Candida Infections

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<u>Question 1:</u> You get a call from the Microbiology Lab to inform you of positive blood cultures. You are told that one of your patients has ½ blood cultures growing yeast.

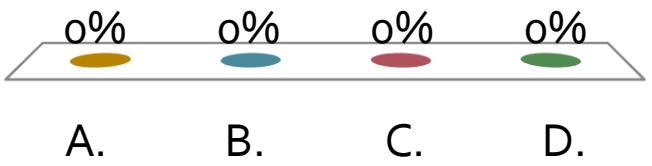
What do you do next?

A. Tell them "Thanks for the message" and go about your day.

B. Tell them that "it's probably a contaminant and do nothing more.

C. Repeat blood cultures x 2

D. Repeat blood cultures x 2, then start empiric antifungal treatment.



Answer: Repeat blood cultures x 2 and start empiric antifungal treatment.

Yeast in the blood is NEVER EVER, EVER a contaminant!

Candida Infections

- Range from local mucous membrane infections to widespread dissemination with multisystem organ failure
- Normal flora in GI or GU tract, but may invade and cause disease if imbalance
- One of the most important determinants of the type of infection caused by *Candida* is the immune response of the host

Candida Infections

- The most benign infections are due to local overgrowth on mucous membranes
  - Oropharyngeal infection (thrush)
  - Vaginitis
- Persistent mucous membrane infections occur in those with deficiencies in cell-mediated immunity (e.g.. AIDS)

Candida Infections

- Invasive focal infections most often occur after hematogenous spread or when anatomic abnormalities or devices are present
  - Endocarditis
  - Meningitis
  - Pyelonephritis
- Can progress to widespread visceral dissemination and multi-organ system failure in the neutropenic host or in severely ill patients

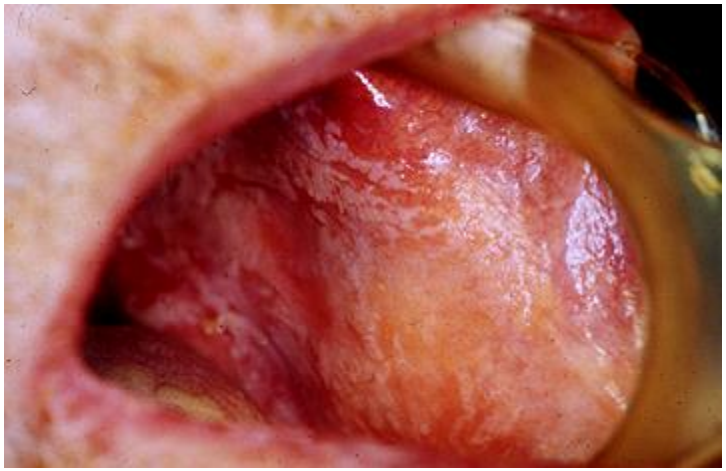
Candida Infections

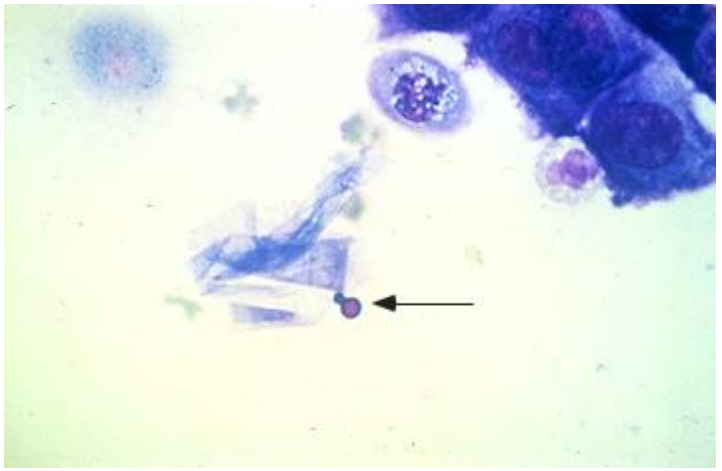
- The different *Candida* species can produce all of the clinical syndromes
  - *C. albicans* is most common
- Important to identify the infecting organism because it will help to guide treatment

