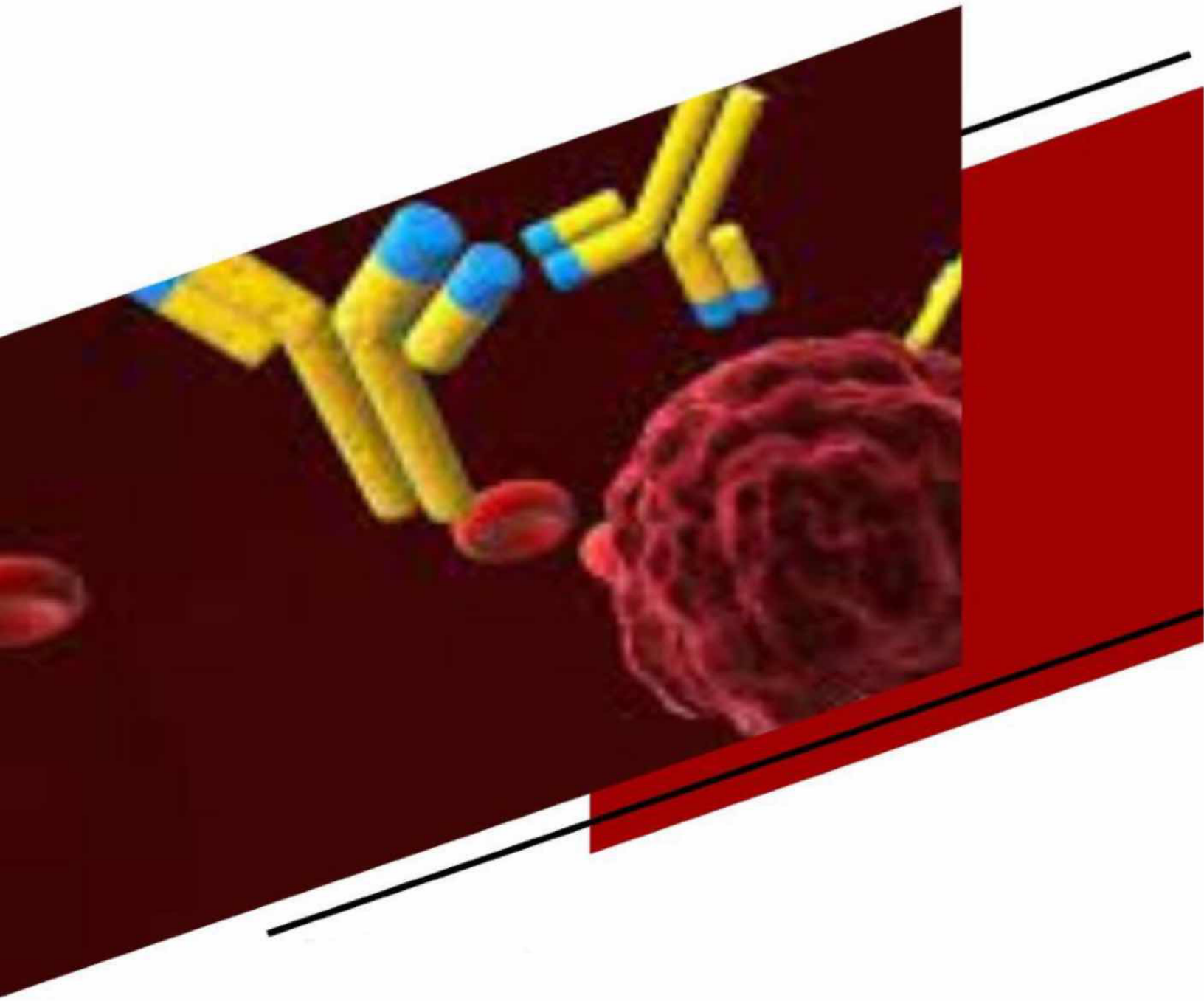
Doctor 021

IMMUNOLOGY

Sheet no.21



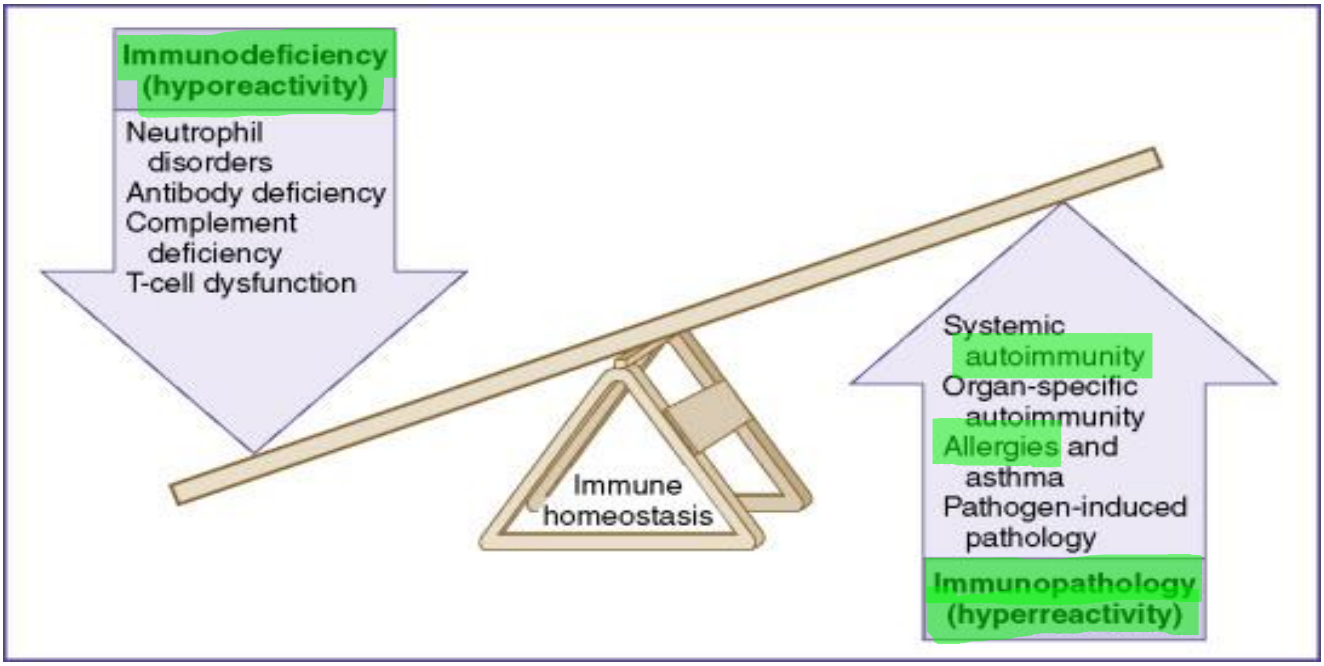
Doctor :Anas Abu-Humaidan

Immune system malfunction

Defects or malfunctions in either the innate or adaptive immune response can provoke illness or disease. Such disorders are generally caused by (ways of immune system malfunction):-

1. **autoimmunity** that makes immune system inappropriately reactive against self-antigens
2. **hypersensitivity reaction**: overactive or aggressive immune response toward foreign antigens
3. ineffective immune responses (known as **immunodeficiency**).

Note:- meningitis cause mainly isn't the pathogen itself, but the immune response against pathogen and destruction of tissue to clear pathogen and restore homeostasis



Immunodeficiency

Immunodeficiency results from a failure or absence of elements of the immune system, including lymphocytes, phagocytes, and complement system. These immunodeficiencies can be either primary or secondary.

****In immunodeficiency we can't count proper immune response against pathogen that leads to**

➔increase risk of infections

➔certain types of cancer (Many of these cancers appear to be caused by oncogenic viruses, such as the Epstein-Barr virus)

➔sometimes immunodeficiency can to autoimmunity as well.

**** example of immunodeficiency that is associated with autoimmunity**

SLE (systemic lupus erythematosus)

- the cause:- complement deficiency in C1q, C2 & C4 predisposes to SLE
- **C1q** bind to apoptotic cells and facilitate their phagocytosis
- in SLE C1q, C2 & C4 deficiency → improper clearance of apoptotic cells so it will accumulate → propagate proliferation of autoreactive T cells to antigen → autoimmunity

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1) The congenital, or primary immunodeficiency: -

genetic defects that result in an increased susceptibility to infection that is frequently manifested early in infancy and childhood but is sometimes clinically detected later in life.

While many might have some form of a primary immunodeficiency, only a small proportion are affected severely enough for development of life-threatening complications

2) secondary immune deficiency disease

occurs when the immune system is compromised due to **an environmental factor** e.g:

- HIV: advanced stage of immunodeficiency syndrome
- Age: very young and very old
- Cancer and cancer treatment
