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## THE IMPORTANCE OF GENUS *CANDIDA* IN HUMAN SAMPLES\*

**ABSTRACT:** Microbiology is a rapidly changing field. As new researches and experiences broaden our knowledge, changes in the approach to diagnosis and therapy have become necessary and appropriate. Recommended dosage of drugs, method and duration of administration, as well as contraindications to use, evolve over time all drugs. Over the last 2 decades, *Candida* species have emerged as causes of substantial morbidity and mortality in hospitalized individuals. Isolation of *Candida* from blood or other sterile sites, excluding the urinary tract, defines invasive candidiasis. *Candida* species are currently the fourth most common cause of bloodstream infections (that is, candidemia) in U.S. hospitals and occur primarily in the intensive care unit (ICU), where candidemia is recognized in up to 1% of patients and where deep-seated *Candida* infections are recognized in an additional 1 to 2% of patients. Despite the introduction of newer anti-*Candida* agents, invasive candidiasis continues to have an attributable mortality rate of 40 to 49%; excess ICU and hospital stays of 12.7 days and 15.5 days, respectively, and increased care costs. Postmortem studies suggest that death rates related to invasive candidiasis might, in fact, be higher than those described because of undiagnosed and therefore untreated infection. The diagnosis of invasive candidiasis remains challenging for both clinicians and microbiologists. Reasons for missed diagnoses include nonspecific risk factors and clinical manifestations, low sensitivity of microbiological culture techniques, and unavailability of deep tissue cultures because of risks associated with the invasive procedures used to obtain them. Thus, a substantial proportion of invasive candidiasis in patients in the ICU is assumed to be undiagnosed and untreated. Yet even when invasive candidiasis is diagnosed, culture diagnosis delays treatment for 2 to 3 days, which contributes to mortality. Interventions that do not rely on a specific diagnosis and are implemented early in the course of *Candida* infection (that is, empirical therapy) or before *Candida* infection occurs (that is, prophylaxis) might improve patient survival and may be warranted. Selective and nonselective administration of anti-*Candida* prophylaxis is practiced in some ICUs. Several trials have tested this, but results were limited by low statistical power and choice of outcomes. Thus, the role of anti-*Candida* prophylaxis for patients in the ICU remains controversial. Initiating anti-*Candida* therapy for patients in the ICU who have suspected infection but have not responded to antibacterial therapy (empirical therapy) is practiced in some hospitals. This practice, however, remains a subject of

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considerable debate. These patients are perceived to be at higher risk from invasive candidiasis and therefore are likely to benefit from empirical therapy. Nonetheless, empirical anti-*Candida* therapies have not been evaluated in a randomized trial and would share shortcomings that are similar to those described for prophylactic strategies. Current treatment guidelines by the Infectious Diseases Society of America (IDSA) do not specify whether empirical anti-*Candida* therapy should be provided to immunocompetent patients. If such therapy is given, IDSA recommends that its use should be limited to patients with *Candida* colonization in multiple sites, patients with several other risk factors, and patients with no uncorrected causes of fever. Without data from clinical trials, determining an optimal anti-*Candida* strategy for patients in the ICU is challenging. Identifying such a strategy can help guide clinicians in choosing adequate therapy and may improve patient outcomes. In our study, we developed a decision analytic model to evaluate the cost-effectiveness of empirical anti-*Candida* therapy given to high-risk patients in the ICU, defined as those with altered temperature (fever or hypothermia) or unexplained hypotension despite 3 days of antibacterial therapy in the ICU.

KEY WORDS: *Candida*, species, human samples, candidiasis

## INTRODUCTION

**Background:** *Candida* species are ubiquitous fungi and are the most common fungal pathogens that affect humans. The growing problem of mucosal and systemic candidiasis reflects the enormous increase in the pool 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 (1).

The increased prevalence of local and systemic disease caused by *Candida* species has resulted in numerous new clinical syndromes, primarily dependent 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. Management of serious and life-threatening invasive candidiasis remains severely hampered by delays in diagnosis and the lack of reliable diagnostic methods that allow detection of both fungemia and tissue invasion by *Candida* species.