Candida Infections

- Local mucocutaneous infections
  - Oropharyngeal candidiasis
    - Infants
    - Denture wearers
    - Recent antibiotics, chemotherapy, or radiation
    - AIDS
    - Xerostomia
    - Inhaled glucocorticoids
    - Most patients asymptomatic
    - White plaques on buccal mucosa, palate, tongue, or under dentures
    - Dx: scrape lesions with tongue blade; Gram stain or KOH prep will show budding yeasts with or without pseudohyphae

Candida Infections

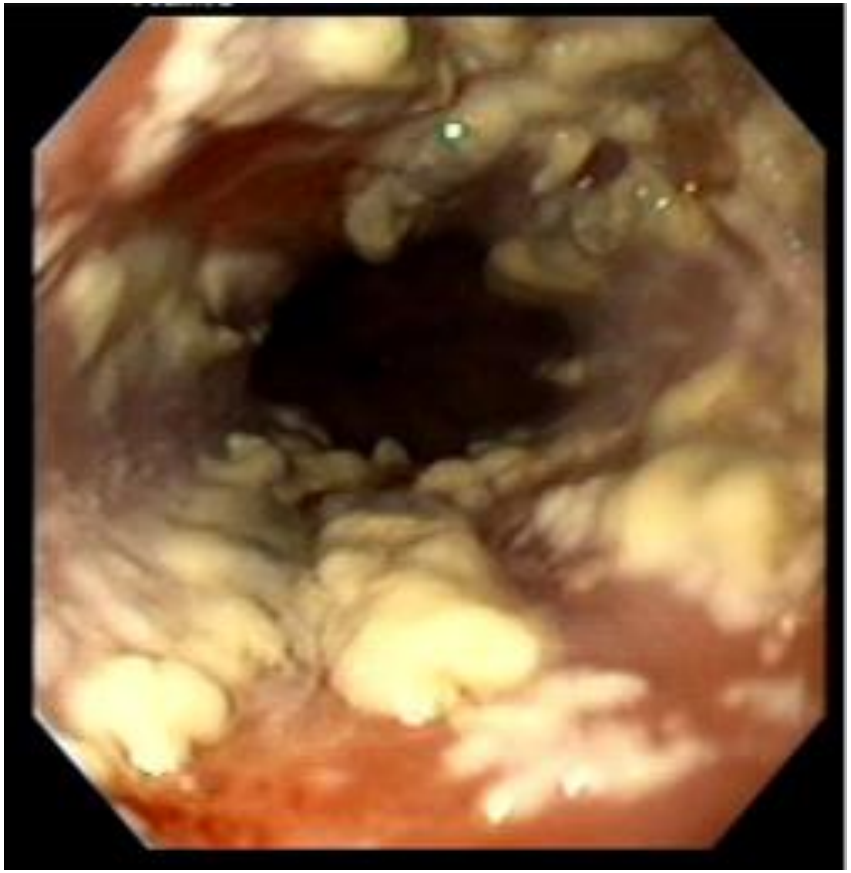




Candida Infections

- Local mucocutaneous infections
  - Esophagitis
    - Most common in HIV-infected patients, considered an AIDS-defining illness
    - Hematologic malignancies
    - Thrush may or may not be present
    - Almost all patients will complain of odynophagia and will localize their pain to the retrosternal area
    - Dx: white plaque-like lesions made on endoscopy; biopsy will show yeast invading mucosal cells

