Opportunistic Systemic Mycoses - Candidiasis

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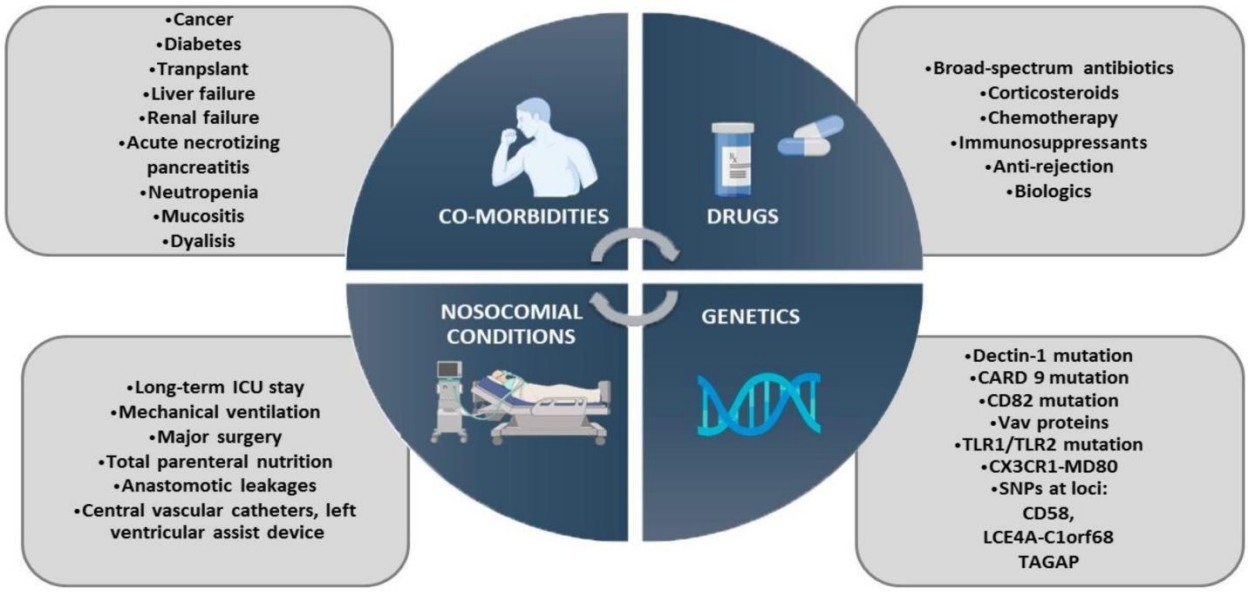
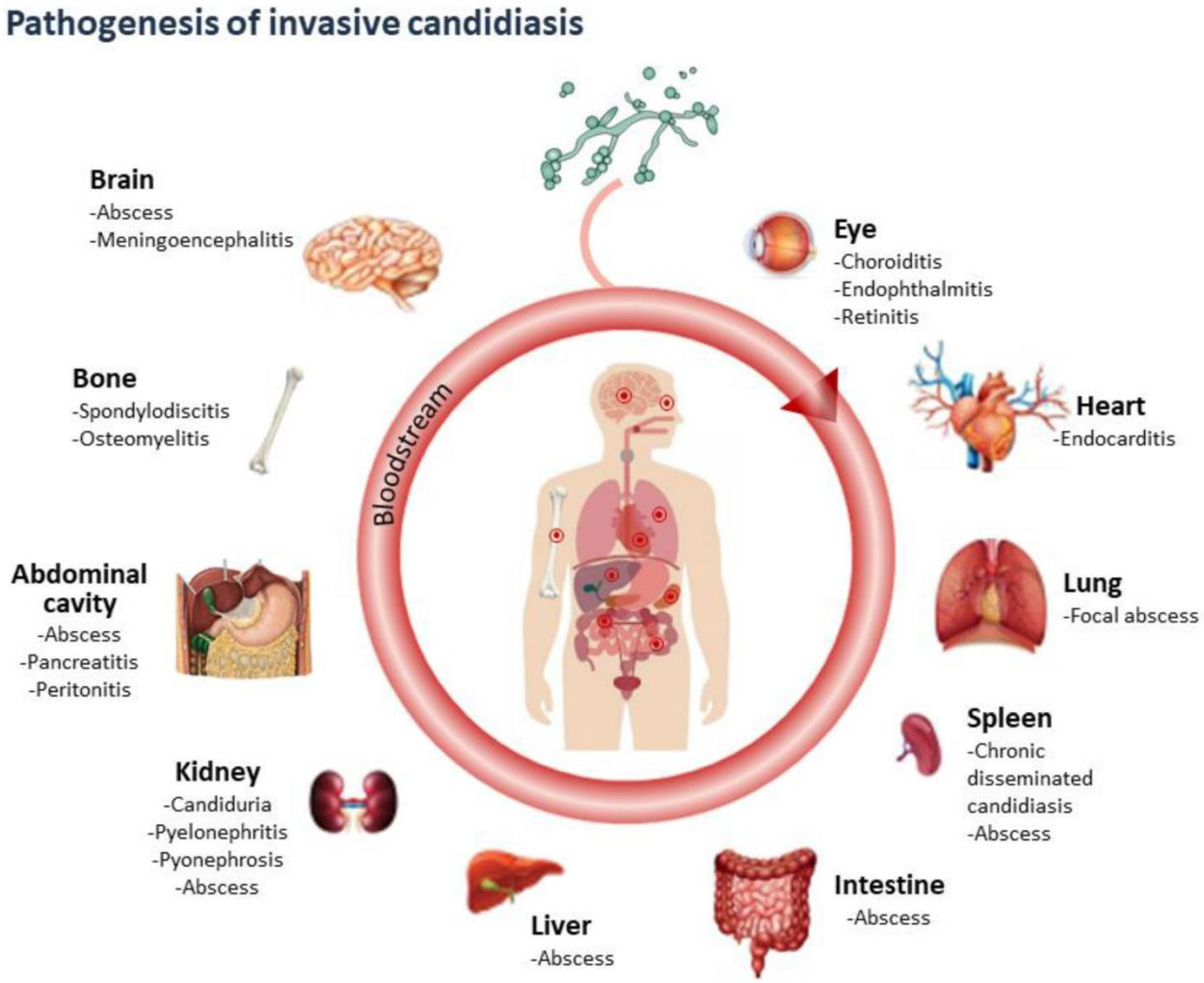
Candidiasis

