Primary Immunodeficiencies	
Pathophysiology	• Genetic defects in the adaptive (B- or T-cell) or innate (phagocytes, complement) immune systems lead to recurrent infections • Over 200 distinct disorders: B cell defects (65%), combined B and T cell deficiencies (15%), phagocytic disorders (10%), T cell deficiencies (5%), and complement deficiencies/others (5%)
Epidemiology	The overall incidence is 1:10000, and overall prevalence is 1:2000.
Clinical	• Can be nonspecific and broad • **Constitutional**: Poor growth, failure to thrive • **GI**: chronic diarrhea. • **Derm**: Atopic and non-atopic dermatitis, severe diaper rash, neonatal rash, anhydrosis, as well as delayed separation of the umbilical cord (LAD) • **Immuno**: Recurrent infections, autoimmunity • Family history of consanguinity or family history of immunodeficiency or unexplained childhood deaths puts a child at higher risk of having or developing a primary immunodeficiency
Physical Exam	• **Vital signs**: Growth parameters • **General exam**: Note dysmorphisms, including teeth and hair (abnormal in NEMO). Look for infectious sources (sinusitis, otitis, pneumonia, thrush, diaper rash) • **HEENT exam**: Note tonsils (absent in XLA) and examine for thrush and other signs of infection such as sinusitis or recurrent otitis media • **CV exam**: Note any cardiac anomalies including heart sounds, pulses, perfusion, and overall volume status as cardiac anomalies can be a part of certain syndromes associated w/ immuno-deficiency syndromes (e.g.: DiGeorge Syndrome) • **Respiratory**: Note symmetry of lung exam, quality of air entry, and lung sounds as pulmonary anomalies may be a manifestation of immunodeficiency syndromes • **GI**: A thorough GI exam including abdominal exam for elements like hepatosplenomegaly and rectal exam for possible anal atresia is important • **GU**: Primary immunodeficiencies can also lead to GU anomalies; assess for absence/presence of appropriate male/female organs in the correct number • **Derm exam**: Skin exam for eczema/dermatitis (i.e. WAS, SCID, hyper IgE syndrome) as well as erythroderma (Omenn Syndrome). Note telangiectasia (AT), warts, granulomas, poor wound healing or ulcers • **Neuro**: A thorough neuro exam may also hint at the etiology of an immunodeficiency (ataxia-telangiectasia), an infection such as meningitis, or may help elucidate an alternate cause of symptoms
Diagnosis	• **Initial labs**: CBC w/ differential (note especially lymphopenia), chem7, albumin, urinalysis, ESR, CRP, quantitative immunoglobulins (IgG, IgA, IgM, IgE), specific vaccine antibody studies (tetanus, HiB, pneumococcal). • **Follow-up labs**: HIV testing. B- and T-cell subset, complement screening (C3, C4, AH50, CH50), vaccine challenge (administer pneumococcal or other vaccine and measure titers 4-6 weeks later), Dihydrorhodamine (DHR) assay (CGD). Leukocyte adhesion defect testing (LAD). • **Advanced lab analysis**: T cell proliferation studies (mitogen, antigen), T and B cell memory panels, NK cell function assays, Toll-like receptor assays. Immunodeficiency genetic panel. Whole exome or whole genome sequencing.
Treatment	Varies widely based upon the deficiency. Common therapies include prophylactic antibiotics, IVIG, bone marrow transplant.

Indications for a Primary Immunodeficiency Evaluation

- ≥8 ear infections w/i one year
- >2 serious sinus infections w/i one year
- >2 pneumonias w/i one year
- FTT, poor weight gain, or abnormal growth parameters
- Abnormal physical exam suggestive of syndrome
- Recurrent skin or organ abscesses
- Persistent thrush (mouth/skin), at >12 months of age
- Severe or overwhelming infection
- Infection w/ unusual organisms
- Need for intravenous antibiotics to clear infections
- Infections w/ opportunistic organisms (Aspergillus, Pneumocystis)
- Severe forms of viral infections (HSV, VZV, EBV)
- Complications from a live vaccine
- A family history of primary immunodeficiency
- Abn. TRECs on newborn screen x2
- Abn. screening CBC (profound leukopenia, lymphopenia, eosinophilia)

