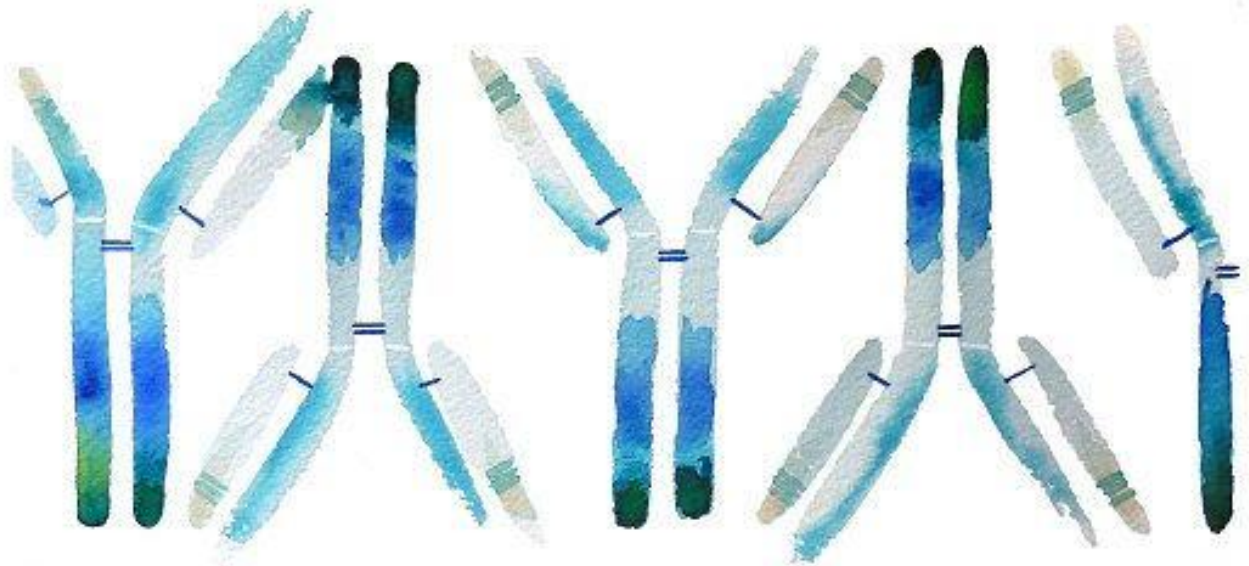
Medical Immunology



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Lecture 21

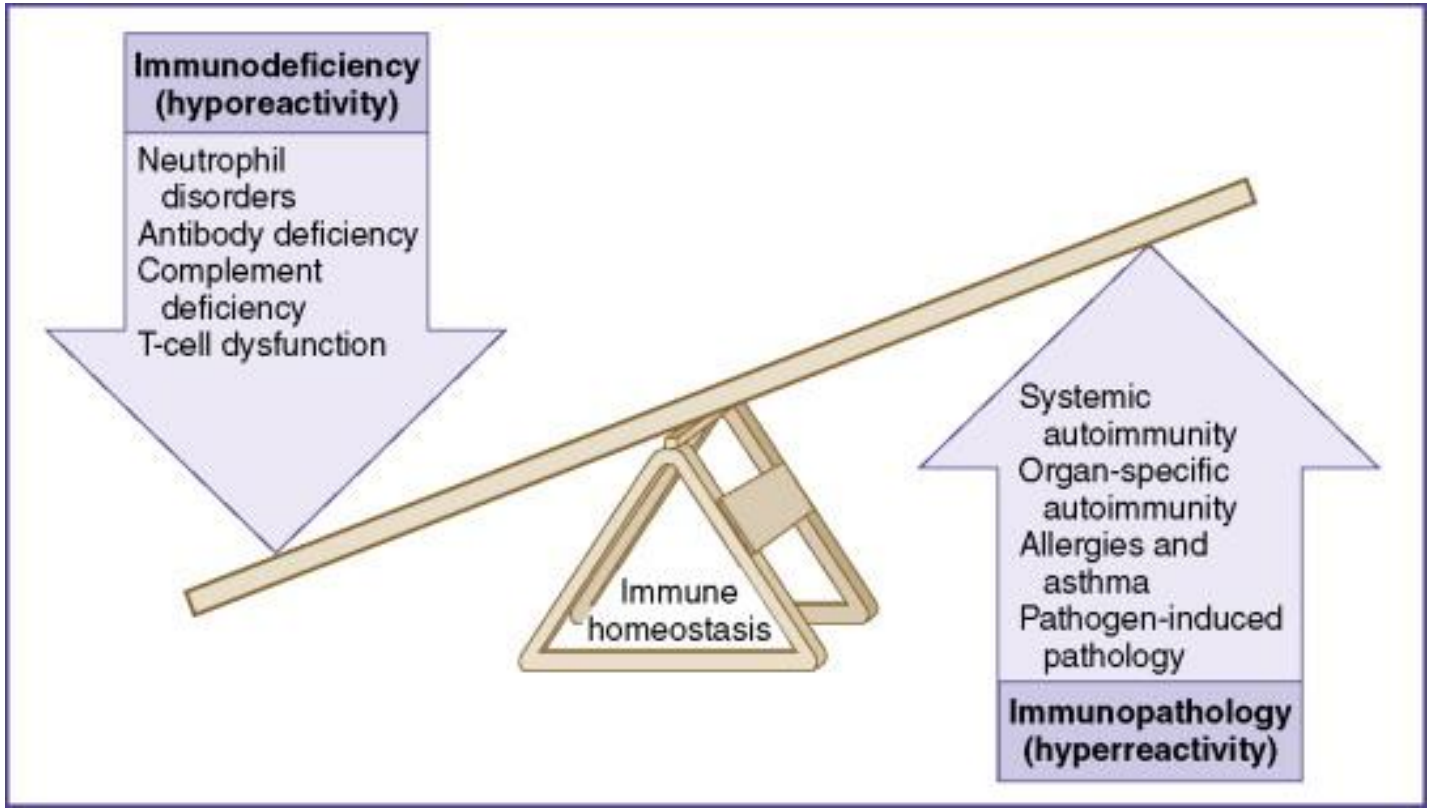
Primary immunodeficiencies

In this lecture we will discuss:

- Examples of primary immunodeficiencies

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 an overactive immune response (known as **hypersensitivity reactions**), an inappropriate reaction to self (known as **autoimmunity**) or ineffective immune responses (known as **immunodeficiency**).



Immunodeficiencies

- **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**.

- The **congenital**, or **primary**, immunodeficiencies are **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 immunodeficieny, only a small proportion are affected severely enough for development of life-threatening complications.

- A secondary immune deficiency disease occurs when the immune system is compromised due to **an environmental factor**.