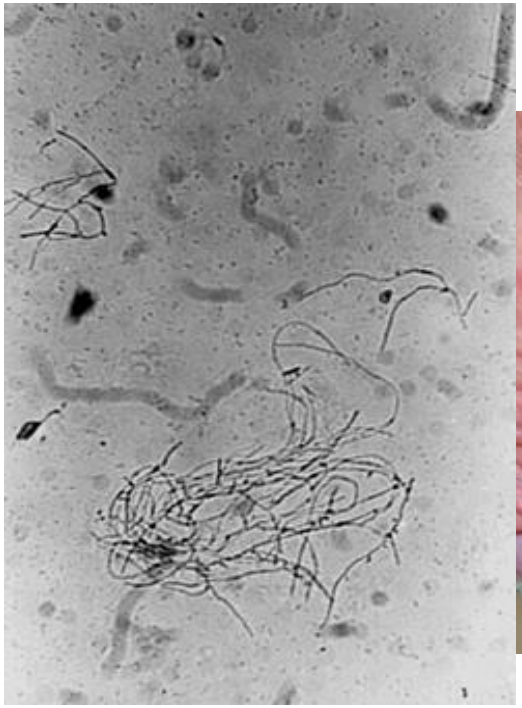
Candida Infections

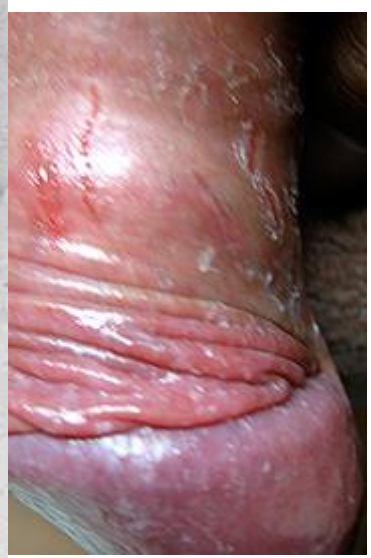


Candida Infections

- Local mucocutaneous infections
  - Vulvovaginitis
    - Most common mucocutaneous infection
    - Increased estrogen levels (OCP, pregnancy)
    - Other risk factors include recent antibiotic use, glucocorticoids, diabetes, HIV, IUD's, and diaphragm use
    - Classic symptoms include itching, white discharge
    - Other symptoms include dyspareunia and dysuria
    - Diagnosis made clinically, can do a wet mount or KOH prep to confirm
  - Balanitis
    - White patches on penis
    - Severe burning and itching
    - Can spread to thighs, gluteal folds, buttocks, and scrotum

Candida Infections





Candida Infections

- Invasive infection
  - Risk factors
    - Immunosuppression
    - Severe illness (ICU)
    - Hematologic malignancies
    - Solid organ or stem cell transplant recipients
    - Chemotherapy

