The Physician Pharmacist: Immunology

B-Cell Disorders			
X-Linked Agammaglobulinemia (Bruton's Dx)	-Defect in BTK (tyrosine Kinase) gene -failure of B cell precursors to become B-cells (no B-cell maturation) -X-linked (commonly males)	-recurrent bacterial + enteroviral infxns after 6 months (decreased maternal IgG)	-Absent B cells in peripheral blood -low Immunoglobulins of ALL classes -Absent/scanty lymph nodes + tonsils -**Primary follicles + germinal centers absent** -Live Vaccines **Contraindicated**
Selective IgA Def	-cause unknown -MOST Common immunodeficiency	-MOST asymptomatic -Airway/GI infxns, Autoimmune Dx, Atopy, Anaphylaxis to IgA blood products	-decreased IgA w/ normal IgG, IgM levels -increased susceptibility to **Giardiasis** -can cause false negative celiac dx tests
Common Variable Immunodeficiency	-Defect in B-cell differentiation	-ddx usually after Puberty -increased risk of autoimmune dx, Bronchiectasis, Lymphoma, Sinopulmonary infxns	-low Plasma Cells + Immunoglobulins
T-Cell Disorders			
Thymic Aplasia	-22q11 microdeletion; failure of 3rd + 4th pharyngeal pouches to develop → absent thymus + parathyroids -**DiGeorge Syndrome** = thymic, parathyroid, cardiac defects (Truncus Arteriosus, Tetralogy of Fallot) -**Velocardiofacial Syndrome** = palate, facial, cardiac defects	-**CATCH-22: C**ardiac defects, Abnormal facies, Thymic Hypoplasia (T-cell def - recurrent fungal/viral infxns), Cleft palate, Hypocalcemia (secondary to low PTH - causing Tetany - Chevostoks, Troussous)	-Low T cells -Low PTH -Low Ca2+ serum -thymic shadow absent on CXR
IL-12 Receptor Def	-decreased Th1 response; Autosomal recessive	-Disseminated mycobacterial + fungal infxns; may present after admin of BCG vaccine	-Low IFN-g -Most common cause of Mendelian susceptibility to mycobacterial dx (MSMD)
Autosomal Dominant Hyper-IgE Syndrome (Job Syndrome)	-def of **Th17** cells due to **STAT3** mutation -**impaired recruitment of PMNs** to sites of infection	-Cold (noninflamed) staph **A**bscesses -Retained **B**aby Teeth -**C**oarse Facies -**D**ermatologic Eczema -Increased Ig**E** -Bone **F**ractures (from minor traumas)	-High IgE -High Eos -"ABCDEF to get the Job"
Chronic Mucocutaneous Candidiasis	-impaired cell-mediated immunity against Candida (fungal) -Classic form caused by defects in **AIRE**	-persistent non invasive Candida albicans infxns of skin + mucous membranes	-Absent in vitro T-cell proliferation in response to Candida Antigens -Absent Cutaneous rxn to Candida Antigens

