthyroidism (TSI): IgG Ab reactive with TSH receptors. Low TSH & TRH - High T3 / T4

Often presents during stress (eg, pregnancy). Associated with HLA-DR3 and HLA-(B8)

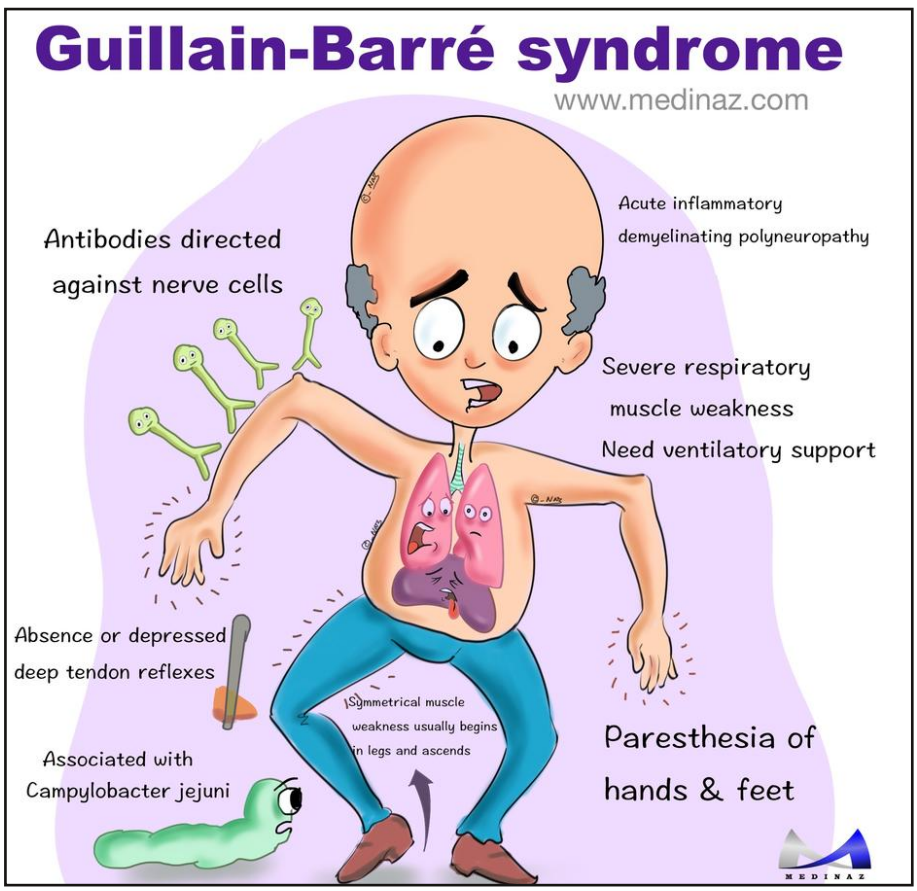


Guillain-Barre Syndrome

Polyneuritis following viral infection/ autoimmune (ascending muscle weakness & paralysis; usually self-limiting)

Associated with infections (eg, Campylobacter jejuni, viruses [eg, Zika]) that destroys Schwann cells by inflammation and demyelination of peripheral nerves

Facial paralysis (usually bilateral) and respiratory failure are common



Hashimoto thyroiditis

Most common cause of hypothyroidism in iodine-sufficient regions

An **autoimmune** disorder with antithyroid peroxidase (antimicrosomal) and antithyroglobulin antibodies

Associated with HLA- DR3,risk of non-Hodgkin lymphoma (typically of B-cell origin).

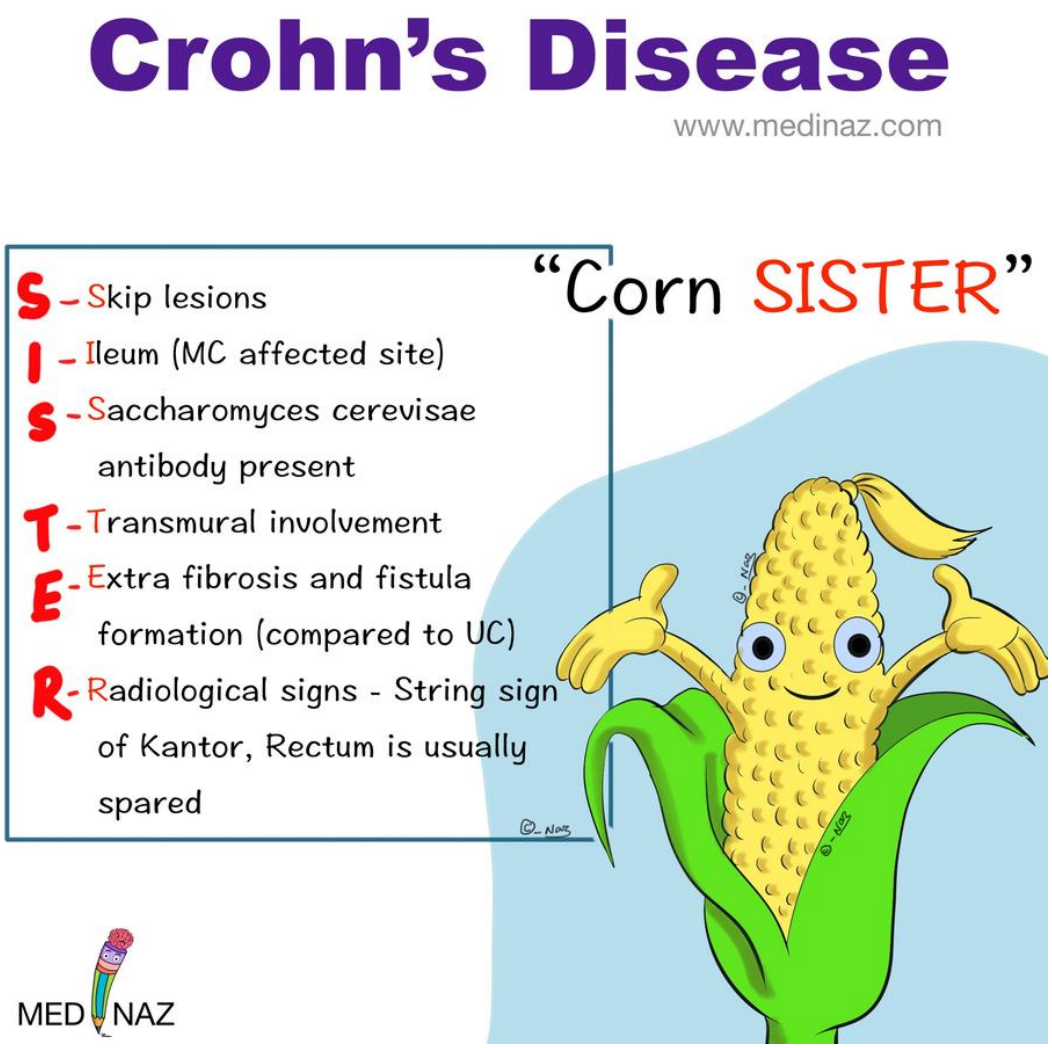
May be hyperthyroid early in course due to thyrotoxicosis during follicular rupture

Histology: Hürthle cells, lymphoid aggregates with germinal centers

Findings: moderately enlarged, nontender thyroid.

Crohn Disease

Any portion of the GI tract, usually the **terminal ileum** and **colon**
It is also called Skip lesions (rectal sparing)
Transmural inflammation – fistulas
Cobblestone mucosa, creeping fat, bowel wall thickening linear ulcers, fissures



Radiological appearance on barium meal follow through is known as "String sign of Kantor" because of the decreased lumen in the affected part of intestine
Non-caseating granulomas and lymphoid aggregates. Th1 mediated
Diarrhea that may or may not be bloody

Complications:-
Malabsorption/malnutrition, colorectal cancer (increase risk with pancolitis)
Fistulas (eg, enterovesical fistulae, which can cause recurrent UTI and pneumaturia)
Perianal fistula is the **most common** fistula seen
Phlegmon/abscess, strictures (causing obstruction), perianal disease

Extraintestinal manifestations:-
Rash (pyoderma gangrenosum, erythema nodosum), eye inflammation (episcleritis, uveitis), oral ulcerations (aphthous stomatitis), arthritis (peripheral, spondylitis)
Kidney stones (usually calcium oxalate), gallstones. May be +ve for anti-Saccharomyces cerevisiae antibodies (ASCA)

Treatment:-
Corticosteroids, azathioprine, antibiotics (eg, ciprofloxacin, metronidazole), infliximab, adalimumab

Multiple Sclerosis

• Autoimmune inflammation and demyelination of CNS (brain and spinal cord) with subsequent axonal damage.