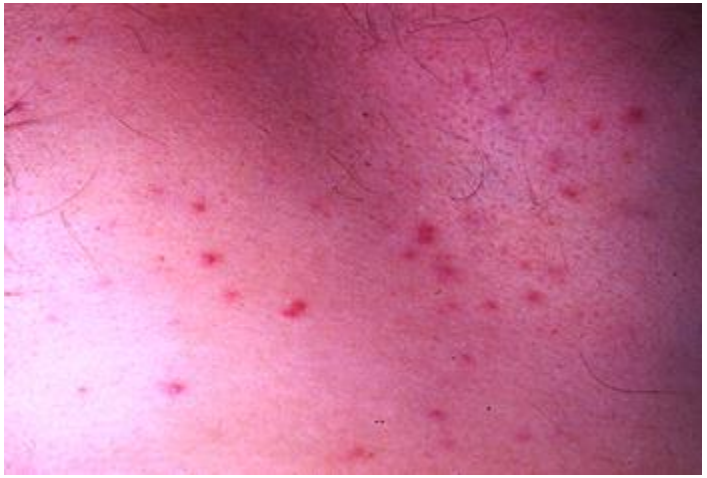
Candida Infections

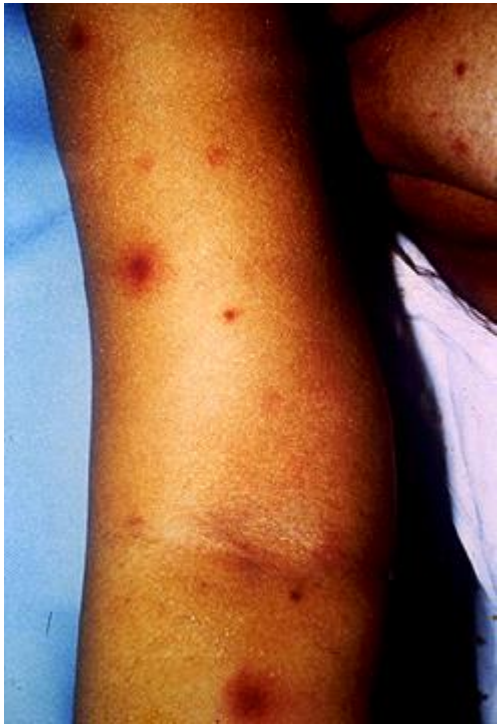
- Invasive infection
  - ICU patients account for the greatest number of episodes of candidemia at most hospitals
    - Highest risk units: Trauma, burn, neonatal
    - Other risk factors associated with invasive candidiasis in ICU patients are:
      - Central venous catheters
      - TPN
      - Broad-spectrum antibiotics
      - High APACHE scores
      - ARF, particularly if requiring HD
      - Prior surgery, especially GI surgery
      - GI tract perforations and anastomotic leaks

Candida Infections

- Invasive infection
  - Clinical manifestations vary
  - Candidemia: Candida species in blood
  - Invasive candidiasis: visceral sites involved
  - Hematogenous spread:
    - Eye, skin lesions
    - Muscle abscesses (uncommon)
    - Lesions look like clusters of painless pustules on an erythematous base and can occur anywhere on the body

Candida Infections





Candida Infections

- Invasive infection
  - In addition to peripheral signs of involvement, may have signs of multi-organ system failure
  - Microabscesses may be present in kidneys, heart, liver, spleen, lungs, eyes, brain
- Chronic disseminated candidiasis
  - Seen in patients with hematologic malignancies who have just recovered from a neutropenic episode
  - Classic presentation: persistent fever (frequently high and spiking) in a patient who was recently neutropenic and whose neutrophil count is now normal
    - RUQ pain, anorexia, nausea, vomiting
    - Labs typically show an elevated alkaline phosphatase
    - MAY OCCUR IN ABSENCE OF POSITIVE BLOOD CULTURES
    - Diagnosis established with imaging (U/S, CT, MRI), will see lucencies in liver, spleen, kidneys

Candida Infections

- Treatment of candidemia and invasive candidiasis
  - Candida in a blood culture should NEVER be viewed as a contaminant and should ALWAYS prompt a search for the source of candidemia
    - Can be a manifestation of disseminated candidiasis or may be due to colonization of an indwelling catheter
  - Candidemia ALWAYS requires treatment with an antifungal agent
  - It should NEVER be assumed that removal of a catheter alone is adequate therapy for candidemia

Candida Infections

- Treatment
  - Mortality rates are high in patients with candidemia and are highest in those who were not treated with an antifungal drug
  - PROMPT INITIATION OF THERAPY IS VERY IMPORTANT

Candida Infections

- Treatment
  - Antifungal agents
    - Drug classes: polyenes, azoles, echinocandins
  - Polyenes
    - Amphotericin B, liposomal amphotericin B, and amphotericin B lipid complex
    - Disrupts fungal wall synthesis by binding to sterols
    - May be fungistatic or fungicidal depending on concentration and sensitivity of pathogen
    - Polyenes demonstrate rapid cidal activity in vitro against most species of *Candida*
      - Exception: *Candida lusitaniae* (susceptible to azoles and echinocandins)

Candida Infections

- Treatment
  - Polyenes
    - Associated with significant nephrotoxicity
    - Lipid based compounds have much less toxicity than Ampho B
    - Recommended dose for candidemia: 3 – 5 mg/kg IV q 24 (liposomal formulation)
    - Adverse effects
      - Infusion related reactions: nausea, vomiting, chills, fever, headache
      - Premedicate with Tylenol and Benadryl, usually given 30 minutes before Ampho B infusion
      - Other adverse effects included phlebitis, electrolyte abnormalities
      - Anaphylaxis extremely rare
    - Drug interactions with other nephrotoxic agents, digoxin