B and T Cell Disorders			
Severe Combined Immunodef (SCID)	Several types; -Defective IL-2R gamma chain (most common) **-Adenosine Deaminase def** -RAG mutation → VDJ recombination defect	-Failure to thrive -chronic diarrhea -thrush -recurrent viral, bacterial, fungal, protozoal infxns	-decreased T-cell receptor excision circles (TRECs) -Absence of Thymic Shadow (CXR) -Germinal centers absent w/ LN biopsy -T cells absent (Flow cytometry)
Ataxia-Telangiectasia	-defects in **ATM** gene → **failure to detect DNA damage** -leads to failure to halt progression of cell cycle → mutations accumulate	-Triad: **Ataxia** (Cerebellar Defects), **Angiomas** (Telangiectasia), **IgA def.** -increased sensitivity to radiation (Limit Imaging studies (CT/X-ray)	-High **AFP** -Low IgA, IgG, IgE -Lymphopenia -Cerebellar atrophy -High risk for Lymphoma + Leukemia
Hyper-IgM Syndrome (HIMS)	-most due to defective **CD40L** on Th cells -causes **Class switching defect** -X-linked recessive	-severe pyogenic infxns early in life -opportunistic infxns (Pneumocystis, Cryptosporidium, CMV)	-Normal or elevated IgM -Low/non-existent IgG, IgA, IgE -Failure to make Germinal Centers
Wiskott-Aldrich Syndrome (WAS)	-mutation in **WAS** gene → leukocytes and platelets unable to reorganize actin cytoskeleton -**defective antigen Presentation** -X-linked recessive	**WATER:** **-Wiskott-Aldrich** **-Thrombocytopenia** **-Eczema** **-Recurrent** (Pyogenic) infxns -increased risk of autoimmune dx + malignancy	-decreased to normal IgG, IgM -elevated IgE, IgA -Fewer and smaller platelets
Phagocyte Dysf			
Leukocyte Adhesion Def (Type I) (LAD1)	-defect in **LFA-1** integrin (CD18) protein on phagocytes -**impaired migration + chemotaxis** -autosomal recessive	-**Late separation** (>30 days) of umbilical cord -**Absent pus** -**Dysfunctional PMNs** → recurrent skin + mucosal bacterial infxns	-**increased neutrophils** in blood absence of PMNs at infxn sites → impaired wound healing
Chediak-Higashi Syndrome (CHS)	-defect in lysosomal trafficking (LYST) -**microtubule dysfunction in phagosome-lysosome fusion**	**PLAIN**: -Progressive neurodegeneration -Lymphohistiocytosis -Albinism (partial) -recurrent Infxns -Neuropathy (peripheral)	-**Giant granules** in Granulocytes + Platelets -Pancytopenia -Mild coagulation defects
Chronic Granulomatous Dx (CGD)	-**Defect in NADPH Oxidase** → less ROS (Superoxide) + decreased respiratory burst in PMNs	-increased susceptibility to **catalase (+)** organisms -recurrent infxns + granulomas	-Abnormal dihydrorhodamine test (less green fluorescence) -Nitroblue Tetrazolium dye reduction test is USELESS… **fails to turn blue**

-Encapsulated Bugs = **SHINE SKiS** = Pseudomonas, Strep pneuo, Heamophilus, Influenza type B, Neisseria men., E. coli, Salmonella, Kleb, group B Strep

Transplant Rejection:

Hyperacute (minutes)	**Acute (weeks-months)**	**Chronic (Years)**	**GVHD (varies)**
-pre-existing antibodies react to donor antigen **-Type II HSR** -Activates complement -widespread thrombosis of Graft vessels Ischemia + fibrinoid necrosis -Organ cannot be saved	-Cellular: CD8+ T cells/CD4 activated against donor MHCs **-Type IV HSR** -Humoral: similar to hyperacute, except antibodies develop after transplant associated w/ **C4d** deposition -vasculitis of graft vessels w/ dense interstitial Lymphocytic Infiltrate -Prevent/reverse w/ immunosuppression	-CD4+ T-cells respond to recipient APCs presenting Donor Peptides, including allogeneic MHC **-Type II and IV HSR** -Recipient T cells react + secrete cytokines → proliferation of vascular smooth muscle, Parenchymal atrophy, interstitial fibrosis -Dominated by **Arteriosclerosis** (Chronic Allograft Nephropathy, Bronchiolitis Obliterans, Accelerated Atherosclerosis, Vanishing Bile Duct Syndrome)	-Grafted immunocompetent T-cells proliferate in Immunocompromised host + reject HOST cells (severe organ dysf.) -**Type IV HSR** -Maculopapular Rash -Jaundice -Diarrhea -Hepatosplenomegaly -Common in Bone Marrow Transplants -Mild GVHD is actually beneficial (Graft-vs-Tumor Effect) - kills off any remaining tumor cells -Irradiate blood products prior to transfusion to prevent/limit GVDH

