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The Crux

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CONTENTS

Editorial

Candidiasis is a fungal infection due to any species of yeasts in the genus *Candida* or those that were formerly classified in genus *Candida* but are now classified in the genus *Candidozyma*. When it affects the mouth (oral candidiasis) it is commonly known as **thrush**. Signs and symptoms include white patches on the tongue or other areas of the mouth and throat. Other symptoms may include soreness and problems swallowing. When it affects the vagina, it may be referred to as a **yeast infection** or **thrush**. Signs and symptoms include genital itching, burning, and sometimes a white "cottage cheese-like" discharge from the vagina. Yeast infections of the penis are less common and typically present with an itchy rash. Very rarely, yeast infections may become invasive, spreading to other parts of the body. This may result in fevers, among other symptoms. Finally, candidiasis of the esophagus is an important risk factor for contracting esophageal cancer in individuals with achalasia.

More than 20 types of Candida may cause infection with *Candida albicans* being the most common. Infections of the mouth are most common among children less than one month old, the elderly, and those with weak immune systems. Conditions that result in a weak immune system include HIV/AIDS, the medications used after organ transplantation, diabetes, and the use of corticosteroids. Other risk factors include during breastfeeding, following antibiotic therapy, and the wearing of dentures. Vaginal infections occur more commonly during pregnancy, in those with weak immune systems, and following antibiotic therapy. Individuals at risk for invasive candidiasis include low birth weight babies, people recovering from surgery, people admitted to intensive care units, and those with an otherwise compromised immune system.

TROUBLESHOOTING and **UNDERSTANDING** have everything to do with Fungi while **BOUQUET** is all about FUN but nothing to do with FUNgal.

DISEASE DIAGNOSIS

CANDIDIASIS

Background

Candidiasis is caused by infection with species of the genus *Candida,* predominantly with *Candida albicans. Candida* species are ubiquitous fungi that represent the most common fungal pathogens that affect humans. The growing problem of mucosal and systemic candidiasis reflects the enormous increase in the number of patients at risk and the increased opportunity that exists for *Candida* species to invade tissues normally resistant to invasion. *Candida* species are true opportunistic pathogens that exploit recent technological advances to gain access to the circulation and deep tissues. The increased prevalence of local and systemic disease caused by *Candida* species has resulted in numerous new clinical syndromes, the expression of which depends primarily on the immune status of the host. *Candida* species produce a wide spectrum of diseases, ranging from superficial mucocutaneous disease to invasive illnesses, such as hepatosplenic candidiasis, *Candida* peritonitis, and systemic candidiasis. The management of serious and life-threatening invasive candidiasis remains severely hampered by delays in diagnosis and the lack of reliable diagnostic methods that prevent the early identification of candidemia and invasive candidiasis. The growing significance of fungal infections has prompted the publication of a fungal priority pathogens list by WHO (WHO PPPL), analog to a previous bacterial pathogens priority list. The list classifies organisms as critical, high or medium, considering both research and development needs and perceived public health importance. Both *C albicans* and *C auris* are in the critical priority group. Advances in medical technology, chemotherapeutics, cancer therapy, and organ transplantation have greatly reduced the morbidity and mortality of life-threatening disease. Patients who are critically ill and in medical and surgical ICUs have been the prime targets for opportunistic nosocomial fungal infections, primarily due to *Candida* species. Studies suggest that the problem is not under control and, in fact, show it is worsening. On a daily basis, virtually all physicians are confronted with a positive *Candida* isolate obtained from one or more various anatomic sites. High-risk areas for *Candida* infection include neonatal, pediatric, and adult ICUs, both medical and surgical. *Candida* infections can involve any anatomic structure.

Pathophysiology

Candida species are yeastlike fungi that can form true hyphae and pseudohyphae. For the most part, *Candida* species are confined to human and animal reservoirs; however, they are frequently recovered from the hospital environment, including on foods, countertops, air-conditioning vents, floors, respirators, and medical personnel. They are found as commensals of diseased skin and normal mucosal membranes of the gastrointestinal, genitourinary, and respiratory tracts, since early in life. *Candida* species also contain their own set of well-recognized but poorly characterized virulence mechanisms that contribute to their ability to cause infection. The main virulence factors include the following:

- Surface molecules that permit adherence of the organism to other structures (eg, human cells, extracellular matrix, prosthetic devices)
- Acid proteases and phospholipases that involve penetration and damage of cell envelopes
- Ability to convert to a hyphal form (phenotypic switching)
- Upregulation of alternative carbon utilization pathways (metabolic adaptation)
- Induction of differential stress resistance responses (superoxidedismutases)
- Masking of cell wall components for immune evasion

As with most fungal infections, host defects play a significant role in the development of candidal infections. Host defense mechanisms against *Candida* infection and their associated defects that allow infection are as follows:

- Intact mucocutaneous barriers - Wounds, intravenous catheters, burns, ulcerations
- Phagocytic cells -Granulocytopenia
- Polymorphonuclear leukocytes - Chronic granulomatous disease
- Monocytic cells -Myeloperoxidase deficiency
- Complement -Hypocomplementemia
- Immunoglobulins -Hypogammaglobulinemia
- Cell-mediated immunity - Chronic mucocutaneous candidiasis, diabetes mellitus, cyclosporin A, corticosteroids, HIV infection
- Mucocutaneous protective bacterial flora - Broad-spectrum antibiotics

Risk factors associated with mucocutaneous, invasive or systemic candidiasis include the following :

- Granulocytopenia
- Bone marrow transplantation
- Solid organ transplantation (liver, kidney)
- Parenteral hyperalimentation
- Hematologic malignancies
- Foley catheters
- Solid neoplasms
- Recent chemotherapy or radiation therapy
- Corticosteroids, TNF-α inhibitors, tocilizumab (IL-6 inibitor, elevated risk of candidemia during the COVID-19 pandemic), IL-17A- and IL-23-targeted biologics (secukinumab, ustekinumab)
- *Clostridioides difficile* infection
- Broad-spectrum antibiotics
- Burns
- Prolonged hospitalization
- Severe trauma
- Recent bacterial infection
- Recent surgery
- Gastrointestinal tract surgery
- Central intravascular access devices
- Premature birth
- Hemodialysis
- Acute and chronic renal failure
- Mechanical ventilation for longer than 3 days

The first step in the development of a candidal infection is colonization of the mucocutaneous surfaces, followed by proliferation of yeast blastospores and hyphae formation with activation of fungal virulence factors. All of the conditions outlined above are associated with increased colonization rates. The routes of candidal invasion include (1) disruption of a colonized surface (skin or mucosa), allowing the organisms access to the bloodstream, and (2) persorption via the gastrointestinal wall, which may occur following massive colonization with large numbers of organisms that pass directly into the bloodstream.

