Primary Immunodeficiencies

- not rare like once thought (4x more than CF and same incidence as leukemia/lymphoma)
- not only occurs in young children (sometimes pts present when adults b/c symptoms are mild and missed)
- not always severe clinical symptoms (sometimes symptoms are of same severity as found in normal pts but just occur more frequently)
- effective therapy exists for almost every immunodeficiency but is most beneficial when instituted before there has been damage to organs
- many times unusually severe infections with low virulence pathogens
- Ig (parasite), T-cell (fungal, intracellular bacteria, viral), neutrophil (bacteria)
- Acquired 2/2 immunosuppressants (eg. Anti-TNF leads to Tb, Histo, Zoster, PCP, lymphoma, etc)
- Spectrum of Clinical Manifestations:
    - *(1) Infections*
        - a. not so much more severe but more frequent and chronic
        - b. not so much at a single anatomic site but involving multiple sites within the same organ/system (eg. several lobes in lung) or even multiple organs/systems (eg. ear, sinus, pharynx, bronchi, lungs)
        - c. many times these infections have complications
        - d. many times the pathogens are organisms which usually have low virulence
    - *(2) Autoimmune Disorders*
        - a. the underlying abnormality that leads to the development of the immunodeficiency also leads to faulty discrimination b/t "self" and "non-self" and therefore autoimmune diseases develop
        - b. Examples: autoimmune hemolytic anemia
    - *(3) Gastrointestinal Disorders*
        - a. these disorders are not always 2/2 GI infections but are sometimes 2/2 to some intrinsic problem with the GI system itself resulting in chronic diarrhea esp from parasites (esp Giardia), fungi (esp Candida), bacteria (esp Mycobacteria)
        - b. Examples: IBD, gluten sensitive enteropathy, atrophic gastritis w/ pernicious anemia, nodular lymphoid hyperplasia
    - *(4) Hematologic Disorders*
        - a. these disorders are not always 2/2 autoimmune disorders but are sometimes 2/2 to some intrinsic problem with blood cells resulting in anemia, leucopenia, and thrombocytopenia

(1) Adaptive Immunity
- a. B-cell (50%)
- b. T-Cell (10%)

(2) Innate Immunity
- a. Phagocytes (20%)
- b. Complement (5%)

NB Combined (20%)

B-Cell (Humoral) Dysfunction						
Type of Infection • polysaccharide encapsulated bacteria (Streptococcus, Staphylococcus, Haemophilus, Enterococcus) and Giardia			*Tests* 1st • #: measure IgA,G,D,E,M levels aka Quantitative Serum Ig • #: measure total lymphocyte number • Fxn: Ab titers after immunization w/ protein Ags (eg. Tetanus, Diptheria, Rubella, Rubeola, Polio) 2nd • #: measure IgG subclasses esp if you suspect IgG deficiencies but the overall value is normal • #: measure B-cell number based on CDs • Fxn: Ab titers after immunization w/ polysaccharides (eg. Haemophilus, Pneumococcus)			
Primary B-Cell Dysfunction	**Bruton's Agammablobulinemia**	**Common Variable Immunodeficiency**	**IgG Subclass Immunodeficiency**	**Antibody Immunodeficiency**	**Hyper IgM Syndrome**	**Selective IgA Immunodeficiency**
Genetics	X-linked	most are sporadic but sometimes clusters in families	Sporadic	Sporadic	X-linked	most are sporadic but sometimes clusters in families, extremely common w/ prevalence of 1/750
Mechanism	mutation of tyrosine kinase gene which is required for B-cell differentiation therefore NO mature B-cells form and thus NO Abs are made (however there may be some "junk" Abs)	variable degree of defective T-cell regulation of B-cell differentiation, proliferation, and Ab production resulting in LOWER amounts of IgG	partial deficiency of Abs in one IgG subclass (children = 1,2,4 vs Adult = 3)	missing certain Abs in each IgG subclass	mutation of CD40 resulting in defective communication b/t T-cells and B-cells such that IgM cannot isotype switch to IgG,D,E,A hence hyper IgM and hypo IgG,D,E,A	IgA <5mg/dl (note that many people do not meet this requirement but still have low enough levels that are clinically significant) also recently it has been found that many pts previously diagnosed with selective IgA deficiency also some IgG subclass deficiency
Ig	NO Ig	Decreased IgG	Decreased Some IgG	Variable	Decreased IgG/D/E/A Increased IgM	Decreased IgA <5mg/dL
Specific Infection	normal for first few months of life until mother's Ab disappear with infant developing frequent and/or severe 1° respiratory and gastrointestinal infections esp Giardia/Rotavirus 2° meningitis, sepsis, arthritis, osteomyelitis	1° respiratory AND gastrointestinal infections esp Giardia, Bacterial Overgrowth	1° respiratory infections	1° respiratory infections	1° respiratory infections	1° respiratory AND gastrointestinal infections esp Giardia
Other Pathology	None	*** Celiac Disease*** autoimmune hemolytic anemia, ITP, leucopenia, pernicious anemia, persistent splenomegaly, CVD			Many Autoimmune Disorders	*** Celiac Disease *** Juvenile rheumatoid arthritis, SLE, thyroiditis, pernicious anemia, NHL