Candidiasis is a primary or secondary mycotic infection caused by members of the genus Candida and other related genera. The clinical manifestations may be acute, subacute or chronic to episodic. Involvement may be localized to the mouth, throat, skin, scalp, vagina, fingers, nails, bronchi, lungs, or the gastrointestinal tract, or become systemic as in septicemia, endocarditis and meningitis. In healthy individuals, Candida infections are usually due to impaired epithelial barrier functions and occur in all age groups, but are most common in the newborn and the elderly. They usually remain superficial and respond readily to treatment. Systemic candidiasis is usually seen in patients with cell-mediated immune deficiency, and those receiving aggressive cancer treatment, immunosuppression, or transplantation therapy.



Risk Factors Predisposing to Invasive Candidiasis, categorized into four Groups: Co-Morbidities, Nosocomial Conditions, Drugs and Human Genetic Factors.



Virulence Factors: A combination of virulence factors and fitness attributes promotes Candida virulence.

1- Polymorphism: The ability of C. albicans to undergo morphological transitions allows it to adapt to different growth conditions, adhere to biotic and abiotic surfaces, invade cells and tissue, and escape from immune cells.

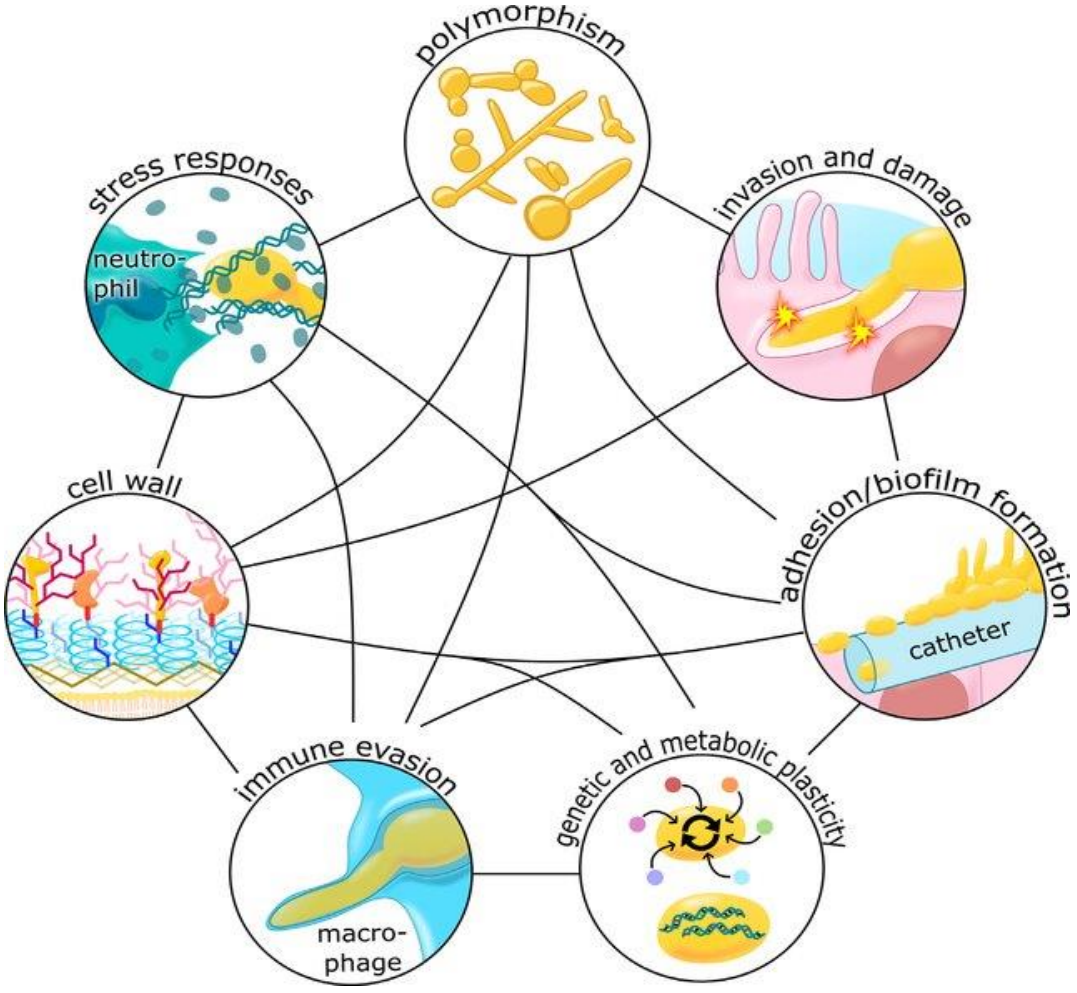
2- Invasion and damage: A combination of induced endocytosis and active penetration promotes fungal invasion of host tissues, and the accumulation of the toxin, candidalysin, in the invasion pocket leads to pore formation and host cell damage.

3- Adhesion/biofilm formation: The battery of adhesins promotes fungal adhesions to biological and abiotic surfaces, which can lead to the development of biofilms, for example on medical devices such as catheters.

4- Genetic and metabolic plasticity: Candida albicans displays a high degree of metabolic flexibility, which allows it to adapt rapidly to diverse host niches. This fungus also displays great genetic plasticity, which permits rapid evolutionary adaptation to selective pressures and stresses such as exposure to antifungal drugs.