Candida Infections

- Treatment
  - Polyenes
    - Besides *Candida* infections, Ampho B used in treatment of fungal infections caused by *Aspergillus* spp, *Zygomycetes*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*, and *Sporothrix schenckii*
    - Fungal isolates RESISTANT to Ampho B include:
      - Organisms that cause chromoblastomycosis (*Fonsecaea*, *Cladophiliophora)*
      - *Aspergillus terreus*
      - *Scedosporium spp (Pseudallescheria boydii)*
      - Some *Fusarium* species

Candida Infections

- Treatment
  - Azoles
    - Include fluconazole, itraconazole, voriconazole, posaconazole
    - Fluconazole widely used for treatment of candidiasis
      - Excellent safety profile, available IV and PO
      - Inexpensive (generic)
      - Candidemia dosing: 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) po daily
    - Voriconazole
      - Activity against *Candida* species superior compared to fluconazole
      - Much better activity against *C.krusei*
      - Also available IV and PO, need to monitor drug levels which can be difficult sometimes
      - Expensive
      - Side effects: mostly ocular (floaters)
      - Voriconazole is the treatment of choice for what fungal infection?

Candida Infections

- Treatment
  - Azoles
    - Posaconazole
      - Newest azole, available in oral (solution and tablet) and IV formulation
      - Approved for use as a prophylactic agent for fungal infections in stem cell transplant recipients with GVHD and in patients with prolonged neutropenia
      - Approved for ORAL candidiasis, not systemic candidiasis
      - Ridiculously expensive
    - Azoles interact with multiple cytochrome P450 enzymes
    - Echinocandins may be preferred if patients are taking meds metabolized through the cytochrome P450 pathway

Candida Infections

- Treatment
  - Echinocandins
    - Include caspofungin, anidulafungin, and micafungin
    - Have excellent activity against most *Candida* species
    - Approved for treatment of candidemia and other forms of invasive candidiasis
    - Preferred over azole agents for initial treatment of candidemia if *C.glabrata* or *C.krusei* are identified or suspected
      - *C.glabrata* and *C.krusei* often resistant to fluconazole

Candida Infections

- Treatment
  - Echinocandins
    - Noncompetitive inhibitors of 1,3-beta-D-glucan (cell wall component)
    - Active in vitro against almost all species of Candida
      - High MIC's for *C.parapsilosis* and *C.guillermondii*
    - NO activity against *Cryptococcus* or *Trichosporon* species
    - Side effects: fever, thrombophlebitis, headache, elevated transaminases

Candida Infections

- Treatment
  - Echinocandins
    - Not well absorbed orally and must be given IV
      - Caspofungin: loading dose 70 mg IV x 1, followed by 50 mg IV q 24; need to reduce dose with hepatic dysfunction
      - Anidulafungin: loading dose 200 mg IV x 1, followed by 100 mg IV daily; no adjustments made for hepatic or renal dysfunction
      - Micafungin: 100 mg IV q 24, no loading dose

Candida Infections

- Treatment
  - If etiologic agent has yet to be identified, approach to therapy influenced by these factors:
    - Is the patient known to be colonized with resistant Candida species?
    - Has the patient developed candidemia despite antifungal prophylaxis?
    - What is the proportion of candidemias due to resistant species within that particular hospital?
    - Is the patient also at risk for mold infections?

Candida Infections

- Treatment
  - Neutropenic patients
    - Antifungal therapy most commonly initiated in the case of a persistent fever that has failed to respond to antibiotics
    - Think about starting antifungal treatment after 4-7 days in febrile neutropenic patients receiving antibiotics
    - Most neutropenic patients who receive empiric antifungal therapy are treated with an echinocandin, liposomal Ampho B, or voriconazole
      - Fluconazole may be used in those patients who are clinically stable, have no history of azole exposure, and who are in institutions where *C.glabrata* or *C.krusei* are not commonly isolated

Candida Infections

- Treatment
  - Non-neutropenic patients
    - 2009 IDSA guidelines recommend that empiric antifungal treatment be considered in critically ill patients who are at risk for invasive candidiasis and who have persistent fevers despite antibiotic therapy; supported in 2016 update
    - Remember to assess for risk factors
      - Central lines, TPN, hemodialysis, trauma/burn, broad spectrum antibiotics, and recent surgery
    - Empiric therapy should ONLY be given to those who are felt to be at substantial risk for invasive candidiasis
    - Recommend using an echinocandin or fluconazole, depending on risk of resistant *Candida* species
      - Polyene may be used if there is documented intolerance to other antifungals