Classification of Primary Adaptive Immunodeficiencies

B-cell (Humoral)		
Diseases	• X-linked agammaglobulinemeia • Transient hypogammaglobuniema of infancy • IgA deficiency	• IgG deficiency • IgG subclass deficiency • Specific antibody deficiency
Clinical Manifestations	• Generally presents <12 mo old (3-6 mo, due to loss of maternal antibody) • Bacterial infxn (sinusitis, otitis, pneumonia) • Abscesses (recurrent) • Bronchiectasis	• Chronic diarrhea or gastroenteritis • Failure to thrive • Enteroviral meningoencephalitis (chronic)
Organisms	Encapsulated: • S pneumo • HiB • N meningitides • Salmonella typhii	Also: • S Aureus • Pseudomonas • Enteroviral meningoence-phalitis
Vaccine Issues	Do not give live vaccines for severe defects. Vaccination not necessary if on IgG replacement Effectiveness of other vaccines is uncertain	
T-cell Defects (Cellular)		
Diseases	• DiGeorge Syndrome • SCID (T-/B+)	
Clinical Manifestations	• Typically presents at birth/early infancy. • Mucocutaneous candidiasis • Severe viral infections • Opportunistic infections • Fungal infections	• Bacterial infections • Warts or severe eczema • Chronic diarrhea • Failure to thrive
Organisms	• Candida • PJP • Mycobacterium	• VZV, HSV, CMV infections • Salmonella typhii
Vaccine Issues	Do not give live virus vaccines if substantial T cell defect	

Classification of Primary Adaptive Immunodeficiencies

Combined B/T Cell Defect		
Diseases	• SCID (T-/B-) • CVID • Omenn syndrome • Wiskott-Aldrich syndrome • Ataxia-telangiectasia • Hyper IgM syndrome	• X-linked lymphoproliferative disease (XLP) • NEMO (NK-kappa B essential modifier) deficiency • Hyper IgE syndrome • DOCK8 deficiency • ZAP70 deficiency
Clinical Manifestations	• Typically presents in 1st year of life. XLP/CVID can present as teens/adults. • Infections (sinusitis, otitis, pneumonia) • Abscesses (recurrent) • Chronic diarrhea or gastroenteritis • Failure to thrive	• Mucocutaneous candidiasis • Viral/opportunistic infections • Fungal infections • Increased cancer risk • WAS: eczema, sinusitis • AT: telangiectasias, int. disability
Organisms	• Candida • PJP • Mycobacterium	• VZV, HSV, CMV infections • Encapsulated bacteria
Vaccine Issues	Do not give live vaccines (OPV, BCG, smallpox, YF, live influenza, MMR, MMRV, rotavirus). Effectiveness of other vaccines is uncertain.	
Phagocytic Defects		
Diseases	• Chronic granulomatous disease (CGD) • Chediak-Higashi syndrome (CHS) • Lymphocyte adhesion deficiency (LAD)	
Clinical Manifestations	• Typically presents in infancy • Poor wound healing • Delayed separations of the umbilical cord (LAD) • Lymphadenitis/abscesses	• Catalase (+) bacterial infections (CGD) • Candidiasis • Chronic gingivitis, oral disease • Hepatosplenomegaly
Organisms	Catalase-(+) bacteria: • S aureus • Pseudomonas • Burkholderia cepacia • Nocardia • Enterobacteria erratia and Klebsiella)	Fungal infections: • Aspergillus • Candida albicans
Vaccine Issues	• Live viral vaccines contradindicated in CH & LAD, but OK in CGD • Live bacterial vaccines are contraindicated. Other vaccines are safe/ effective	

Classification of Primary Adaptive Immunodeficiencies continued on next page →

Classification of Primary Adaptive Immunodeficiencies		
Complement Defects		
Diseases	**Classical pathway**: C1q, Cqr, C1s, C2, C4 Hereditary angioedema (C1-est) C2: most common in Causasians	**Lectin pathway**: MBL, M-/L-/H-ficolin, CL-11, MASPs **Alternative pathway**: Factors D, B, and properdin
Clinical Manifestations	• Can present at any age • Angioedema of the face, lips, hands, feet, GI tract, throat (C1-inh) • Recurrent sinopulmonary infections • Bacteremia/pyogenic bacterial infections	• Meningitis • Autoimmune disease (lupus-like) • Often autosomal dominant inheritance • Associated w/ atypical HUS
Organisms	• Encapsulated bacteria • Neisseria	
Vaccine Issues	• No vaccine contraindications • Refer to CDC guidelines re: additional vaccinations for protection against encapsulated bacteria	

