Microbiology

- Eukaryotic cells that differ from human cells in a few ways: (1) membrane sterol is ergosterol not cholesterol, (2) they have cell walls but not like prokaryotic walls made of peptidoglycan rather they are made of glucans and chitin, (3) they are saprophytic in that they decompose organic material for energy, (4) they have a very long doubling time hence presenting as chronic infections
    - Types (monomorphic = either M or Y vs dimorphic = switch from infectious cold M w/ spores to warm Y when in body)
        - (1) Mold: tubular/multicellular septated/non-septated hyphae, reproduce by turning the end of hyphae into conidia aka spore which releases, germinates, and proliferates forming new hyphae, NB molds are generally resistant to azoles
        - (2) Yeast: round/unicellular, reproduce by budding, NB if budding is not complete then psuedohyphae can form
- Dx
    - Cutaneous Fungi: scrap skin even toe nail clippings, treat w/ KOH to remove all organic material except fungi, direct microscopic examination w/ Wood's lamp, then send for Cx if needed
    - Systemic/Opportunistic Fungi: get tissue biopsy, treat w/ KOH to remove all organic material except fungi, stain tissue w/ India Ink and observe under light microscopy, culture mold in Sabouraud Agar and yeast in Blood Agar
        - **fungal complement fixation** = Histo/Blasto/Coccidio/Asp (panel of fungal chronic IgG serology to see if immunocompromised pt has been exposed to various fungi in past and will be predisposed to reactivation b/c of immunocompromised state)
        - **beta-D-glucan aka Fungitell** (a general component of all fungi and such can be used as a general screen for a fungal infection, order when you can't get a tissue sample but you suspect a fungal process is present, false negative with crypto)
        - **urine histo ag, serum crypto ag, serum galactogamon** (false positive with zosyn)
- Tx
    - b/c fungi are eukaryotes there are only few targets for antifungal therapy, the most effective anti-fungals target ergosterol (a sterol like cholesterol but only found in fungal membranes)
    - Polyenes/Azoles/Echinocandins/Squalene Epoxidase Inhibitors + Flucytosine/Microtubule Inhibitors: synergistic effect b/c polyenes make fungus more permeable to flucytosine and also flucytosine allows for lower levels of amphotericin needed to be effective
    - Polyenes + Azoles + Echinocandins + Squalene Epoxidase Inhibitors: antagonistic effect b/c azoles decrease [ergosterol] therefore less ergosterol for polyenes to act one
    - **Polyenes**
        - Mechanism: amphipathic drug w/ nonpolar end associating w/ ergosterol while polar end associating w/ each other forming an aqueous channel leading to cell lysis
        - Systemic Mycoses
            - Amphotericin B (Fungizone)
            - Uses: any serious systemic mycoses (IV and IT)
            - SEs
                - **Acute Infusion Reaction**: "shake & bake" (rigors & fever), myalgia, anorexia, N/V, chest/ab/back/flank/leg pain, thrombophlebitis, rare hypotension, very rare severe dyspnea and focal pulmonary infiltrates due to pulmonary edema
                    - 2/2 proinflammatory cytokine release (not histamine)
                    - subsides after awhile, decreases w/ repeated infusions, better w/ central vs peripheral infusion
                    - it is recommended that a pt be tested w/ a small dose (1mg) but this is rarely done
                    - premedicate w/ Tylenol (for fever), Benadryl (b/c no histamine release not really effective), meperidine (for chills), steroids (b/c cytokine release is occurring), heparin (for thrombophlebitis) (NB in theory NSAID should be helpful b/c of cytokine release but not given b/c of nephrotoxicity)
                - **Chronic Nephrotoxicity** (low TI, never exceed 1.5mg/kg/d): Type I RTA, Decreased Erythropoeitin, profound HypoK/Mg
                    - use newer formulations of amphotericin B which have larger volume of distribution, more rapid clearance, higher tissue concentration, and less SEs especially nephrotoxicity but very $$$$
                        - Amphotericin B Lipid Complex – ABLC (Abelcet) ampho B w/ lipid bilayer ribbons
                        - Liposomal Amphotericin B – L-AmB (AmBisome) ampho B w/in a lipid bilayer vessel
                        - Amphotericin B Colloidal Dispersion – ABCD (Amphotec) ampho B w/ cholesteryl sulfate complex
        - Topical Mycoses
            - Nystatin (Mycostatin, Nilstat)
                - Uses: Dermatophytosis, Thrush, Vaginitis (PO Swish & Swallow/Spit and Top Ointment)

