General

- NB PCP prophylaxis (Bactrim DS QMWF)
- Drug Reactions: Immunologic Reactions (below), Toxic, Idiosyncratic

Immunologic Reactions (Gell & Coomb's Classification)		
Type	**Mechanism**	**Examples**
I (Immediate Hypersensitivity)	Sensitized Mast Cells bind floating Ag via IgE and cross-link triggering degranulation of vasoactive substances and production of chemotaxins	AR, Asthma, Atopic Dermatitis, Hives/Wheal/Flare Anaphylaxis (Severe Type I Allergic Reaction) • Causes o Meds: PCN, etc (75%) o Bites/Stings: hymenoptera stings aka bees, yellow jackets, hornets, wasps, etc (15%) o Contact: latex, etc (5%) o Foods (refer) (5%) o Heme: blood products, seminal fluid, etc (5%) o NB a new emerging one is delayed onset contrast allergy • S/S (severe w/in minutes to mild w/in several hours, 20% have biphasic S/S w/ 2nd phase occurring 8-72hrs later which is characterized by eosinophilia) o Derm: utricaria/angioedema of skin/airway/conjunctiva, flushing, pruritus o Pulm: b/c of edema above you can get stridor and bronchospasm w/ wheezing o GI: crampy ab pain, N/V, diarrhea o CV: hypoTN • Dx: mainly clinical but there is eosinophilia, elevated serum tryptase/histamine (only transiently elevated right after episode therefore draw blood quickly) • Tx: IM Epi Pen, Complete Histamine Blockade, Steroids, IVF/Pressors, Airway Protection, IVF, Bronchodilators, Teach Pt • DDx o Anaphylactoid Rxn: looks like anaphylaxis and is due to degranulation of mast cells induced directly by offending agent and NOT by IgE, most commonly associated w/ osmotic shift from radiocontrast media (seen in 5-10% of pts, 2/2 osmolality of contrast and not iodine in contrast and thus no cross-reactivity w/ iodine in seafood, premedicate w/ prednisone 50mg PO at 13hrs, 7hrs, 1hr, H2B and diphenhydramine 50mg PO at 1hr before administration), meds (NSAIDs, narcotics, etc), dialysis, physical stimuli (cold, exercise), etc o Mastocytosis: consider in pts w/ recurrent unexplained anaphylaxis, S/S 2/2 mast cell substance release: histamine = GI/Derm, PGD2 = flushing, bronchoconstriction, Heparin = bleeding, Neutral Protease = hepatic fibrosis and bone lesions, ("urticaria pigmentosa" = multiple light brown plaques that when rubbed result in urtication aka Darier's Sign, "Telengiectasia Macularis Eruptiva Perstans" = brown macules w/ telengectasias) o ACE-I Angioedema o Hereditary Angioedema (refer) o Flushing Syndromes (red man syndrome, carcinoid, post-menopausal, VIPoma)
II (Cytotoxic)	IgG bind FIXED-Ag (aka human tissue) and trigger phagocytosis and complement activation	Various Autoimmune Diseases (Goodpasture's, Graves, AIHA, etc)
III (Immune Complex)	IgG bind Non-FIXED-Ag and trigger IC formation followed by deposition in tissue and neutrophil chemotaxis and necrosis called leukocytoclastic vasculitis (NB obviously not all IC cause Type III reactions rather reactions only occur when [Ag] > [Ig])	Various Autoimmune Diseases (SLE, Hashimoto's, RA, etc) Serum Sickness (systemic Type III reaction, occurs 5d after exposure to protein Ag like other animal serum or more commonly now recombinant murine non-humanized antibodies, causing F, urticaria, arthralgia, proteinuria, LAD, seen in non-immunized pts) Arthus Reaction (local Type III reaction in skin, occurs 1d after Ag exposure, causing skin edema and necrosis, seen in prior immunized pts)
IV (Delayed Hypersensitivity)	Sensitized T-cells bind floating Ag triggering release of lymphokines	Transplant Rejection, TB/fungal/viral infections, Contact Dermatitis, Hypersensitivity Pneumonitis, etc