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

Immunodeficiencies/ overview

- In immunodeficiency there is a history of: **Recurrent** infections, infections caused by **rare microorganisms**, and **Opportunistic** infections.

- Patients with immunodeficiencies are also **susceptible to certain types of cancer**. Many of these cancers appear to be caused by oncogenic viruses, such as the Epstein-Barr virus.

- The immune defects observed are usually **heterogeneous in their clinical presentation**, 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.

Immunodeficiencies/ CONGENITAL (PRIMARY) IMMUNODEFICIENCIES

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

Immunodeficiencies/ Defects in 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.

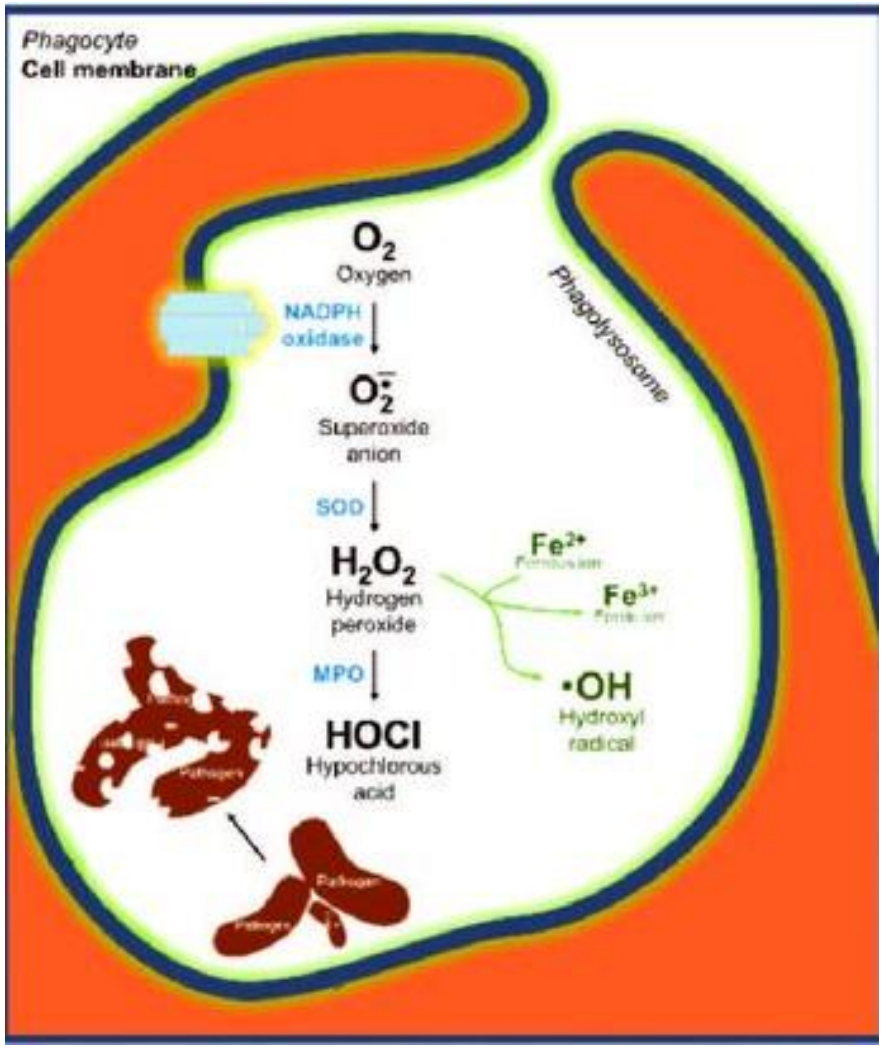
Immunodeficiencies/ Defective Microbicidal Activities of Phagocytes