5- Stress responses: Candida albicans activates robust stress responses following exposure to host imposed stresses, including ROS and RNS, which enhances fungal survival following immune attack, for example. Cell wall: As well as maintaining cell morphology, the robust cell wall provides protection against host-imposed stresses including changes in osmolarity.

6- Immune evasion: Candida albicans has evolved a variety of immune evasion strategies that include the modulation of PAMP exposure at the cell surface to evade immune recognition, and phagocytic escape mechanisms to evade killing by innate immune cells.



Clinical manifestations:

Neonatal and congenital candidiasis:

Low birth weight and age, prolonged intravascular catheterization and the use of antibiotic drugs are the principle predisposing conditions for systemic candidiasis in neonates. Blood cultures are often positive and there is also a high incidence of meningitis. Renal complications due to fungus ball formation in the ureters or renal pelvis may also occur. Congenital candidiasis acquired in utero is usually confined to the skin in the form of a generalized erythematous vesicular rash, however intrauterine candidiasis may also result in abortion.

Oesophageal candidiasis:

Oesophageal candidiasis is frequently associated with AIDS and severe immunosuppression following treatment for leukemia or solid tumors. Concomitant oral candidiasis is often present. Oesophagitis may also lead to septicemia and disseminated candidiasis. Symptoms include burning pain in the substernal area, dysphagia, nausea and vomiting. The clinical diagnosis relies on radiological and endoscopic findings, which usually shows white mucosal plaques with erythema resembling those seen in oral candidiasis. Herpes simplex or cytomegalovirus (CMV) infection may also be present and the clinical diagnosis may need to be confirmed by histopathology and culture.