- Diabetes mellitus: if glucose levels aren't controlled→ immunodeficiency
- Organ transplant: immunosuppressive therapy

Secondary immunodeficiencies **are far more common** than **primary** immunodeficiencies.

In immunodeficiency there is a history of (the picture of immunodeficiency):

1. **Recurrent** infections
2. infections caused by **rare microorganisms** e.g: fungal infection
3. **Opportunistic** infections (more severe than normal individual, maybe it becomes invasive and it isn't treated properly)

If you got the history of immunodeficiency, you should first think about secondary immunodeficiency because it's much more common than primary then you think about primary immunodeficiency

If the patient is young (infant or child) you should first think about primary immunodeficiency but later on we think about secondary when the patient exposed do environmental factors

The immune defects observed are usually heterogeneous in their clinical presentation (the type of infection can lead you to where the defect is. for example, GI infection can lead you to the place of the pathogen while recurrent skin infection lead you to another place. Also the pathogen give you a clue to what the immunodeficiency is), and their prognosis depends on the severity of the immune defect.

More than 120 inherited primary immunodeficiency diseases have been discovered in the past five decades, and the precise genetic defect in many of these diseases has now been identified. Why? Because there are many points in the immune system (proteins, receptors, etc..) that can be mutated and many steps in immune response can go wrong, which results in large number of immunodeficiency diseases.

In different congenital immunodeficiencies, the causative abnormality may be in components of the **innate causative system**, at different stages of **lymphocyte development**, or in the **responses of mature lymphocytes** to antigenic stimulation

we will talk about some of these immunodeficiency diseases: ↓

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❶ innate immunity

- Innate immunity constitutes the first line of defense against infectious organisms.
- Two important mediators of innate immunity are **phagocytes** and **complement**, both of which also participate in the effector phases of adaptive immunity.
- Therefore, congenital disorders of phagocytes and the complement system result in recurrent infections.

