

Candidiasis

(We highly recommend reading the Dr notes as they contain some highly imp info not in the main lec)

Lecture objectives:

- Acquire the basic knowledge about Candida as a pathogen
- know the main infections caused by Candida species
- Identify the clinical settings of such infections
- Know the laboratory diagnosis, and treatment of these infections.

Color index:

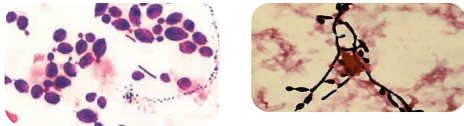
- Important
- Doctors' note
- Extra
- Found in Females' slides
- Found in Males' slides

- Candida is a unicellular yeast fungus.
- It is imperfect reproducing by budding

❖ Morphology¹

Microscopy

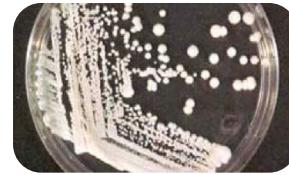
Round **budding** yeast cells, and **Pseudohyphae**.



Will appear as Gram + bacteria (violet in color) but they are larger in size with buds

Culture

Creamy colony, fast growing on **Sabouraud Dextrose agar (SDA)**, Blood agar (48 hr)



SDA: Creamy white colonies

❖ Species

- There are many species of Candida (>150)
- The common species are:
Candida albicans (Most common), C. parapsilosis, C. tropicalis, C. glabrata, C. krusei

❖ Human commensal “Normal flora”



Oral cavity



Gastrointestinal tract



Skin



Genitourinary tracts e.g.
Vagina, urethra

¹- Almost all candida have the same morphology, so you can't differentiate candida species by morphology.

The disease: Candidiasis

❖ Definition:

- Any infection caused by any species of the yeast fungus *Candida*.
- The most common invasive fungal infections in immunocompromised patients
- 4th most common cause of nosocomial **bloodstream infection** “Septicemia”

❖ Modes of transmission:

1. **Endogenous:** “Usually normal flora” (More Common)
 - a. Colonization precedes infection
 - b. Antibiotic suppression of normal flora, fungal overgrowth
2. **Exogenous:** Very rare, could be from the environment in hospitals.

❖ Pathogenesis:

- **Opportunistic Fungal infections:**
 - Alteration in : Immunity¹ , Normal physiology² , Normal flora³
 - Damage in the barriers e.g. Skin, Intestinal mucosa. If damaged by Burns, Abdominal surgery or central lines, yeast cells will get the chance to reach the blood and cause septicemia.
 - **Clinical : Spectrum of disease:**

Mucous membrane infections	Cutaneous infections	Other diseases
<ul style="list-style-type: none">• Oral Thrush (oropharyngeal)• Esophagitis• Vaginitis	<ul style="list-style-type: none">• Paronychia (skin around nail bed)• Onychomycosis (nails)• Diaper rash• Chronic mucocutaneous candidiasis :<ul style="list-style-type: none">○ Children with T-cell abnormality	<ul style="list-style-type: none">• Urinary tract infection• Candidemia which may disseminate⁵ (systemic, invasive) to:<ul style="list-style-type: none">○ Endophthalmitis (eye)⁴, Liver and spleen, Kidneys, Skin, Brain, Lungs and Bone

❖ Chronic mucocutaneous candidiasis:

- Heterogeneous group of immune system defects → impaired cell-mediated immunity(T-cell dysfunction.) against *Candida* sp. Classic form caused by defects in AIRE.
- Patients are born with defects in their immune system, so they are more susceptible to candida infections, They usually develop very severe cutaneous candidiasis (common in Skin and nails).
- It's Chronic, so it's more difficult to treat.