Basic Immunology

- General
  - **Cytokines**

        - Pro-Inflammatory Cytokines: IL-1 (secreted by macrophages, stimulates T, B, neutrophils, etc), 2 (secreted by Th, stimulates Tc), 3 (secreted by Th, stimulates BM), 4 (secreted by Th, stimulates B), 5 (secreted by Th, stimulates B), 8 (neutrophil chemotactic factor), 12, 13, 18, 23, alpha/beta/gamma-IFN (secreted by Th, stimulates macrophages and place cells in an antiviral state), TNF-alpha/beta (secreted by macrophages/Th, stimulates T/B), LTB4
            - APR are IL-1/IL-6/TNF then ESR/CRP
            - First Neutrophils then Lymphocytes (release cytokines which enhance immune response) then Mast/Baso (release other mediators)
        - Anti-Inflammatory Cytokines: IL-10,11, PGE2, PGJ2, PGI, NO, TGF
    - **MHC (Major Histo Compatibility) Genes** code for **HLA (Human Leukocyte Antigen) Ags** which are transmembrane proteins found on certain human cells and are used to present NON-self proteins to T-cells
        - **Class I (A,B,C)** are found on ALL cells except RBC/Hepatocytes/Muscle, present to CD8+ T-cells
        - **Class II (DP, DQ, DR)** are found on NO cells except APCs (refer below), present to CD4+ T-cells
- **Innate** (rapid acting, non-specific, no memory, generic ready-made receptors)
    - **Lymphoid Cells**
        - **NK-Cells** (similar to T CD8+ cells in that they kill viral infected cells and neoplastic cells)
    - **Myeloid Cells**
        - **Monocyte Cells aka Antigen Presenting Cells (APCs)** (eat pathogens and present Ags)
            - **Macrophages**
            - **Dendritic Cells**
            - **Langerhan Cells**
        - **Basophil/Mast Cells** (activated by IgE and release performed pro-inflammatory mediators)
    - **Complement Pathway** (refer below)
- **Acquired** (opposite)
    - **Lymphoid Cells (produced in BM and thymus and then localized into lymphoid tissue including LNs, spleen, Waldeyer's ring, MALT)**
        - **Cell Mediated T Cells**
            - **CD4+:** kill exogenous pathogens (Ags are presented by MHC-HLA-DR2/3/4 after the pathogen is phagocytosed by APCs)
                - **Th1** (produce IL-2/gamma-IFN which activates CD8+Tc/macrophages, also mediates delayed type hypersensitivity)
                - **Th2** (produce IL-4 which stimulates B-cells to differentiate into Plasma cells and make Ab)
            - **CD8+:** kill viral infected cells and neoplastic cells (Ags are presented by MHC-HLA-A/B/C)
        - **Humoral B Cells** (bacterial/extra-cellular-viral pathogen) B-Epitope (bound by Ig by B-cells)
            - **Memory Cells:**
            - **Plasma Cells:** produce Ig
                - Fab end (variable amino end that binds/inactivates bacteria) and Fc end (constant carboxyl end that binds/activates complement and opsonization aka phagocytosis) NB can also be divided into light/heavy chains
                - G (secondary/chronic response, inactivation/complement/opsonization, only one that crosses placenta), A (prevents bacteria attachment to mucosa), M (primary/acute response, hemagglutination, RF, etc), D (surface of B-cells), E (Type I Hypersensitivity, Parasites)
    - **Myeloid Cells**
        - **Granulocytes Cells**
            - **Neutrophil**
            - **Eosinophil**
    - **Complement Pathway**
        - **(1) Classical Pathway**: IgG-Ab Complex → C1 → C4/2a →
        - **(2) Lectin Pathway**: Pathogen Surface → C4b/2a →
        - **(3) Alternative Pathway**: Pathogen Surface →
        - = C3b/Bb → C5/6/7/8/9 aka Membrane Attack Complex (MAC)
        - NB Levels
            - Low Levels (consumed during various inflammatory processes like SLE, Glomerulopathy, Endocarditis, etc)
            - High Levels (?)
            - NO C1/2/4 (hereditary angioedema, bacterial infections but mild b/c the alternative pathway is still working, early onset rheumatoid dz), NO C3 (severe bacterial infections), NO C5/6/7/8/9 (severe bacterial infections esp *Neisseria* infections)

Immunostimulants

- All work in a generalized fashion and have limited effectiveness
- Used in cancer, infection, immunodeficiencies

- BCG (injected in melanoma which attracts inflammatory cells with the hope that there will be a spill-over effect with killing of cancer cells), Vaccine, C.diff (IVIG), Levamisole (CRC), IFN (HCV/HBV)

Immunosuppressants (refer to liver transplant)