Defect in phagocyte

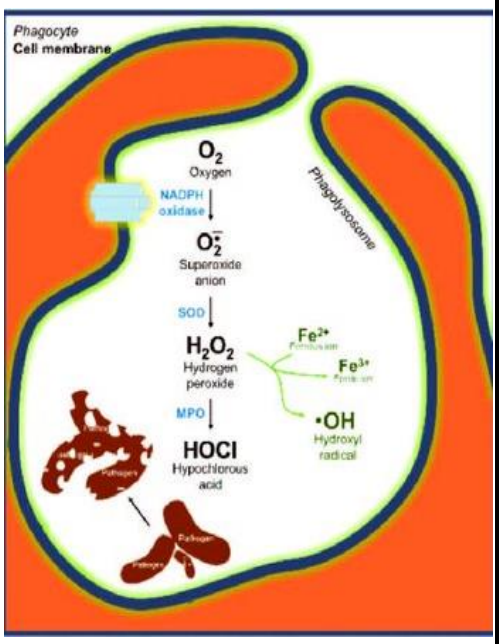
When phagocyte isn't able to reach infection site because of defect in chemokine secretion or in adhesion molecule (integrin mutation) that is called **leukocyte adhesion defect** leading to
→ abnormal leukocyte function because it can't reach infection site
→ patient can't overcome the disease easily
→ patient can't form pus because there is no leukocytes in the infected tissue

Pus: immune cells that reach to the infection site and die in the tissue

Defect ROS-radical oxygen species (free radicals), oxidative burst or lysosomal enzymes that are important of killing microbes.

Immunodeficiencies/ Defective Microbicidal Activities of Phagocytes

◆Chronic Granulomatous Disease◆



♦ it is caused by mutations in components of the phagocyte oxidase (phox) enzyme complex (the enzyme that is responsible of forming ROS from O_2)

♦ A rare disease, probably 1 in a million

♦Results in defective production of superoxide anion, one of several reactive oxygen species from which we form other ROS, which constitute a major microbicidal mechanism of phagocytes leading to failure to kill phagocytosed microbes (especially those producing catalase which convert H_2O_2 to H_2O and O_2) or kill it at much lower efficiency.

♦ Patients may have H_2O_2 from pathways other than O_2^- → H_2O_2 but if the pathogen has catalase, it will overcome another immune mechanism so the risk of chronic infections becomes higher

♦ in this disease, macrophages and neutrophils can ingest the pathogen but can't kill it, which result in granuloma formation

Chronic Granulomatous Disease

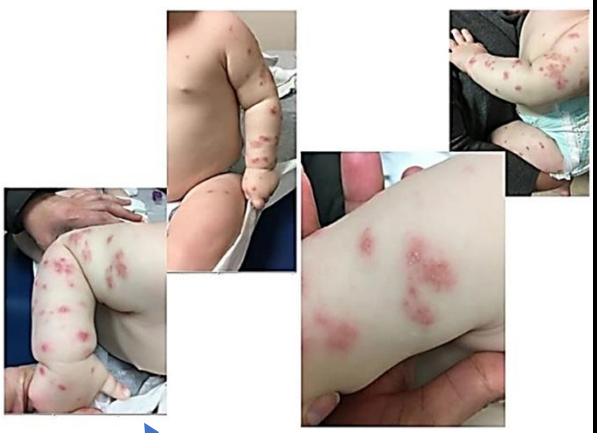
- Because it is a genetic disease- not curable
- Because of the formation of granuloma

♦Because the infections aren't controlled by phagocytes, they stimulate chronic cell-mediated immune responses, **resulting in T cell–mediated macrophage activation and the formation of granulomas** composed of activated macrophages mainly, neutrophils & CD4 helper T cells

♦Helper T cells stimulate the macrophages to kill the phagocytosed pathogen

♦This histologic appearance is the basis for the name of the disorder. The disease is often fatal, even with **aggressive antibiotic therapy** (all you can do)

Try to limit the exposure to infectious pathogens specially in severe immunodeficiency



♦IFN-γ therapy is now commonly used for the treatment of X-linked CGD along with antibiotic therapy

♦ IFN-γ is a cytokine important in stimulating macrophages to kill intracellular microbe even though they cannot perform proper oxidative burst, they can still form other digestive enzymes

Recurrent skin infections

severe

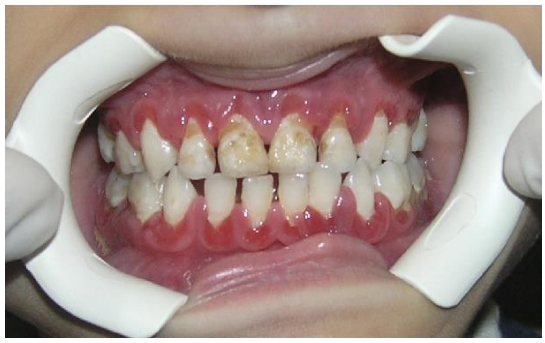
Present in infants (early in life) → primary immunodeficiency