Gastrointestinal candidiasis:

Patients with acute leukemia or other hematological malignancies may have numerous ulcerations of the stomach and less commonly the duodenum and intestine. Perforation can lead to peritonitis and hematogenous spread to the liver, spleen and other organs. Colonization and invasion of the stomach or intestinal mucosa is often accompanied by the excretion of large numbers of yeasts which may be detected in stools.

Pulmonary candidiasis:

Pulmonary candidiasis can be acquired by either hematogenous dissemination causing a diffuse pneumonia or by bronchial extension in patients with oropharyngeal candidiasis. Aspiration of yeasts from the oral cavity has also been reported in infants. Pulmonary candidiasis is difficult to diagnose due to non-

specific radiological and culture findings and most patients, especially those with granulocytopenia, present at autopsy. The presence of yeasts in alveolar lavage or sputum specimens is not specific and blood cultures may also be negative. Unfortunately, only histopathology can provide a definitive diagnosis and this is not always possible in patients with coagulation problems.

Peritonitis:

Candida peritonitis can result from colonization of indwelling catheters used for peritoneal dialysis (CAPD) or gastrointestinal perforation due to ulcers, diverticular colitis, surgery or intra-abdominal neoplasm. Symptoms include fever, abdominal pain, tenderness and a cloudy peritoneal dialysate containing greater than 100 leukocytes/mm3. Candida peritonitis usually remains localized to the abdominal cavity unless patients are severely immunosuppressed.

Urinary tract candidiasis:

Transient asymptomatic candiduria may occur during antibiotic or corticosteroid treatment which promotes the growth of Candida, throughout the gastrointestinal and genital tracts, and most lower urinary tract infections result from local spread of yeasts from these sites. This condition is most common in women. Candida cystitis or bladder colonization may be caused by prolonged catheterization with concomitant antibiotic treatment, diabetes and glycosuria, anatomical uropathy, previous bladder endoscopy or surgery, diabetic neurogenic bladder, chronic outlet obstruction from prostatic hypertrophy, or pelvic irradiation for cervical cancer.

Renal candidiasis (pyelonephritis) is usually the result of either an ascending infection or more frequently, hematogenous dissemination from another organ focus. Symptoms include fever, rigors, lumbar pain and abdominal pain. The development of a fungus ball in the renal pelvis, although rare may complicate the infection. Predisposing factors for this include constriction of the urinary tract, localized papillary necrosis, urethral or bladder catheters and diabetes. Even though, up to 80% of patients with disseminated candidiasis also have renal infection and associated candiduria, urine cultures alone are not a reliable method for diagnosis of disseminated infection.

The practical problem in a patient with candiduria is to distinguish between colonization and/or contamination and infection. Therefore, it is important to determine whether renal function is present or whether infection is confined to the bladder. Mycological findings are usually inconclusive which makes the clinical parameters important. The following criteria are suggestive of renal infection; the isolation of yeasts in urine specimens obtained by suprapubic aspiration, positive blood cultures and a positive immunodiffusion precipitin test result or serological conversion in a patient with iatrogenic predisposing factors and/or an underlying illness.

It should be noted that many clinicians do not recommend suprapubic aspirates as they are invasive and require additional expertise, especially in immunocompromised patients. Laboratories are also advised on the need to report the isolation of any yeasts from urine specimens obtained from high risk immunosuppressed patients.

Meningitis:

Candida meningitis is a rare entity, predominantly seen in low birthweight neonates with septicemia and in patients with hematological malignancies, complicated neurosurgery or intracerebral prosthetic devices such as ventriculoperitoneal shunts. Symptoms include a feverish meningeal irritation. Diagnosis in the neonate requires a high index of suspicion by the clinician to the possibility of meningitis as a sequel to septicemia. The detection of Candida cells in smears and its isolation from CSF is often difficult.

Hepatic and hepatosplenic candidiasis:

Hepatosplenic candidiasis occurs in patients with severe neutropenia, usually acute leukemia. Symptoms include fever, hepatosplenomegaly and increased blood concentrations of alkaline phosphatases. Histopathology shows diffuse hepatic and/or splenic necrotic lesions or abscesses containing small numbers of pseudohyphae. However, blood and biopsy cultures are usually culture negative. A definitive diagnosis is often difficult due to the inability to adequately biopsy these patients.