• **Can present with:**
Acute optic neuritis (painful unilateral visual loss associated with Marcus Gunn pupil)

• Brain stem/cerebellar syndromes (eg, diplopia, ataxia, scanning speech, intention tremor, nystagmus/INO (bilateral > unilateral)

• **Pyramidal tract** weakness

• **Spinal cord syndromes** (eg, electric shock-like sensation along spine on neck exion [Lhermitte phenomenon], neurogenic bladder, paraparesis, sensory manifestations affecting the trunk or one or more extremity).

• Symptoms may exacerbate with increased body temperature (eg, hot bath, exercise).

• **Relapsing** and **remitting** is most common clinical course.

• Most often affects women in their 20s and 30s; more common in Caucasians living farther from equator.

• **IgG level** and **myelin basic protein** in CSF.

• Oligoclonal bands are diagnostic.

• MRI is **gold standard**. Periventricular plaques (areas of oligodendrocyte loss and reactive gliosis).

• Multiple white matter lesions disseminated in space and time

• Stop relapses and halt/slow progression with disease-modifying therapies (eg, β-interferon, glatiramer, natalizumab).

• Treat acute areas with IV steroids.

• Symptomatic treatment for neurogenic bladder (catheterization, muscarinic antagonists), spasticity (baclofen, GABAB receptor agonists), pain (TCAs, anticonvulsants).

Myasthenia Gravis

Most common **NMJ**(Neuromuscular junction) disorder

Autoantibodies to postsynaptic ACh receptor and decreased ACh receptors (in muscles)

Women are affected more commonly than men (W:M = 3:2)

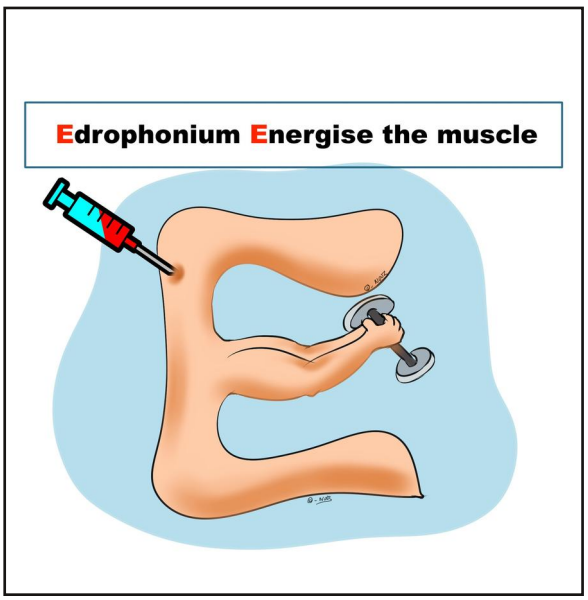
Classic presentation:

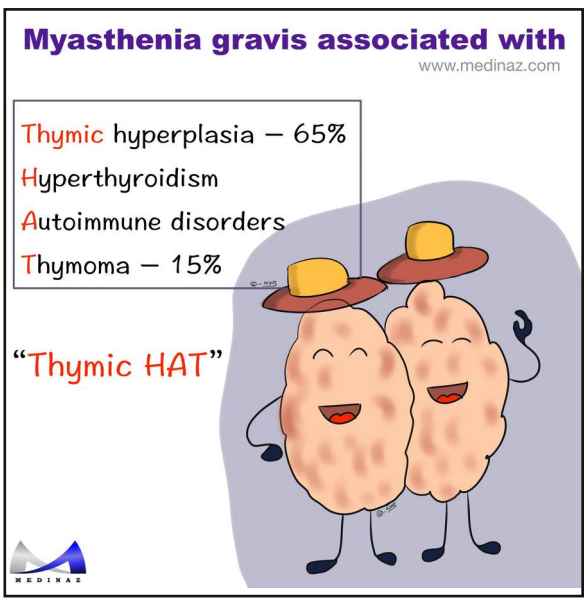
Ptosis, diplopia, weakness (respiratory muscle involvement can lead to dyspnea)

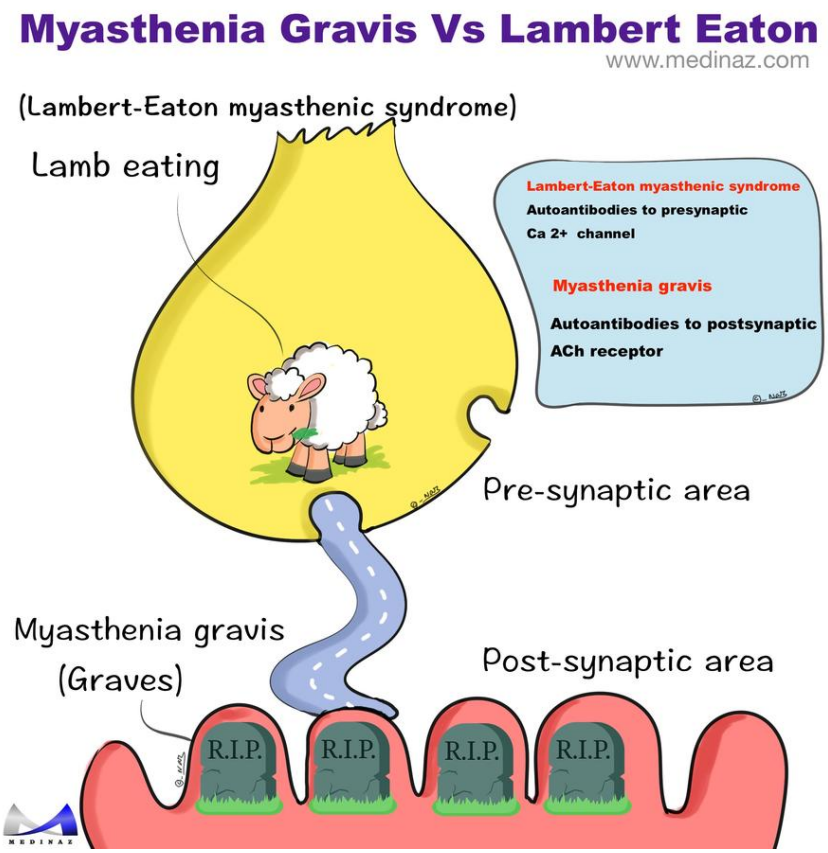
Facial weakness produces a "snarling" expression when the patient attempts to smile

Worsens with muscle use

Improvement after edrophonium (tensilon) test.







Associated with:

Thymic hyperplasia – 65%

Thymoma – 15%

Hyperthyroidism

Autoimmune disorders

(Hashimoto's thyroiditis, Grave's disease,

Rheumatoid arthritis, SLE etc)

HLA subtypes associated with MG – B8

Concept box

- Edrophonium to diagnose
- Pyridostigmine to treat (Mn. Py**rid**osti**gm**ine gets **rid** of **m**yasthenia **g**ravis)
- Most **sensitive** test - Single fibre electromyography
- Most **specific** test - Antibodies to ACh Receptors

Lambert-Eaton myasthenic syndrome

Uncommon

Autoantibodies to presynaptic Ca2+ channel decrease ACh release

Classic presentation:
Proximal muscle weakness, autonomic symptoms (dry mouth, impotence)
Improves with muscle use

Associated with:

- Small cell lung cancer
- AChE inhibitor has minimal effect

Sjögren syndrome

Autoimmune disorder characterized by destruction of exocrine glands (especially lacrimal and salivary) by lymphocytic infiltrates

Predominantly affects perimenopausal and postmenopausal women (40–60 years old).