Immunosuppressants				
Cyclosporine	-**Calcineurin inhibitor** = binds cyclophilin -Blocks T-cell activation by preventing **IL-2** transcription	Psoriasis, RA	**-Nephrotoxicity** -HTN -Hyperlipidemia -Neurotoxicity (w/ Taco) -Gingival Hyperplasia (Cyclo Only) -Hirsutism (Cyclo Only) -DM (w/ Taco)	BOTH are Extremely Nephrotoxic
Tacrolimus (FK506)	-**Calcineurin Inhibitor** = binds FK506 binding protein (FKBP) -Blocks T-cell activation by preventing **IL-2** transcription	Immunosuppression after solid organ transplant		
Sirolimus	**-mTOR** inhibitor; binds FKBP -blocks T-cell activation + B-cell differentiation by preventing response to **IL-2**	Kidney transplant rejection ppx (Sir Basil's)	-Pancytopenia -Insulin resistance -Hyperlipidemia -**NOT nephrotoxic**	
Basiliximab	-**IL-2R Blocker**		-Edema, HTN, Tremor	
Azathioprine	-Antimetabolite to **6-MP** -inhibits lymphocyte proliferation by blocking nucleotide synth	-RA, Crohns, Glomerulonephritis	-Pancytopenia	-6-MP degraded by Xanthine Oxidase (toxicity increased if given w/ Allopurinol)
Mycophenolate Mofetil	-Reversibly inhibits **IMP dehydrogenase** -Purine synth blocked in B/T cells	-Glucocorticoid sparing RA drug	-GI upset -Pancytopenia -HTN, Hyperglycemia -Less nephrotoxic/Neurotoxic	-associated w/ Invasive CMV infxns

Glucocorticoids	Inhibit NF-KB -suppress both B and T cell function via decreased transcription of Cytokines -Induces T-cell apoptosis	-everything	-Cushing Syndrome -Osteoporosis -Hyperglycemia -Amenorrhea, -Adrenal Insuff/ Atrophy -Peptic Ulcers -Psychosis -Cataracts -Avascular necrosis of femoral head	-Demargination of WBCs causes artificial leukocytosis -adrenal insuff may develop if abruptly stopped w/ chronic use
Bone Marrow Stimulation				
<u>Erythropoietin</u> -Tx animals -increased risk of Thromboembolic events + HTN (not used if Hgb > 10)	**<u>Colony Stimulating Factors</u>:** -Filgrastim (G-CSF) -Tx Leukopenia; recovery of Granulocyte and Monocyte Counts		**<u>Thrombopoietin</u>** -Romiplostim (TPO analog) -Elthrombopag (TPO receptor agonist) -Tx autoimmune thrombocytopenia (Platelet Stimulator)	

SLE - Lupus:

-Autoimmune dx
- F > M
-AA > White
-Cause unknown

-Abs against nuclear material (Antinuclear ANtibodies (**ANA)**)
-(+) ANA is very suggestive

-(+) anti-double stranded DNA (anti-dsDNA) = higher risk for Glomerulonephritis)

-(+) Anti-Sm Abs (target Small nuclear ribonucleoproteins - splicosome) = very specific for lupus

-Antibody-Antigen Complexes circulate in plasma (many deposit into tissue)
-**Type III HSR**
-complexes activated Complement; **Low C3/C4** levels (Hypocomplementemia), Low CH50 test

Antiphospholipid Syndrome (APS); occur in association w/ lupus (but can happen in other dx)
-Antibodies against proteins in phospholipids
-Increased risk of **Arterial thrombosis** + venous, DVT, Stroke, Fetal loss
-Elevated PTT
-False (+) Syphilis (RPR/VDRL)
-Antiphospholipid Antibodies:
1. Anti-Cardiolipin - RPR false (+)
2. Lupus anticoagulant - PTT interfer
3. Anti-B2 Glycoprotein

-Disease of FLARES, followed by remission

Sxs:
-**Malar Rash (Butterfly)** - often after Sunlight
-Discoid Lesion (forearm)
-**Raynaud's** = vasospasm of arteries to fingers (if severe can lead to ulceration
-Mouth ulcers
-Arthritis
-Serositis (Pleura inflammation - painful inspiration; Pericardial inflam - Pericarditis)
-"Penias" = Anemia, Thrombocytopenia, Leukopenia = all **Type II HSR**
-Lupus Cerebritis
-**Diffuse Proliferative Glomerulonephritis** (most common + nephritic syndrome)
-Membranous Glomerulonephritis (Less common - nephrotic syndrome)