- Defective Microbicidal Activities of Phagocytes: Chronic Granulomatous Disease

- **Chronic granulomatous disease (CGD)** is caused by mutations in components of the phagocyte oxidase (phox) enzyme complex.

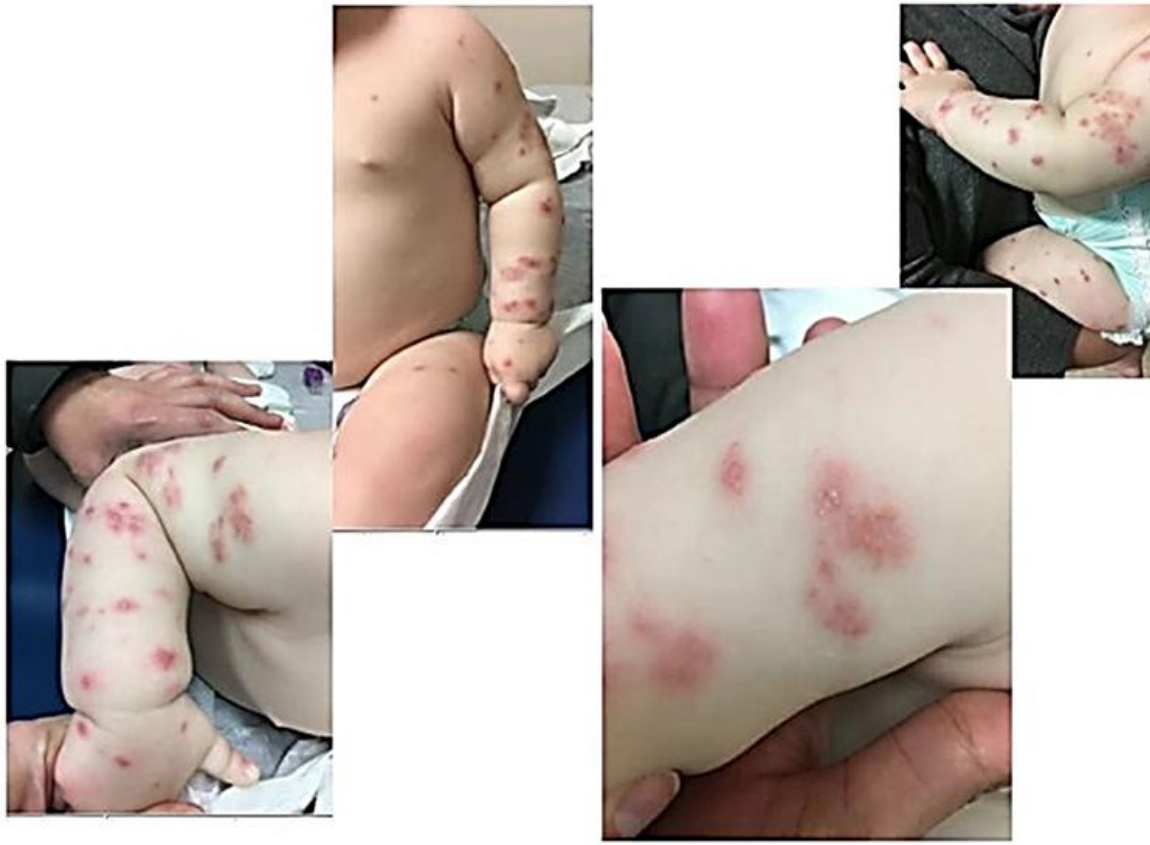
- A rare disease, probably 1 in a million.