Types:

Primary - occurs in the absence of another autoimmune disease

Secondary - occurs in the setting of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and scleroderma

Clinical features:
• Patients with SS also have higher levels of cariogenic and acidophilic bacteria such as Lactobacillus acidophilus and Streptococcus mutans
Inflammatory joint pain

• **Keratoconjunctivitis sicca** (tear production and subsequent corneal damage)

• **Xerostomia** (decreased saliva production)

• Presence of antinuclear antibodies

• Rheumatoid factor (can be in the absence of rheumatoid arthritis)

• Antiribonucleoprotein antibodies: SS-A (anti-Ro) and/or SS-B (anti- La)

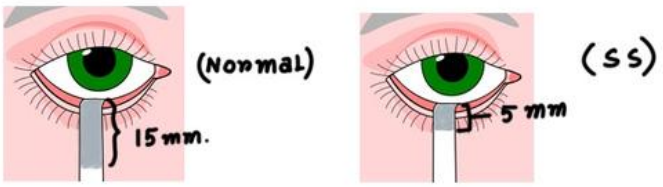
• Bilateral parotid enlargement

Diagnosis:

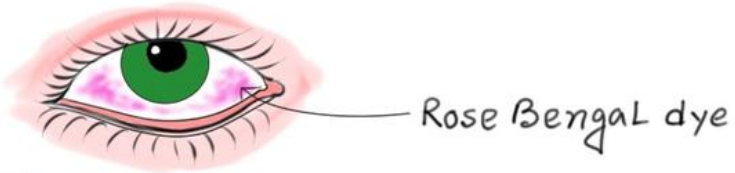
Sjogren's syndrome Diagnosis

Ophthalmic tests

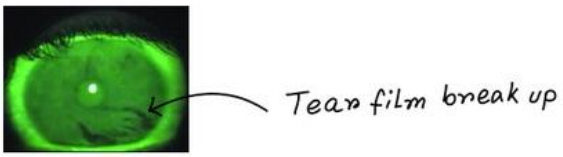
1. **Schirmer's test:** In normal patient 15mm of filter paper is wetted when placed in lower conjunctival sac for 5 minutes, but in SS only 5 mm.



2. **Rose Bengal dye test:** Denuded and damaged areas of cornea can be visualised clearly with this dye.



3. **Break up time test:** A slit lamp is used and interval between complete blink and appearance of dry spot on the cornea is noted.



Salivary gland tests

1. Saliva flow rate is diminished in SS.

Extra Points

- **Anti-SSA** and **anti-SSB** may also be seen in SLE
- +Ve Anti-SSA in **pregnant women** with SLE – Increase risk of **congenital heart block** in the newborn.
- SS patients are at an increased risk of developing a **NHL**, most commonly mucosa-associated B-cell lymphomas (**MALT** lymphomas) involving the **salivary glands**

2. Minor salivary gland biopsy taken from lower labial mucosa.

Focus score: ≥ 1 focus per 4 mm^2

3. Scintigraphy: Technetium pertechnate 99m, in SS diminished uptake and excretion of isotope in saliva.

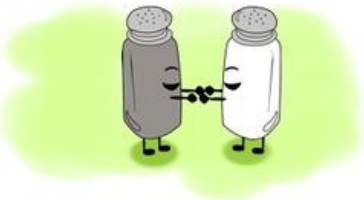
4. Sialography appearance:

"Branchless fruit laden tree"

"Cherry blossom"

"Snow storm appearance"

5. MRI shows Salt and Pepper appearance of the enlarged salivary glands.



6. Immunological tests: Presence of auto antibody against anti-SS A and anti-SS B.

Scleroderma

Autoimmune disorder characterized by **fibroblast stimulation** and **collagen deposition** in the skin and internal organs, manifesting as puffy, taut skin without wrinkles, fingertip pitting

Most commonly affected organ - Skin

Other affected organs - GIT, Kidney, Heart, Muscle & Lungs

More commonly seen in - Females

Categories:

Diffuse scleroderma -
•Characterized by presence of anti-DNA topoisomerase antibodies (scl-70)

Widespread skin involvement at onset with rapid progression and early visceral involvement

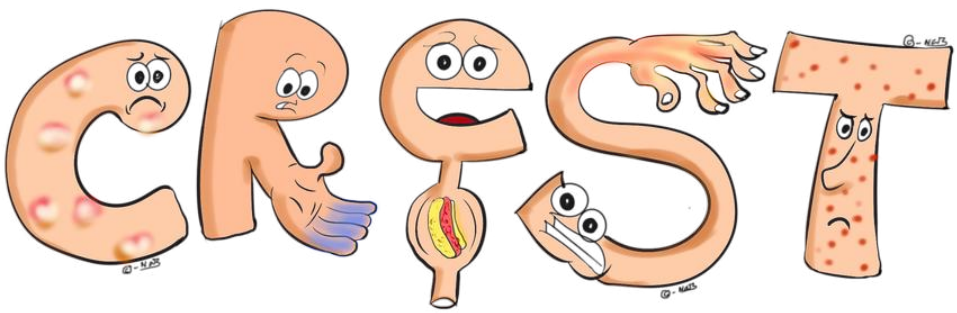
Limited scleroderma -

•Characterized by presence of anti-centromere antibodies

•Skin involvement often confined to fingers, forearm, and face

•Late visceral involvement

•Some patients develop **CREST** syndrome



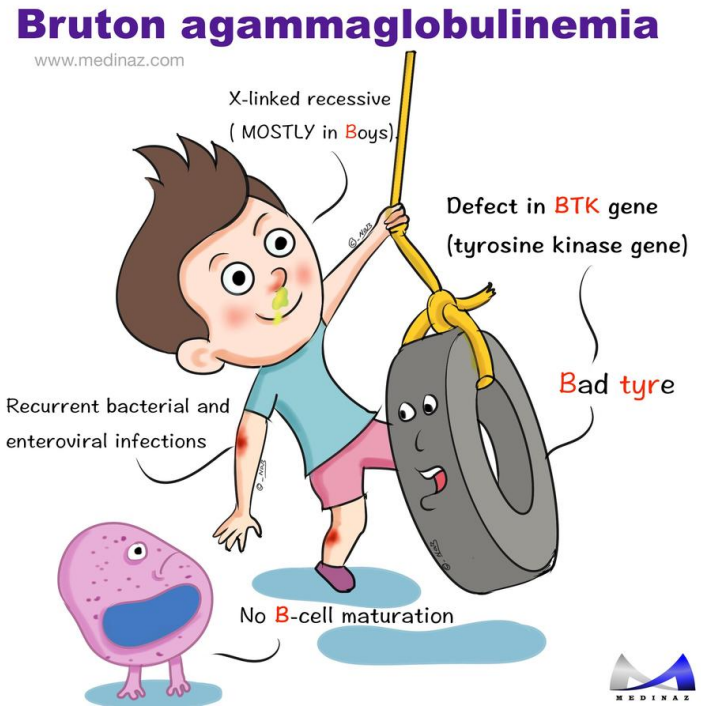
Key points

CREST syndrome:
Calcinosis cutis, anti-Centromere antibody, **R**aynaud phenomenon,
Esophageal dysmotility, **S**clerodactyly, and **T**elangiectasia

B-cell disorders

X-linked (Bruton) agammaglobulinemia

- Defect in BTK, a tyrosine kinase gene
- No B-cell maturation
- X-linked recessive (in Boys)



- Recurrent bacterial and enteroviral and parasite (Giardia lamblia) infections after 6 months
- Fist 6-month protection is due to maternal antibodies
- Peripheral blood – Absence of B cells
- Decrease Ig of all classes
- Absent/scanty lymph nodes and tonsils
- **Live vaccines** contraindicated