        - SEs: no systemic absorption hence only N/V
    - **Azoles**
        - Mechanism: inhibits conversion of lanosterol to ergosterol (ademethylase) resulting in increased lanosterol incorporation into fungal membranes but they do not pack as well as ergosterol resulting in increased permeability and cell lysis, NB requires gastric acid to absorb therefore take w/ "Coca-Cola" and no PPI
        - SEs: Inhibits P450 (decreased aldosterone, cortisol, sex steroids and decreased metabolism of drugs), GI (ab pain, N/V), Liver (various toxicity), Skin Rash
        - Systemic Mycoses (IV/PO)
            - 1st: ketoconazole (Nizoral) (first one, cheapest but more SEs)
                - Use: endocrine problems given its SEs
                - SEs: most SEs
            - 2nd: itraconazole (Sporanox)
                - Use: Endemic Mycoses, Local Candida, Dermatophytosis
                - SEs: ?
            - 3rd: fluconazole (Diflucan)
                - Use: ABOVE + Cryptococcal Meningitis b/c best CSF penetration
                - SEs: alopecia of scalp and pubic crest
            - 4th: voriconazole (Vfend)
                - Use: ABOVE + Invasive Aspergillosis and Systemic Candida
                - SEs: self-limited various transient visual disturbances w/ IV infusion, don't use in CKD
            - 5th: posaconazole (Noxafil) (last line Tx when all other antifungals have failed)
                - Use: ABOVE + Mucormycosis and Zygomycetes
                - SEs: ?
        - Cutaneous Mycoses (Top)
            - clotrimazole (Desemex, Lotrimin, Mycelex)
                - Use: Dermatophytosis
            - miconazole (Monistat)
                - Use: Vaginitis
            - Others: econazole (Nizoral), oxiconazole (Oxistat), seruconazole (Ertaczo)
- **Echinocandins**
    - Types: caspofungin (Cancidas) (many drug interactions), micafungin (Mycamine) (less drug interactions), anidulafungin (Eraxis) (no drug interactions) IV (no PO)
    - Mechanism: inhibits synthesis of beta-1,3-D-glucan a critical component of fungal cell walls
    - Use: systemic mycoses (esp invasive aspergillosis, systemic candidiasis, febrile neutropenia) NB no activity against endemic mycosis
    - SEs: Infusion Reaction (flushing, pruritus, headache, fever, chills, N/V, diarrhea), Liver (increased LFTs), Drug-Drug Reaction (surprisingly not that toxic given its profound antifungal effect in comparison to amphotericin)
- **RNA Synthesis Inhibitors**
    - Types: flucytosine aka 5-FC (Ancobon) PO
    - Mechanism: converts to fluorouracil aka 5-FUTP which competes w/ uracil in RNA synthesis (NB resistance occurs quickly)
    - Uses: systemic mycoses (esp w/ amphotericin B to Tx cryptococcal dz)
    - SEs: significant hence its limited use, GI (diarrhea, anorexia, N/V), Liver (increased LFTs), BM (pancytopenia), Skin Rash
- **Squalene Epoxidases Inhibitors**
    - Types: terbinafine (Lamisil) PO/Cream/Powder, butenafine (Lotrimin) Cream/Powder
    - Mechanism: inhibits conversion of squalene to lanosterol (epoxidase) resulting in decreased ergosterol (similar to azoles)
    - Uses: Dermatophytosis
    - SEs: Liver (various toxicity), Eye (retinal/lens changes), Drug-Drug Interaction
- **Microtubule Inhibitors**
    - Types: griseofulvin (Grifulvin) PO, tolnalfate (Tinactin) Cream/Powder
    - Mechanism: interferes w/ microtubule function preventing mytosis
    - Uses: Dermatophytosis
    - SEs: Teratogenic/Carcinogenic, Confusion, Headaches, Increased Warfarin Metabolism, Potentiates EtOH Intoxication

<u>Cutaneous Fungi</u> (Mold) (refer)

- 1st: OTC treatment of bad and prophylaxis of normal nails (OTC topical antifungal cream, Gold Bond Powder/Cream benzoyl peroxide, discard old shoes, pedicures/manicures particularly by podiatrists) NB w/o Tx it will progress to other nails, Meds: Polyenes, Azoles, Squalene Epoxidase Inhibitors, Microtubule Inhibitors
- 2nd: Rx topical: cicloporix (Penlac)
- 3rd: Rx systemic: terbinafine (Lamisil), itraconazole/fluconazole/ketoconazole x6-14wks (finger-toe), follow LFTs
- NB even after Tx nails cosmetically still look bad but nonetheless stop Tx especially if repeat KOH prep is negative
- NB consider Lotrisome which is a combo of antifungal and steroids for small skin lesions that look like they have an inflammatory component also or consider addition of abx if there is a super infection

<u>Opportunistic Fungi</u> (Yeast) (not virulent in immunocompetent hosts)