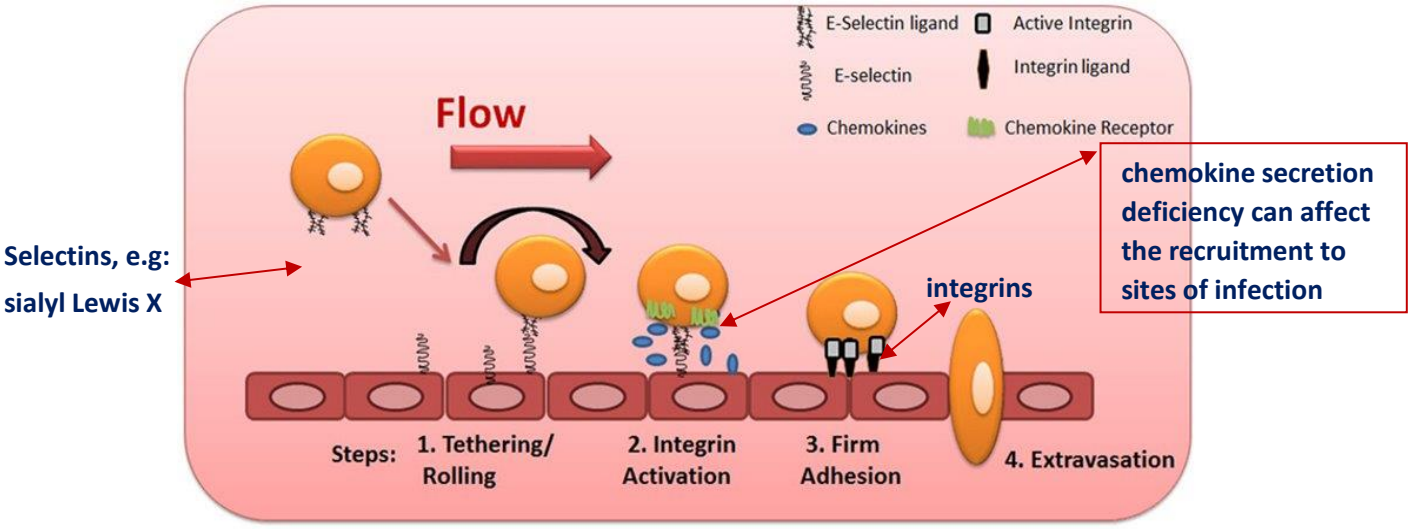
Immunodeficiencies/ Leukocyte Adhesion Deficiencies

→The leukocyte adhesion deficiencies (LAD) are a group of autosomal recessive disorders caused by defects in leukocyte and endothelial adhesion molecules

→These diseases are characterized by a **failure of leukocyte, particularly neutrophil, recruitment to sites of infection**, resulting in severe **periodontitis** (gum infection) and other recurrent infections starting early in life, and the inability to make **pus** (page 3 in this sheet).

→There are different types of LAD such as LAD 1 (The molecular basis of the defect is absent or deficient expression of the β2 integrins) and LAD 2 (results from an absence of sialyl Lewis X, the tetra saccharide carbohydrate ligand on neutrophils and other leukocytes that is required for binding to E-selectin and P-selectin.





Immunodeficiencies/ Complement Deficiencies

■Genetic deficiencies in classical pathway components, including C1q, C1r, C4, C2, and C3, have been described; **C2 deficiency** is the most common human complement deficiency (C2 deficiency predispose to SLE).

it is found that C1q, C1r, C4, C2 aren't severe immunodeficiency and sometimes you live without knowing that you have a deficiency in those molecules, because of the alternative pathway that can compensate with the deficiency of in classical pathway components

■But C3 deficiency is the heart of the complement system, both alternative and classical pathway aim to form C3 convertase that break down C3

C3A is an anaphylatoxin that promote inflammation and C3b is an opsonin

Deficiency of C3 is associated with frequent serious pyogenic bacterial infections that may be fatal, illustrating the central role of C3 in opsonization.

■Deficiencies in components of the alternative pathway, including properdin and factor D, result in increased

→properdin and factor D deficiency is more important than C1q, C1r, C4, C2 deficiency, so it seems that alternative pathway is more important than classical pathway in fighting infections

■ Deficiencies in the terminal complement components, including C5, C6, C7, C8, and C9, have also been described. Interestingly, the only consistent clinical problem in these patients is a propensity for disseminated infections by Neisseria bacteria, including *Neisseria meningitidis* ***(causes meningitis)*** and *Neisseria gonorrhoeae* ***(causes gonorrhoeae & STD)***

➢we conclude that terminal complement components are important in fighting Neisseria bacteria

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◎Neisseria gonorrhoeae isn't only shown in ①terminal complement deficiencies, also it is associated with ②giving a drug that inhibit C_5

C_5 inhibitor, a monoclonal antibody that binds C5 and prevents its cleavage. a drug to treat a disease associated with the absence of a complement regulatory protein (**paroxysmal nocturnal hemoglobinuria**).

*this disease causes lysis of RBCs by the action of complement, and to inhibit this action we give this drug (C_5 inhibitor)

*it has a warning of serious meningococcal infection. So before taking this drug, patients must get vaccinated against Neisseria meningitidis and Neisseria gonorrhoeae.also, Prophylactic Antibiotics

Soliris® (eculizumab) Concentrated solution for intravenous infusion
Initial U.S. Approval: 2007

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris and may become rapidly life-threatening or fatal if not recognized and treated early (5.1).

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).
- Immunize patients with a meningococcal vaccine at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection. (See *Serious Meningococcal Infections* (5.1) for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program (5.2).

INDICATIONS AND USAGE

Soliris is a complement inhibitor indicated for:

- The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis (1.1).
- The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (1.2).

Immunodeficiencies/ Defects in NK Cells & Other Leukocytes: The Chédiak- Higashi Syndrome

→The Chédiak-Higashi syndrome is a rare autosomal recessive disorder characterized by recurrent infections by pyogenic bacteria.

→ caused by:-

mutations in the gene encoding the **lysosomal trafficking regulator protein LYST**

→ result in: -

①defective phagosome-lysosome fusion in neutrophils and macrophages (causing reduced resistance to infection mainly skin infection) look at picture 1 ↓

Not only the immune system uses lysosomal trafficking regulator protein, also other systems use this protein or only lysosomes for certain functions, so the syndrome doesn't only affect the immune system, but it affects other systems and organs

②defective melanosome formation in melanocytes (causing albinism-look at picture 1 ↓)

③lysosomal abnormalities in cells of the nervous system (causing nerve defects)

④platelets problems (leading to bleeding disorders).

