Approach to Immunodeficiency in Pediatrics

When to suspect immunodeficiency?

1. manifestations of a specific immune disorder.
2. family history of early infant death or a known immunodeficiency disorder.
3. Unusual, chronic, or recurrent infections such as
    A. 1 or more systemic bacterial infections (sepsis, meningitis)
    B. 2 or more serious respiratory or documented bacterial infections (cellulitis, abscesses, draining otitis media, pneumonia, lymphadenitis) within 1 yr
    C. Serious infections occurring at unusual sites (liver, brain abscess)
    D. Infections with unusual pathogens (Pneumocystis jiroveci, Aspergillus, Serratia marcescens, Nocardia, Burkholderia cepacia)
    E. Infections with common childhood pathogens but of unusual severity.

When to suspect immunodeficiency?

- Additional clues to immunodeficiency include
  - FTT with or without ch. diarrhea
  - persistent infections after receiving live vaccines
  - chronic oral or cutaneous moniliasis

Characteristic clinical pattern in some primary immunodeficiency

In newborn and child (0-6 months)	Diagnosis
Hypocalcaemia, heart disease, unusual faces	DiGeorge anomaly
Delayed umbilical cord detachment, leukocytosis, recurrent infections	Leukocyte adhesion defect
Diarrhea, pneumonia, thrush, failure to thrive	Severe combined immunodeficiency
Maculopapular rash, alopecia, lymphadenopathy	Severe combined immunodeficiency with graft-versus-host disease
Bloody stools, draining ears, eczema	Wiskott-Aldrich syndrome
Mouth ulcers, neutropenia, recurrent infections	XL-Hyper IgM syndrome

Characteristic clinical pattern in some primary immunodeficiency

Infancy and young children (6 m-5 y)	Diagnosis
Severe progressive infectious mononucleosis	X-linked lymph proliferative syndrome
Recurrent cutaneous and/or systemic staphylococcal abscesses, coarse facial features	Hyper-IgE syndrome
Persistent thrush, nail dystrophy, endocrinopathies	Chronic mucocutaneous candidiasis
Short stature, fine hair, severe varicella	Cartilage hair hypoplasia with short-limbed dwarfism
Oculocutaneous albinism, recurrent infection	Chédiak-Higashi syndrome
Lymphadenopathy, dermatitis, pneumonia, osteomyelitis	Chronic granulomatous disease

Characteristic clinical pattern in some primary immunodeficiency

In older children (>5 years) and adults	Diagnosis
Progressive dermatomyositis with chronic enterovirus encephalitis	X-linked agammaglobulinemia
Sinopulmonary infections, neurologic deterioration, telangiectasia	Ataxia-telangiectasia
Recurrent neisserial meningitis	C6, C7, or C8 deficiency
Sinopulmonary infections, malabsorption, splenomegaly, autoimmunity	Common variable immunodeficiency
Candidiasis with raw egg ingestion	Biotin-dependent cocarboxylase deficiency

Initial Screening Immunologic Testing of the Child with Recurrent Infections

- **CBC with differentiation and ESR**
  - Absolute lymphocyte count (ALC); normal result rules against T-cell defect
  - Absolute neutrophil count(ANC); normal result rules against congenital or acquired neutropenia and [usually] both forms of leukocyte adhesion deficiency, in which elevated counts are present even between infections
  - Platelet count; normal result excludes Wiskott-Aldrich syndrome
  - Howell-Jolly bodies; absence rules against asplenia

Initial Screening Immunologic Testing of the Child with Recurrent Infections

- **Screening tests for B cell defects**
  - Immunoglobulin (Ig) A measurement; if abnormal, IgG and IgM measurement
  - Isohemagglutinins
  - Antibody titers to blood group substances, tetanus, diphtheria, *Haemophilus influenzae*, and pneumococcus
- **Screening tests for T cell defects**
  - Absolute lymphocyte count; normal result indicates T-cell defect unlikely
  - Flow cytometry to examine for the presence of naïve T cells (CD3+CD45RA+ cells)
- **Screening tests for phagocytic cell defects**
  - Absolute neutrophil count
  - Respiratory burst assay
- **Screening tests for complement deficiency**
  - CH50

Primary Defects of Antibody Production

Primary Defects of Antibody Production

- Most frequent.
- Selective absence of serum and secretory immunoglobulin (Ig)A is the most common defect.
- Recurrent infections with encapsulated bacteria.