- ***Candida* spp (Yeast but they have psuedohyphae)**

- Epidemiology: normal commensals in the 10%-vagina/20%-mouth/50%-GI, not typically found on skin, RFs: neutropenia, DM, immunosuppression, broad-spectrum abx, intravascular catheters esp TPN, IVDU, ab surgery, renal failure
- Type of spp. (always speciate, in general increasing resistance esp if on prophylactic therapy and/or HIV+, therefore try another drug in same class or try different class)
  - C. albicans (50%)
  - C. glabrata (10-25%) increasing azole/ampho resistance
  - C. parapsilosis (10-25%) increasing echinocandin resistance
  - C. tropicalis (10-25%)
  - C. krusei (1%) increasing fluconazole resistance
  - C. lusitania (1%) increasing ampho resistance
- Types of Infections
  - Skin
    - S/S: pruritic pustular maceration w/ confluent satellite lesions in moist occluded/intertriginous skin
    - Tx: Nystatin Cream/Pill and if that doesn't work then Azole Cream and treat Sx w/ Castellani's paint
    - Px: keep area dry and wash w/ benzoyl peroxide and powder miconazole
  - Mucosa
    - S/S: thrush (easily removable creamy white exudate covering erythematous base) vs atrophy (erythema) vs angular cheilitis in oropharynx/esophagus/vagina
    - Tx: oropharynx (Nystatin Swish & Spit/Swallow, Clotrimazole Troche aka lozenge that dissolves in mouth, Fluconazol Swish & Spit/Swallow or PO pill), esophagus (refer to HIV), vagina (terconazole 0.8% crm 1 applicatorful PV qhs x3d)
    - Px: Diflucan Qwk
    - NB if deeper/chronic/severe then consider HIV, DM, Immunosuppression or Chronic Mucocutaneous Candiasis (presents in first 2yrs of life, associated w/ PGS)
  - Candiduria
    - S/S: ?
    - Tx: change catheter, if neutropenic or symptomatic or pregnant or undergoing urologic procedure then Tx w/ oral or IV fluconazole or bladder irrigation w/ AmphoB
  - Candidemia
    - S/S: sepsis w/ MOF
    - Tx
      - Non-Neutropenic/HD-Stable/No Recent Azole Exposure: remove all catheters, Tx for 14d after first negative Blood Cx and S/S resolved w/ IV fluconazole
      - Neutropenic/HD-Unstable/Recent Azole Exposure: remove all catheters, Tx until non-neutropenic and HD stable w/ IV Caspofungin or Ampho B
    - Complications w/ Dissemination to
      - eye (check eye exam)
      - valves (check TTE)
      - liver/spleen (esp seen in acute leukemics)
      - peripheral/central veins ( )
      - vertebra ( )

- ***Cryptococcus neoformans* aka Crypto**
  - Epidemiology: HIV pt inhales pigeon droppings
  - S/S: lung dz (subclinical to resp failure w/ cavitary lesions) with subsequent dissemination to CNS (meningoencephalitis) and skin ("cannon ball" lesions) (degree of infection all depends on how immunocompromised the pt is)
  - Dx: Cx/Stain of body fluid/tissue, CSF (very high opening pressure, low glucose, high protein, lympho-pleocytosis) serum/CSF latex cryptococcal Ag, distinctive large halo capsule seen on India Ink
  - Tx:
    - Subclinical Pulm Dz = observation w/o Tx is enough
    - Clinical Pulm Dz = fluconazole for several months depending on immune state
    - CNS/Skin Dz = IV Ampho B and PO 5-FU x2wks then PO fluconazole 400mg QD x10wks and if HIV+ then 200mg QD until CD4>300, consider serial LP to reduce pressure to <20cm of H2O or consider a temporary lumbar drain or VP shunt
- **Zygomycosis aka *Mucor* spp., *Rhizopus spp.*, *Absidia* spp., *Cunninghamella* spp.**
  - Epidemiology: diabetics in DKA, immunosuppressed esp leukemics
  - Mech: proliferate in the walls of blood vessels and cause infarction
  - S/S: black necrotic lesions around eyes/nose/palate that can extend intracranially
  - Dx: Bx
  - Tx: IV Ampho B + surgical debridement
- ***Aspergillus* spp.**
  - Epidemiology: common mold floating everywhere in the environment
  - Aspergillus spp.
    - *A. fumigates* (most common, least resistant to Amphotericin)
    - *A. flavus*
    - *A. niger*