Autoimmune diseases (eg. SLE, Dermatomyositis) occur in upto 20% of cases

Selective IgA deficiency

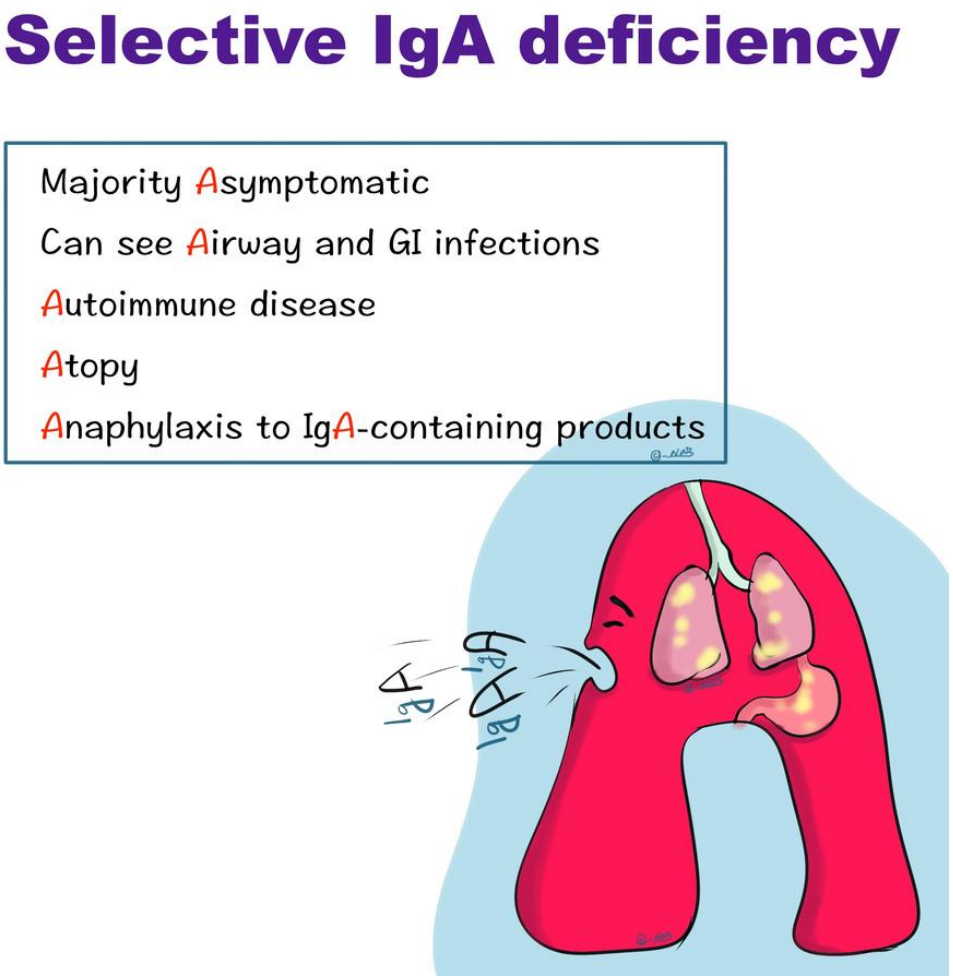
- **Most common** 1° immunodeficiency

- Pathogenesis is due to a block in the terminal differentiation of IgA secreting B-cells to plasma cells

- Majority Asymptomatic. Can see Airway and GI infections, Autoimmune disease, Atopy, Anaphylaxis to IgA-containing products

- Decrease IgA with normal IgG, IgM levels.

- ncrease susceptibility to giardiasis.



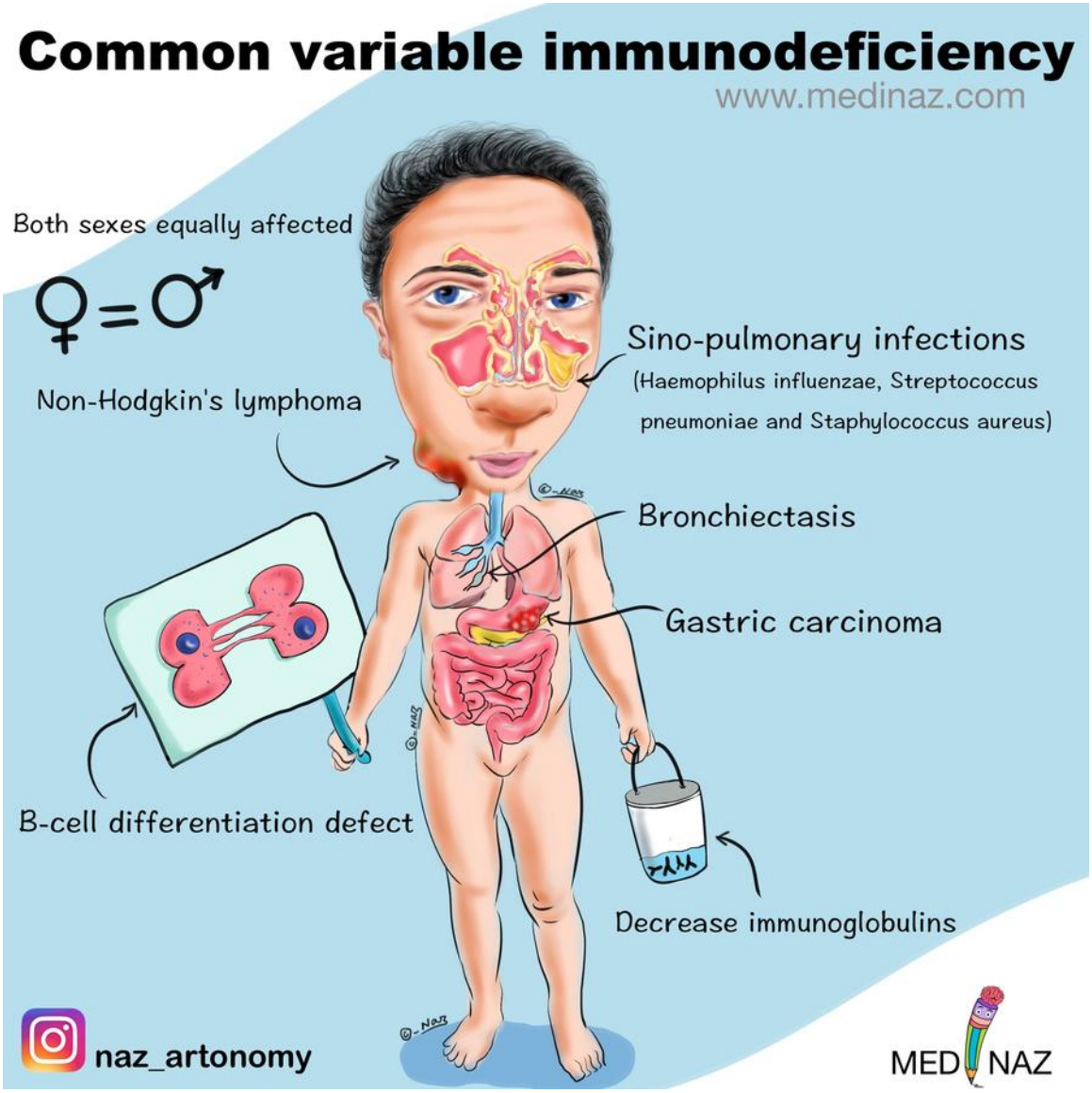
Common variable immunodeficiency

- B-cell differentiation defect

- Both sexes equally affected

- Cause is unknown in most cases (Mutations in the genes encoding ICOS, TACI, CD19, CD20, CD21, CD80 and BAFFR have been identified as causative of CVID)

Usually presents in 2nd and 3rd decade of life



•Risk of autoimmune disease, bronchiectasis, lymphoma, sinopulmonary infections

•Associated malignancies, particularly Non-Hodgkin's lymphoma and gastric carcinoma