- Results in **defective production of superoxide anion**, one of several reactive oxygen species, which constitute a major microbicidal mechanism of phagocytes leading to **failure to kill phagocytosed microbes (especially those producing catalase)**.



Immunodeficiencies/ Defective Microbicidal Activities of Phagocytes

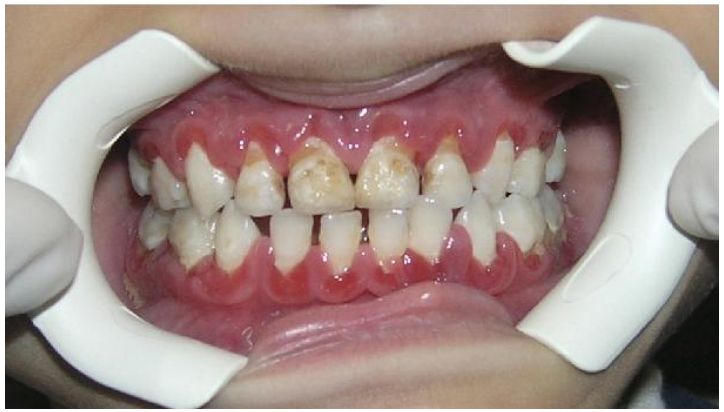
- Because the infections are not controlled by phagocytes, they stimulate chronic cell-mediated immune responses, **resulting in T cell–mediated macrophage activation and the formation of granulomas** composed of activated macrophages.



- This histologic appearance is the basis for the name of the disorder. The disease is often fatal, even with **aggressive antibiotic therapy**.