Characteristics of Selected Immunodeficiencies		
Disorder	**Category**	**Characteristics**
Ataxia Telangiectasia (AT)	Combined B- and T- cell	Progressive cerebellar ataxia, oculocutaneous telangiectasia, diminished/ absent deep tendon reflexes. Intellectual disability. Defect in the ATM gene (11q22.3). Elevated serum AFP. Inc risk of malignancy (i.e. leukemia, lymphoma). Avoid radiation (CT, x-rays)
Chediak-Higashi Syndrome (CHS)	Phagocytic	Neutropenia, oculocutaneous albinism. Recurrent skin and sinopulmonary infections. Severe gingivitis and periodontal disease, adenopathy, progressive neurologic findings. Most patients enter “accelerated phase” resembling lymphohistiocytosis. Defect in CHS1 gene (1q42.1-q42.4). Blood smear shows characteristic giant cell granules.
Chronic Granulomatous Disease (CGD)	Phagocytic	Recurrent bacterial infections, often w/ encapsulated and catalase-positive organisms, due to inability of neutrophils to generate oxidative burst. Also prone to infections w/ fungi. Can see recurrent granulomas and abscesses, both superficial and deep-seated. Majority are X-linked, also autosomal recessive forms. Abnormal DHR.
Common Variable Immunodeficiency (CVID)	Combined B- and T- cell	Can present in childhood or adolescence/adulthood. Recurrent sinopulmonary infections, opportunistic infections, autoimmune diseases. Can see granulomas, hepatosplenomegaly, bronchiectasis. Impaired B cell differentiation w/ hypogammaglobulinemia and poor response to polysaccharide vaccines (ie tetanus, pneumococcal). Mutations in a number of geneshave been described in subsets of patients.
DiGeorge Syndrome	T-cell	Heterogeneous T-cell disorders, ranging from normal immune system to severe T-cell immunodeficiency w/ SCID-like features (in 0.5% or less). Abnormal development of the 3rd and 4th pharyngeal pouches, leading to thymic hypoplasia, hypoparathyroidism, congenital heart disease, characteristic facies. Most common genetic defects = del. 22q11.2 & 10p13-14.