-**Libman-Sacks (Marantic) Endocarditis** (Nonbacterial inflammation of valves w/ classic Mitral valve lesions on BOTH sides of the valve)

Neonatal Lupus:
-maternal antibodies transfer to Fetus
-Associated w/ **Maternal Sjogren's Syndrome** (+SSA/Ro)
-present @ birth or first few weeks
-Rash (NOT malar) - face/scalp
-**Congenital Complete Heart Block**; slow HR in < 50s, often Tx w/ Pacemaker

Ddx: "need 4 of the following"
1. **Malar rash**
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Serositis
7. Cerebritis
8. **Renal dx**
9. "Penias"
10. (+) ANA
11. (+) Anti-dsDNA or Anti-Sm or Anti-phospholipid

DILE:
1. INH
2. Hydralazine
3. Procainamide

-has Anti-Histone Antibodies
-resolves after stopping drug

Tx:
-steroids
-avoid sunlight

Prognosis:
-renal failure
-infection (immunosup from Tx)
-Coronary Dx

Rheumatoid Arthritis (RA):

-Autoimmune dx
-inflam of joints
-W > men
-Commonly associated w/ Sjogren's

-Synovium = lines joints + tendon sheaths; secreting Hyaluronic acid to lubricate joint space
-**Pannus** = Synovial Hypertrophy due to infiltration of inflammatory cells/granulation tissue (increased synovial fluid, eroding into cartilage, bone)
-Antibody Mediated (**Type III HSR)**

MCP and PIP joints involved (DIP spared - unlike OA)

Prognosis:
-higher rates of Coronary Dx (leading COD)
-Amyloidosis (deposits in kidneys)
-Chronic/Untreated = Ulnar Deviation + Swan Neck Deformity (hyperextended PIP and flexed MCP)

Sxs:
-**Symmetric Joint Inflammation**
-gradual onset (pain, stiffness, swelling)
-**Morning Stiffness (>1hr after rising)** (improves w/ use)
-Fever/Systemic sxs
-**Baker's Cyst** (Popliteal Cyst) = rupture causes DVT like sxs
-Pleuritis +Pericarditis
-SQ Nodules (RF+ pts ONLY) - Elbow, central necrosis w/ palisades
-Episcleritis = Red painful eye
-Scleritis = bilateral, deep ocular pain when moving eye
-Uveitis = eye issues (floaters etc)
-Osteoporosis

Felty Syndrome:
1. Splenomegaly
2. Neutropenia
3. RA

-Seen in severe dx and chronic sxs (classic Triad)

Ddx:
-(+) Rheumatoid Factor (RF) = antibodies against **Fc portion of IgG antibody** (can be positive in other dx)
-Citrullinated Peptides (ACA) = used to confirm
-Elevated CRP + ESR
-Strong association w/ **HLA-DR4**

Tx:
-NSAIDs
-Steroids
-DMARDs
1. MTX
2. Aza
3. Cyclosporine
4. Hydroxychloroquine
5. Sulfasalazine
6. Leflunomide
7. TNF-a Inhibs:
    a. Infliximab
    b. Adalimumab
    c. Golimumab
    d. Etanercept

Sulfasalazine: (5-ASA)
-colonic bacteria process it

Leflunomide:
-inhibits Dihydroorotate Dehydrogenase (Pyrimidine Synth)

Infliximab: (TNF-a)
-PPD screening (reactivation of TB risk)

Scleroderma:

-Autoimmune dx
-"systemic sclerosis"
-F > M
-Onset 30-50 yo

-Endothelial cell damage → antibody production → Fibroblast Activation (Excessive Collagen Deposition)

Diffuse Scleroderma:
-**skin thickening**
-**Raynaud's** Phenomenon (often 1st sign)
-Early involvement of Visceral Organs (Renal, GI, Heart - pericarditis, myocarditis, Joint pains)
-Pulmonary HTN** (Right Heart Failure)
-Interstitial Lung Dx (fibrous tissue in lungs)

Scleroderma Renal Crisis:
-life threatening complication of Diffuse Scleroderma
-Acute worsening of renal function + HTN
-Tx = ACEI