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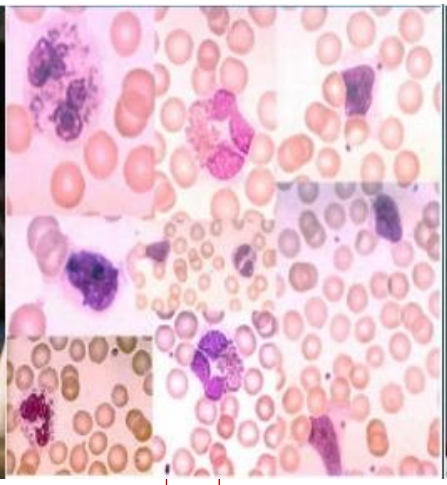

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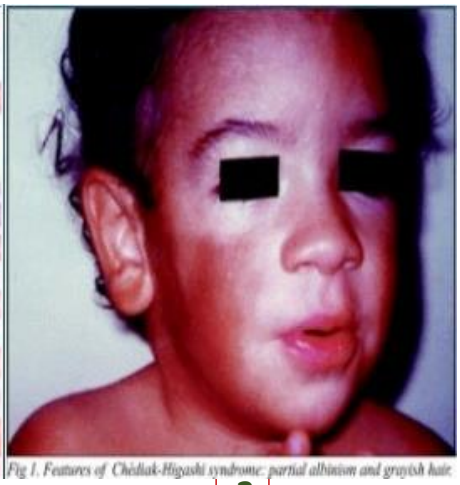

Fig 1. Features of Chédiak-Higashi syndrome: partial albinism and grayish hair.

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→In picture 2, you can see immune cells filled with lysosomes and granules because there is a problem in trafficking them to the cell membrane

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TABLE 20–2 Congenital Disorders of Innate Immunity

Disease	Functional Deficiencies	Mechanism of Defect
Chronic granulomatous disease	Defective production of reactive oxygen species by phagocytes; recurrent intracellular bacterial and fungal infections	Mutation in genes of phagocyte oxidase complex; phox-91 (cytochrome b_{588} α subunit) is mutated in X-linked form
Leukocyte adhesion deficiency type 1	Defective leukocyte adhesion and migration linked to decreased or absent expression of β_2 integrins; recurrent bacterial and fungal infections	Mutations in gene encoding the β chain (CD18) of β_2 integrins
Leukocyte adhesion deficiency type 2	Defective leukocyte rolling and migration linked to decreased or absent expression of leukocyte ligands for endothelial E- and P- selectins, causing failure of leukocyte migration into tissues; recurrent bacterial and fungal infections	Mutations in gene encoding a GDP-fucose transporter required for the synthesis of the sialyl Lewis X component of E- and P- selectin ligands
Leukocyte adhesion deficiency type 3	Defective leukocyte adhesion and migration linked to defective inside-out signaling and therefore defective integrin activation	Mutations in gene encoding KINDLIN-3
Chédiak-Higashi syndrome	Defective vesicle fusion and lysosomal function in neutrophils, macrophages, dendritic cells, natural killer cells, cytotoxic T cells, and many other cell types; recurrent infections by pyogenic bacteria	Mutation in LYST leading to defect in secretory granule exocytosis and lysosomal function
Toll-like receptor signaling defects	Recurrent infections because of defects in TLR and CD40 signaling and defective type I interferon production	Mutations in NEMO, UNC93B, MyD88, IκBα, and IRAK-4 compromise NF-κB activation downstream of Toll-like receptors

IRAK-4, IL-1 receptor–associated kinase 4; LYST, lysosomal trafficking protein; NEMO, NF-κB essential modulator.

❷Adaptive/ Severe Combined Immunodeficiencies

→we can have problems in adaptive immunity (B cells and T cells formation)

→Which is more severe, B cell or T cell problems?

The problem in T cells is bigger than B cells, because T cells are required in B cell activation (germinal center formation, long lived plasma cells formation)→ so you will have a combined problem in B & T cells

→Congenital immunodeficiencies that **affect both humoral and cell-mediated immunity** are called **combined immunodeficiencies**, and a subset of these in which **most peripheral T cells are missing** or defective are known as **severe combined immunodeficiencies** (SCIDs)

→SCID results from **impaired T lymphocyte development** with or without defects in B cell maturation

→About 50% of SCIDs are autosomal recessive; the rest are X-linked.

→example on severe combined immunodeficiency? **DiGeorge syndrome**

DiGeorge syndrome

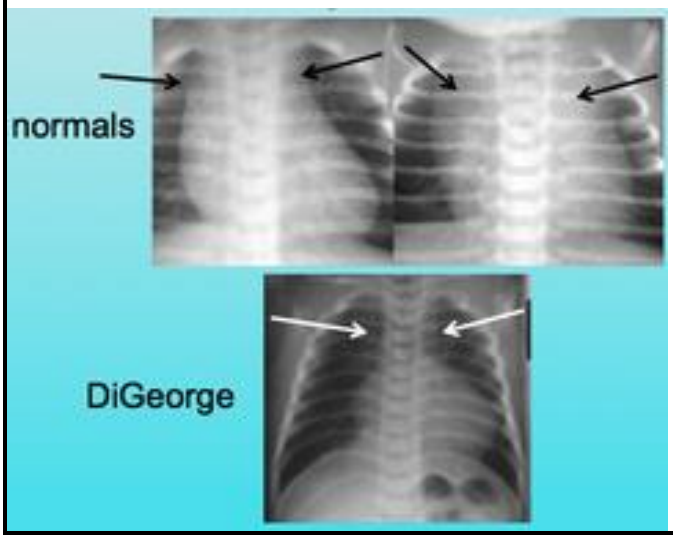
→This selective T cell deficiency is due to a **congenital malformation** that results in **defective development of the thymus** and the **parathyroid glands** as well as other structures that develop from the third and fourth pharyngeal pouches during fetal life.