- **IFN-γ therapy** is now commonly used for the treatment of X-linked CGD

Immunodeficiencies/ Leukocyte Adhesion Deficiencies

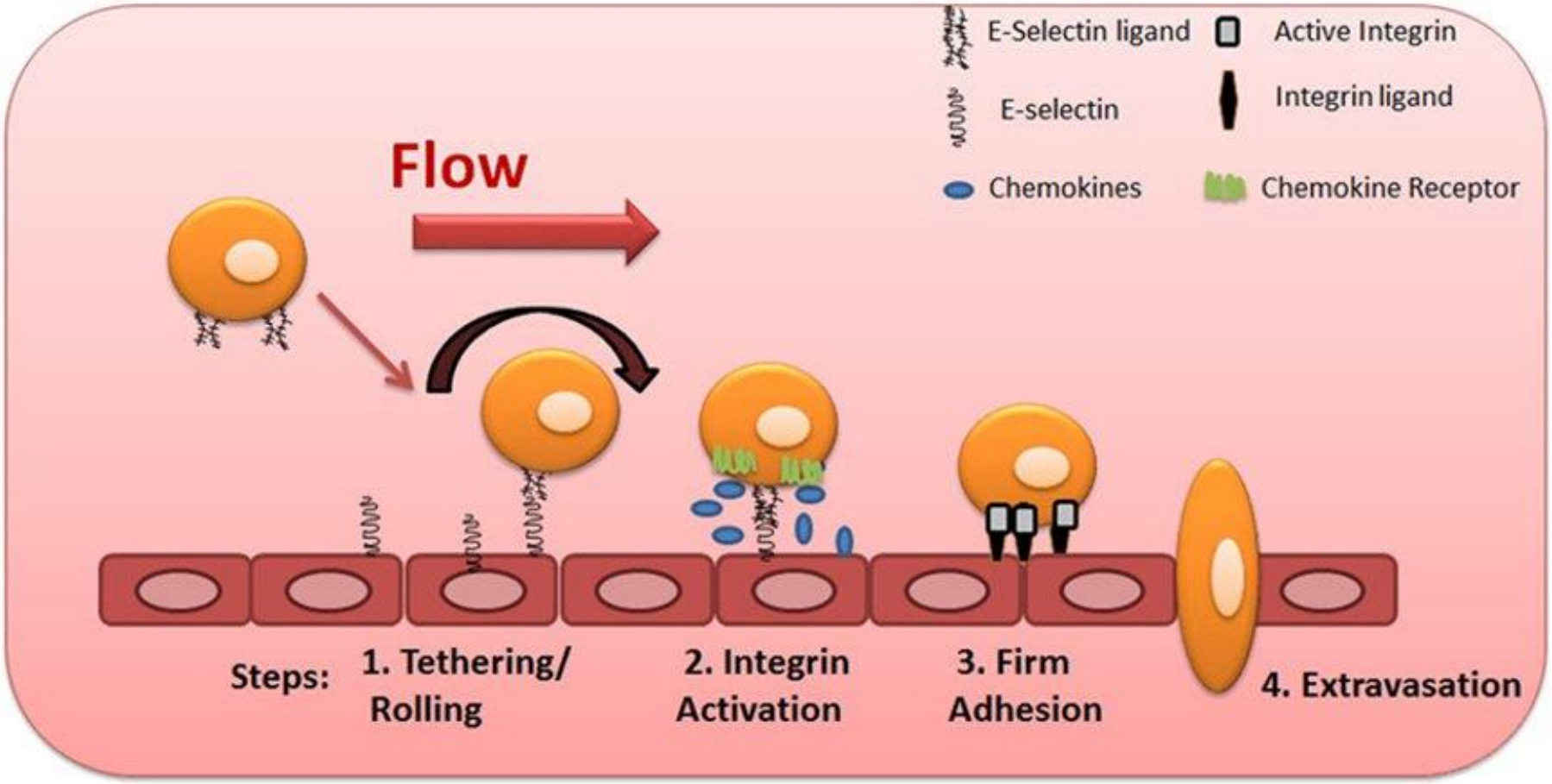


- The leukocyte adhesion deficiencies (LAD) are a group of autosomal recessive disorders caused by defects in leukocyte and endothelial adhesion molecules

- These diseases are characterized by a **failure of leukocyte, particularly neutrophil, recruitment to sites of infection**, resulting in severe **periodontitis** and other recurrent infections starting early in life, and the inability to make pus.

- 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 tetrasaccharide carbohydrate ligand on neutrophils and other leukocytes that is required for binding to E-selectin and P-selectin.

Immunodeficiencies/ Leukocyte Adhesion Deficiencies



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.

- 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

- 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* and *Neisseria gonorrhoeae.*

Immunodeficiencies/ Complement Deficiencies

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).

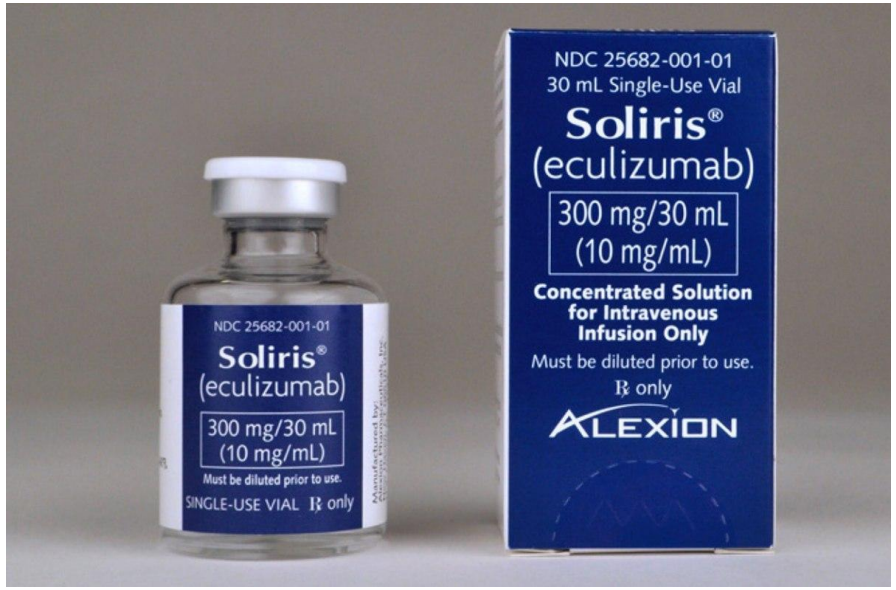
- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).**
- **Immunize patients with a meningococcal vaccine at least 2 weeks prior to administering the first dose of Soliris, unless 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:

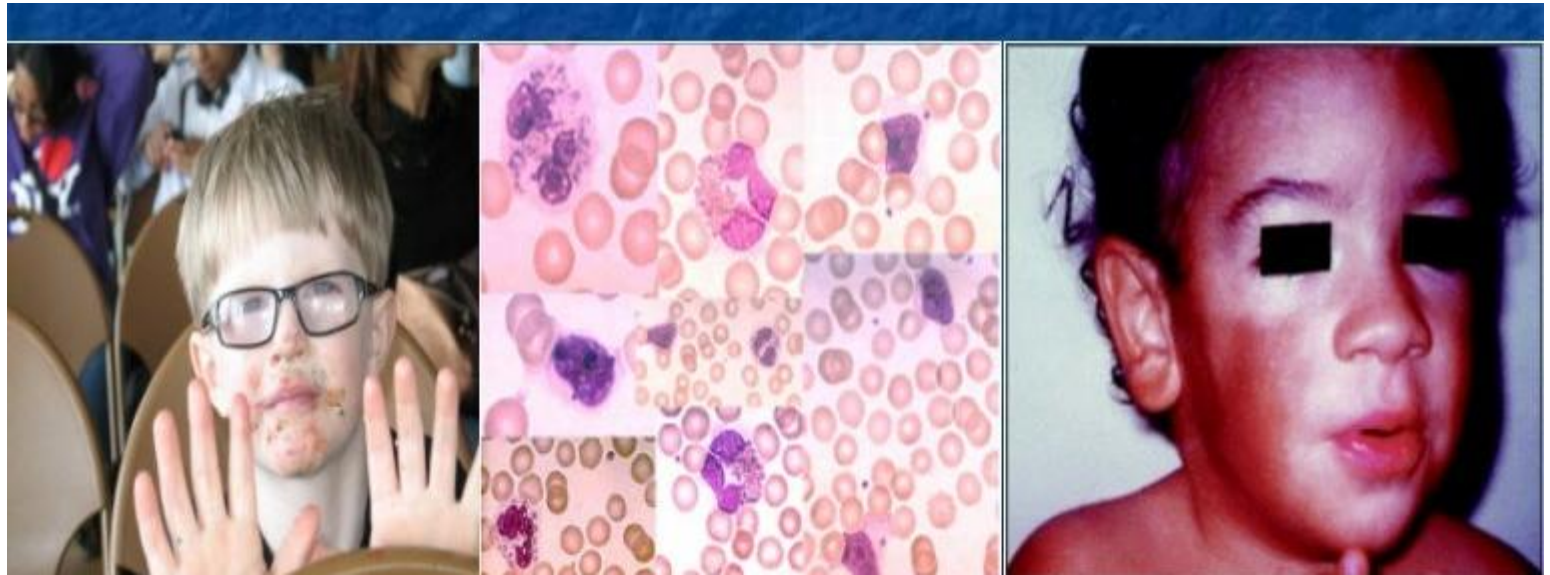
- The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis (1.1).
- The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (1.2).



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

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

This disease is caused by mutations in the gene encoding the **lysosomal trafficking regulator protein LYST**, resulting in defective phagosome-lysosome fusion in neutrophils and macrophages (causing reduced resistance to infection), defective melanosome formation in melanocytes (causing albinism), and lysosomal abnormalities in cells of the nervous system (causing nerve defects) and platelets (leading to bleeding disorders).



Immunodeficiencies/ Defects in Innate Immunity

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.

Immunodeficiencies/ Severe Combined Immunodeficiencies

- 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.

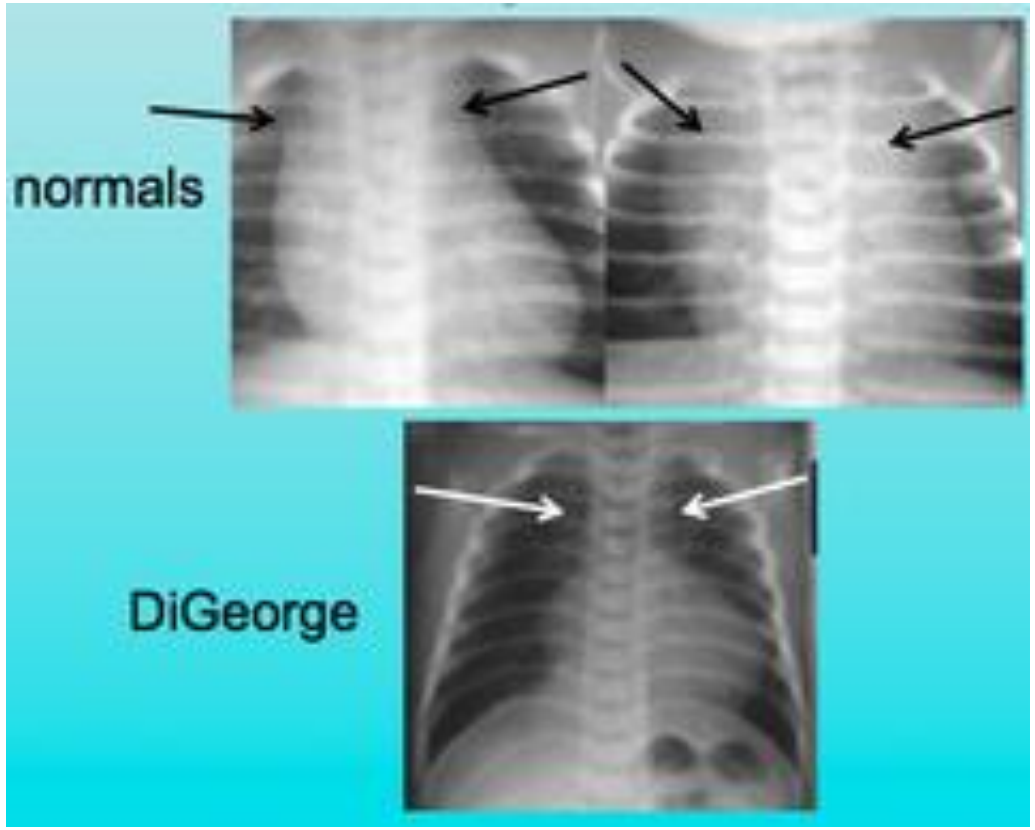
- About 50% of SCIDs are autosomal recessive; the rest are X-linked.