Frequency

International

Similar rates of mucocutaneous and systemic candidiasis/candidemia have been observed worldwide. In fact, throughout the world, *Candida* species have replaced *Cryptococcus* species as the most common

fungal pathogens affecting immunocompromised hosts. The frequency of non-albicans Candida causing candidemia and invasive candidiasis has grown, an observation also found in the United States. As for the most recent years (last 10 years), it is unclear whether there is a continued increase, as variable trends are reported from different countries. COVID-19 pandemic did show an association with increased risk of candidemia, probably related to increased use of CVCs.

Mortality/Morbidity

Mucocutaneous candidiasis: Most candidal infections are mucocutaneous and, as such, do not cause mortality. However, in patients with advanced immunodeficiency due to HIV infection, these mucosal infections can become refractory to antifungal therapy and may lead to severe oropharyngeal and esophageal candidiasis that initiates a vicious cycle of poor oral intake, malnutrition, wasting, and early death.

Candidemia and disseminated candidiasis: Mortality rates associated with these infections have not improved markedly and remain in the range of 30-40%. Systemic candidiasis causes more case fatalities than any other systemic mycosis. More than a decade ago, investigators reported the enormous economic impact of systemic candidiasis in hospitalized patients. Candidemia is associated with considerable prolongation in hospital stays (70 d vs 40 d in comparable patients without fungemia). Although mucocutaneous fungal infections, such as oral thrush and *Candida*esophagitis, are extremely common in patients with AIDS, candidemia and disseminated candidiasis are uncommon.

Sex

Neither sex is predisposed to candidal colonization; however, VVC is the second most common cause of vaginitis in women.

Age

Persons at the extremes of age (neonates and adults >65 y) are most susceptible to candidal colonization. Mucocutaneous candidiasis is also more prevalent in neonates and older adults. Very-low-birth-weight and extremely-low-birth-weight infants are at high risk for blood culture–proven late-onset candidiasis (defined as sepsis that develops after age 72 h).

Clinical Presentation

History

Candidiasis can cause a wide spectrum of clinical syndromes, as described below. The clinical presentation can vary depending on the type of infection and the degree of immunosuppression. This section is referred mainly to systemic and invasive forms of candidiasis. For a more detailed discussion, several others chapter are available at emedicine.medscape.com (cutaneous candidiasis, mucosal candidiasis, chronic mucocutaneous candidiasis, pediatric candidiasis, candidiasis in emergency medicine).

Cutaneous candidiasis syndromes

Generalized cutaneous candidiasis: This is an unusual form of cutaneous candidiasis that manifests as a diffuse eruption over the trunk, thorax, and extremities. The patient has a history of generalized pruritus, with increased severity in the genitocrural folds, anal region, axillae, hands, and feet. Physical examination reveals a widespread rash that begins as individual vesicles that spread into large confluent areas.

Intertrigo: The patient has a history of intertrigo affecting any site in which skin surfaces are in close proximity, providing a warm and moist environment. A pruritic red rash develops. Physical examination reveals a rash that begins with vesiculopustules that enlarge and rupture, causing maceration and fissuring. The area involved has a scalloped border with a white rim consisting of necrotic epidermis that surrounds the erythematous macerated base. Satellite lesions are commonly found and may coalesce and extend into larger lesions.

Erythema, maceration, and satellite pustules in the axilla, accompanied by soreness and pruritus, result in a form of intertrigo. Courtesy of Matthew C. Lambiase, DO.

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Metastatic skin lesions: Characteristic skin lesions occur in approximately 10% of patients with disseminated candidiasis and candidemia. The lesions may be numerous or few and are generally described as erythematous, firm, nontender macronodular lesions with discrete borders. Biopsy specimens of these lesions demonstrate yeast cells, hyphae, or pseudohyphae, and cultures are positive for *Candida* species in approximately 50% of cases.

*Candida*folliculitis: The infection is found predominantly in the hair follicles and, rarely, can become extensive.

Paronychia and onychomycosis: Paronychia and onychomycosis frequently are associated with immersion of the hands in water and with diabetes mellitus. The patient has a history of a painful and erythematous area around and underneath the nail and nail bed. Physical examination reveals an area of inflammation that becomes warm, glistening, tense, and erythematous and may extend extensively under the nail. It is associated with secondary nail thickening, ridging, discoloration, and occasional nail loss.

Chronic mucocutaneous candidiasis

Chronic mucocutaneous candidiasis describes a group of *Candida* infections of the skin, hair, nails, and mucous membranes that tends to have a protracted and persistent course.

History: Most infections begin in infancy or during the first 2 decades of life; onset in people older than 30 years is rare. Most patients survive for prolonged periods and rarely experience disseminated fungal infections. The most common cause of death is bacterial sepsis.

Chronic mucocutaneous candidiasis frequently is associated with endocrinopathies, such as the following:

- Hypoparathyroidism
- Addison disease
- Hypothyroidism
- Diabetes mellitus
- Autoimmune antibodies to adrenal, thyroid, and gastric tissues (approximately 50%)
- Thymomas
- Dental dysplasia
- Polyglandular autoimmune disease

- Antibodies to melanin-producing cells

Physical examination: Findings reveal disfiguring lesions of the face, scalp, hands, and nails. This is occasionally associated with oral thrush and vitiligo.

White plaques are present on the buccal mucosa and the undersurface of the tongue and represent thrush. When wiped off, the plaques leave red erosive areas. Courtesy of Matthew C. Lambiase, DO.

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Gastrointestinal tract candidiasis

Oropharyngeal candidiasis

The patient usually has a history of HIV infection, wears dentures, has diabetes mellitus, or has been exposed to broad-spectrum antibiotics or inhaled steroids. Patients are frequently asymptomatic. However, symptoms may include the following:

- Sore and painful mouth
- Burning mouth or tongue
- Dysphagia
- Whitish thick patches on the oral mucosa

Physical examination reveals a diffuse erythema and white patches that appear on the surfaces of the buccal mucosa, throat, tongue, and gums. The following are the 5 types of oropharyngeal candidiasis (OPC) :

- Membranous candidiasis: This is one of the most common types and is characterized by creamy-white curdlike patches on the mucosal surfaces.
- Erythematous candidiasis: This is associated with an erythematous patch on the hard and soft palates.
- Chronic atrophic candidiasis (denture stomatitis): This type is thought to be one of the most common forms of the disease. The presenting signs and symptoms include chronic erythema and edema of the portion of the palate that comes into contact with dentures.
- Angular cheilitis: An inflammatory reaction, this type is characterized by soreness, erythema, and fissuring at the corners of the mouth.

Soreness and cracks at the lateral angles of the mouth (angular cheilitis) are a frequent expression of candidiasis in elderly individuals. Courtesy of Matthew C. Lambiase, DO.

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- Mixed: A combination of any of the above types is possible.