Limited Scleroderma (CREST): "minimal skin dx"
-better prognosis but Higher Pulmonary Dx
1. **Calcinosis:**
    a. Bumps on elbows, knees, fingers
    b. Ddx w/ X-ray
2. **Raynaud's**
3. **Esophageal Dysmotility**
    a. Dysphagia
    b. LES Hypotonia (heartburn)
4. **Sclerodactyly:**
    a. Puffy fingers, hard to bend, shiny skin, loss of wrinkles
5. **Telangiectasias:**
    a. Skin lesions, dilated capillaries

Primary Biliary Cirrhosis:
-associated w/ Limited Scleroderma, Sjogren's, SLE, RA
-sxs = jaundice, fatigue, itching
-elevated conj Bili + Alk Phos

Ddx:
1. (+) ANA = not specific
2. Anti-Topoisomerase I (**Anti-Scl-70**) = Diffuse
3. **Anti-RNA Polymerase III Ab** = Diffuse dx (high risk of Renal Crisis)
4. **Anti-Centromere Antibody** (ACA) = CREST/Limited Dx

Tx:
-aimed at organs affected (CCBs for Raynauds, PPIs for GI, Pulm HTN drugs)
-not usually immunosuppressants

Sjogren's Syndrome: -Autoimmune disorder -destruction of lacrimal/salivary glands -F > M	-Lymphocyte mediated (**Type IV HSR**) -Biopsy of salivary gland = **Lymphocytic sialadenitis** -Primary vs. Secondary = Associated w/ RA, Lupus, and Primary Biliary Cirrhosis Sxs: -Dry eyes (Keratoconjunctivitis sicca) or feeling or dirt/debris in eye -Dry mouth (Xerostomia): difficulty to each dry foods, bad breath, tooth cavities -Xerosis: Dry scaly skin -Arthralgias/Arthritis -Raynaud's Phenomenon	DDx: 1. ANA - non specific 2. RF 3. Anti-SS-A (Ro) 4. Anti-SS-B (La) 5. Schirmer Test: a. Measure tears/wetting 6. Salivary Gland Scintigraphy (Nuclear) 7. Whole Sialometry (spit measure vol) 8. Clinical Sxs -Oral/Eyes -Must have Histopathology or Autoantibodies (Can't just be sxs)	Tx: -Tooth hygiene -Artificial Tears -Pilocarpine **B-Cell Lymphoma:** -increased risk -Unilateral Swollen Gland **Neonatal Lupus** (greatest risk involves + SSA or SSB) -Atypical Rash -Congenital Complete Heart Block (requiring Pacer)

Vasculitis - Inflammation of BVs (Lymphocytes in BV walls)

-**Palpable Purpura** = "if seen in a question stem, we are talking about Vasculitis"
=DOES NOT blanch when pressed (extravasation of blood into skin), Small vessel inflammation, Raised

Large Vessel: (TATA)			
Temporal Arteritis	-"Giant Cell Arteritis" = **granulomatous** -Narrowing of temporal artery system -HA, Jaw claudication (painful chewing) -**Ophthalmic Artery Occlusion (Blindness)**	-High ESR -DDx = Biopsy of Temporal Artery (finding granulomas) -Tx Empirically w/ High dose steroids (don't wait for biopsy)	Classic Presentation: 1. **Elderly Female w/ HA** 2. **Pain on Chewing** 3. **High ESR**
Takayasu's Arteritis	-**Granulomatous** thickening of Aortic arch + branches -Pulseless Dx: Proximal great vessels (BP difference btw arms/legs), Bruits over arteries	-Tx = Steroids	Classic: 1. **Young, Asian Women** 2. **Weak pulses in one arm** 3. **High ESR**

Medium Vessel: (PKB)			
Polyarteritis Nodosa	-Immune Complex Mediated (IC) = **Type III HSR** -Hep B+ -Nerves = Motor/Sensory Deficits -Skin = Nodules, Palpable Purpura -Kidneys = Renal Failure	-Constrictions and Aneurysms (BUT commonly found in Kidney, Liver, Mesenteric arteries….NOT coronary) -**Rosary Sign** = Beads on a string -Tx = Steroids + Cyclophosphamide	Classic: 1. **Hep B (+)** 2. Bizarre constellation of sxs (Nerve defects, skin nodules, purpura, renal failure)