Immunodeficiencies/ Severe Combined Immunodeficiencies/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

Immunodeficiencies/ Severe Combined Immunodeficiencies/DiGeorge syndrome



- Humans with DiGeorge syndrome suffer from T cell deficiency because of mutations in genes required for thymus development.

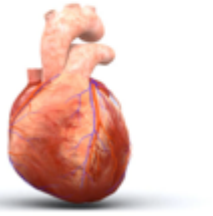
DiGeorge Syndrome

CATCH-22

Cardiac abnormalities
Abnormal facies
Thymic absence/abnormality, **T** cell abnormality
Cleft palate
Hypocalcemia
Chromosome **22**

Microdeletion in chromosome 22

Thymic hypoplasia → Hypocalcemia → Neonatal Seizure or Tetany



Congenital heart defect | Abnormal facies | Cleft palate

Immunodeficiencies/ Severe Combined Immunodeficiencies

- 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.

Immunodeficiencies/ Severe Combined Immunodeficiencies

TABLE 20–3 Severe Combined Immunodeficiencies

Disease	Functional Deficiencies	Mechanism of Defect
Defects in cytokine signaling		
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

Immunodeficiencies/ Severe Combined Immunodeficiencies

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	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.

Immunodeficiencies/ 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**

- The most common is selective **IgA deficiency**, which affects about 1 in 700 Caucasians and 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

Immunodeficiencies/ Antibody Deficiencies: Defects in B Cell Development and Activation

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*

Immunodeficiencies/ Antibody Deficiencies: Defects in B Cell Development and Activation

- ***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**

- **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.

Immunodeficiencies/ Antibody Deficiencies: Defects in B Cell Development and Activation

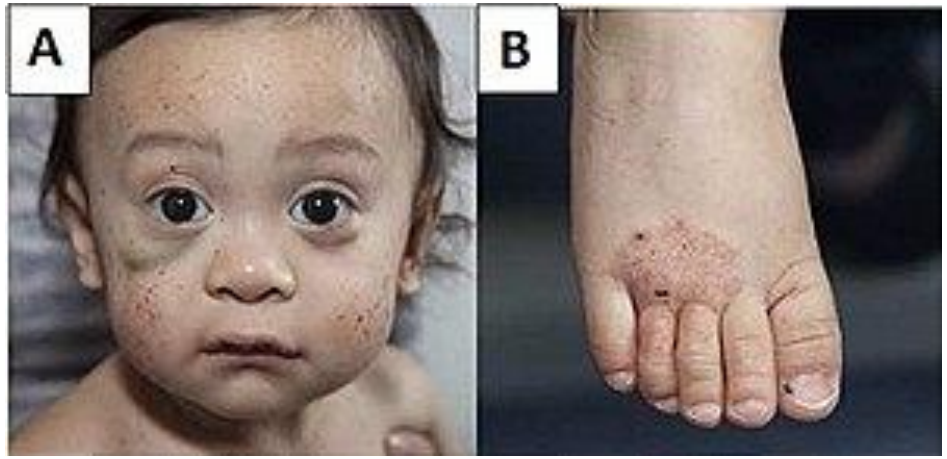
- The X-linked hyper-IgM syndrome is caused by mutations in the gene encoding the T cell effector molecule CD40 ligand (CD154).

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.

Immunodeficiencies/ Defects in T Lymphocyte Activation and Function

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 eczema, thrombocytopenia (reduced blood platelets), and susceptibility to bacterial infection.