Esophageal candidiasis

The patient's history usually includes chemotherapy, the use of broad-spectrum antibiotics or inhaled steroids, the presence of HIV infection or hematologic or solid-organ malignancy. Patients may be asymptomatic or may have 1 or more of the following symptoms:

- Normal oral mucosa (>50% of patients)
- Dysphagia
- Odynophagia
- Retrosternal pain
- Epigastric pain
- Nausea and vomiting

Physical examination almost always reveals oral candidiasis.

Nonesophageal gastrointestinal candidiasis

The patient usually has a history of neoplastic disease of the gastrointestinal tract. The esophagus is the most commonly infected site, followed by the stomach. Less commonly, patients have chronic gastric ulcerations, gastric perforations, or malignant gastric ulcers with concomitant candidal infection. The small bowel is the third most common site of infection (20%). The frequency of candidal infection in the small bowel is the same as in the large bowel. Approximately 15% of patients develop systemic candidiasis. Physical examination findings vary depending on the site of infection. The diagnosis, however, cannot be made solely on culture results because approximately 20-25% of the population is colonized by *Candida*. The following symptoms may be present:

- Epigastric pain
- Nausea and vomiting
- Abdominal pain
- Fever and chills
- Abdominal mass (in some cases)

Respiratory tract candidiasis

The respiratory tract frequently is colonized with *Candida* species, especially in hospitalized patients. Approximately 20-25% of ambulatory patients are colonized with *Candida* species.

Laryngeal candidiasis: This is an uncommon form of invasive candidiasis that sometimes results in disseminated infection. It primarily is seen in patients with underlying hematologic or oncologic malignancies. The patient may present with a sore throat and hoarseness. The physical examination findings generally are unremarkable, and the diagnosis frequently is made with direct or indirect laryngoscopy.

Candida tracheobronchitis: This also is an uncommon form of invasive candidiasis. Most patients with *Candida* tracheobronchitis are HIV-positive or are severely immunocompromised. Most patients with *Candida* tracheobronchitis report fever, productive cough, and shortness of breath. Physical examination reveals dyspnea and scattered rhonchi. The diagnosis generally is made with bronchoscopy.

Candida pneumonia: This rarely develops alone and is associated with disseminated candidiasis in rare cases. The most common form of infection is multiple lung abscesses due to the hematogenous dissemination of *Candida* species. The high degree of *Candida* colonization in the respiratory tract greatly complicates the diagnosis of *Candida* pneumonia. The history reveals risk factors similar to those of disseminated candidiasis, along with reports of shortness of breath, cough, and respiratory distress. Physical examination reveals fever, dyspnea, and variable breath sounds, ranging from clear to rhonchi or scattered rales.

Genitourinary tract candidiasis

Vulvovaginal candidiasis (VVC): This is the second most common cause

of vaginitis. The patient's history includes vulvar pruritus, vaginal discharge, dysuria, and dyspareunia. Approximately 10% of women experience repeated attacks of VVC without precipitating risk factors. Physical examination findings include a vagina and labia that usually are erythematous, a thick curdlike discharge, and a normal cervix upon speculum examination.

Candida balanitis: Patients report penile pruritus along with whitish patches on the penis. *Candida* balanitis is acquired through direct sexual contact with a partner who has VVC. Physical examination initially reveals vesicles on the penis that later develop into patches of whitish exudate. The rash occasionally spreads to the thighs, gluteal folds, buttocks, and scrotum.

Dry, red, superficially scaly, pruritic macules and patches on the penis represent candidal balanitis. Courtesy of Matthew C. Lambiase, DO.

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Candida cystitis: Many patients are asymptomatic. However, bladder invasion may result in frequency, urgency, dysuria, hematuria, and suprapubic pain. *Candida* cystitis may or may not be associated with the use of a Foley catheter. Physical examination may reveal suprapubic pain; other findings are unremarkable.

Asymptomatic candiduria: Most catheterized patients with persistent candiduria are asymptomatic, similar to noncatheterized patients. Most patients with candiduria have easily identifiable risk factors for *Candida* colonization. Thus, invasive disease is difficult to differentiate from colonization based solely on culture results because approximately 5-10% of all urine cultures are positive for *Candida*. Clinical assessment is required to decide whether antifungal medication is indicated.

Ascending pyelonephritis: The use of stents and indwelling devices, along with the presence of diabetes, is the major predisposing risk factor in ascending infection. Most patient report flank pain, abdominal cramps, nausea, vomiting, fever, chills, and hematuria. Physical examination reveals abdominal pain, costovertebral-angle tenderness, and fever.

Fungal balls: This is due to the accumulation of fungal material in the renal pelvis. The condition may produce intermittent urinary tract obstruction with subsequent anuria and ensuing renal insufficiency.

Hepatosplenic candidiasis (chronic systemic candidiasis)

Hepatosplenic candidiasis is a form of systemic candidiasis in patients with an underlying hematologic malignancy and neutropenia and develops during the recovery phase of a neutropenic episode. The patient's history includes the following:

- Fever unresponsive to broad-spectrum antimicrobials
- Right upper quadrant pain
- Abdominal pain and distension
- Jaundice (rare)

Physical examination findings include right upper quadrant tenderness and hepatosplenomegaly (< 40%).

Systemic candidiasis

Systemic candidiasis can be divided into 2 primary syndromes: candidemia and disseminated candidiasis (organ infection by *Candida* species). Deep organ infections due to *Candida* species generally are observed as part of the disseminated candidiasis syndromes and may involve one or more organs.

Candidemia

Candida species are a frequent cause of bloodstream infection, having been reported as the fourth most commonly isolated organism in blood cultures. *Candida* infection generally is considered a nosocomial infection. The patient's history commonly reveals the following:

- Several days of fever that is unresponsive to broad-spectrum antimicrobials; frequently the only marker of infection
- Prolonged intravenous catheterization
- A history of several key risk factors (see Pathophysiology)
- Possibly associated with multiorgan infection

Physical examination results may include the following:

- Fever
- Macronodular skin lesions (approximately 10%)
- Candidal endophthalmitis (approximately 10%)
- Occasionally, septic shock (hypotension, tachycardia, tachypnea)

Other causes of candidemia without invasive disease include the following:

- Intravascular catheter-related candidiasis: This entity usually responds promptly to catheter removal and antifungal treatment.
- Suppurative thrombophlebitis: This is associated with prolonged central venous catheterization. Suppurative thrombophlebitis manifests as fever and persistent candidemia despite appropriate antifungal therapy and catheter removal. Sepsis and septic shock may develop.
- Endocarditis: The frequency of endocarditis has recently increased. *Candida* species, primarily *C albicans* and *Candidaparapsilosis* (>60% of cases), are the most common cause of fungal endocarditis. The aortic and mitral valves most are commonly involved. The endocarditis may be exogenous (due to direct inoculation during surgery) or endogenous (due to hematogenous dissemination during bloodstream invasion). *Candida* endocarditis is associated with 4 main risk factors, including intravenous heroin use (frequently associated with *C parapsilosis* infection), chemotherapy, prosthetic valves (approximately 50%), and prolonged use of central venous catheters. The physical examination reveals a broad range of manifestations, including fever unresponsive to antimicrobials, hypotension, shock, new or changing murmurs, and large septic emboli to major organs, a characteristic of fungal endocarditis.