Candida Infections

- Mortality
  - One study of 230 patients with candidemia showed that the number of days that passed from notification of the first positive culture for yeast to initiation of fluconazole correlated with increased mortality
    - Day 0: 15%, Day 3: 41%
  - Other factors associated with increased mortality:
    - Higher APACHE scores
    - Inadequate fluconazole dosing
    - Retention of central line
    - ICU patients: diabetes mellitus, immunosuppression, mechanical ventilation
    - Non-ICU patients: glucocorticoids at time positive culture drawn

Candida Infections

- Following patients with candidemia
  - Daily blood cultures after initiation of therapy to document clearance
  - If blood cultures remain positive, need to look for metastatic focus of infection
    - Abscess
    - Endocarditis
  - Patients with candidemia should have a dilated eye exam, preferably by an ophthalmologist, within the first week of therapy in non-neutropenic patients to establish if endophthalmitis is present. For neutropenic patients, it is recommended to delay the examination until neutrophil recovery.
  - Patients with CVC's in place should have them removed

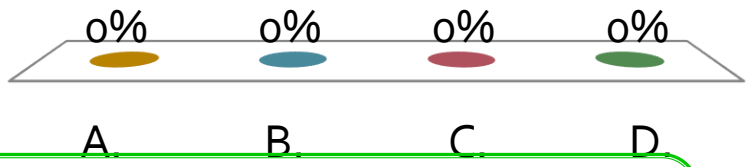
Candida Infections

- Duration of therapy
  - Appropriate duration of therapy hasn't been studied
  - Recommend a minimum of 2 weeks after blood cultures become negative
  - All patients should have resolution of symptoms attributable to candidemia AND resolution of neutropenia before therapy discontinued
  - In candidemia with metastatic focus of infection, formal ID consult is warranted

Question 2: You are reviewing urinalysis and culture results on one of your patients. The patient is a 76 year old white female admitted with abdominal pain. You see that U/A shows 26 WBC's, small leukocyte esterase, negative nitrates, and 136 squamous epithelial cells. Culture results are showing > 100K yeast. The culture was collected as a clean catch sample.

What do you do next?

A. Start Fluconazole
B. Start and echinocandin
C. Repeat U/A and culture
D. Repeat U/A and culture but ask for a straight cath sample



Answer: Repeat U/A and culture, but ask for a straight cath sample.

- There is no such thing as a clean catch in a 76 year old lady.
- U/A and culture results obtained via clean catch in the elderly population are almost always abnormal.
- Echinocandins DO NOT get into the urine

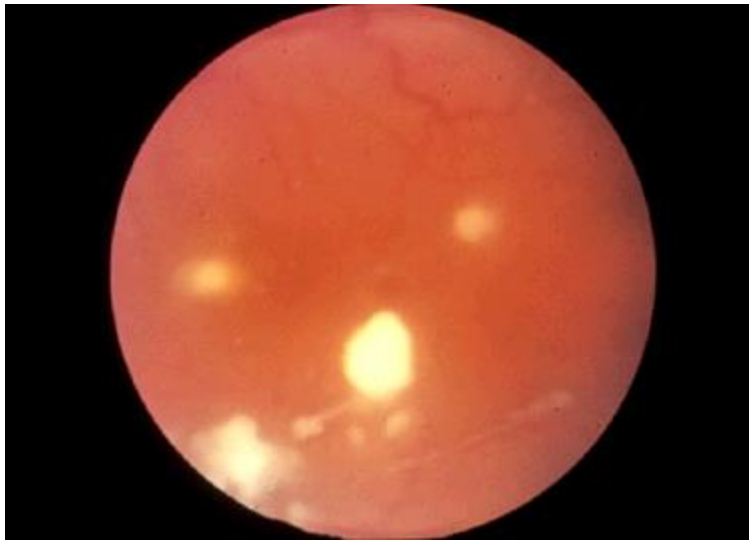
Candida Infections

- Invasive focal infections
  - UTI
    - Candiduria very common in hospitalized patients
    - Difficult to distinguish colonization from infection of the bladder
    - Bladder infection and kidney infection must be distinguished, but can coexist
    - Renal infection more often due to hematogenous seeding; usually seen in setting of disseminated candidiasis
    - Ascending infection develops more insidiously, usually unilateral, and can be complicated by development of an obstructing fungus ball