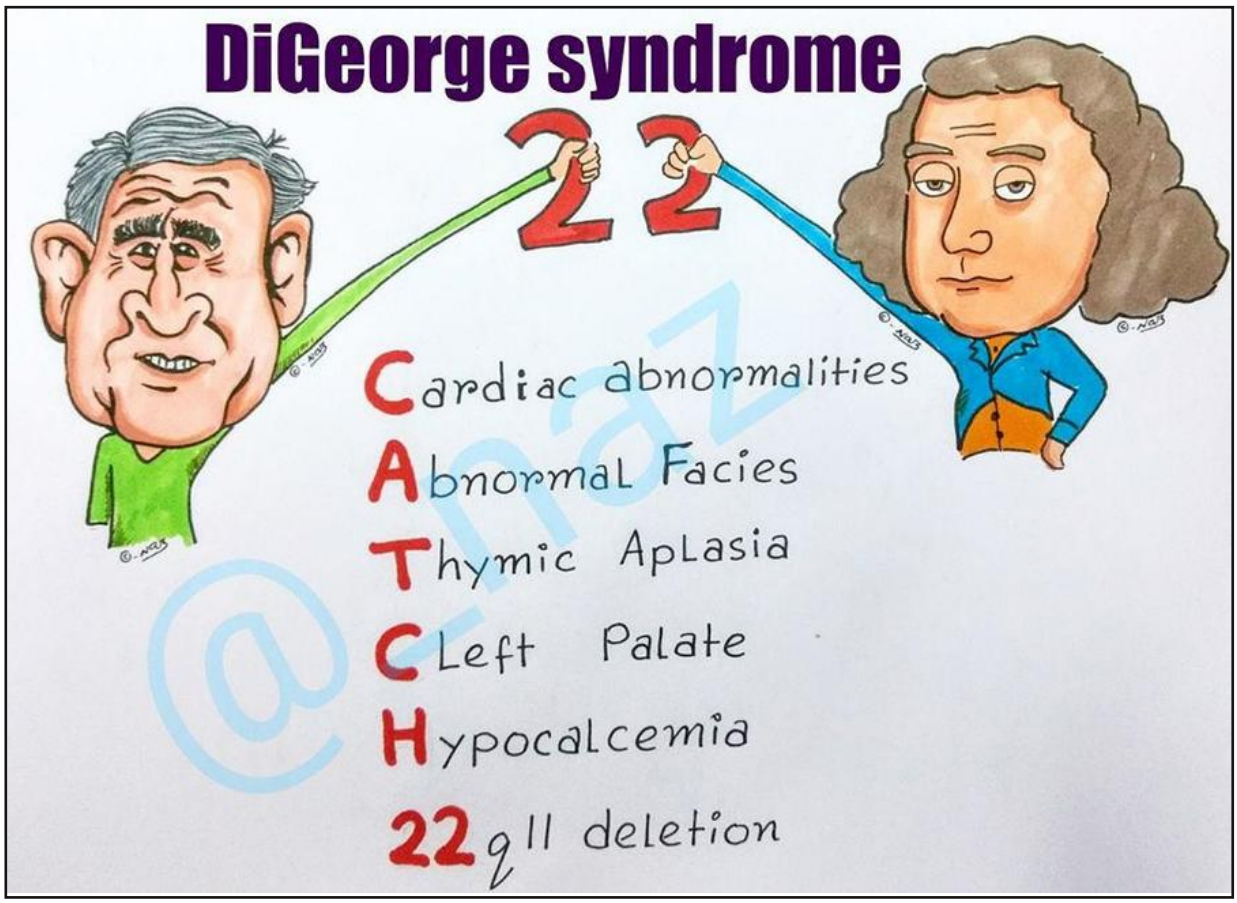
•The microorganisms that most frequently cause infections in CVID are bacteria Haemophilus influenzae, Streptococcus pneumoniae and Staphylococcus aureus

•Decrease **plasma cells** and **immunoglobulins** (Specially IgG, IgM and IgA)

T-cell disorders

DiGeorge syndrome

- Failure to develop 3rd and 4th pharyngeal pouches due to 22q11 deletion
- Absent thymus and parathyroid glands
- **Tetany** due to hypocalcemia
- **Recurrent** viral/fungal infections due to T-cell deficiency
- **Conotruncal abnormalities** (eg, tetralogy of Fallot, truncus arteriosus)
- Decrease T-cells, PTH, & Ca2+
- Thymic shadow absent on CXR.



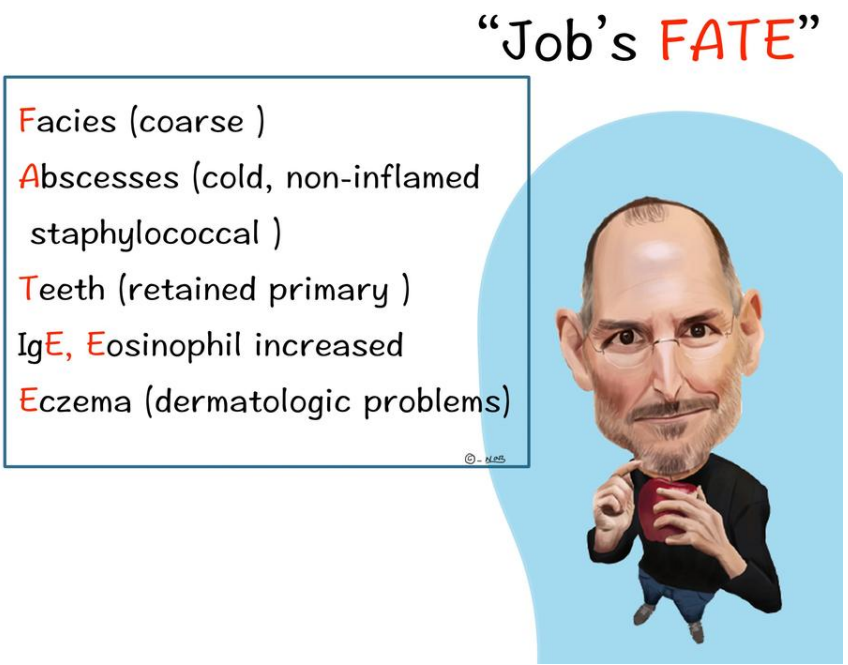
IL-12 receptor deficiency

- Autosomal recessive
- Decrease Th1 response
- Disseminated mycobacterial and fungal infections; may present after administration of BCG vaccine.
- Decreased IFN-γ

Autosomal dominant hyper-IgE syndrome (Job syndrome)

- Deficiency of Th17 cells due to STAT3 mutation
- Impaired recruitment of **neutrophils** to sites of infection
- Coarse Facies, cold (noninflamed) staphylococcal Abscesses, retained primary Teeth, IgE, Dermatologic problems (eczema). Bone fractures from minor trauma
- Increased IgE and Eosinophils

Hyper - IgE Syndrome (Job Syndrome)



Chronic mucocutaneous candidiasis

- T-cell dysfunction
- Can result from congenital genetic defects in IL-17 or IL-17 receptors
- Noninvasive **Candida albicans** infections of skin and mucous membranes
- Absent in vitro T-cell proliferation in response to Candida antigens
- Absent cutaneous reaction to Candida antigens

B- & T-cell disorders

Severe combined immunodeficiency

- Several types including defective IL-2R gamma chain (most common, X-linked recessive)
- Adenosine deaminase deficiency (autosomal recessive)
- Also Recombinase-activating genes mutation, JAK3 mutation, class II MHC deficiency (Bare lymphocyte syndrome)
- Failure to thrive, chronic diarrhea, thrush. Recurrent viral, bacterial, fungal, and protozoal infections
- Decrease T-cell receptor excision circles (TRECs)
- Absence of thymic shadow (CXR), germinal centers (lymph node biopsy), and T cells (flow cytometry)
- Treatment: avoid live vaccines, give antimicrobial prophylaxis and IVIG; bone marrow transplant curative (no concern for rejection)

Ataxia-telangiectasia

Autosomal recessive

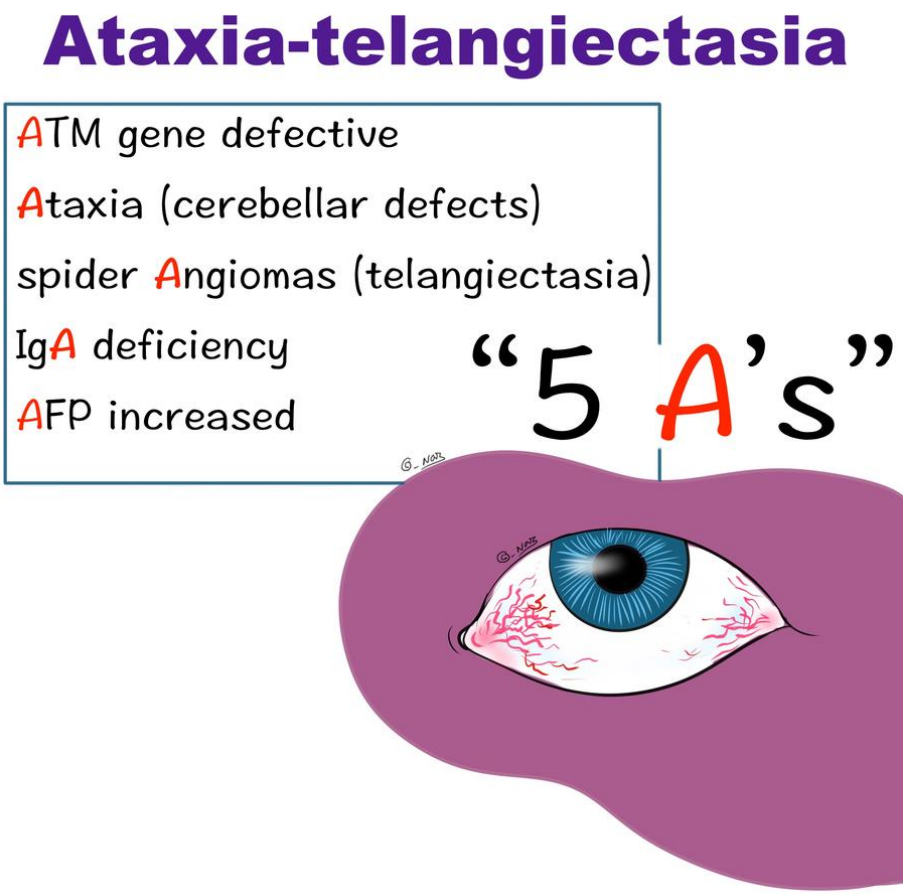
Defects in ATM gene - failure to detect DNA damage failure to halt progression of cell cycle - mutations accumulate

Triad: cerebellar defects (Ataxia), spider Angiomas (telangiectasia), IgA deficiency

Increase AFP

Decrease IgA, IgG, and IgE.
Lymphopenia, cerebellar atrophy

Increase risk of lymphoma and leukemia.