Disseminated candidiasis

This is frequently associated with multiple deep organ infections or may involve single organ infection. Unfortunately, blood cultures are negative in up to 40-60% of patients with disseminated candidiasis. The history of a patient with presumptive disseminated candidiasis reveals a fever unresponsive to broad-spectrum antimicrobials and negative results from blood culture. Physical examination reveals fever (may be the only symptom) with an unknown source and associated sepsis and septic shock.

Candida endophthalmitis

The 2 primary forms of *Candida*endophthalmitis are the exogenous form and the endogenous form. Exogenous endophthalmitis is associated

with either accidental or iatrogenic (postoperative) injury of the eye and inoculation of the organism from the environment. Endogenous endophthalmitis results from hematogenous seeding of the eye. It has been found in about 10% of patients with documented candidemia. Recently, newer studies have shown a decreasing incidence of *Candida* endophthalmitis, possibly due to an increased awareness of this complication and the initiation of early or empiric antifungal therapy. It is important to note that hematogenous candidal endophthalmitis is a marker of disseminated candidiasis.

The patient's history reveals a broad range of manifestations, including the following.

- Eye injury
- Ophthalmic surgery
- Underlying risk factors for candidemia
- Asymptomatic and detected upon physical examination
- Ocular pain
- Photophobia
- Scotomas
- Floaters

Physical examination reveals fever.

Funduscopic examination reveals early pinhead-sized off-white lesions in the posterior vitreous with distinct margins and minimal vitreous haze. Classic lesions are large and off-white, similar to a cotton-ball, with indistinct borders covered by an underlying haze. Lesions are 3-dimensional and extend into the vitreous off the chorioretinal surface. They may be single or multiple.

Renal candidiasis

This is frequently a consequence of candidemia or disseminated candidiasis. The patient's history includes fever that is unresponsive to broad-spectrum antimicrobials. Frequently, patients are asymptomatic and lack symptoms referable to the kidney. Physical examination findings generally are unremarkable, and the diagnosis is made with a urinalysis and with a renal biopsy. Otherwise, this condition commonly is diagnosed at autopsy.

CNS infections due to *Candida* species

CNS infections due to *Candida* species are rare and difficult to diagnose. The 2 primary forms of infection include the exogenous infection and the endogenous infection. The exogenous infection results from postoperative infection, trauma, lumbar puncture, or shunt placement. The endogenous infection results from hematogenous dissemination and thus involves the brain parenchyma and is associated with multiple small abscesses (eg, disseminated candidiasis). As with other organ infections due to *Candida* species, patients usually have underlying risk factors for disseminated candidiasis. CNS infections due to *Candida* species frequently are found in patients hospitalized for long periods in ICUs. The spectrum of this disease includes the following:

- Meningitis
- Granulomatous vasculitis
- Diffuse cerebritis with microabscesses
- Mycotic aneurysms
- Fever unresponsive to broad-spectrum antimicrobials
- Mental status changes

Physical examination reveals the following:

- Fever
- Nuchal rigidity
- Confusion
- Coma

Candida arthritis, osteomyelitis, costochondritis, and myositis

Candidal musculoskeletal infections once were unusual; recently, they have become less so, possibly due to the increased frequency of candidemia and disseminated candidiasis. The pattern of involvement is similar to the pattern observed in bacterial infections. The infection may be divided into exogenous or endogenous forms. The exogenous infection is due to the direct inoculation of the organisms, such as postoperative infection or trauma. Affected sites include the following:

- Ribs and leg bones (patients < 20 y)
- Vertebral column and paraspinal abscess (adulthood)
- Flat bones (any age group)
- Sternum - Generally observed postoperatively after cardiac surgery

The patient frequently is asymptomatic, and the history reveals risk factors typical of disseminated candidiasis, as well as pain localized over the affected site. The physical examination findings frequently are unremarkable but may reveal tenderness over the involved area, erythema, and bone deformity, occasionally in association with a draining fistulous tract. Diagnostic work up is complicated by non-specific clinical presentation, yield of diagnostic methods and degree of clinical suspicion.

Arthritis: *Candida* arthritis generally is a complication of disseminated candidiasis but may be caused by trauma or direct inoculation due to surgery or steroid injections. Most cases are acute and begin as a suppurative synovitis. A high percentage of cases progress to osteomyelitis. In addition, *Candida* arthritis after joint replacement is not uncommon.

Osteomyelitis: *Candida* osteomyelitis originates either exogenously or endogenously. The exogenous infection is due to direct inoculation of the organisms via routes such as postoperative infection, trauma, or steroid injections. The endogenous form is a complication of candidemia or disseminated candidiasis. In most cases due to hematogenous seeding, the vertebral disks are involved and frequently progress to discitis with contiguous extension into the vertebrae body. Other bones affected include the wrist, femur, scapula, and proximal humerus.

Costochondritis: This is an uncommon form of infection and also has 2 modes of infection. *Candida* costochondritis usually is due to hematogenous infection spread or direct inoculation during surgery (median sternotomy). Costochondritis frequently is associated with pain localized over the involved area.

Myositis: *Candida* myositis is uncommon but is frequently associated with disseminated candidiasis. Most patients are neutropenic and report muscular pain.

Myocarditis-pericarditis

This infection usually is due to direct hematogenous spread in association with candidemia and rarely is due to the direct extension from the sternum or the esophagus. Myocarditis-pericarditis occurs as diffuse abscesses scattered throughout the myocardium surrounded by normal cardiac tissue. In patients with disseminated candidiasis, the rate of *Candida* myocarditis-pericarditis has been documented as high as 50%. The patient history reveals serious complications in 10-20% of cases without valvular disease. Physical examination reveals fever, hypotension, shock, tachycardia, and new murmurs or rubs (or recent changes in previously detected murmurs).

Candida peritonitis

The patient history frequently reveals an association with gastrointestinal tract surgery, viscous perforation, or peritoneal dialysis. *Candida* peritonitis tends to remain localized, disseminating into the bloodstream in only 15% of cases. The range of manifestations is broad and includes fever and chills, abdominal pain and cramping, nausea, vomiting, and constipation. The isolation of *Candida* species from the peritoneal fluid in surgical patients needs to be carefully evaluated.

Physical examination may reveal the following:
- Fever
- Abdominal distention
- Abdominal pain
- Absent bowel sounds
- Rebound tenderness
- Localized mass

*Candida*splenic abscess and hypersplenism
Both are manifestations of disseminated candidiasis and are usually simultaneously associated with liver involvement. Manifestations of hypersplenism are common (see Hepatosplenic candidiasis).

Candida cholecystitis
This is uncommon and is generally associated with bacterial cholangitis and ascending cholangitis. In general, *Candida* cholecystitis is diagnosed at the time of surgery when a culture is obtained.