Kawasaki Dx	-Skin, Lips, tongue (Strawberry tongue) -psalms, soles, → later desquamates -Coronary Artery Aneurysms (start 3-4 weeks after acute phase) -Acute Phase = Fever, Arthritis Sxs are very similar to **Scarlet Fever** (Strep Pyogenes) = different b/c SF has SORE THROAT + Sandpaper Skin	-Tx = IVIG + **ASA** (one case where we still give to children) **Reye's Syndrome:** -encephalopathy, liver failure, fatty infiltration -Vomiting, confusion, seizures, coma -follows Viral Illness (Influenza/Varicella) -Mitochondrial insult	Classic: 1. **Asian Child** 2. **Strawberry tongue** 3. **Coronary Artery Aneurysms**
Buerger's Dx	-"Thromboangiitis Obliterans" -Male smokers -Poor blood flow to hands/feet (Gangrene, Autoamputation of Digits - just falls off, Superficial Nodular Phlebitis) -Raynaud's Phenomenon -Segmental thrombosing vasculitis	-Tx: Smoking Cessation	Classic: 1. **Smokers Hands**

Small Vessel: (CS, WG, MP, HSP)

Churg-Strauss	-Asthma (often refractory to Tx) -Sinusitis -Neuropathy -High Eos -Tx = steroids / cyclophosphamide -Palpable Purpura	Classic: 1. **Asthma** 2. **High IgE/Eos** 3. **p-ANCA**
Wegener's Granulomatosis (w/ Polangitis)	-Upper and Lower Airway dx -Palpable Purpura -**Granulomatous Dx** -kidney dx	Classic: 1. **Sinusitis / Otitis Media** 2. **Lungs - Hemoptysis** 3. **Kidneys** 4. **c-ANCA**
Microscopic Polyangiitis	Just Like Wegner's except; -No upper airway dx (Sinusitis) -p-ANCA -NO Granulomas	Classic: 1. **Lungs - Hemoptysis** 2. **Kidneys** 3. **p-ANCA**

^^^^ANCA Mediated Dx = Antineutrophil Cytoplasmic Antibodies
-ANCA = antibodies attacking Neutrophil proteins

-c-ANCA (Cytoplasmic) = Proteinase 3 (PR3) Antibodies (Wegener's Only)

-p-ANCA (Perinuclear) = Myeloperoxidase (MPO) antibodies

-All have Pulmonary Involvement
-All have Renal Involvement
1. Crescentic MPGN
2. "Pauci-Immune" = Paucity of Ig (negative Immunofluorescent staining)
3. Nephritic Syndrome, Proteinuria, Hematuria

-All Tx w/ Steroids + Cyclophosphamide

Henoch-Schonlein Purpura (HSP)	-Most common childhood systemic vasculitis -often follow URI -Associated w/ IgA (Vasculitis from IgA complex deposition - IgA Nephropathy) -C3 Deposition	-Skin = Palpable Purpura on butt/legs -GI = abdominal pain, melena -Kidney = Nephritis -Tissue Biopsy = shows IgA deposition around BVs of Kidneys -Self-limiting (no Tx needed)	Classic: **1. Child** **2. Classic w/ Recent URI** **3. Palpable Purpura** **4. Melena**
Goodpasture's Syndrome	-Antibody to **Collagen** (**Type II HSR**) -Antibodies to alpha-3 chain of **type IV collagen (kidney/lungs)** -Anti-GBM -Anti-Alveoli	-Hemoptysis + Nephritic Syndrome -**Linear (+) IF** (IgG, C3): ***NOTE****: All the ANCAs above are "Pauci-Immune" meaning they will have a negative Immunofluorescence staining pattern*	Classic: **1. Young adult** **2. Male** **3. Hemoptysis** **4. Hematuria**

References:

1. **Le, Tao and Bhushan, Vikas.** First Aid for the USMLE Step 1 2021, Fourteenth edition. New York: McGraw-Hill Education, 2021.