Endocarditis, myocarditis and pericarditis:

Endocarditis is the most common form of cardiac candidiasis. Pre-existing valvular disease with concomitant intravenous catheterization and antibiotic treatment, intravenous drug abuse, heart surgery and valve prosthesis are the most common predisposing factors. Clinical symptoms include fever, murmur, congestive heart failure, anemia and splenomegaly. Blood cultures are often positive and echocardiology and serology for the detection of Candida antibodies (immunodiffusion precipitin tests) are other useful diagnostic procedures. Myocardial abscesses, arterial emboli and purulent pericarditis are additional rare complications of Candida septicemia or surgery.

Candidemia (Candida septicemia) and disseminated candidiasis:

Candidemia has been defined as the presence of yeasts in the blood with or without visceral involvement. Hematogenous dissemination may then occur to one or more other organ systems with the formation of numerous microabscesses. Candida species have been reported to cause up to 15% of cases of septicemia seen in hospital patients.

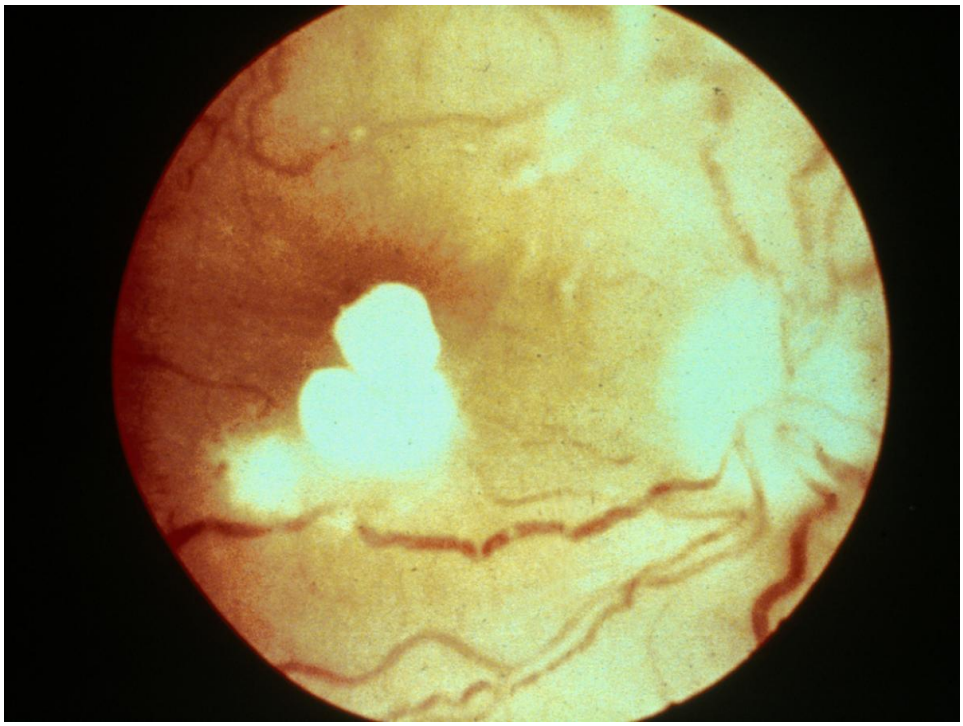
Predisposing factors include intravenous catheters, use of antibacterial drugs, urinary catheters, surgical procedures, corticosteroid therapy, neutropenia, severe burns, parental nutrition, and chemotherapy induced impairment of oropharyngeal or gastrointestinal mucosa. A characteristic presentation is antibiotic resistant fevers in the neutropenic patient with tachycardia and dyspnea. Hypotension is also common and skin lesions may also occur.

When yeasts are isolated from blood or from tissue biopsies a diagnosis is straightforward, however this is not often the case. Blood cultures often remain negative even in patients dying from proven disseminated candidiasis, especially in the granulocytopenic patient. If at all possible, suspected foci should be aspirated, including articular, peritoneal, CSF, or even vitreal specimens; and liver and/or lung biopsies should also be performed. However histopathology is more often not a viable option because biopsies are contraindicated due to the patients underlying illness. Finally, the detection of yeasts from more accessible no-sterile sites, like urine, is too common to be of diagnostic value. In this situation, of clinically suspected unproven disseminated candidiasis, only cutaneous and/or ocular lesions

can rapidly confirm the diagnosis. Specific, reliable serological tests are still not generally available. Empiric antifungal treatment is usually initiated in these cases.