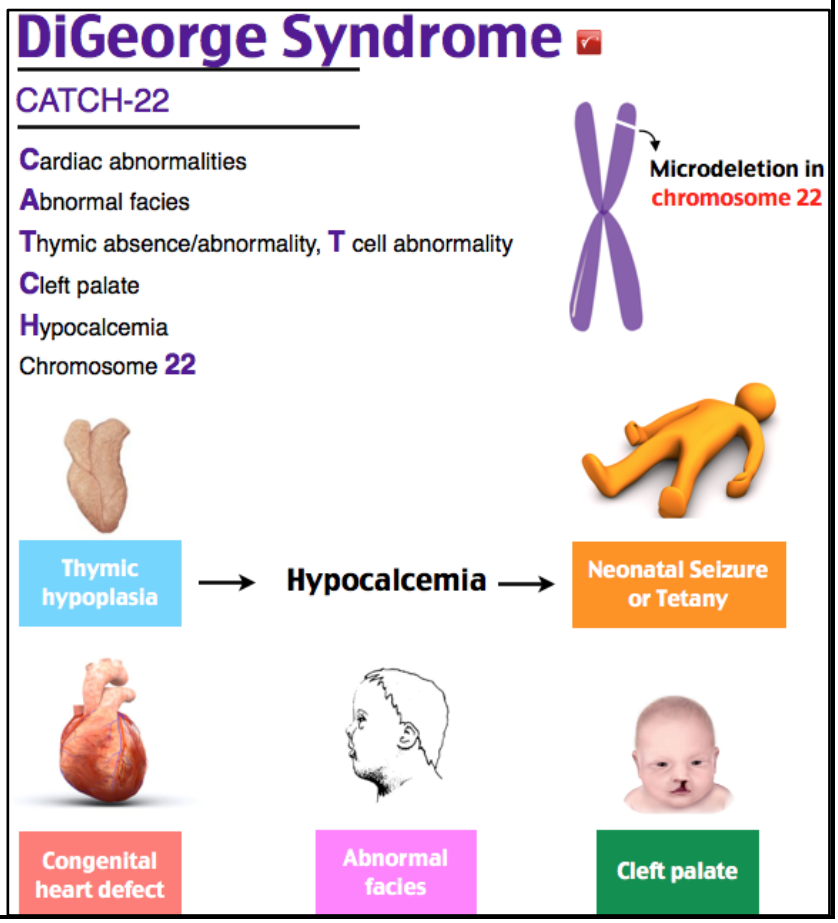
→The immunodeficiency associated with DiGeorge syndrome can be corrected by fetal thymic transplantation or by bone marrow transplantation. Such treatment is usually not necessary. however, because T cell function tends to improve with age in a large fraction of patients so they won't be at risk of severe infection – probably T cells mature somewhere else and probably there Is thymic remnant where they can mature

◎in this syndrome: mutations in genes required for thymus development →improper development of T cell→ deficiency and reduced function of T cells

◎Patients have problems in parathyroid so they will develop hypocalcemia

◎Look at the picture CATCH-22





◎In the “nude” mouse strain, which has been widely used in immunology research, a mutation in the gene encoding a transcription factor causes a failure of differentiation of certain types of epithelial cells that are required for normal development of the thymus and hair follicles. Consequently, these mice lack T cells and hair.

◎they are used to study severe combined immunodeficiency & immune system response to various infections

◎also they are used in studying xenotransplants

Other Severe Combined Immunodeficiencies

✦ Severe Combined Immunodeficiencies can result from problems in cytokine signalling (IL-2)

Problem in IL-2 can lead to defect in activation and proliferation of T cells

✦mutations in RAG1 & RAG2 → defect VDJ recombination (aromatic recombination of B & T cells) → leads to Severe Combined Immunodeficiencies

TABLE 20–3 Severe Combined Immunodeficiencies

Disease	Functional Deficiencies	Mechanism of Defect
Defects in cytokine signaling	because B cells don't depend on IL-2 as much as T cells do	
X-linked SCID	Marked decrease in T cells; normal or increased B cells; reduced serum Ig	Cytokine receptor common γ chain mutations; defective T cell development in the absence of IL-7–derived signals
Autosomal recessive forms	Marked decrease in T cells; normal or increased B cells; reduced serum Ig	Mutations in *IL2RA, IL7RA, JAK3*
Defects in nucleotide salvage pathways		
ADA deficiency	Progressive decrease in T, B, and NK cells; reduced serum Ig	ADA deficiency caused by mutations in the gene, leading to accumulation of toxic metabolites in lymphocytes
PNP deficiency	Progressive decrease in T, B, and NK cells; reduced serum Ig	PNP deficiency caused by mutations in the gene, leading to accumulation of toxic metabolites in lymphocytes
Defects in V(D)J recombination		
RAG1 or RAG2 deficiency recombination*	Decreased T and B cells; reduced serum Ig; absence or deficiency of T and B cells Both decrease	Cleavage defect during V(D)J recombination; mutations in *RAG1* or *RAG2*
Double-stranded break repair and checkpoint	Decreased T and B cells; reduced serum Ig; absence or deficiency of T and B cells	Failure to resolve hairpins during V(D)J recombination; mutations in *ARTEMIS,* DNA-PKcs, *CERNUNNOS, LIG4, NBS1, MRE11, ATM*
Defective thymus development		
Defective pre-TCR checkpoint	Decreased T cells; normal or reduced B cells; reduced serum Ig	Mutations in *CD45, CD3D, CD3E, ORAI1* (CRAC channel component), *STIM1*
DiGeorge syndrome	Decreased T cells; normal B cells; normal or reduced serum Ig	22ql 1 deletion; T-box 1 (*TBX1*) transcription factor mutations
FoxN1 deficiency	Thymic aplasia with defective thymic cell development	Recessive mutation in *FOXN1*
Other defects		
Reticular dysgenesis	Decreased T, B, and myeloid cells	Mutation in *AK2*