Treatment	IV-Ig	IV-Ig	IV-Ig	IV-Ig	IV-Ig	IV-Ig but sometimes it can react with existing IgA and cause an anaphylactic reaction
Secondary B-Cell Dysfunction	**Premature Birth** **Plasmapharesis** **Leukemias** **Chemotherapy**					

T-Cell (Cell-Mediated) Dysfunction			
Type of Infection • Opportunistic intracellular bacteria, fungi, parasites, viruses		*Tests* 1st • #: measure total lymphocyte number • Fxn: Delayed-Type IV Hypersensitive (DTH) Skin Test (panel of ubiquitous Ags are given subcutaneously but (1) note that a + response does not indicate that pt has normal T-cell response to ALL Ags as in Chronic Mucocutaneous Candiasis and (2) note that a + response requires prior exposure and sensitization therefore a problem in young children) 2nd • #: measure T-cell number (and subtypes: total-CD2/3, helper-CD4, cytotoxic/suppressor-CD8) based on CDs • Fxn: Ab titers after immunization w/ protein Ags (eg. Tetanus, Diptheria, Rubella, Rubeola, Polio) b/c B-cell fxn requires good T-cell fxn	
Primary T-Cell Dysfunction	**DiGeorge Syndrome**	**Chronic Mucocutaneous Candiasis**	**Purine Nucleoside Phosphorylase Deficiency**
Genetics	unknown genetics		
Mechanism	mutation on 22q leading to defect of pharyngeal pouches resulting in defects of: (1) Thymus (thymus dysplasia = T-cell deficiency = infection) (2) PTH (hypoPTH = hypoCa) (3) Heart (congenital heart defects)	defect in specific T-cells against *Candidiasis*	
Specific Infection	Candida		
Other Pathology		polyendocrinopathy (which actually leads to greater morbidity than the immune dysfxn)	
Treatment	Stem Cell Transplant	Stem Cell Transplant	Stem Cell Transplant
Secondary T-Cell Dysfunction	**Malnutrition/Aging** **Immunosuppresants (steroids, XRT, cyclosporine, cytotoxic drugs)** **Infection (HIV, Measles, CMV, TB)** **Malignancies (Leukemia)**		

Phagocyte Dysfunction		
Type of Infection • skin, subcutaneous, deep tissue, dental, reticoendothelial infections		*Tests* 1st • #: measure total phagocytic numbers • Fxn: Nitroblue Tetrazolium Reduction Test (measures whether an oxidizing agent such H2O2 is present (from phagocytes) by whether normal phagocytes can convert yellow tertazolium to its reduced blue form) 2nd • Fxn: Phagocytic Assay, Chemotaxis Assay, Bactericidal Assay
Primary Phagocyte Dysfunction	**Leukocyte Adhesion Deficiency (LAD)**	**Chronic Granulomatous Disease (CGD)**
Genetics	aut rec	X-linked
Mechanism	defective ICAM cell adhesion molecule resulting in inability to chemotax but there is normal respiratory burst and phagocytosis	defective enzyme resulting in inability to generate respiratory burst but there is normal chemotaxis and phagocytosis resulting in granuloma formation in lungs, LNs, soft tissues, bone, and skin
Specific Infection		infections with catalase + bacteria recurrent lymphadenitis, hepatic abscesses, osteomyelitis +FHx
Other Pathology		
Treatment		gamma-IFN
Secondary Phagocyte Dysfunction	**Leukemias** **Chemotherapy**	

Complement Dysfunction (refer)

Combined Dysfunction				
Primary Complement Dysfunction	**Severe Combined Immunodeficiency Disorder (SCID)**		**Wiskott-Aldrich Syndrome**	**Ataxia Telengectasia (AT) Immunodeficiency**
Genetics	X-linked	aut rec	X-linked	aut rec
Mechanism	mutation of IL-2 receptor resulting in inability for immune cells to communicate and proliferate therefore inquire when there is severe leukepenia (<1000) in a very young child	mutation of adenosine deaminase resulting in accumulation of precursors that are toxic to immune cell therefore…	(1) Eczema (2) thrombocytopenia (3) immunodeficiency • variable humoral dysfunction (high IgA,E, low IgM) • variable cell-mediated dysfunction	Defective DNA repair mechanisms that evolves over time such that early on pts are normal but over time develop overt immunodeficiency (1) ataxia (2) telengectasia (3) immunodeficiency • variable humoral dysfunction (low IgA,E,G) • variable cell-mediated dysfunction
Specific Infection	all kinds of infections	all kinds of infections	all kinds of infections	all kinds of infections
Other Pathology	failure to thrive			Lymphomas & Leukemias Breast Cancer *** these cancers can develop even in carriers ***

Treatment	Gene Therapy (but pts develop leukemias b/c you are inserting genes into blood cell lines) BM Transplantation	Enzyme Replacement Therapy (but very expensive) Gene Therapy	BM Transplant	IV-Ig