Characteristics of Selected Immunodeficiencies		
Disorder	**Category**	**Characteristics**
DOCK8 Deficiency	Combined B- and T- cell	Autosomal recessive form of hyper IgE syndrome w/ a distinct genetic cause and unique features compared to autosomal dominant form. Autosomal recessive. Presents in childhood w/ atopic dermatitis, severe food allergies, asthma, recurrent sinopulmonary infections and otitis. Often extensive cutaneous viral infections (HSV, warts, molluscom). Frequent skin infections and abscesses (S Aureus). Candidiasis. Inc risk of malignancy, especially viral-associated (HPV, HSV, EBV). Low B and T cell counts, very high serum IgE and eosinophilia, however few cases reported w/ normal IgE levels. Defect is in the DOCK8 gene (9p24). Treatment is bone marrow transplant.
Hyper IgE Syndrome	Combined B- and T- cell	Recurrent bacterial infections of the skin and upper and lower respiratory tracts. Abnormal features (not often presents until adulthood): coarse/ thickened facial features, frontal bossing, wide alar base of nose, high arched palate. History of prolonged retention of primary teeth, increased fractures w/ minor trauma, eczema. Labs show elevated IgE, eosinophilia. Dominant negative mutations in STAT3.
Severe Combined Immunodeficiency (SCID)	Combined B- and T- cell, depending on the type	Presents in the first 3-12 months of life. Abnormal newborn screen (low TRECs). Recurrent infections (bacterial, virus, fungus), failure to thrive, recurrent fevers, chronic diarrhea, poor growth, infections caused by vaccines. Definitive diagnosis by absolute T cell count <300, abnormal T cell proliferation studies, OR presence of maternal T cells in circulation. Multiple genetic defects (RAG1, RAG2, ADA, Artemis, IL2RG). Immunologic emergency, needs positive pressure room, urgent work-up and evaluation for bone marrow transplant.
Selective IgA Deficiency	IgA	Most patients (85-90%) are asymptomatic. Occasional susceptibility to recurrent infections, malignancy, autoimmune disease. Theoretical increased risk of anaphylaxis to blood products; however, this is controversial and rarely seen.
Wiskott-Aldrich Syndrome	Combined B- and T- cell	Triad: thrombocytopenia, eczema, chronic otitis media/sinusitis. On exam: severe eczema, petechiae. Defect in the WAS gene (Xp11.23). Increased risk of autoimmune disease, malignancy (i.e. lymphoma).
X-linked Agammaglobulin-emia (XLA)	B-cell	Defect of B cell maturation resulting in complete absence of B cells/ hypogammaglobulinemia. Recurrent bacterial infections. Exam notable for absent tonsils and lymph nodes. Defect in BTK gene (Xp22). Autosomal recessive forms also. Treatment is IgG replacement
X-linked Lymphoprolifer-ative Disease (XLP)	Combined T- and B- cell	X-linked recessive. Presentation is typically in childhood. Most commonly presents w/ a fulminant EBV infection (often w/ hepatitis, hepatosplenomegaly, liver failure), often causing secondary hemophagocytic lymphohistiocytosis or aplastic anemia. About 1/3 of XLP patients have dysgammaglobulinemia. Inc risk of malignancy, esp. lymphoma. Death is from lymphoma or HLH.. Caused by mutation in XLP/SH2D1A (Xq25) gene encoding for signaling protein called. SAP- defects impair both cellular and humoral immunity, Treatment is bone marrow transplant.
ZAP-70-related SCID	T-, B+ cell	Autosomal recessive. Presents in the first 2 years of life., generally age 6-12 months Similar to SCID w/ recurrent infections, opportunistic infections, chronic diarrhea, failure to thrive. However, patients have normal lymphocyte count and detectable lymphoid tissue. Diagnosis by T cell subsets: CD8+ cells are low/absent, CD3+ and CD4+ are normal or high. Defect is a mutant ZAP-70 gene (2q11.2), involved in T cell receptor signaling and T cell function. Treatment is bone marrow transplant.

Specific Antibody Deficiencies

	Presentation	Labs					
		IgG	IgA	IgM	IgG subclass	Vaccine response	B cells
IgG Subclass Deficiency	Recurrent severe infections (controversial)	NL	NL	NL	At least 1 is low	LOW	NL
Selective IgA Deficiency	Asymptomatic or associated w/ autoimmune, GI, atopic disorders	NL	LOW	NL	NL	NL OR LOW	NL
Hyper IgM Syndrome	Severe infections, including PJP	LOW	LOW	NL OR HIGH	LOW	LOW	NL
Specific Antibody Deficiency	Often asymptomatic	NL	NL	NL	NL	LOW	NL
CVID	Recurrent infections	LOW	NL OR LOW	NL OR LOW	LOW	LOW	NL

Characteristics of Selected SCID disorders

Type	Gene defects		Treatment
T-, B+ SCID	• IL2RG (most common form, X-linked) • JAK3 • IL7RA • IL2RA	• CD3D/E/Z • PTPRC • CORO1A • ZAP70	Bone marrow transplant or gene therapy (IL2RG)
T-, B- SCID	• RAG1/RAG2 (common) • Artemis (common) • Adenosine deaminase (ADA, common) • PRKDC	• AK2 • LIG4 • Cernunnos (NHEJ1)	• Bone marrow transplant or gene therapy (ADA) • ADA can be treated w/ gene therapy or enzyme replacement

Diagnostic Approach to Primary Immunodeficiencies

Initial Labs (Most Cases)	**Next step** (Include w/ initial labs if suspicious of specific disorder)	**Advanced** (Depending on specific history)
• CBC w/ differential • Quantitative immunoglobulins (IgG, IgA, IgM, IgE) • Specific antibody studies (tetanus, HiB [PRP], pneumococcal)	• B- and T-cell subsets • T cell proliferation studies (mitogen, antigen) • Complement screening (CH50, AH50, C3, C4) • DHR (dihydrorhodamine assay for CGD)	• T and B cell memory panels • NK cell function assay • Toll-like receptor studies • Specific genetic testing