Causes
Over 200 species of *Candida* exist in nature; thus far, only a few species have been associated with disease in humans.

The medically significant *Candida* species include the following:
- *C albicans,* the most common species identified (50-60%)
- *Candida glabrata* (renamed *Nakaseomyces glabrata,* previously known as *Torulopsis glabrata*)* (15-20%)
- *C parapsilosis* (10-20%)
- *Candida tropicalis* (6-12%)
- *Candida krusei* (renamed *Pichia kudriavzeveii*)* (1-3%)
- *Candida kefyr* (< 5%)
- Candida guilliermondi (*Meyerozyma guilliermondii*)* (< 5%)
- *Candida lusitaniae* (*Clavispora lusitaniae*)* (< 5%)
- *Candida dubliniensis,* primarily recovered from patients infected with HIV
- *Candida auris*
- *Candida haemulonii*

* We will still use the former names in the present discussion. While sequencing data is rapidly changing fungal nomenclature, old names are still linked to medical considerations, such as clinical presentation and diagnostic and therapeutic approaches. As renaming of fungal species makes its way into medical practice we will prioritize newer names. *C glabrata* and *C albicans* account for approximately 70-80% of *Candida* species recovered from patients with candidemia or invasive candidiasis. *C glabrata* has recently become very important because of its increasing incidence worldwide, its association with fluconazole resistance in up to 20% of clinical specimens, and its overall decreased susceptibility to other azoles and polyenes. *C krusei* is important because of its intrinsic resistance to ketoconazole and fluconazole (Diflucan); it is also less susceptible to all other antifungals, including itraconazole (Sporanox) and amphotericin B. Another important *Candida* species is *C lusitaniae;* although not as common as other *Candida* species, *C lusitaniae* is of clinical significance because it may be intrinsically resistant to amphotericin B, although it remains susceptible to azoles and echinocandins. *C parapsilosis* is also an important species to consider in hospitalized patients. It is especially common in infections associated with vascular catheters prosthetic devices. Additionally, in vitro analyses have shown that echinocandins have a higher minimum inhibitory concentration (MIC) against *C parapsilosis* than other *Candida* species. The clinical relevance of this in vitro finding has yet to be determined. *C tropicalis* has frequently been considered an important cause of candidemia in patients with cancer (leukemia) and in those who have undergone bone marrow transplantation. *C auris* is a globally emerging invasive *Candida* species with a number of problematic characteristics: it has virulent factors that facilitate infections, is associated with a high mortality rate and healthcare-associated outbreaks, is often resistant to multiple antifungal drugs, and can be difficult to identify with conventional diagnostic laboratory methods. *C auris* may present drug resistance to two different classes of antifungals in more than 40% of cases and three.class resistance of about 4%. *C auris* has already been reported in over 60 countries as of December 2023. The CDC has issued a global clinical alert for this fungus and has asked laboratories to report *C auris* cases and to send isolates to state and local health departments and to the CDC. The figures have increased rapidly. Between initial identification and February, 2019, 587 cases of *C auris* infection had been reported in the United States. In 2022 only, 2377 cases were reported. A 2020 report from the US Centers for Disease Control and Prevention described 3 chronically ill people in New York who were identified as having pan-resistant *C auris* infection. The report stated that the pan-resistant *C auris* infection developed after the patients had received antifungal medications, including echinocandins, a class of drugs that targets the fungal cell wall. *C haemulonii* is another emerging species, closely related to *C auris,* and has occasionally reported as cause of systemic or invasive candidiasis. It also shares some pathogenic and drug-resistance features. A significant proportion of cases has been reported form tropical regions.

Diagnostic Considerations
Diagnostic considerations include the following:
- Cutaneous candidiasis - Dermatitis (contact, allergic), folliculitis
- Gastrointestinal tract candidiasis - Esophagitis due to herpes simplex virus, herpes zoster, induced by radiation, gastroesophageal reflux disease
- Respiratory candidiasis - Bacterial pneumonia, viral pneumonia, tracheitis, *Aspergillus* pneumonia
- Genitourinary tract candidiasis - Bacterial cystitis or pyelonephritis
- Candidemia - Bacterial sepsis, bacterial endocarditis
- Disseminated candidiasis - Bacterial meningitis, bacterial sepsis, bacterial endocarditis, tuberculosis
- Chronic mucocutaneous candidiasis - HIV-seropositive state, chronic granulomatous disease
- Hepatosplenic candidiasis - Hepatic abscess, cholelithiasis, cholecystitis, acalculous cholecystitis, ascending cholangitis, graft versus host disease, granulomatous hepatitis, relapsed malignancy

Differential Diagnoses
- Abdominal Abscess
- Aspergillosis
- Bacterial Sepsis
- Cryptococcosis
- Septic Shock

Candidiasis Workup
Laboratory Studies
Unfortunately, results from the routine laboratory studies are often nonspecific and not very helpful. Clinicians are required to act definitively and early based on a high index of suspicion. In the past, many patients with life-threatening candidiasis died without receiving antifungal therapy. Systemic candidiasis should be suspected in patients with persistent leukocytosis and either persistent neutropenia or other risk factors and who remain febrile despite broad-spectrum antibiotic therapy. To be effective, antifungal therapy should be provided early and empirically in such high-risk patients. Cultures of nonsterile sites,

although not useful for establishing a diagnosis, may demonstrate high degrees of candidal colonization. Always consider positive culture results from sterile sites to be significant and evidence of infection. In September 2014, the FDA gave marketing approval for the T2Candida Panel and T2Dx Instrument (T2Candida), the first direct blood test for detecting five *Candida* species that cause bloodstream infections (*C albicans* and/or *C tropicalis*, *C parapsilosis*, *C glabrata* and/or *C krusei*). T2Candida can use single blood sample to identify these five yeasts within 3-5 hours, whereas traditional testing methods can take up to 6 days to detect, and even longer to identify, *Candida* species. Therefore, this test potentially allows earlier administration of appropriate antifungal therapy and may reduce disease severity and/or the mortality risk from sepsis. However, blood cultures should be used to confirm T2Candida results owing to the potential for false-positive results. Approval was based on a study of 1500 patients, in which T2Candida correctly categorized almost 100% of negative specimens as negative for the presence of *Candida*, and another study of 300 blood samples with specific concentrations of yeast, in which the test correctly identified the organism in 84-96% of positive samples. The serum (1,3)β-D-glucan detection assay (Glucatell, Fungitell) is a nonculture assay that was approved for use in the United States in May 2004. This assay measures the level of β-glucan (a fungal cell wall component). In a large multicenter study, the assay yielded a high specificity and positive predictive value with highly reproducible results.