Dx of: Primary Defects of Antibody Production

- Serum immunoglobulin levels
- Antibody titers to protein and polysaccharide antigens.
- A simple screening test for B-cell defects is the measurement of serum immunoglobulin (Ig) A
- Patients found to be agammaglobulinemic should have their blood B cells enumerated by flow cytometry

Primary Defects of Antibody Production

1. X-linked agammaglobulinemia
2. Common variable immunodeficiency (CVID)
3. Selective IgA deficiency
4. Selective IgG subclass deficiencies
5. Hyper-IgM syndrome

X-linked agammaglobulinemia

- Patients with X-linked agammaglobulinemia (XLA), also called Bruton agammaglobulinemia, have a profound defect in B-lymphocyte development
- The primary defect in XLA is the failure of pre-B cells to differentiate into mature B lymphocytes
- Only 10% of patients are girls.

X-linked agammaglobulinemia

Clinical Manifestations

- Most boys with XLA remain well during the 1st 6-9 mo of life.
- They acquire infections with extracellular pyogenic organisms
- Infections include sinusitis, otitis media…...

X-linked agammaglobulinemia

Diagnosis

- Lymphoid hypoplasia is found on physical examination
- serum concentrations of IgG, IgA, IgM, and IgE are far below the 95% confidence limits
- Levels of natural antibodies to type A and B red blood cell polysaccharide antigens (isohemagglutinins) and antibodies to antigens given during routine immunizations are abnormally low in this disorder
- **Flow cytometry** demonstrates the absence of circulating B cells.

Common variable immunodeficiency CVID

- CVID is a syndrome characterized by hypogammaglobulinemia with phenotypically normal B cells.
- Most of the patients usually do not become symptomatic until 15-35 years of age.
- CVID patients have an increased risk of developing autoimmune diseases, lymphatic and gastrointestinal malignancies, malabsorption and granulomatous inflammation.

Common variable immunodeficiency

- The diagnosis of CVID is based on :
  - low IgG levels
  - IgM and IgA levels may present in significant amounts or absent
  - Poor specific antibody responses to immunizations
  - T cell and B cell enumeration are usually normal
  - Some patients may have abnormal T cell function

Selective IgA deficiency

- Most common immunodeficiency disorder.
- Infections occur predominantly in the respiratory, gastrointestinal, and urogenital tracts.
- Intestinal giardiasis is common.
- Serum concentrations of other immunoglobulins are usually normal
- IgA deficiency is associated with **Celiac.**

Selective IgA deficiency

- The incidence of autoantibodies, autoimmune diseases, and malignancy is increased.
- Only 5-times washed Packed RBC should be administered to patients with IgA deficiency.
- Many intravenous immunoglobulin (IVIG) preparations contain sufficient IgA to cause anaphylactic reactions.

Hyper-IgM syndrome HIM

- The hyper-IgM syndrome is characterized:
  - normal or elevated serum IgM levels
  - low or absent IgG, IgA, and IgE serum levels, indicating a defect in the class-switch recombination (CSR) process.
- HIM presents with recurrent sinopulmonary infections and Pneumocystis carinii pneumonia (PCP).
- The unique susceptibility to opportunistic infections and neutropenia with high IgM levels distinguishes HIM from XLA or other hypogammaglobulinemias.

Hyper-IgM syndrome

- Treatment:
  - IVIG
  - trimethoprim-sulfamethoxazole to prevent PCP.
  - stem cell transplantation.
- Prognosis: worse than in other forms of hypogammaglobulinemia.