1- e.g. AIDS, Steroid medications, Diabetes, Chemotherapy.
2- e.g. Aging, pregnancy (Have more risk for developing vaginitis)
3- e.g. Broad spectrum Abx (e.g. Ampicillin, Aminoglycosides (except for streptomycin), Tetracyclines)
4- Especially in children.
5- Especially in neutropenic patients

1- Oropharyngeal Candidiasis :

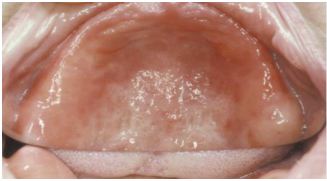
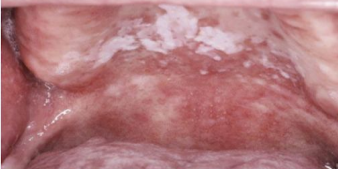
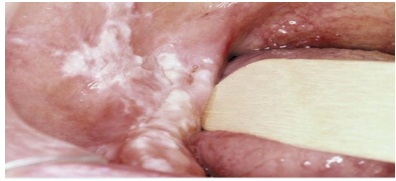
- **Oral thrush:**

- **White** or grey Pseudomembranous **patches** on oral surfaces **especially tongue and palate** with underlying erythema.
- Common in **neonates ,infants** , elderly, **Patients on broad spectrum Abx,** **Asthmatic patients**(because they use steroid medications) and In immunocompromised hosts¹e.g.AIDS.



Oral thrush

- **Forms of oral candidiasis:**

1- Erythematous form	2-Pseudomembranous-erythematous form.	3- Hyperplastic form:
 <p>Sometimes we don't see white patches, we see something called erythematous candidiasis(redness and inflammation). It usually occurs in old people using dentures.</p>	 <p>Both White patches and erythematous lesions.</p>	 <p>White patches but difficult to remove unlike oral thrush, That was mistaken for leukoplakia</p>

2- Esophagitis

3- Vulvovaginitis : “70% of women develop this, at least once in life”

- Common in pregnancy, diabetics, use of contraceptives.
- Thick discharge, itching irritation .
- Lesion appear as white patches on vaginal mucosa

1-Usually Immunocompromised hosts present with esophagitis as well.

1- Intertriginous candidiasis:

- Infections of skin folds eg. axilla, buttock, toe web, under breast.
- Erythematous lesion, dry or moist or whitish accompanied by itching and burning.

2- Nail infections:

- Onychomycosis and paronychia



Pulmonary Candidiasis

- Primary pneumonia is **less common** and could be a result of Aspiration
- Secondary pneumonia commonly seen with hematogenous candidiasis
 - Immunocompromised patients
- Isolation of Candida from **sputum¹, Bronchoalveolar lavage (BAL) is not always significant**
 - Clinical features
 - Radiology,
 - Other Lab investigations



1- Positive sputum for candida isn't diagnostic because candida is usually found in the normal flora of the mouth, BAL is better than sputum.

- Candida is the fourth in causing nosocomial bloodstream infections (BSI)
- Increased colonization (endogenous or exogenous factors)
- Damage in host barriers by **catheters¹**, trauma, **surgery**
- Immunosuppression
- **Central venous catheters (CVC)**
- Disseminated candidiasis (involvement of any organ):
 - **Septic shock → Has bad prognosis (Death)**
 - Meningitis
 - Ocular involvement (retinitis)
- Fever could be the only clinical manifestation:
 - Usually the scenario is a patient in the ICU and has central lines, develops fever. What's your first intervention? First Think of bacteria, so start with bacterial Abx, if there's no response, think about yeast.

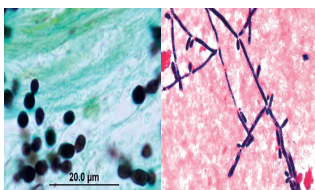
Rank	Pathogen	BSI per 10,000 admissions	% BSI			% Crude Mortality		
			Total (n=20,978)	ICU (n=10,515)	Non-ICU (n=10,515)	Total	ICU	Non-ICU
1.	CoNS	15.8	31.3	35.9	26.6	20.7	25.7	13.8
2.	S aureus	10.3	20.2	16.8	23.7	25.4	34.4	18.9
3.	Enterococcus spp	4.8	9.4	9.8	9.0	33.9	43.0	24.0
4.	Candida spp	4.6	9.0	10.1	7.9	39.2	47.1	29.0
5.	E coli	2.8	5.6	3.7	7.6	22.4	33.9	16.9
6.	Klebsiella spp	2.4	4.8	4.0	5.5	27.6	37.4	20.3
7.	P aeruginosa	2.1	4.3	4.7	3.8	38.7	47.9	27.6
8.	Enterobacter spp	1.9	3.9	4.7	3.1	26.7	32.5	18.0
9.	Serratia spp	0.9	1.7	2.1	1.3	27.4	33.9	17.1
10.	A baumannii	0.6	1.3	1.6	0.9	34.0	43.4	16.3

- Mortality rate: Almost 50%.
- Note that candida has higher mortality rate than bacteria.