Ocular candidiasis:

Candida endophthalmitis is often associated with candidemia, indwelling catheters or drug abuse, however it is rare in patients with severe neutropenia. Lesions are often localized near the macula and patients complain of cloudy vision. Exogenous Candida endophthalmitis is rare, but cases have been reported following ocular trauma or surgery. Similarly, conjunctival and corneal infections have also been recorded following trauma.



Endophthalmitis due to *Candida*.

Osteoarticular candidiasis:

Arthritis may be a late sequel of candidemia in neonates or neutropenic patients. Prosthetic or rheumatoid joints are also prone to infection by Candida either by hematogenous spread or direct inoculation during surgery or intra-articular corticosteroid injection. The knee is the main site involved with pain on weight bearing or on full extension. The diagnosis depends on the isolation of yeasts from joint fluid obtained by needle aspiration or from synovial biopsies.

Other forms of candidiasis:

As candidiasis is an iatrogenic, nosocomial infection which is usually endogenous in origin many other clinical manifestations may occur, especially in the debilitated patient. For example, the reported cutaneous, ocular and arthritic manifestations reported in heroin addicts; fever, rash and myalgia associated with leukemia patients; Candida cholecystitis; Candida prostatitis; pancreatic abscesses; epiglottitis and osteomyelitis, to name a few.

Summary of clinical groups and/or predisposing factors for invasive candidiasis.

1- Neutropenia (especially >7 days). 2- Hematological malignancy.
3- Solid tumor malignancy. 4- Postsurgical intensive care patients.
5- Prolonged intravenous catheterization.
6- Broad-spectrum or multiple antibiotic therapy.
7- Diabetes mellitis. 8- Parental nutrition. 9- Severe burns.
10- Neonates. 11- Corticosteroid therapy. 12- Intravenous drug abuse.

Laboratory diagnosis:

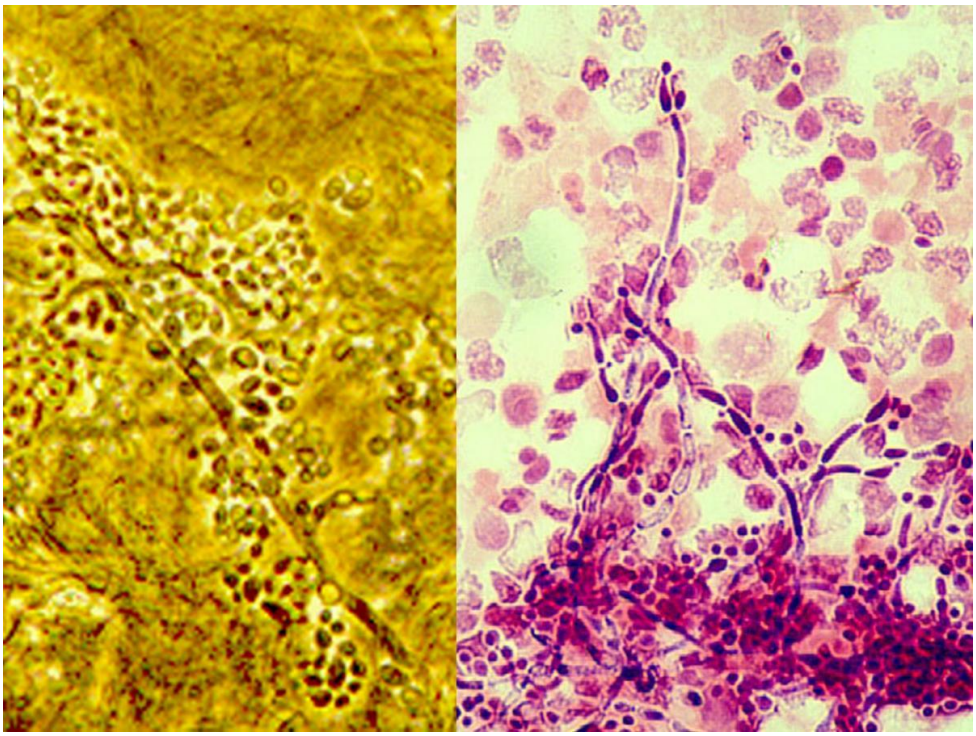
Clinical material:

Skin and nail scrapings; urine, sputum and bronchial washings; cerebrospinal fluid, pleural fluid and blood; tissue biopsies from various visceral organs and indwelling catheter tips.