Mucocutaneous candidiasis

For a wet mount, scrapings or smears obtained from skin, nails, or oral or vaginal mucosa are examined under the microscope for hyphae, pseudohyphae, or budding yeast cells. A potassium hydroxide smear, Gram stain, or methylene blue is useful for direct demonstration of fungal cells. Cultures from affected nails may help identify the etiologic agent responsible for onychomycosis versus other noninfectious causes.

Candidemia and disseminated candidiasis

Blood cultures are helpful but yield positive results in only 50-60% of cases of disseminated infection. Urinalysis may be helpful and may show either colonization or renal candidiasis. Cultures of nonsterile sites, although not useful for establishing a diagnosis, may be useful for initiating antifungal therapy in patients with fever that is unresponsive to broad-spectrum antimicrobials. Therefore, appropriate interpretation is required. Positive results from blood cultures and cultures from other sterile sites always imply the presence of invasive disease. Positive results from sterile sites should always be taken as significant and should always prompt treatment. Gastrointestinal, respiratory, and urinary tract cultures that are positive for *Candida* may not always represent invasive disease. However, these should be considered sites of colonization.

Cutaneous candidiasis: Using a wet mount, scrapings or smears obtained from skin or nails can be examined under microscopy for hyphae, pseudohyphae, or budding yeast cells. Potassium hydroxide smears are also useful.

Genitourinary candidiasis: A urinalysis should be performed. Evidence of WBCs, RBCs, protein, and yeast cells is common. Additionally, urine fungal cultures are useful.

Respiratory tract candidiasis

Sputum Gram stain may demonstrate WBCs and yeast cells. Sputum cultures may demonstrate *Candida* species. Lung biopsy is mandatory to definitively establish the diagnosis of respiratory tract candidiasis because of the high frequency of yeast colonization of the respiratory tract.

Gastrointestinal candidiasis

Endoscopy with or without biopsy is necessary to establish the diagnosis.

Focal hepatosplenic candidiasis

Serum alkaline phosphatase levels are commonly elevated.

Species identification

C albicans, C dubliniensis, and *Candida stellatoidea* can be identified morphologically via germ-tube formation (hyphae are produced from yeast cells after 2-3 h of incubation) or biochemical assays. CHROMagar *Candida* allows for the presumptive identification of several *Candida* species by using color reactions in specialized media that demonstrate different colony colors depending on the species of *Candida.* API20C and API32C are biochemical assays that allow for the identification of the different *Candida* species with more precision. These assays evaluate the assimilation of numerous carbon substrates and generate profiles used in the identification of different fungal species. *The C albicans* peptide nucleic acid (PNA) fluorescence in situ hybridization (FISH) test can be used to identify *C albicans in* 24-48 hours when the probe is added to smears that are made directly from the blood culture bottle and followed by hybridization. A newer version of this test now allows for the simultaneous identification of either *C albicans* or *C glabrata*. MALDI-TOF MS, which stands for Matrix Associated Laser Desorption/Ionization Time of Flight Mass Spectrometry, is a rapid identification system for blood cultures has increased its use in recent years in most hospitals. After the isolation of the organism, MALDI-TOF MS takes 10 to 15 min to identify. MALDI-TOF MS can be used for antifungal susceptibility tests.(ref 74, Delavy; ref 73, Alves)

Antifungal susceptibility testing

In vitro susceptibility testing for *Candida* species is now standardized using the Clinical Laboratory Standards Institute (CLSI) microbroth dilution (CLSI M27-A2, 2002) or the disk diffusion (CLSI M44-P, 2003) methodology. This was formerly known as the National Committee for Clinical Laboratory Standards (NCCLS) microbroth dilution. These methods may be helpful in guiding difficult therapeutic decisions. Most of the difficult decisions involve antifungal-refractory oral or esophageal candidiasis in patients with advanced HIV disease.

Nonculture *Candida* detection assays

The *Candida* mannan assay yields a sensitivity of 31%-90% (less for non-*albicans Candida* species). The *Candida* heat labile antigen assay yields a sensitivity of 10%-71%. The D-arabinitol assay yields a sensitivity of 50% but is not useful for infection with *C krusei* or *C glabrata*. The enolase assay yields a sensitivity of 55%-75%, which improves with serial testing. The (1,3) β-D-glucan assay is an amebocyte lysis assay with a sensitivity of 75-100% and a specificity of 88%-100%. It is a broad-spectrum assay that detects *Aspergillus, Candida, Fusarium, Acremonium,* and *Saccharomyces* species. β-D-glucan is a cell wall component in a wide variety of fungi and can be detected based on its ability to activate factor G of the horseshoe crab coagulation cascade. The Fungitell assay may be used in the evaluation of invasive fungal infections caused by the fungi mentioned above. The assay does not detect infections caused by *Cryptococcus neoformans* or Zygomycetes. Molecular assays such as the polymerase chain reaction (PCR) assay and DNA probes are still under development and in the early investigational phases, but they appear promising. A new, rapid test for *Candida* infections of the bloodstream may cut patient mortality from 40% to 11% by diagnosing candidemia 25 times faster than blood culture can and quickly identifying the *Candida* species that is causing the infection. The new test, T2Candida, uses polymerase chain

reaction (PCR) assay to amplify *Candida* DNA in blood, with the genetic material hybridizing to superparamagnetic nanoparticles coated with complementary DNA. The nanoparticles aggregate into "micro clusters," which greatly alter a T2 magnetic resonance (T2MR) signal.

Histologic Findings

Fixed tissues can be stained with hematoxylin and eosin. In addition, fungal hyphae may be demonstrated with Grocott silver-methenamine, methylene blue, or periodic acid-Schiff staining (PAS). The classic appearance demonstrates the *Candida* species as either round or ovoid yeast cells, hyphae, or pseudohyphae. Tissues may show inflammatory and necrotic changes.

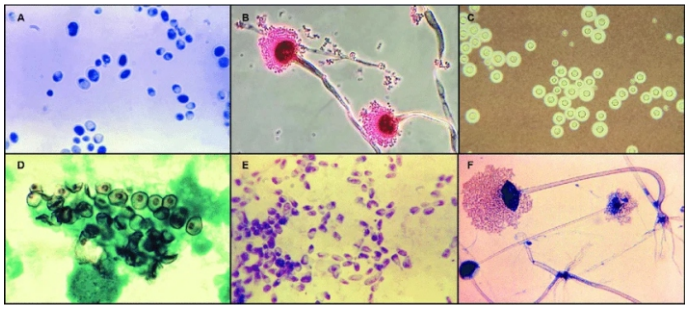
Management

Management of candidiasis includes the following:

- Cutaneous candidiasis - Most localized cutaneous candidiasis infections can be treated with any number of topical antifungal agents (e.g., clotrimazole, econazole, ciclopirox, miconazole, ketoconazole, nystatin)
- Chronic mucocutaneous candidiasis - This condition is generally treated with oral azoles
- Oropharyngeal candidiasis - This can be treated with either topical antifungal agents or systemic oral azoles
- Esophageal candidiasis - Treatment requires systemic therapy with oral azoles, such as fluconazole, itraconazole, and voriconazole
- VVC - Topical antifungal agents or oral fluconazole can be used
- *Candida* cystitis - In non catheterized patients, *Candida* cystitis should be treated with fluconazole; in catheterized patients, the Foley catheter should be removed or replaced; if the candiduria persists after the catheter changes, then patients can be treated with fluconazole.