X-Linked lymphoproliferative disease

- XLP disease, also referred to as Duncan disease is an X-linked recessive trait characterized by an inadequate immune response to infection with Epstein-Barr virus (EBV).
- The mean age of presentation is <5 yr.
- XLP has an unfavorable prognosis; 70% of affected boys die by age 10 years.

Treatment of B-Cell Defects

- Antibiotics
- IVIG monthly
  - (IVIG or SCIG).
  - Anaphylactic reactions if patient has :CVID or IgA deficiency.

Primary Defects of Cellular Immunity

Primary Defects of Cellular Immunity

- T-cell more severe than B-cell (antibody deficiency disorders)
- Die at infancy or childhood.
- T cells and T-cell subpopulations can be enumerated by **flow cytometry**
- Flow cytometry

Thymic Hypoplasia; DiGeorge syndrome

- Dysmorphogenesis of the 3rd and 4th pharyngeal pouches during early embryogenesis, leading to hypoplasia or aplasia of the thymus and parathyroid glands.
- Suspected if: hypocalcemic seizures during the neonatal period
- The **CATCH 22 syndrome** (*c*ardiac, *a*bnormal facies, *t*hymic hypoplasia, *c*left palate, *h*ypocalcemia) includes the broad clinical spectrum of conditions with 22q11.2 deletions.
- **Partial or complete DiGeorge syndrome**

Thymic Hypoplasia; DiGeorge syndrome

- 1/3 of complete DiGeorge syndrome have CHARGE association
- Concentrations of serum immunoglobulins in DiGeorge syndrome are usually normal
- Absolute lymphocyte counts are usually only moderately low for age
- Thymic tissue, when found, contains Hassall corpuscles, a normal density of thymocytes, and corticomedullary distinction
- Lymphoid follicles are usually present

CHARGE Association

- **C** – Coloboma
- **H** – Heart
- **A** – Atresia of Chonae
- **R** – Retardation of growth and/or development
- **G** – Genital : Undesedended testicle, hypospadias or hypogonadism
- **E** – Ear: deafness and abnormally bowl-shaped and concave ears, known as "lop ears".

Thymic Hypoplasia; DiGeorge syndrome

Clinical Manifestations

- Children with **partial thymic** hypoplasia may have little trouble with infections and grow normally
- Patients with **complete DiGeorge** syndrome resemble patients with severe combined immunodeficiency
- Complete DiGeorge is fatal without treatment
- A T-cell count should be obtained on all infants born with primary hypoparathyroidism, CHARGE syndrome, truncus arteriosus, and interrupted aortic arch

- Rx: thymic tissue transplants.

Primary Combined Antibody and Cellular Immunodeficiencies

Severe Combined Immunodeficiency SCID

- Gene mutation
- All patients with SCID have very small thymuses
- Spleen are depleted of lymphocytes.
- Lymph nodes, tonsils, adenoids, and Peyer patches are absent or extremely underdeveloped

Severe Combined Immunodeficiency

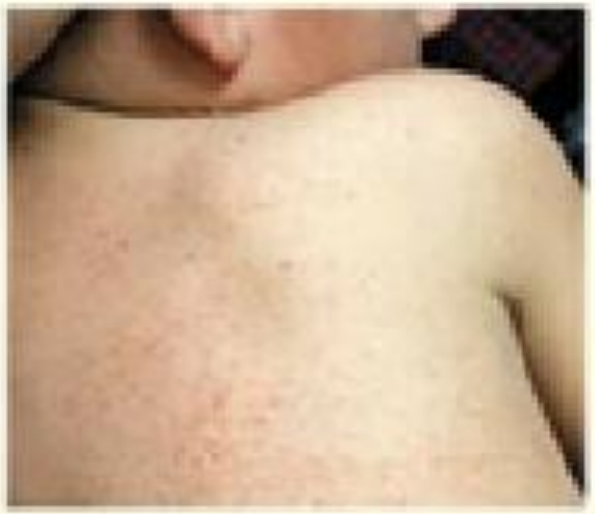
- Clinical manifestation
  - Affected infants present within the 1st few mo of life
  - recurrent or persistent diarrhea, pneumonia, otitis media, sepsis, and cutaneous infections.
  - Growth may appear normal initially.
  - Persistent infections with opportunistic lead to death.
  - At risk for severe or fatal graft-versus host disease (GVHD)