        - *A. terrens* (least common, most resistant to Amphotericin)
    - Types of Infections
        - Chronic
            - Allergic
                - Allergic Broncho Pulmonary Aspergillosis (ABPA)
                    - Pt: severe refractory asthmatics
                    - CXR: migratory upper lobe infiltrates → central bronchiectasis → fibrosis
                    - S/S: bad asthma with brown colored sputum
            - Saprophytic
                - Aspergilloma aka "Fungus Ball"
                    - Pt: underlying lung dz w/ cavities from TB, etc
                    - CXR: cavity w/ ball
                    - S/S: asymptomatic to hemoptysis
                    - Dx: 50% + Sputum Cx, CT (mobile intracavitary mass w/ air crescent)
                    - Tx: antifungals have NO role?, embolization or surgery if hemoptysis
            - Invasive
                - Necrotizing Tracheitis/Pneumonitis
                    - Pt: COPD, immunosuppression
                    - S/S: productive cough, B symptoms
                    - Dx: CT (infiltrates, nodules, pleural thickening), Lung Bx
                    - Tx: AmphoB
        - Acute
            - Allergic
                - Hypersensitivity Pneumonitis
                    - Pt: asthmatics
                    - CXR: bronchiectasis, fibrosis
                    - S/S:
            - Saprophytic
                - Pulmonary Aspergillosis
                    - Pt: underlying lung dz
                    - CXR: halo sign around peripheral nodules with air-crescentic appearance
                    - S/S:
            - Invasive
                - Invasive Aspergillosis
                    - Pts: immunocompromised esp neutropenic, HIV, s/p transplant
                    - Organs: Sinuses, CNS, Heart, Kidneys
                    - Tx: AmphoB
    - Dx
        - Basic Labs
            - Eosinophilia
            - + Skin Test to Aspergillus
            - Increased IgE (>1000ng/mL) and IgG (esp specifically for Aspergillus)
        - Serum Tests
            - Galactomannan ELISA (?)
                - Ag: specific antigen found in Aspergillus
                - High False – (not sensitive)
                - NB spot lab that is done at Baylor and takes two days to come back
        - Tissue Bx much better than BCx
        - CXR (refer above)
    - Treatment
        - Allergic: High Dose Steroids and Itraconazole (follow IgE to determine duration of Tx)
        - Saprophytic: Surgical Resection for Fungus Ball (no medical therapy)
        - Invasive: prophylaxis (Posaconazole) vs treatment (Voriconazole is the DOC NOT Ampho which is 2nd line)

- **PCP (Bacteria) (refer)**
- ***Actinomyces isrealii* & *Nocardia asteroides* (GPR that resemble fungi in that they grow long branching into filaments resembling hyphae)**
    - Actinomyces (anaerobic, normal flora of mouth/skin, trauma leads to eroding cervicofacial fistulizing abscesses w/ pus revealing yellow sulfur granules, seen in immunocompetent pts, Tx w/ PenG and surgical debridement)
    - Nocardia (aerobic, + AFB, not normal flora only found in soil, inhalation leads to TB like disease w/ brain abscesses and meningitis, seen in immunocompromised pts, Tx w/ Bactrim)

<u>Endemic Fungi</u> (Dimorphic) (not opportunistic in that they possess innate virulence that allows them to infect immunocompetent pts however severe disseminated disease occurs in immunocompromised pts, dimorphic fungi existing as mold in cool soil and yeast in warm

tissue, acquire from inhalation of soil, can mimic TB, Dx: complement fixation, Ag, Cx, Tx: IV Ampho B followed by PO Itraconazole indefinitely if HIV+ and CD4 <150, NB in some cases of subclinical pulmonary dz can just be Tx w/ Itraconazole)

- **Histoplasmosis (*Histoplasma capsulatum*)**
    - Epidemiology: Central/SE US esp where there are bird/bat droppings and at Mississippi/Ohio River Valleys (also Central/South America, Southeast Asia)
    - S/S: acute pulmonary dz (subclinical or flu-like illness) then chronic pulmonary dz (B Symptoms, bilateral upper lung cavities similar to TB, productive cough) then disseminated dz if immunocompromised (B Symptoms, HSM, **Fibrosing Mediastinal LAD w/ compression of adjacent structures**, **palate/GI Ulcers**, SM, Skin, BM w/ pancytopenia, Bone, Heart)
- **Coccidiomycosis (*Coccidioides immitis*)**
    - Epidemiology: soil of SW US esp San Joaquin Valley in California (also Central/South America)
    - S/S: acute pulmonary dz (subclinical or flu-like illness) then chronic pulmonary dz (B symptoms, cavitary nodules, productive cough) then disseminated dz if male/immunocompromised/pregnant/diabetic (B symptoms, Bone, **Skin w/ E. nodosum,** CNS w/ meningitis) NB LOOKS VERY MUCH LIKE **SARCOID**
- **Blastomycosis (*Blastomyces dermatitides*)**
    - Epidemiology: **Central/SE/MW** US
    - S/S: acute pulmonary dz (subclinical or flu-like illness) then chronic pulmonary dz (B symptoms, productive cough, pleuritic cp) then disseminated dz if immunocompromised (B Symptoms, **Skin w/ Warty Lesions w/ Central Ulceration**, Bone, CNS, **Prostate/Epididymis/Testes**) NB least common but highest M&M
- **Paracoccidiomycosis (*Paracoccidioides brasiliensis*)**