1 - Always remember that Central lines are one of the major risk factors for developing candidiasis.

Specimen depend on site of infection: e.g. UTI → Urine, Meningitis→ CSF etc.
Swabs. Urine, Blood, Respiratory specimens, CSF, vitreous sample, vaginal swabs.

Method	Description
Direct Microscopy	<ul style="list-style-type: none"> ● Stain: Gram stain, KOH, Giemsa, GMS¹, or PAS stained smears. ● Budding yeast cells and pseudohyphae will be seen in stained smear or KOH.
Culture	<ul style="list-style-type: none"> ● Media: SDA & Blood agar at 37oC, ● Creamy moist colonies in 24 - 48 hours.
Blood Culture (If patient is febrile and you suspect septicemia)	<ul style="list-style-type: none"> ● Uses: <ul style="list-style-type: none"> ○ Detection of circulating microorganisms in <u>septicemia</u> ● Description : <ul style="list-style-type: none"> ○ Different types of blood culture bottles and blood volumes required: <ul style="list-style-type: none"> ■ Pediatric aerobic (0.5–4 mL blood) ■ Adult aerobic (5–10 mL blood) ■ Anaerobic (5–10 mL blood) ● Two sets of cultures before starting antibiotics is ideal
Serology	<ul style="list-style-type: none"> ● Patient serum <ul style="list-style-type: none"> ○ Test for Antigen , e.g. Mannan² antigen using ELISA ○ Test for Antibodies e.g. Anti-mannan antibodies
PCR	<ul style="list-style-type: none"> ● For detection of nucleic acid.



Direct microscopy



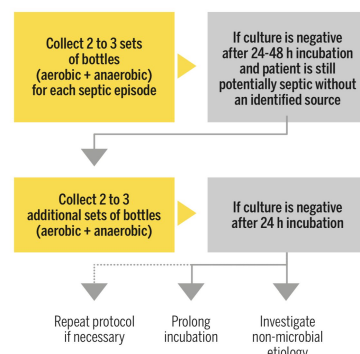
Culture



Blood Culture

EXTRA info about blood culture:

Adapted from Baron EJ, Tenover FC, Tenover FC. *Cumitech 10, Blood Cultures IV*. Coordinating ed., E.J. Baron. ASM Press, Washington, D.C. 2005.



Everything must be done aseptically to prevent false positive results. Note: *Brucella* sp. require 21 days of incubation

1- Grocott-Gomori's methenamine silver stain

2- Mannan is a polysaccharide and polymer of the sugar mannose that is a highly immunogenic component of the *Candida* cell wall. So if serology is positive mannan antigen this indicates a *Candida* infection (specific for *Candida*).

Laboratory diagnosis of yeast

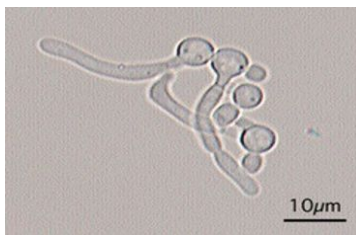
- Because *C. albicans* is the most common species to cause infection

The following tests are used to identify *C. albicans*:

1

Germ tube test¹:

Formation of germ tube when cultured in serum at 37oC

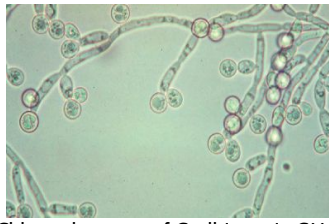


Germ tube test

2

Corn meal Agar :

Chlamyospore production in corn meal Agar



Chlamyospores of *C. albicans* in CMA

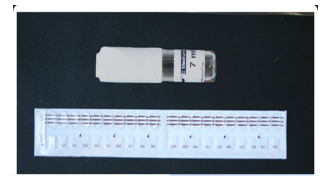
3

Cycloheximide :

Resistance to 500 µg/ml Cycloheximide

- If these 3 are positive this yeast is *C. albicans*, If negative, then it could be any other yeast, we can do:

- Carbohydrate assimilations and fermentation.²
 - Commercial kits available for this like: API 20C, API 32C
- Culture on Chromogenic Media (**CHROMagarTM** Candida)



Carbohydrates assimilation test , API 20C

◆ Candida species :

- Candida albicans*

Agar	Morphology	Picture
Sabouraud Agar	Creamy white yeast , may be dull, dry irregular and heaped up, glabrous and tough	
Chromagar	producing green pigmented colonies on specially designed medium to speciate certain yeasts based on color they produce	

1- We add the yeast to serum, and keep the sample in the incubator for 2hr and 30 min, only candida albicans will germinate and produce germ tubes.