Severe Combined Immunodeficiency

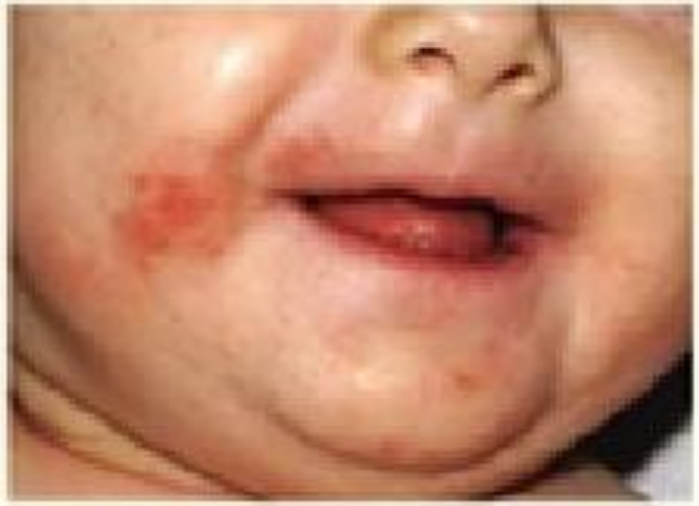
- All molecular types of SCID lack T cells
- Serum immunoglobulin concentrations are low or absent
- Analyses of lymphocyte populations and subpopulations demonstrate distinctive phenotypes for the various genetic forms of SCID.

Severe Combined Immunodeficiency

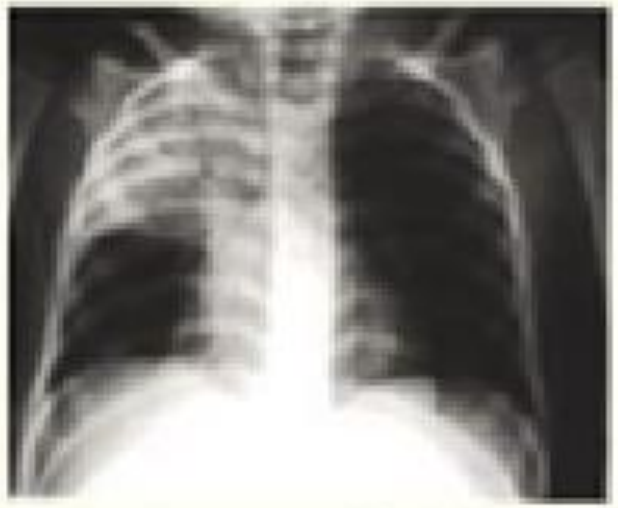
- SCID is a true pediatric emergency.
- >92% of cases can be treated successfully with hematopoietic stem cell transplantation.



Petechiae due to thrombocytopenia



Eczema



Pneumonia and other infections

Wiskott-Aldrich syndrome

- Wiskott-Aldrich syndrome is characterized by:
  - **Atopic dermatitis**
  - **Thrombocytopenic purpura** with normal-appearing megakaryocytes but small defective platelets
  - Undue susceptibility to infection.

Wiskott-Aldrich syndrome

- Patients often have prolonged bleeding
- Atopic dermatitis and recurrent infections usually develop during the 1st yr of life
- Survival beyond the teens is rare
- Patients with this defect uniformly have an impaired humoral immune response to polysaccharide antigens
- The predominant immunoglobulin pattern is a low serum level of IgM, elevated IgA and IgE, and a normal or slightly low IgG concentration

Wiskott-Aldrich syndrome

- Good supportive care
- Aggressive management of eczema
- platelet transfusion for serious bleeding episodes
- Bone marrow or cord blood transplantation is the treatment of choice

Ataxia-telangiectasia

- Ataxia-telangiectasia is a complex syndrome with immunologic, neurologic, endocrinologic, hepatic, and cutaneous abnormalities

- The most prominent clinical features are
  - progressive cerebellar ataxia
  - oculocutaneous telangiectasias
  - chronic sinopulmonary disease
  - high incidence of malignancy
  - variable humoral and cellular immunodeficiency.