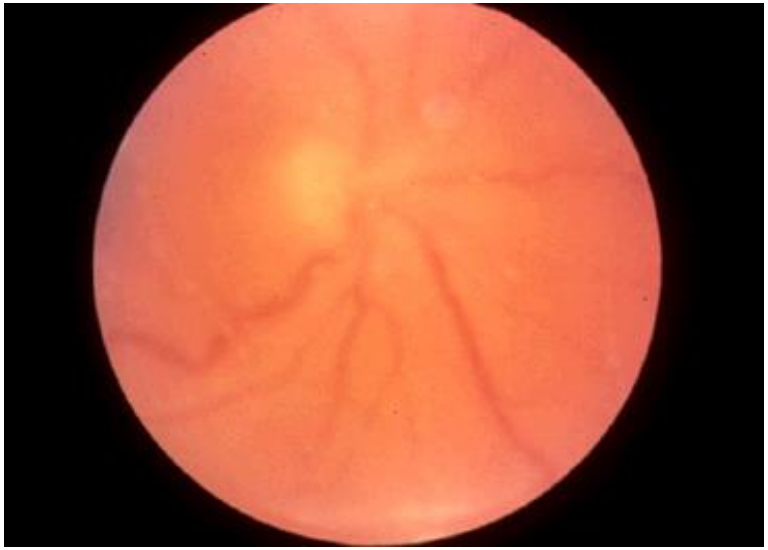
Candida Infections

- Invasive focal infections
  - Endophthalmitis
    - Develops exogenously through eye trauma or eye surgery or endogenously through seeding of the retina or choroid as a complication of candidemia
    - Primary presenting symptom is a decrease in visual acuity
    - Classic findings of chorioretinoid involvement are focal, glistening, white, infiltrative mound-like lesions on retina
    - Vitreal haze present when extension to vitreous
    - Can be sight-threatening if not treated

Candida Infections



Endophthalmitis



Vitritis

Candida Infections

- Invasive focal infections
  - Osteoarticular infections
    - Infect bones and joints through hematogenous seeding, inoculation during trauma, intraarticular injection, surgery, or injection drug use
    - Most infections are of native joints
    - Among patients with osteomyelitis, site of involvement varies with age:
      - Adults: vertebrae
      - Children: long bones
    - These infections become symptomatic months after an episode of candidemia or surgical procedure; manifestations more subtle than bacterial infections at same sites

Candida Infections

- Invasive focal infections
  - Osteoarticular infections
    - Candida arthritis: pain and decreased ROM
    - Candida osteomyelitis: local pain
    - Diagnosis: culture of infected site
      - Arthrocentesis: arthritis
      - Bone biopsy: osteomyelitis
    - A single colony of Candida seen in arthrocentesis or bone biopsy should be considered pathogenic and not a contaminant

Candida Infections

- Invasive focal infections
  - Meningitis
    - Can present as a chronic meningitis as a manifestation of disseminated candidiasis, a complication of ventricular drainage devices, and as an isolated chronic meningitis
    - Can enter CNS through hematogenous seeding, at time of craniotomy, or through VP shunt
    - Symptoms same as in acute bacterial meningitis
      - Sepsis, multi-organ system failure in neonates
      - Fever only in those who are neutropenic
    - Look for other signs of hematogenous seeding

Candida Infections

- Invasive focal infections
  - Meningitis ctd.
    - Dx: lumbar puncture
    - Diagnosis often difficult to establish because Candida usually present in low numbers; often need large volume LP's to get enough sample to detect it

Candida Infections

- Invasive focal infections
  - Endocarditis
    - Most common cause of fungal endocarditis
    - Seen in patients with prosthetic heart valves, IVDU, and in those with indwelling central catheters and prolonged fungemia
    - Clinical manifestations: fever, new murmur, heart failure
    - Larger vegetations than in bacterial endocarditis; peripheral embolization more likely
    - Dx: TEE
    - CT surgery consult