Transplant

- Process
  - Preliminary Screen for Contraindications (no comorbities, no psych dz, no cancer/infection (but not HIV/HCV!!!) b/c immunosuppression could accelerate cancer/infection, evidence of non-compliance, obesity)
  - Full Eval (heart, etc)
  - HLA/ABO Typing
  - NB "paired exchange" is the new matching process
- Types: autograft (from same person as in CABG), allograft (from the same species), xenograft (from a different species), SOT (solid organ transplant) vs BMT (bone marrow transplant)
- HLA Matching: ideal is 6/6 but you can go as unmatched as 4/6, there is a 1/4 chance that a sibling is 6/6, children and parents can only be 3/6 which is not good enough therefore only sibling or un-related donor
- SOT: Liver, Kidney, Heart, Lung, Intestine, Pancreas
  - Liver (refer)
  - Kidney: most common transplant, transplanted into abdominal R/LLQ and connected to femoral (you can actually feel it on PEx), original kidneys are left in place, only 50% of ESRD are on transplant list and only 2% actually get an organ, transplanted pt (5/1000 die/yr) live longer than those on HD (200/1000 die/yr), once you reach 106d post transplant survival is very good, grafts typically last 7yrs w/ chronic allograft failure 2/2 (1) usual AKI causes, (2) chronic rejection, (3) chronic cyclosporine induced nephropathy, (4) recurrent renal dz esp FSGS/MPNG/HUS, (5) new renal dz esp ant-GBM, there are specific unique infections including BK virus (notorious for reactivating in transplanted kidneys causing nephropathy, you have clue cells on UA, check PCR of serum/urine, Tx w/ leflunomide + cidofovir + decrease immunosuppression) and CMV (mono like illness, check PCR of serum/urine, Tx w/ antiviral), pts often have anemia, erythrocytosis, low vitD, etc
- BMT
  - autologous (stem cells from pt, low r/o GVHD but low GVT high r/o cancer relapse, used in cancers with no BM involvement like lymphoma, plasma cell dyscrasia, AML, germ cell tumors, amyloidosis, certain autoimmune dz, 2% mortality) vs allogenic (stem cells from donor, can be related vs non-related, high GVT and low r/o cancer relapse but high r/o GVHD, used in leukemias, MDS, MPD and nonmalignant disorders like severe aplastic anemia, hemoglobinopathies, PNH, inherited metabolic disorders, immunodeficiencies, 10% mortality)
  - CD34+ stem cells can be harvested from (1) BM thru a process similar to a BM Bx from the posterior iliac crest, (2) peripheral blood has some circulating stem cells but mobilization of more cells to circulate can be done w/ certain meds (most common,) or (3) umbilical cord blood
  - after harvesting the pt undergoes myeloablation with super high dose chemo and whole body radiation (something which cannot be done unless stem cells are available) which wipes out the cancer but also the BM then the stem cells are engrafted thru a central venous line where they magically go to the BM
  - Complications are 2/2 the effects of the myeloablative process OR interaction b/w donor and recipient immune systems
  - Early Complications (<100d)
    - Acute GVHD (refer to GI)
    - Early Infections (refer)
    - Primary Graft Failure (pts initially are normally neutropenic/pancytopenic for a while after engraftment but if counts don't recover after a few weeks then graft failure must be entertained)
    - Myeloablative SEs: pancytopenia, mucositis w/ diarrhea and N/V, rash, alopecia, peripheral neuropathy, hemorrhagic cystitis, microangiopathy, interstitial pneumonitis (alveolar damage resulting in hypoxia, diffuse pulmonary infiltrates, and occasionally Diffuse Alveolar Hemorrhage (DAH))
  - Late Complications (>100d)
    - Relapse
    - Chronic GVHD (refer to GI)
    - Late Infections (refer) Tx/Px: same as above
    - Secondary Graft Failure (pts are no longer neutropenic but still pancytopenic indicating that engraftment was successful but the new BM is now being attacked by immunocompetent host cells aka graft rejection or there is non-immune mediated process like a CMV infection)
    - Myeloablative SEs: cataracts, infertility, hypothyroidism, avascular necrosis of bone, secondary cancers
- Post-Transplant Complications
  - Rejection
    - Hyperacute: 2/2 ABO incompatibility occurring w/in minutes resulting in deadly SIRS
    - Acute: 2/2 HLA incompatibility occurring w/in first 3 months resulting in organ dysfunction which must be confirmed on Bx
    - Chronic: 2/2 MHC incompatibility
  - Viral Induced Malignancy (refer)
  - Infection (can be newly acquired pathogens or reactivation of harbored opportunistic bugs in pt or transplanted organ, S/S of infection can be very atypical, vaccinate and give prophylaxis for nocardia (bactrim), CMV (gancyclovir), PCP (bactrim), Candida (fluconazole), HSV (acyclovir))

- 0-1mo: nl bugs related to surgical procedure, normal **nosocomial** infections, **HSV** (usually a little bit later on like right at 1mo, reactivation occurs in 2/3 of pts)
- 1-6mo: immunosuppresion leads to susceptibility to bugs that do not usually cause dz in otherwise healthy pts, Viral (**CMV**, HSV, HB/CV, VZV, HHV-6/7, Influenza, Parainfluenza, BKV, JCV, Adenovirus, RSV), Bacteria (**Nocardia**, **Mycobacterial, Listeria**, Legionella, Salmonella), Protozoa (**Strongoloides, Toxo**), Fungi (**Aspergillus**, **Candida,** Histo/Coccidio,/Blasto)
- >6mo: Viral (**CMV**), Fungal (**Crypto**, Aspergillus), Protozoa (**PCP**), Bacteria (encapsulated bacteria and normal community acquired infections)
- NB studies are now showing that one can transplant a HIV pt as long as they are well controlled