ADA, adenosine deaminase; AK2, adenylate kinase 2; ATM, ataxia-telangiectasia mutated; CRAC, calcium release activated channel; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; LIG4, DNA ligase 4; MRE11, meiotic recombination homologue 11; NBS1, Nijmegen breakpoint syndrome 1; PNP, purine nucleoside phosphorylase.
*Hypomorphic mutations in *RAG* genes and in *ARTEMIS* can contribute to Omenn's syndrome.

Antibody Deficiencies: Defects in B Cell Development and Activation

✦Whereas defects in T cell development or in both T and B cell development contribute to the SCID phenotype more circumscribed defects in B cells result in disorders in which the primary abnormality is in antibody synthesis (Low level of antibodies in general or certain types of antibodies)

✦The most common is selective IgA deficiency, which affects about 1 in 700 Caucasians & is thus **the most common primary immunodeficiency** known. The clinical features are variable. Many patients are entirely normal; others have occasional respiratory infections and diarrhea; and rarely, patients have severe, recurrent infections leading to permanent intestinal and airway damage it isn't always manifest and patients can live a normal life without problems(it isn't serious)

✦IgA deficiency → mucus infection (respiratory tract or GI tract) → easily food poisoning and diarrhea

✦ IgA deficiency affects about 1 in 700 Caucasians & maybe 1 in 500 Saudi Arabians → we conclude that difference in races can lead to difference in certain immune pathways and severity of immunodeficiencies

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People who have deficiency in all classes of antibodies

→**How can we decrease the recurrent of severe infections?** By giving them antibodies either directing to a specific pathogen or a pooled serum Igs against several pathogens

Common variable immunodeficiency is a group of heterogeneous disorders defined by reduced levels of serum Ig, impaired antibody responses to infection or vaccines, and increased incidence of infections

X-linked agammaglobulinemia

→***X-linked agammaglobulinemia.*** The disease is characterized by the absence of **gamma globulin** in the blood, as the name implies. It is one of the most common congenital immunodeficiencies and the prototype of a failure of B cell maturation.

→Patients with X-linked agammaglobulinemia usually **have low or undetectable serum Ig reduced or absent B cells** in peripheral blood and lymphoid tissues, **no germinal centers** in lymph nodes, and no plasma cells in tissues. The maturation, numbers, and functions of T cells are generally normal.

→The infectious complications of X-linked agammaglobulinemia are greatly reduced by periodic (e.g., weekly or monthly) injections of **pooled gamma globulin preparations**

Note:- *agammaglobulinemia, is caused by mutations or deletions in the gene encoding an enzyme called Bruton tyrosine kinase (Btk) that results in a failure of B cells to mature beyond the pre-B cell stage in the bone marrow*

The X-linked hyper-IgM syndrome

It is caused by mutations in the gene encoding the T cell effector molecule CD40 ligand (CD154).

CD40 ligand present on T cells and it has a receptor on B cells (CD40 receptor), for activating B cells properly and form germinal centers

If this gene is defect, there is no enough signal for the formation of germinal centers, results in decreasing class switching → increase IgM

Defects in T Lymphocyte Activation and Function

Wiskott-Aldrich syndrome

Variable degrees of T and B cell immunodeficiency occur in certain congenital diseases with a wide spectrum of abnormalities involving multiple organ systems.

One such disorder is **Wiskott-Aldrich syndrome**, an X-linked disease characterized by ①eczema, ②thrombocytopenia (lead to bleeding under the skin)

③ (reduced blood platelets), and ④ susceptibility to bacterial infection

A) Multiple face petechiae and a hematoma under the right eye (left in image).