Candida Infections

- Invasive focal infections
  - Peritonitis and intraabdominal infections
    - Frequently contribute to polymicrobial infections that occur following GIT perforation, anastomotic leaks after bowel surgery, or acute necrotizing pancreatitis
    - Can also complicate continuous peritoneal dialysis in those patients with ESRD
    - *C. albicans* is the most predominant species isolated in intraabdominal infections, although *C.glabrata* on the rise
    - Symptoms of peritonitis include fevers, chills, abdominal pain
    - Can progress to bloodstream infection with sepsis and abscess formation requiring drainage

Candida Infections

- Invasive focal infections
  - Peritonitis and intraabdominal infections, ctd.
    - Diagnosis: CT or U/S guided aspiration or deep cultures obtained during surgery
    - Culture of *Candida* species from indwelling drain NOT adequate for diagnosis; more reflective of colonization inside drain rather than in fluid collection itself

Candida Infections

- Invasive focal infections
  - Pneumonia
    - Very rare
    - Positive cultures from bronchoscopy/BAL more likely colonization or contamination of sample rather than true infection
  - Empyema
    - Mostly seen in patients with malignancies
    - Usually nosocomial
    - Most of these patients also have/had candidemia

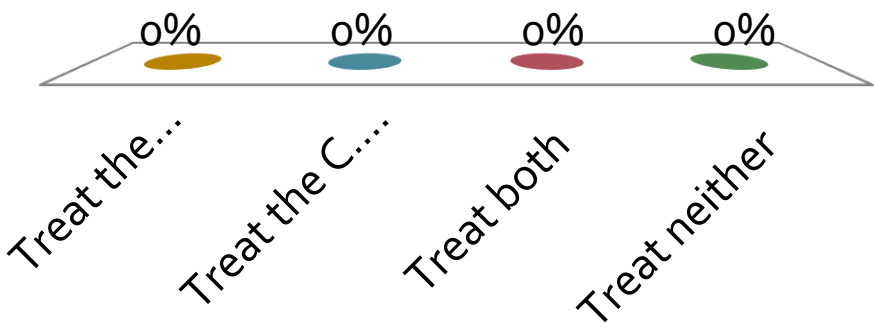
Candida Infections

- Invasive focal infections
  - Mediastinitis
    - Almost always occurs after surgical procedure
    - Sx: chest wall erythema, drainage, sternal instability
  - Pericarditis
    - Rare, life-threatening
    - Complication of surgery or contiguous spread from adjacent focus
    - Hematogenous spread can occur
    - *C.albicans* most common pathogen

<u>Question 3</u>: You are called by the Microbiology lab regarding a positive stool culture. The patient is a 46 year old white male admitted with diarrhea. Stool culture is showing *Campylobacter* and *C.albicans*.

What do you do next?

A. Treat the *Campylobacter*
B. Treat the C. *albicans*
C. Treat both
D. Treat neither



Answer: Treat the Campylobacter

Treat the Campylobacter

- Candida species are part of the normal flora of the GI tract.
- Isolation from stool cultures represents colonization and not infection.

Candida Infections

- Take Home Points
  - Yeast in the blood is NEVER a contaminant. Always follow up with repeat blood cultures and a workup to evaluate for disseminated disease (TEE to r/o endocarditis, Ophthalmology consult)
  - Ask Microbiology what yeast looks like
    - If they says it's *Candida*, ask them to do a germ tube test
      - Germ tube positive: *C.albicans*
      - Germ tube negative: another *Candida* species

Candida Infections

- First line treatment if it's *Candida*: echinocandin
  - Can adjust therapy as needed once sensitivities return
- If yeast in blood does NOT look like *Candida*, start with Ampho B (lipid formulation); premedicate if needed
- *Candida* is part of the normal flora of the GI and GU tract. Careful investigation is needed to determine if *Candida* is actually causing disease or is just a colonizer. More often than not, it's a colonizer.

References

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