Hyper-IgM syndrome

X-linked recessive.

Most commonly due to defective CD40L on Th cells - class switching defect;

Severe pyogenic infections early in life; opportunistic infection with Pneumocystis, Cryptosporidium, CMV.

Normal or increased IgM.

Decreased IgG, IgA, IgE.

Failure to make germinal centers.

Nezelof syndrome

Autosomal recessive condition characterized by cellular immunodeficiency resulting from thymus hypoplasia

In some patients B-cells are normal, whereas in others a B-cell deficiency is secondary to the T-cell defect

Affected individuals suffer from chronic diarrhea, viral and fungal infections, and a general failure to thrive

Wiskott-Aldrich syndrome

X-linked recessive

Mutation in *WASp gene*; leukocytes and platelets unable to reorganize actin cytoskeleton - defective antigen presentation

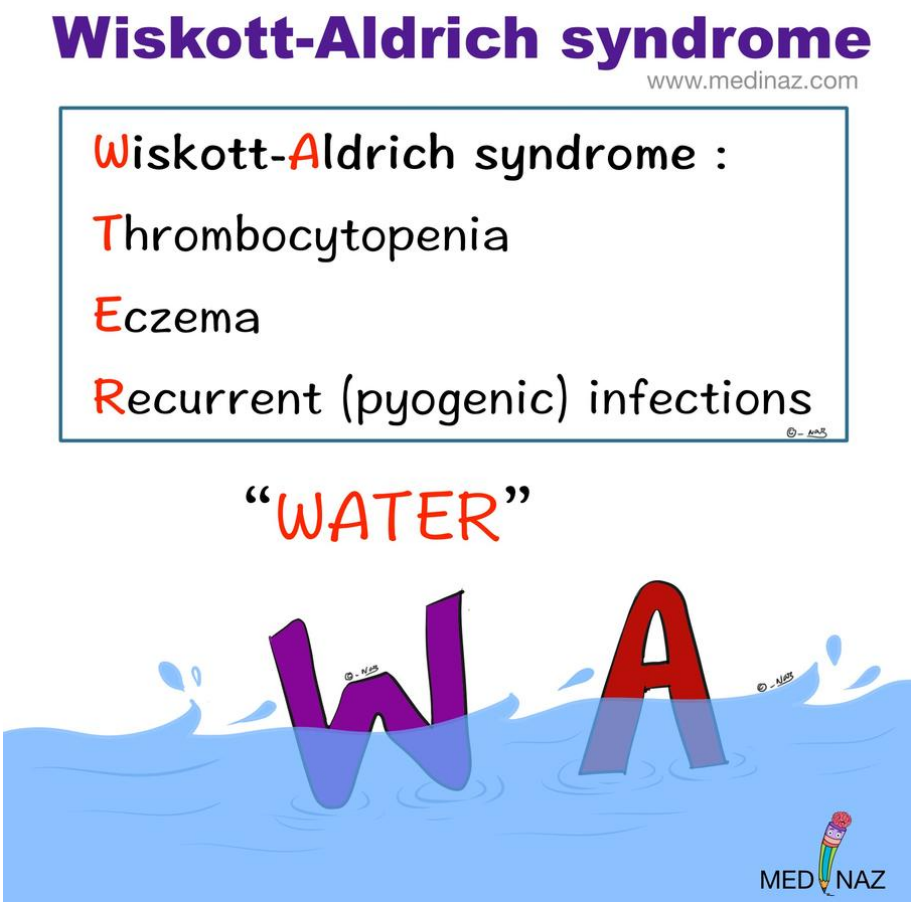
Thrombocytopenia, Eczema, Recurrent (pyogenic) infections.

Increase risk of autoimmune disease and malignancy

Decrease to normal IgG, IgM

Increase IgE, IgA

Fewer and smaller platelets



Phagocyte Dysfunction

Leukocyte adhesion deficiency (type 1)

• Autosomal recessive

• Defect in **LFA-1 integrin** (CD18) protein on phagocytes; impaired migration and chemotaxis

• Recurrent skin and mucosal bacterial infections, absent pus, impaired wound healing, delayed (> 30 days) separation of umbilical cord.

• Increase neutrophils in blood but absence of neutrophils at infection sites

Chédiak-Higashi syndrome

• Autosomal recessive.

• Defect in lysosomal trafficking regulator gene (LYST).

• Microtubule dysfunction in phagosome-lysosome fusion

• Progressive neurodegeneration

• Lymphohistiocytosis

• Albinism (partial)

• recurrent pyogenic Infections by staphylococci and streptococci

• peripheral Neuropathy

• Giant granules in granulocytes and platelets.

• Pancytopenia

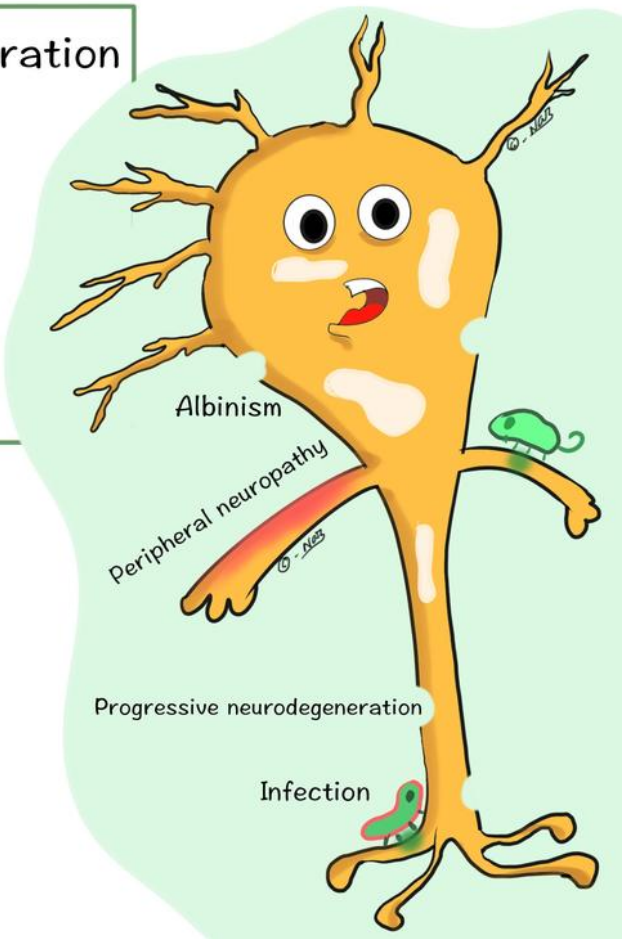
• Mild coagulation defects.

Chédiak-Higashi syndrome

www.medinaz.com

Progressive neurodegeneration
Lymphohistiocytosis
Albinism (partial)
Infections
Neuropathy (peripheral)

"PLAIN"



MEDINAZ

Chronic granulomatous disease

• X-linked form most common

• Defect of NADPH oxidase – decrease reactive oxygen species (eg, superoxide) and decrease respiratory burst in neutrophils

• Increase susceptibility to catalase +ve organisms

• Abnormal dihydrorhodamine (flow cytometry) test (decrease green fluorescence).