Direct microscopy:

(a) Skin and nails should be examined using 10% KOH and Parker ink or calcofluor white mounts; (b) Exudates and body fluids should be centrifuged and the sediment examined using either 10% KOH and Parker ink or calcofluor white mounts and/or gram stained smears; (c) Tissue sections should be stained using Periodic acid-Schiff (PAS) digest, Grocott's methenamine silver (GMS) or Gram stain.

Note *Candida* may be missed in H&E stained sections. Examine specimens for the presence of small, round to oval, thin-walled, clusters of budding yeast cells (blastoconidia) and branching pseudohyphae. *Candida* pseudohyphae may be difficult to distinguish from *Aspergillus* hyphae when blastoconidia are not observed as often happens in liver biopsies.



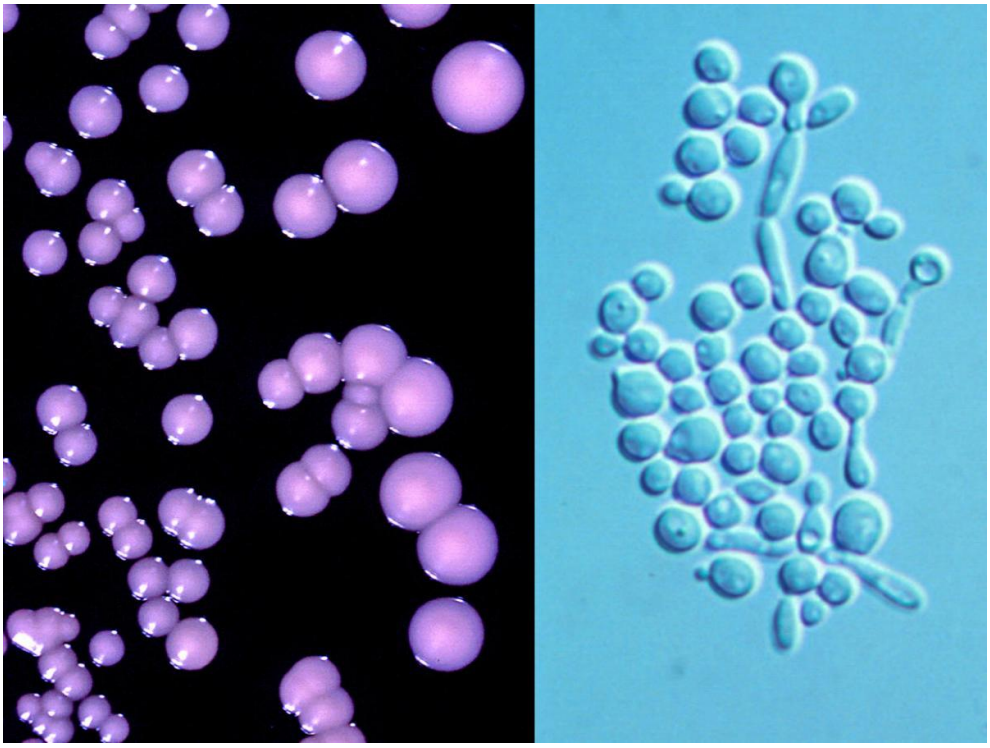
10% KOH mount showing the presence of budding yeast cells and pseudohyphae in a skin scraping and a PAS stained smear showing the presence of budding yeast cells and pseudohyphae in a urine specimen.

Interpretation:

As a rule, a positive direct microscopy from a sterile site, especially a tissue biopsy, should be considered significant, even if the laboratory is unable to culture the yeast. Further, the demonstration of pseudohyphae in scrapings or smears from cutaneous, oral, esophageal and vaginal lesions should be considered significant, provided the clinical manifestations support the diagnosis. However, the finding of just budding yeast cells in such material is of little diagnostic importance. **Note,** pseudohyphae will not be observed in smears when *C. glabrata* is involved and the diagnosis will require additional supporting evidence. Direct microscopy of sterile body fluids, such as CSF, vitreous humor, joint fluid and peritoneal fluid is relatively insensitive and positive culture will usually be required to make a diagnosis.

Culture:

Culture on Sabouraud's dextrose agar (SDA) produces typical creamy white, smooth colonies. Different Candida species are identified by their growth characteristics, sugar fermentation, and assimilation tests. Germ tube is a rapid method for identification of C. albicans and Candida dubliniensis. This test depends on the ability of *C. albicans* to produce germ tube within 2 hours when incubated in human serum at 37°C. This phenomenon is called Reynold–Braude phenomenon.