Treatment of Cellular or Combined Immunodeficiency

- Good supportive care is critical while patients await more definitive therapy.
- **Bone Marrow Transplantation** of MHC-compatible sibling or rigorously T-cell–depleted haploidentical (half-matched) parental hematopoietic stem cells is the treatment of choice for patients with fatal T-cell or combined T- and B-cell defects.
- Of patients with SCID, 92% have survived after T-cell–depleted parental marrow is given soon after birth when the infant is healthy.
- Currently, bone marrow transplantation remains the most important and effective therapy for SCID.

Disorders of Phagocyte Function

Disorders of Phagocyte Function

- Neutrophils are the first-line of defense against microbial invasion.
- Children with phagocytic defects present with deep tissue infection, pneumonia, adenitis, or osteomyelitis.
- **Chemotaxis** and motility defects present with significant skin and mucosal infections.

Leukocyte adhesion deficiency

- Leukocyte adhesion deficiency 1 (LAD-1), 2 (LAD-2), and 3 (LAD-3) are rare autosomal recessive disorders of leukocyte function.
- LAD-1 affects about 1 per 10 million individuals and is characterized by recurrent bacterial and fungal infections and depressed inflammatory responses despite striking blood neutrophilia.
- The neutrophils have significant defects in adhesion, motility, and ability to phagocytose bacteria

Leukocyte adhesion deficiency

- LAD-1 results from mutations of the gene on chromosome 21 encoding CD18 ß2-leukocyte transmembrane integrin subunit.
- This group of leukocyte integrins is responsible for the tight adhesion of neutrophils to the endothelial cell surface, egress from the circulation, and adhesion to iC3b-coated microorganisms
- Neutrophils cannot transmigrate through the vessel wall and move to the site infection.
- Neutrophils that do arrive at inflammatory sites fail to recognize microorganisms opsonized with complement fragment iC3b
- Monocyte function is also impaired

Leukocyte adhesion deficiency

- Children with LAD-2 share the clinical features of LAD-1 but have normal CD11/CD18 integrins.
- Features unique to LAD-2 include: neurological defcts, cranial facial dysmorphism, and absence of the erythrocyte ABO blood group antigen.
- Infections in LAD-2 are milder than that in LAD-1.
- LAD-3 is characterized by a Glanzmann thrombasthenia-like bleeding disorder.

Leukocyte adhesion deficiency

- Children with severe forms of LAD present in infancy with recurrent, indolent bacterial infections.
- Significant neutrophilic leukocytosis, often >25,0000/mm3, is a prominent feature.
- **Delayed separation of the umbilical cord**, usually with associated infection of the cord stump.
- Infected areas characteristically have very little neutrophilic infiltration.

Leukocyte adhesion deficiency

- The pathogens similar to those affecting patients with severe neutropenia:
  - *Staphylococcus aureus*
  - Gram-negative organisms such as *Escherichia coli*.
- Typical **signs of inflammation may be absent**. Pus does not form, and few neutrophils are identified microscopically in biopsy specimens of infected tissues.
- The circulating neutrophil count during infection typically exceeds 30,000/μL and can surpass 100,000/μL

Leukocyte adhesion deficiency

- The diagnosis of LAD-1 is established most readily by **flow cytometric** measurements of surface CD11b/CD18 in stimulated and unstimulated neutrophils.
- Delayed-type hypersensitivity reactions are normal, and most individuals have normal specific antibody synthesis.
- The diagnosis of LAD-2 is established by flow cytometric measurement of sialyl Lewis X (CD15) on neutrophils.