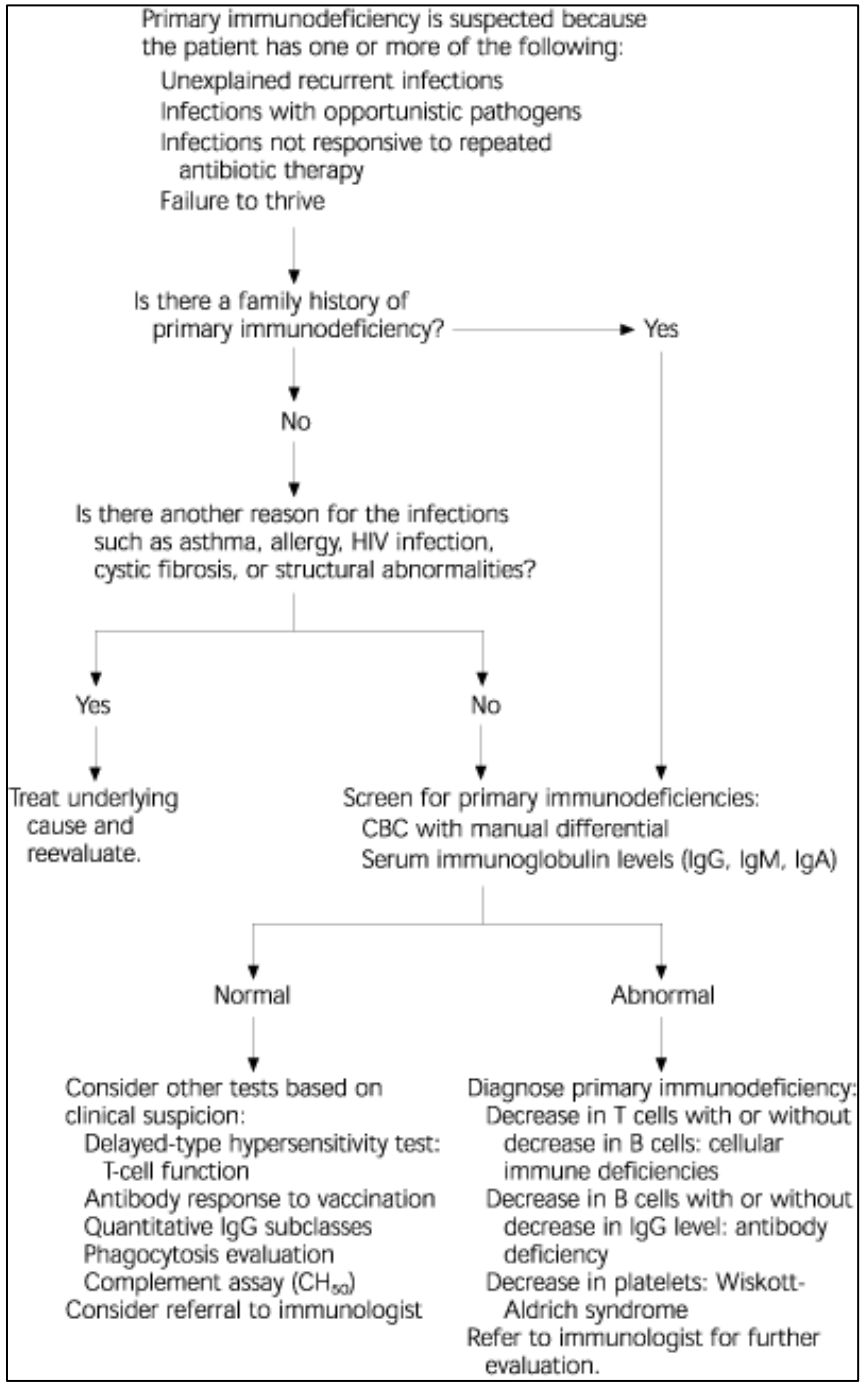
A) Multiple face petechiae and a hematoma under the right eye (left in image).
B) Eczema of the foot.

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.

https://www.ouh.nhs.uk/immunology/diagnostic-tests/tests-catalogue/lymphocyte-function-assay.aspx



Immunodeficiencies/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.

Abstract

Go to:

Severe Combined Immunodeficiency (SCID) involves the lymphocyte lineage and mimics Human Immunodeficiency Virus (HIV) disease common in our region, making it difficult to diagnose and manage effectively. SCID in East Africa stands underdiagnosed because of lack of awareness and diagnostic resources. A case series of three SCID patients admitted to a Tertiary Paediatric Centre in Kenya between 2016 and 2019. The clinical presentations, laboratory findings, management and outcome for each were studied. Three cases were diagnosed between the ages of 4 to 15 months. Two of them were male and one was a female. All had a history of previous sibling death. There was no parental consanguinity. All presented with pneumonia. One of them had vaccine acquired Rotavirus infection and a persistent generalised maculopapular rash. The T, B cell profile was T- B- in two and T- B+ in one case and the immunoglobulins were reduced in all. All the cases were fatal. Thus, Primary immunodeficiency disorders are prevalent in East Africa. A proper clinical history, examination and laboratory tests like a haemogram, peripheral blood film can aid to suspect and diagnose SCID even with limited resources.

Severe combined immunodeficiency: a case series from a paediatric hospital in Kenya

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8363958/

Further reading:

- Cellular and Molecular Immunology. 7th Edition..

Chapter 20. Congenital and Acquired Immunodeficiencies