UNDERSTANDING

COMMON FUNGAL PATHOGENS



Common human fungal pathogens include *Candida* (yeast infections, *C. auris*), *Aspergillus* (respiratory infections), *Cryptococcus* (meningitis), and dimorphic fungi like *Histoplasma* and *Coccidioides* (valley fever). These pathogens often target immunocompromised individuals, causing severe, sometimes fatal, infections.

Top Human Fungal Pathogens (WHO/CDC)

- ***Candida albicans* & *Candida auris*:** Yeast that causes common infections (thrush, yeast infections) and severe, drug-resistant bloodstream infections.
- ***Aspergillus fumigatus*:** A mold prevalent in the environment causing pulmonary aspergillosis.
- ***Cryptococcus neoformans*:** Causes severe lung and brain infections (meningitis), particularly in HIV/AIDS patients.
- ***Histoplasma capsulatum*:** Causes histoplasmosis, a lung infection from spores in soil, bird, and bat droppings.
- ***Coccidioides spp.*:** Causes Valley fever (coccidioidomycosis) in arid regions.
- ***Pneumocystis jirovecii*:** Causes severe pneumonia (PJP) in immunocompromised patients.
- ***Mucormycetes*:** Causes rare but aggressive mucormycosis.

Common Superficial Fungal Infections

- **Ringworm/Tinea:** Includes athlete's foot, jock itch, and nail infections, often caused by *Trichophyton* species.
- **Malassezia:** Causes pityriasis versicolor (skin discoloration).

Key Environmental & Agricultural Fungal Pathogens

- ***Magnaporthe oryzae*:** Causes rice blast disease.
- ***Botrytis cinerea*:** Causes gray mold on fruits and vegetables.
- ***Fusarium spp.*:** Causes vascular wilt in plants.
- ***Batrachochytrium dendrobatidis*:** Causes widespread chytridiomycosis in amphibians.
- ***Pseudogymnoascus destructans*:** Causes white-nose syndrome in bats.

Pathogenic fungi are fungi that cause disease in humans or other organisms. Although fungi are eukaryotic, many pathogenic fungi are microorganisms. Approximately 300 fungi are pathogenic to humans; their study is called "**medical mycology**". Fungal infections are estimated to kill more people than either tuberculosis or malaria—about two million people per year. In 2022 the World Health Organization (WHO) published a list of fungal pathogens which should be a priority for public health action. Markedly more fungi are pathogenic to plant life than those of the animal kingdom. The study of fungi and other organisms pathogenic to plants is called plant pathology.

Pathogens of particular concern

According to the World Health Organization (WHO) in 2022 pathogens of particular concern are:

Critical priority

Cryptococcus neoformans, *Candida auris*, *Aspergillus fumigatus*, *Candida albicans*.

High priority

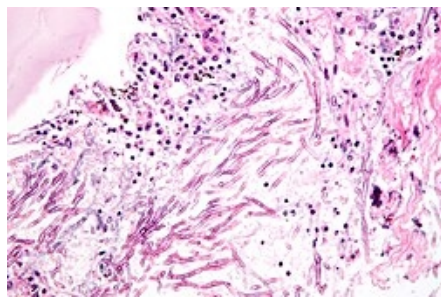
Nakaseomyces glabrata (*Candida glabrata*), *Histoplasma* spp., *eumycetoma* causative agents, *Mucorales*, *Fusarium* spp., *Candida tropicalis, Candida parapsilosis*.

Medium priority

Scedosporium spp., *Lomentospora prolificans*, *Coccidioides* spp., *Pichia kudriavzeveii* (*Candida krusei*), *Cryptococcus gattii*, *Talaromyces marneffei*, *Pneumocystis jirovecii*, *Paracoccidioides* spp.

IMPORTANT PATHOGENIC FUNGI (besides Candida species)

Aspergillus

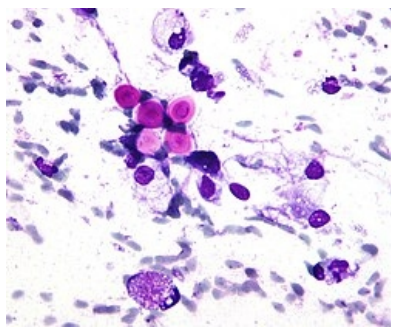


Aspergillosis. H&E stain.

The most common pathogenic species are *Aspergillus fumigatus* and *Aspergillus flavus*. Aspergillus flavus produces aflatoxin which is both a toxin and a carcinogen and which can potentially contaminate foods such as nuts. *Aspergillus fumigatus* and *Aspergillus clavatus* can cause allergic disease. Some *Aspergillus* species cause disease on grain crops, especially maize, and synthesize mycotoxins including aflatoxin. Aspergillosis is the group of diseases caused by *Aspergillus*. The symptoms include fever, cough, chest pain or breathlessness. Usually, only patients with weakened immune systems or with other lung conditions are susceptible.

The spores of *Aspergillus fumigatus* are ubiquitous in the atmosphere. *A. fumigatus* is an opportunistic pathogen. It can cause potentially lethal invasive infection in immunocompromised individuals. *A. fumigatus* has a fully functional sexual cycle that produces cleistothecia and ascospores.

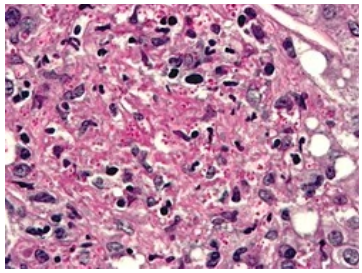
Cryptococcus



Cryptococcus. FNA specimen. Field stain.

Cryptococcus neoformans can cause severe forms of meningitis and meningo-encephalitis in patients with HIV infection and AIDS. The majority of *Cryptococcus* species live in the soil and do not cause disease in humans. *Cryptococcus neoformans* is the major human and animal pathogen. *Papiliotrema laurentii* and *Naganishia albida*, both formerly referred to *Cryptococcus*, have been known to occasionally cause moderate-to-severe disease in human patients with compromised immunity. *Cryptococcus gattii* is endemic to tropical parts of the continent of Africa and Australia and can cause disease in non-immunocompromised people. Infecting *C. neoformans* cells are usually phagocytosed by alveolar macrophages in the lung. The invading *C. neoformans* cells may be killed by the release of oxidative and nitrosative molecules by these macrophages. However some *C. neoformans* cells may survive within the macrophages. The ability of the pathogen to survive within the macrophages probably determines latency of the disease, dissemination and resistance to antifungal agents. In order to survive in the hostile intracellular environment of the macrophage, one of the responses of *C. neoformans* is to upregulate genes employed in responses to oxidative stress. The haploid nuclei of *C. neoformans* can undergo nuclear fusion (karyogamy) to become diploid. These diploid nuclei may then undergo meiosis, including recombination, resulting in the formation of haploid basidiospores that are able to disperse. Meiosis may facilitate repair of *C. neoformans* DNA in response to macrophage challenge.