2- If positive this indicates an infection by yeast. (Not specific, all yeasts are possible including albicans).

Treatment	
Oropharyngeal	<ul style="list-style-type: none"> • Topical Nystatin suspension • Clotrimazole troches • Miconazole • Fluconazole suspension
Vaginitis	<ul style="list-style-type: none"> • Miconazole, • Clotrimazole • Fluconazole
Systemic treatment of Candidiasis (Indications: Septicemia, meningitis or severe UTI)	<ul style="list-style-type: none"> • Fluconazole¹ • Voriconazole¹ • Caspofungin, micafungin, or anidulafungin • Amphotericin²
candidemia	<ul style="list-style-type: none"> • Treat for 14 days after last negative culture and resolution of signs and symptoms • Remove catheters, if possible

- Antifungal susceptibility testing is not done routinely in the microbiology lab, It is done in the following cases:
 - For fungi isolated from sterile samples e.g. Blood, CSF etc.
 - If the patient is not responding to treatment
 - In case of recurrent infections
- Points to consider :
 - **C. glabrata can be less susceptible or resistant to fluconazole³**
 - **C. krusei is resistant to fluconazole³**

1- Only used if species are susceptible.

2- Amphotericin is a broad spectrum anti-fungal, but with candida, if we don't know the exact specie we go with **caspofungin** because it's more safe.

3- Use caspofungin instead.

Quiz

MCQ:

Answers: Q1:C | Q2:C | Q3:D | Q4:B | Q5:A

Q1: C. albicans is recognized in microscopic examination of infected tissues by the presence of:

- A- Spherules containing endospores
- B- Metachromatic granules
- C- Yeasts and pseudohyphae
- D- Asci containing 2–8 ascospores

Q2: A 31-year-old man with AIDS complains of painful swallowing. Physical examination of his oral cavity demonstrates a whitish membrane covering much of his tongue and palate. Endoscopic examination reveals the same whitish membrane covering his esophageal mucosa. Which of the following is the most likely etiologic agent responsible for this patient's symptoms?

- A- Chlamydia
- B- Rickettsia
- C- Fungus
- D- Spirochete

Q3: A 35-year-old, HIV-positive man complains that he has had a "bad" taste in his mouth and discoloration of his tongue for the past 6 weeks. On physical examination, there are areas of adherent, yellow-tan, circumscribed plaque on the lateral aspects of the tongue. This plaque can be scraped off as a pseudomembrane to show an underlying granular, erythematous base. What is the most likely diagnosis?

- A- Aphthous ulcer
- B- Cheilosis
- C- Hairy leukoplakia
- D- Oral thrush

Q4: Which of the following is resistant to fluconazole?

- A- C. Albicans
- B- C. glabrata
- C- C. parapsilosis
- D- C. Tropicalis

Q5: Which of the following tests are used to differentiate C. albicans from other candida?

- A- Germ tube test
- B- Carbohydrate assimilations
- C- Gram stain
- D- macconkey agar

SAQ:

CASE: A patient with diabetes presents to her physician with a white, flaky, adherent substance on the skin under her breasts. Another patient, a woman who has just completed a course of oral Abx, presents with itching and copious vaginal discharge that resembles "cottage cheese". A third patient, with AIDS, presents with white exudate on his oral mucosa and soft palate. The physician diagnoses the same causative microorganism for all three cases.

Q1: What is the most likely diagnosis?

A: Candidiasis

Q2: What is the most likely causative agent?

A: Candida albicans

Q3: How would you confirm that these conditions are caused by the organism you mentioned in Q2?

A: By Germ tube test.

Q4: What media is used for this organism?

A: Sabouraud dextrose agar (SDA)

Q5: Describe its morphology on the media you mentioned in Q4.

A: Creamy white yeast

Members board

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