Typical moist colonies and budding yeast cells of *Candida*.

Interpretation:

A positive culture from blood, or other sterile body fluid, or tissue biopsy should be considered significant. Lysis centrifugation is currently the most sensitive method for the isolation of Candida from blood. However, positive culture from non-sterile specimens such as sputum, bronchial lavage, esophageal brushings, urine, stool, and surgical drains are of little diagnostic value. Similarly, culture of skin or mucous membrane lesions without supporting evidence from direct microscopy is not diagnostic. Candida species are commonly isolated from the mouth, vagina, anus, and less often, moist skin surfaces of normal individuals who do not have candidiasis.

Serology:

Various serological procedures have been devised to detect the presence of Candida antibodies, ranging from immunodiffusion to more sensitive tests such as counter immunoelectrophoresis (CIE), enzyme-linked immunosorbent assay (ELISA), and radioimmunoassay (RIA). However, these are often negative in the immunocompromised patient, especially at the beginning of an infection. The production of four or more precipitin lines in CIE tests has been reported to be diagnostic of candidiasis in the predisposed patient.

Tests for circulating antigen by immunological or non-immunological means have also been developed. Of the non-immunological techniques, use of gas liquid chromography (GLC) to detect mannose derivatives of the cell wall or a metabolic by-product, D-arabinitol, have proved the most useful. The detection of antigen by immunological methods such as ELISA or RIA have been used, however for the small laboratory latex agglutination tests for glycoprotien antigen have proved to be the most useful, although variable results have been reported.
It must be stressed that the interpretation of serological tests for Candida, especially in the neutropenic patient, is often difficult and must be correlated with other diagnostic methods. False-negatives and false-positive results do occur. Hopwood and Evans (1991) provide an excellent review of the current serological methods available.

Indication, usage and explanation of antigen and antibody-based tests for diagnosing invasive candidiasis

Method	Indication	Comments	
		Technical features	Limitations
Candida mannan antigen (MA) and anti-mannan antibody (AMA) Commercial assays - Bio-Rad™ - Serion™ - Dynamiker™ - others	Combined testing of MA/AMA recommended to diagnose IC, candidaemia and deep-seated candidiasis Recommended for the diagnosis of candidaemia to rule out infection To diagnose chronic disseminated candidiasis	Positivity: time advantage of 6–7 days for MA and AMA when compared with blood culture High negative predictive value (>85%) 16 days on average positive before cultures for chronic disseminated candidiasis Heterogeneous results: Platelia™ *Candida* Antigen and Antibody, EIA: Sensitivity and specificity of 55%–89% and 60%–89% Improves by repeated testing and two positive tests for a true positive result Serion Mannan kit, EIA: Sensitivity and specificity of 52%–62% and 54%–98% Dynamiker *Candida* AMA IgM and IgG, EIA: Sensitivity and specificity of 57%–93% and 93%–94%	Different sensitivity for different species: best performance in patients with *Candida albicans*, *Candida glabrata* or *Candida tropicalis* infections Low sensitivity for *Candida krusei* and *Candida parapsilosis* False-positive results in patients with bacteraemia Use of valacyclovir and acyclovir associated with false-positive or borderline results Variable antibody production in immunocompromised patients The exclusive use of MA antigen tests is limited because of low sensitivity (antibody complexing)

Abbreviations: AMA, anti-mannan antibody; IC, invasive candidiasis; MA, mannan antigen.

Treatment:

Antifungal therapy forms the mainstay of treatment of the infections caused by Candida. These agents include azoles (fluconazole, triazole, ketoconazole), nystatin, and amphotericin is becoming increasingly important worldwide .

Identification:

The genus Candida is characterized by globose to elongate yeast-like cells or blastoconidia that reproduce by multilateral budding. Most Candida species are also characterized by the presence of well developed pseudohyphae, however this characteristic may be absent, especially in those species formally included in the genus Torulopsis. Arthroconidia, ballistoconidia and colony pigmentation are always absent. Within the genus Candida, fermentation, nitrate assimilation and inositol assimilation may be present or absent, however, all inositol positive strains produce pseudohyphae.

Scientific classification

Kingdom: Fungi
Division: Ascomycota
Class: Saccharomycetes
Order: Saccharomycetales
Family: Saccharomycetaceae
Genus: Candida (Berkh. 1923)

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