• Nitroblue tetrazolium dye reduction test (obsolete) fails to turn blue.

Shwachman's disease

• It is a rare congenital disorder characterized by neutropenia, exocrine pancreatic insufficiency, bone marrow dysfunction, skeletal abnormalities and short stature

Tuftsin deficiency

• Tuftsin is a tetrapeptide (Thr-Lys-Pro-Arg) produced primarily in the spleen, by the cleavage of the Fc-portion of the heavy chain of IgG

• It stimulates phagocytosis

• Tuftsin deficiency results in increase susceptibility to capsulated organisms

Grafts

Autograft - From self

Syngeneic graft (isograft) - From identical twin or clone

Allograft - From nonidentical individual of same species

Xenograft - From different species

Transplant Rejection

Hyperacute

• Within minutes to hours

• Pre-existing recipient antibodies react to donor antigen (type II hypersensitivity reaction)

• Activate **complement**

• Widespread thrombosis of graft vessels leads to ischemia/necrosis

• Presence of necrosis of **renal cortex**

• Graft must be removed

Acute

• Weeks to months

• **Cellular:** CD8+ T cells and/or CD4+ T cells activated against donor MHCs (type IV hypersensitivity reaction).

• **Humoral:** similar to hyperacute, except antibodies develop after transplant.

• Vasculitis of graft vessels with dense interstitial lymphocytic infiltrate

Key points

• Acute rejection can be prevented/reversed with immunosuppressants like cyclosporine, muromonab and steroids

Chronic

• Months to years

• CD4+ T cells respond to recipient APCs presenting donor peptides, including allogeneic MHC.

• Both cellular and humoral components (type II and IV hypersensitivity reactions).

• Recipient T cells react and secrete cytokines - proliferation of vascular smooth muscle, parenchymal atrophy, interstitial fibrosis. Dominated by arteriosclerosis.

Organ-specific examples:

• Bronchiolitis obliterans (lung)

• Accelerated atherosclerosis (heart)

• Chronic graft nephropathy (kidney)

• Vanishing bile duct syndrome (liver)

Key points

• The initial target of the anti-bodies is the **graft vasculature**

• Hyperacute rejection is **type II** hypersensitivity reaction

• Acute rejection is **type II** + **type IV** hypersensitivity reaction

Graft-versus-host disease (GVHD)

• Grafted immunocompetent T cells proliferate in the immunocompromised host and reject host cells with “foreign” proteins - severe organ dysfunction.

• Type IV hypersensitivity reaction

• Maculopapular rash, jaundice, diarrhea, hepatosplenomegaly.

• Usually in bone marrow and liver transplants (rich in lymphocytes). Potentially beneficial in bone marrow transplant for leukemia (graft-versus-tumor effect)

• **Acute GVHD** is characterized by an erythematous maculopapular rash, persistent anorexia or diarrhea, or both, and by liver disease with increase serum levels of bilirubin, alanine and aspartate aminotransferase, and alkaline phosphatase.

• **Chronic GVHD** resembles an autoimmune disorder with malar rash, sicca syndrome, arthritis, obliterative bronchiolitis and bile duct degeneration and cholestasis

• GVHD developing or persisting beyond 3 months post-transplant is termed Chronic GVHD

Key points

• GVH reaction is observed in skin, intestine and liver leading to skin rash/ dermatitis, diarrhea and jaundice
• **No treatment** is required for **Grade I** acute GVHD
• **Therapy** is required for **Grade II** to **IV** GVHD
• GVHD developing within the first 3 months post-transplant is termed acute GVHD
• The risk of GVHD can be decreased by depletion of T cells from graft

Immunosuppressants

Agents that block lymphocyte activation and proliferation. Reduce acute transplant rejection by suppressing cellular immunity (used as prophylaxis).

Frequently combined to achieve greater efficacy with decrease toxicity.
Chronic suppression increase risk of infection and malignancy.

Cyclosporine

Calcineurin inhibitor; binds cyclophilin. Blocks T-cell activation by preventing IL-2 transcription.

Used in Psoriasis, rheumatoid arthritis.

Toxicities - Nephrotoxicity, hypertension, hyperlipidemia, neurotoxicity, gingival hyperplasia, hirsutism.

Tacrolimus (FK506)
Calcineurin inhibitor; binds FK506 binding protein (FKBP).
Blocks T-cell activation by preventing IL-2 transcription.
Toxicities - Similar to cyclosporine, risk of diabetes
and neurotoxicity;
no gingival hyperplasia or hirsutism.

Sirolimus (Rapamycin)

mTOR inhibitor; binds FKBP.
Blocks T-cell activation and B-cell differentiation by preventing response to IL-2.
Used in Kidney transplant rejection prophylaxis specifically (pancytopenia), insulin resistance, hyperlipidemia; not nephrotoxic.
Synergistic with cyclosporine. Also used in drug-eluting stents

Basiliximab

• Monoclonal antibody; blocks IL-2R.

Side effects - Edema, hypertension, tremor

Azathioprine

• Antimetabolite precursor of 6-mercaptopurine.

• Inhibits lymphocyte proliferation by blocking nucleotide synthesis.

• Used in Rheumatoid arthritis, Crohn disease, glomerulonephritis, other autoimmune conditions.

• **Side effects -** Pancytopenia.
6-MP degraded by xanthine oxidase; toxicity increase by allopurinol.

Mycophenolate Mofetil

• Reversibly inhibits IMP dehydrogenase, preventing purine synthesis of B and T cells.

• Used in Lupus nephritis.

• **Side effects -** GI upset, pancytopenia, hypertension, hyperglycemia.

• Less nephrotoxic and neurotoxic

• Associated with invasive CMV infection.

Glucocorticoids

• Inhibit NF-κB. Suppress both B- and T-cell function by decrease transcription of many cytokines.

• Induce T cell apoptosis.

• Used in Many autoimmune and inflammatory disorders, adrenal insufficiency, asthma, CLL, non-Hodgkin lymphoma.

• **Side effects -** Cushing syndrome, osteoporosis, hyperglycemia, diabetes, amenorrhea, adrenocortical atrophy, peptic ulcers, psychosis, cataracts, avascular necrosis (femoral head).

• Demargination of WBCs causes artificial leukocytosis.

• Adrenal insufficiency may develop if drug is stopped abruptly after chronic use.

Recombinant cytokines and clinical uses

Bone marrow stimulation

Erythropoietin
Agent – Epoetin alfa (EPO analog)
Clinical use - Anemias (especially in renal failure)

Colony stimulating factors
Agent – Filgrastim (G-CSF), Sargramostim (GM-CSF)
Clinical use - Leukopenia; recovery of granulocyte and monocyte counts

Thrombopoietin
Agent – Romiplostim (TPO analog), eltrombopag (TPO receptor agonist)
Clinical use - Autoimmune thrombocytopenia

Immunotherapy

Interleukin - 2
Agent – Aldesleukin
Clinical use - Renal cell carcinoma, metastatic melanoma

Interferon
Agent – IFN-α
Clinical use - Chronic hepatitis C (not preferred) and B, renal cell carcinoma

Agent – IFN-β
Clinical use - Multiple sclerosis

Agent – IFN-γ
Clinical use - Chronic granulomatous disease

Vaccination

Induces an active immune response (humoral and/or cellular) to specific pathogens.

Types :

- Live attenuated vaccine
- Killed or inactivated vaccine
- Subunit
- Toxoid

Live attenuated vaccine :

Microorganism loses its pathogenicity but retains capacity for transient growth within inoculated host

Induces **cellular and humoral responses**

MMR and varicella vaccines can
be given to HIV +ve patients without evidence of immunity if CD4 cell count ≥ 200 cells/ mm3.

Pros: induces strong, often lifelong immunity.