Leukocyte adhesion deficiency

- Early allogeneic hematopoietic stem cell transplantation (**HSCT**) is the treatment of choice for severe LAD-1 and LAD-3.
- Other treatment is largely supportive.
- Some LAD-2 patients have responded to fucose supplementation.
- The severity of infectious complications correlates with the degree of ß2-integrin deficiency.

Chédiak-Higashi syndrome CHS

- Chédiak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by increased susceptibility to infection caused by
  - **defective degranulation of neutrophils**
  - mild bleeding diathesis
  - partial oculocutaneous **albinism**
  - progressive peripheral neuropathy
  - and a tendency to develop a life-threatening form of hemophagocytic lymphohistiocytosis

Chédiak-Higashi syndrome

- The diagnosis of CHS is established by finding large inclusions in all nucleated blood cells.
- The patients have progressive neutropenia and abnormal platelet, neutrophil, and NK function.
- High-dose ascorbic may improve the clinical status of some children in the stable phase.
- The only curative therapy to prevent the accelerated phase is **HSCT.**

Chronic Granulomatous Disease

- CGD is characterized by neutrophils and monocytes capable of normal chemotaxis, ingestion, and degranulation, but **unable to kill catalase positive** microorganisms because of a defect in the generation of microbicidal oxygen metabolites.
- CGD is a rare disease with an incidence of 4-5 per 1 million individuals; it is caused by 4 genes, 1 X-linked and 3 autosomal recessive in inheritance.

Chronic Granulomatous Disease

- They present with recurrent pneumonia, lymphadenitis, hepatic or subcutaneous or other abscesses, osteomyelitis at multiple sites, a family history of recurrent infections, or any infection with an unusual catalase-positive organism.
- The onset of clinical signs and symptoms usually occurs in early infancy
- The most common pathogen is *S. aureus*

Chronic Granulomatous Disease

- Perirectal abscesses and recurrent skin infections.
- Granuloma formation and inflammatory processes are a hallmark of CGD
- More than 80% of CGD patients have positive serology for Crohn disease.
- Persistent fever especially with splenomegaly and cytopenia warrants an evaluation for secondary macrophage activation syndrome (MAS)

Chronic Granulomatous Disease

- Dx: **flow cytometry** using dihydrorhodamine 123 (DHR).
- The nitroblue tetrazolium dye test **(NBT)** is frequently cited in the literature but is now only rarely used clinically.
- HSCT is the only known **cure** for CGD.

Disorders of the complement system

- Suspected if:
  - recurrent angioedema, autoimmune disease, chronic nephritis, hemolytic uremic syndrome, or partial lipodystrophy, or with recurrent pyogenic infections, disseminated meningococcal or gonococcal infection.
- Testing for **total hemolytic complement activity (CH50)** effectively screens for most of the common diseases of the complement system.
- No specific therapy is available at present for genetic deficiencies of the components of the classical, alternative, and lectin complement pathways.
- Give MCV and PCV vaccines

Live Vaccines in Children with Immune deficiency

	Vaccine Use
B cell:	
• Severe(aggama.)	Most live contraindicated (no data for rota and Var)
• Less severe: (IgA, subclass IgG)	live appear safe, caution
T cell:	live contraindicated
Comp deficiency	All safe – give mening.
Cancer Rx	Usually OK 3 mo. p Rx
Phag. Dysfunction	Routine prob. Safe*

Adapted from Table 1.14 Red Book 2009

Vaccines in Persons With Phagocyte Function Abnormalities

- CGD, leukocyte adhesion defects, Myeloperoxidase deficiency
- **Live bacterial (BCG) contraindicated**
- Live viral probably safe
- Inactivated safe and probably effective

Thank you

Suspicion of Immunodeficiency

R/O Common causes of infection	R/O Secondary Immunodeficiency

Consider Primary Immunodeficiency

Note types locations of infections, age of child, and other associated factors

Categories and screen

Predominantly B cell defect	Predominantly T cell defect	Granulocyte defect	Complement defect