B) Eczema of the foot

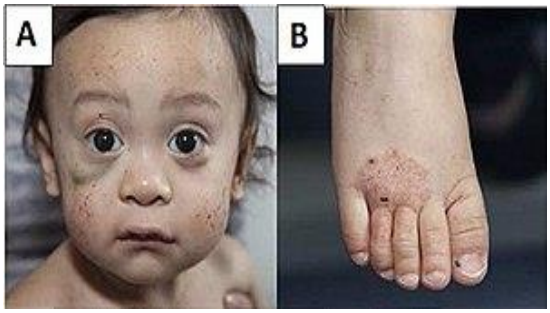


TABLE 20–4 Antibody Deficiencies

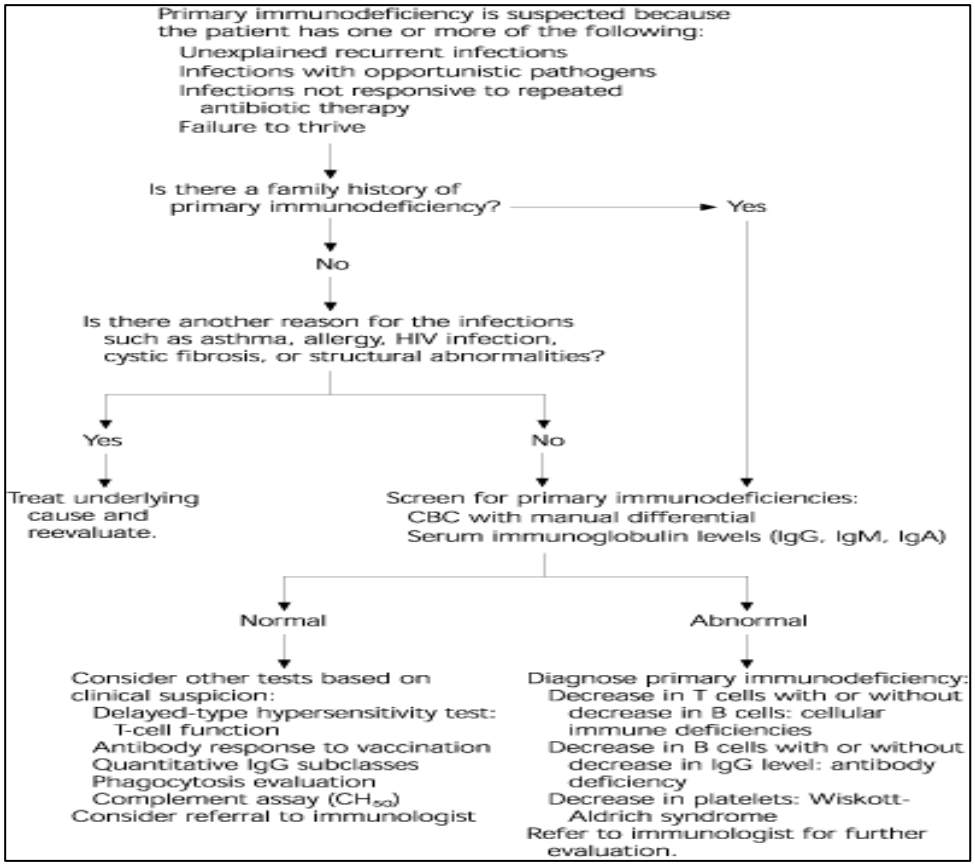
Disease	Functional Deficiencies	Mechanism of Defect
Agammaglobulinemias		
X-linked	Decrease in all serum Ig isotypes; reduced B cell numbers	Pre-B receptor checkpoint defect; Btk mutation
Autosomal recessive forms	Decrease in all serum Ig isotypes; reduced B cell numbers	Pre-B receptor checkpoint defect; mutations in IgM heavy chain (μ), surrogate light chains (λ5), Igα, BLNK
Hypogammaglobulinemias/isotype defects		
Selective IgA deficiency	Decreased IgA; may be associated with increased susceptibility to bacterial infections and protozoa such as *Giardia lamblia*	Mutations in *TACI* in some patients
Selective IgG2 deficiency	Increased susceptibility to bacterial infections	Small subset have deletion in IgH γ2 locus
Common variable immunodeficiency	Hypogammaglobulinemia; normal or decreased B cell numbers	Mutations in *ICOS* and *TACI* in some patients
ICF syndrome	Hypogammaglobulinemia, occasional mild T cell defects	Mutations in *DNMT3B*
Hyper-IgM syndromes		
X-linked	Defects in T helper cell–mediated B cell, macrophage, and dendritic cell activation; defects in somatic mutation, class switching, and germinal center formation; defective cell-mediated immunity	Mutation in *CD40L*
Autosomal recessive with cell-mediated immune defects	Defects in T helper cell–mediated B cell, macrophage, and dendritic cell activation; defects in somatic mutation, class switching, and germinal center formation; defective cell-mediated immunity	Mutations in *CD40, NEMO*
Autosomal recessive with antibody defect only	Defects in somatic mutation and isotype switching	Mutations in *AID, UNG*

AID, activation-induced cytidine deaminase; DNMT3B, DNA methyltransferase 3B; ICF, immunodeficiencies-centromeric instability-facial anomalies; ICOS, inducible costimulator; NEMO, NF-κB essential modulator; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor; UNG, uracil N-glycosylase.

Assessment of immunodeficiencies

➢The immunological investigation of a patient with immunodeficiency includes the assessment of **immunoglobulins**, B and T-**lymphocyte counts**, lymphocyte stimulation assays, quantification of components of the **complement system** and **phagocytic activity.**

➢In addition **microbiological studies** must be done to aid in the assessment of the patient presenting with recurrent infections



Conclusion

➢When evaluating a patient with increased frequency or severity of infections suggesting immunodeficiency, physicians should consider that secondary immunodeficiencies **are far more common than primary** immune defects of genetic cause.

➢Other than primary immune deficiencies. Detailed clinical history might uncover the condition affecting the immune system and causing a secondary immunodeficiency, such as infection, malnutrition, age extremes, concomitant metabolic or neoplastic diseases, use of immunosuppressive drugs, surgery and trauma, and exposure to harsh environmental conditions. Because of its prevalence and clinical progression, HIV infection should be considered and ruled out.

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if we have a baby patient with recurrent infection or rare pathogen, we should test for immunodeficiency. **But first we role out secondary immunodeficiency** because it is more common by asking about organ transplantation or certain drugs or HIV (reasons of immunosuppression)

severe diarrhea, GI infection or respiratory infection→ we think about the common: IGA deficiency →test IgA levels and antibodies in general

skin infection→ test phagocyte activity and production of ROS and test the levels of complement components (C3 &C5) and other tests

if there is a cleft palate → test thymus, level of lymphocytes and antibodies. Also ask about family history (genetic disease)

Good luck