Cons: may revert to virulent form. Often contraindicated in pregnancy and immunodeficiency

Examples

Adenovirus (nonattenuated, given to military recruits), Polio (sabin), Varicella (chickenpox), Smallpox, BCG, Yellow fever, Influenza (intranasal), MMR, Rotavirus

Live attenuated vaccine

www.medinaz.com

Adenovirus
Polio (sabin)
Varicella (chickenpox)
Smallpox
BCG
Yellow fever
Influenza (intranasal)
MMR
Rotavirus

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"Attention! Please Vaccinate Small, Beautiful Young Infants with MMR Regularly"

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Killed or inactivated vaccine

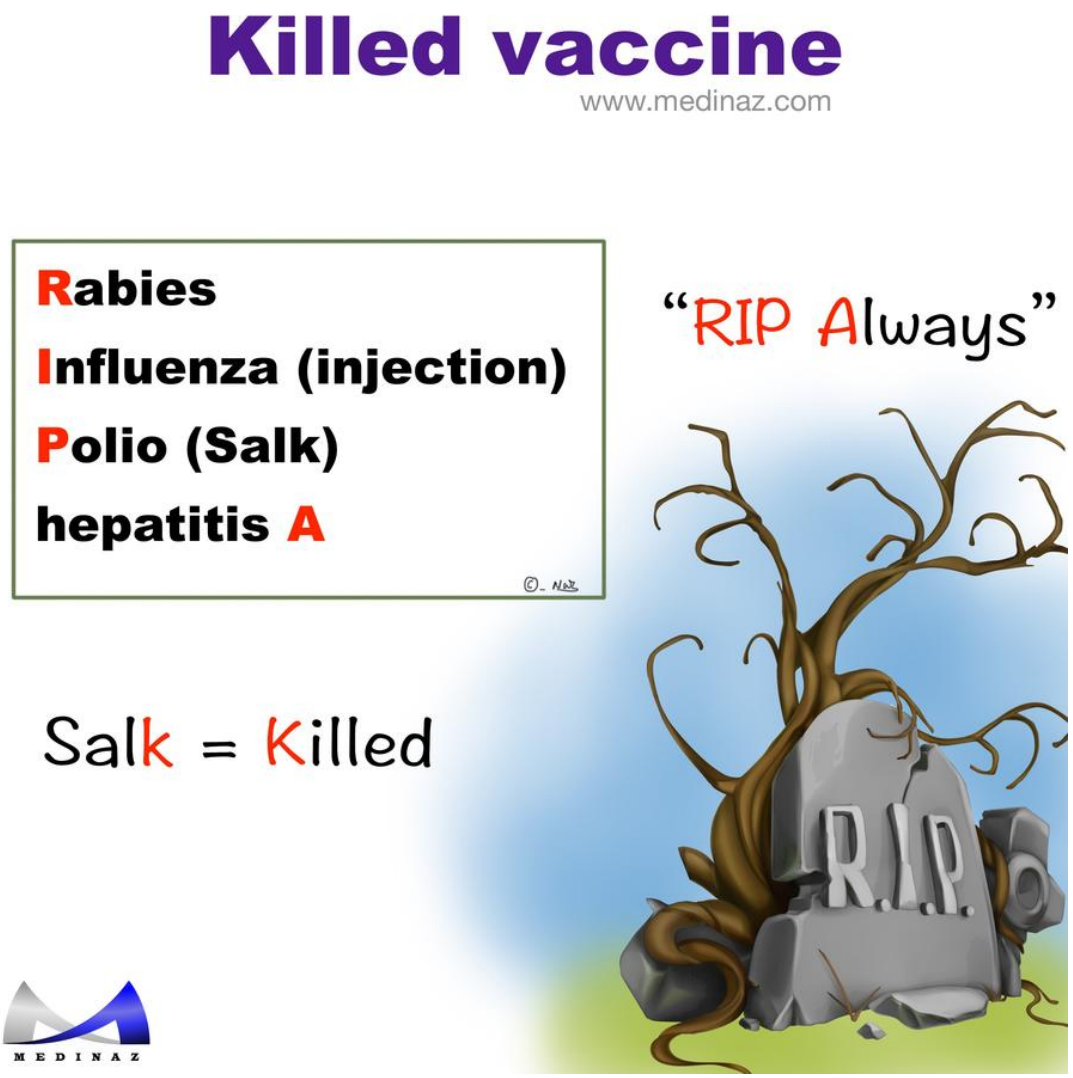
Pathogen is inactivated by heat or chemicals. Maintaining epitope structure on surface antigens is important for immune response

Mainly induces a **humoral response**

Pros: safer than live vaccines

Cons: weaker immune response; booster shots usually required

Examples :
Rabies, Influenza (injection), Polio (Salk), hepatitis A
SalK = Killed RIP Always



Subunit
Includes only the antigens that best stimulate the immune system.

Pros: lower chance of adverse reactions.
Cons: expensive, weaker immune response.

Examples

HBV (antigen = HBsAg),
HPV (types 6, 11, 16, and 18), acellular pertussis (aP), Neisseria meningitidis (various strains), Streptococcus pneumoniae, Haemophilus influenzae type b.

Toxoid

Denatured bacterial toxin with an intact receptor binding site. Stimulates the immune system to make antibodies without potential for causing disease.

Pros: protects against the bacterial toxins.
Cons: antitoxin levels decrease with time, may require a booster.

Examples :
Clostridium tetani, Corynebacterium diphtheriae

Points to Remember

• Cell mediated immunity is mediated by T cells whereas humoral immunity is due to B-cells.

• Helper T cells are positive for CD4 whereas cytotoxic T cells are positive for CD8.

• T cell undergo both positive and negative selection whereas B cells undergo only negative selection

• Antibodies are produced by Plasma cells (modified B cells)

• Th1 produce: IL-2, 1L-12, INF-gamma

• Th2 produce: IL-4, IL-5, IL-6, IL-13

• Production of specific antibodies against particular antigen is due to **Clonal selection**

• NK cells are **not MHC restricted**, not required antibodies

• Markers of NK cells: **CD16** and **CD56**

• Primary function of Toll-like receptors: activation of innate immune system

• Toll-like receptors activate innate immune system by activating transcription factors (NK-kb and AP-1)

• **Toll like receptors** recognise bacterial endotoxin of all gram -ve bacteria **except** leptospira.

• Antigen presenting cells are of 2 types: **Professional APCs** (Dendritic cells, macrophages, Langerhans cells, B cells) and **Non-professional APCs** (Fibroblasts, thymic epithelial cells, endothelial cells)

• Most potent stimulator of naïve T cells is **Langerhans dendritic cells**

• **Superantigens** bind directly to the lateral portion of T cell receptor b chain and MHC II b chain

• MHC molecules previously called as HLA (Human leukocyte antigen) Major function of MHC (HLA): present antigen to T cell for recognition by T cell receptors.

• MHC I is present on all **nucleated cells** and **platelets** (not on RBCs) whereas MHC II is present on the antigen presenting cells (APCs).

• Medullary macrophages **do not** express MHC II

• **Mixed lymphocyte culture** (mixed leukocyte reaction) is used to identify: **MHC II**

• Markers of B cells: CD-10, CD-19, CD-20, CD-21, CD-23, CD-79a

• Markers of memory T cells: CD-45 RO

• Markers of hematopoietic stem cell: CD-34

• Epithelioid granuloma is caused by CD4+ helper T cells

• Allograft is graft from genetically unrelated member of same species Transplant rejection involves both cellular and humoral rejections

• **C4d deposition** in the glomeruli is an indicator of **antibody mediated rejection**

• Hyperacute rejection is due to preformed antibodies

• Mechanism of corneal endothelial graft rejection: cell mediated (type IV) reaction

• Most important target in graft rejection: Blood vessels (endothelitis, necrotizing vasculitis, fibrinoid necrosis)

• Graft vs Host disease occurs when immune competent donor cells (like bone marrow) is transplanted into immunocompromised host

• Most common affected tissue in GVHD: **Skin > Liver > Gut**

• Calcification of long bones is NOT a feature of scleroderma

• Anticentromere antibody is seen with localized scleroderma / CREST syndrome whereas anti-DNA topoisomerase type 1 (anti-Scl 70) is seen with diffuse scleroderma

• **Anti-U1 RNP** antibodies are seen in Mixed connective tissue disease (MCTD)

•Antibodies in Sjogren's syndrome are: Anti-Ro (SSA), Anti-La (SSB)

• **Adenosine deaminase** deficiency is associated with: Severe combined immunodeficiency (SCID)

• Antibodies in Wiskott-Aldrich syndrome: decreased IgM, Increased IgE, normal IgA & IgG

• **Raji cell assay** is used to quantify the circulating immune complexes

• Most commonly affected organ in amyloidosis: Kidney

• Most common cause of death in amyloidosis: **Cardiac failure**

• Characteristic staining feature of amyloidosis: **Apple green birefringence** under polarized light.

Thank You

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