Histoplasma



Histoplasmosis. PASD stain.

Histoplasma capsulatum can cause histoplasmosis in humans, dogs and cats. The fungus is most prevalent in the Americas, India and southeastern Asia. It is endemic in certain areas of the United States. Infection is usually due to inhaling contaminated air.

Pneumocystis

Pneumocystis jirovecii (or Pneumocystis carinii) can cause a form of pneumonia in people with weakened immune systems, such as premature children, patients on immunosuppressive treatment, the elderly and AIDS patients.

Stachybotrys

Stachybotrys chartarum or "black mold" can cause respiratory damage and severe headaches. It frequently occurs in houses and in regions that are chronically damp.

TROUBLESHOOTING

Fungal Culture and Sensitivity:

Troubleshooting fungal culture and sensitivity involves addressing slow growth rates, contamination, low sensitivity (false negatives), and interpreting complex results. Fungal cultures typically require several days to weeks to yield results, with common issues arising from improper specimen collection, transport, or incubation conditions.

Common Issues and Troubleshooting Steps

1. **No Growth/False Negative Results**
   - **Improper Specimen Collection:** Ensure adequate quantity of sample is collected, particularly for blood cultures where 40-60 mL is recommended for optimal sensitivity.
   - **Prior Antifungal Use:** Patients should avoid applying topical antifungal treatments for several days before testing.
   - **Slow Growth/Long Incubation:** Fungi are slow growing. Cultures may need to be held for up to 21 days.
   - **Media Selection:** Ensure appropriate media (e.g., Sabouraud dextrose agar) is used and that media supports the suspected organism (e.g., overlaying olive oil for *Malassezia* spp.).
   - **Temperature Sensitivity:** Transport samples at ambient temperature. Temperatures below 10°C or above 30°C can kill some fungi.
2. **Contamination of Cultures**
   - **Aseptic Technique:** Maintain strict aseptic techniques to avoid bacterial or environmental fungal contaminants.
   - **Contaminants in Sample:** Use antibiotics in the medium to inhibit bacteria, especially in non-sterile sites.
   - **Environmental Control:** Perform procedures in a clean environment, using biological safety cabinets, and check for HVAC issues.
3. **Troubleshooting Sensitivity (AFST: Antifungal Susceptibility Testing) Results**
   - **Standardization Issues:** Ensure testing follows Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines to ensure reproducibility.
   - **Inoculum Size:** Accurate standardization of the inoculum is crucial, as too large or too small a concentration can alter the MIC (Minimum Inhibitory Concentration).
   - **Incubation Time:** Cryptococcus species, for example, may require longer incubation (70–74 hours) compared to Candida (24-48 hours).
   - **Species Identification:** Accurate identification is crucial, as species-specific breakpoints are required for interpretation.

Key Technical Considerations

- **Direct Microscopy:** Always perform a direct KOH mount or Calcofluor White stain, as this can be more sensitive than culture for certain infections.
- **Alternatives for Negative Cultures:** Consider molecular methods (PCR) or serological tests (antigen detection) if cultures are negative despite high clinical suspicion.
- **Interpretation of Results:** A positive culture from a non-sterile site does not always indicate infection; it must be correlated with clinical symptoms, patient status, and direct microscopy.

Troubleshooting Guide Summary

Issue	Potential Cause	Action
No growth	Delayed transport, low sample volume	Ensure proper transport, increase sample volume
Contamination	Improper aseptic technique	Review aseptic procedures, add antibiotics
Slow growth	Incorrect temperature	Incubate at appropriate temperature (usually 25–30°C)
False negative	Prior antifungal use	Pause treatment before sampling

BOUQUET

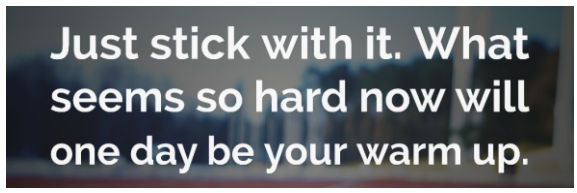
In Lighter Vein

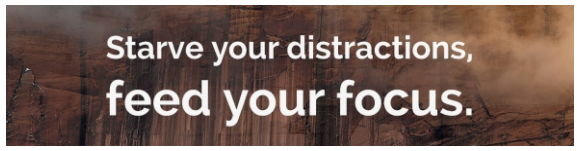
Employee: "Boss I need a raise – there are three companies after me right now."
Boss: "Really? Which ones?"
Employee: "Gas, electric, and water".

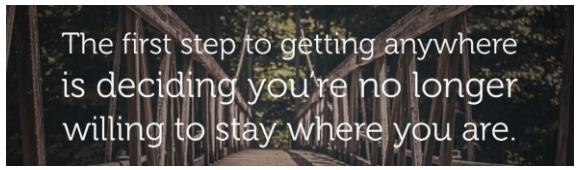
Employee1: "I always give 100% at work:
Employee 2: Really?
Employee1: Yes…10% Monday, 23% Tuesday, 40% Wednesday, 22% Thursday, and 5% Friday."

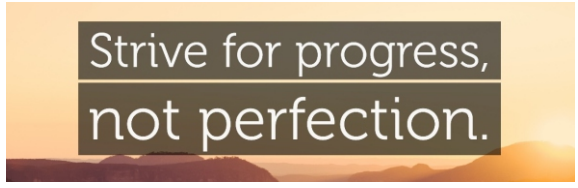
I went for a job interview. The interviewer told me I'd start on Rs.25,000 a month, and then after six months, I'd be on Rs.25,500 a month. I told them I would start in 6 months.

Wisdom Whispers









Brain Teasers

1. **What is the most common causative agent of candidiasis?**
   A. Candida tropicalis
   B. Candida albicans
   C. Candida glabrata
   D. Candida parapsilosis

2. **Which of the following is considered a primary oral candidiasis?**
   A. Median rhomboid glossitis
   B. Chronic mucocutaneous candidiasis
   C. Oral thrush (Pseudomembranous candidiasis)
   D. Candida endocarditis

3. **"Denture stomatitis" is most commonly associated with which organism?**
   A. Streptococcus mutans
   B. Candida albicans
   C. Actinomyces
   D. Fusobacterium

4. **Which condition is a common Candida-associated lesion on the tongue?**
   A. Geographic tongue
   B. Median rhomboid glossitis
   C. Fissured tongue
   D. Hairy tongue

ANSWER: 1-B, 2-C, 3-B, 4-B

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