Advances in medical technology, chemotherapeutics, cancer therapy, and organ transplantation have had a major impact on reducing 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, that it is, in fact, worsening. On a daily basis, virtually all physicians are confronted with a positive *Candida* isolate obtained from one or more various anatomical sites. High-risk areas for *Candida* infection include neonatal, pediatric, and adult ICUs, both medical and surgical. *Candida* infections can involve any anatomical structure (2).

**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 foods, counter tops, air-conditioning vents, floors, respirators, and medical personnel. They are also normal commensals of diseased skin and mucosal membranes of the GI, genitourinary, and respiratory tracts.

*Candida* species also contain their own set of well-recognized virulence factors. Although not well characterized, several virulence factors may contribute to their ability to cause infection. The main virulence factors are surface molecules that permit adherence of the organism to other structures (e.g., human cells, extracellular matrix, prosthetic devices), acid proteases, and the ability to convert to a hyphal form.

As with most fungal infections, host defects also play a significant role in the development of candidal infections. Numerous host defects are associated with candidal infections.

Host defence 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 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
- Broad-spectrum antibiotics
- Burns
- Prolonged hospitalization
- Severe trauma
- Recent bacterial infection
- Recent surgery
- GI tract surgery
- Central intravascular access devices

- Premature birth
- Hemodialysis

The first step in the development of a candidal infection is colonization of the mucocutaneous surfaces. The factors outlined above are all associated with increased colonization rates. The routes of candidal invasion are (1) disruption of a colonized surface (skin or mucosa), allowing the organisms access to the bloodstream, and (2) persorption via the GI wall, which may occur following massive colonization with large numbers of organisms that pass directly into the bloodstream.

### *Frequency*

— **In the US:** *Candida* species are the most common cause of fungal infection affecting immunocompromised patients. Oropharyngeal colonization is found in 30—55% of healthy young adults, and *Candida* species may be detected in 40—65% of normal fecal floras.

Three of every 4 women have at least 1 bout of vulvovaginal candidiasis (VVC) during their lifetime.

In HIV-positive persons who are not receiving highly active antiretroviral therapy (HAART), more than 90% experience oropharyngeal candidiasis (OPC) and 10% have at least 1 episode of esophageal candidiasis.

In persons with systemic infections, *Candida* species are now the fourth most commonly isolated pathogens from blood cultures.

Clinical and autopsy studies have confirmed a considerable increase in the incidence of disseminated candidiasis, reflecting a parallel increase in the frequency of candidemia. This increase is multifactorial in origin and reflects increased recognition of the fungus, a growing population of patients at risk (i.e., patients undergoing complex surgical procedures, patients with indwelling vascular devices), and the improved survival of patients with underlying neoplasms or collagen-vascular disease and patients who are immunosuppressed (3,4).

— **Internationally:** Similar rates of mucocutaneous and systemic candidiasis have been observed worldwide. In fact, throughout the world, *Candida* species have replaced *Cryptococcus* species as the most common fungal pathogens affecting immunocompromised hosts.

### *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 for these infections have not improved much over the past few years and remain in the range of 30—40%. Systemic candidiasis is the cause of 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 of length of stay in the hospital (70 vs. 40 days in patients who are comparable, matched, and nonfungemic). Although mucocutaneous fungal infections, such as oral thrush and *Candida* esophagitis, are extremely common in patients with AIDS, candidemia and disseminated candidiasis are uncommon (5, 6, 7).

**Sex:** Colonization with *Candida* species occurs in equal numbers of males and females. However, in women, VVC is the second most common cause of vaginitis.

**Age:** Candidal colonization is at the highest levels during the age extremes in neonates and in people older than 65 years. In addition, mucocutaneous candidiasis is also more prevalent in neonates and older adults.

**History:** Infections due to *Candida* species can manifest in 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. Clinical syndromes associated with *Candida* infection are the following:

#### *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 where the skin surfaces are in close proximity, providing a warm and moist environment. Pruritic red rash occurs. Physical examination reveals a rash that begins with vesiculopustules, which 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 frequently found and may coalesce and extend into larger lesions (8, 9).

— Metastatic skin lesions: Characteristic skin lesions occur in approximately 10% of patients with disseminated candidiasis and candidemia. The lesions may be numerous or few. Lesions 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 the cases.

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

— Paronychia and onychomycosis: Frequently, paronychia and onychomycosis 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 (10, 11).

### *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 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 is frequently 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.

### *GI tract candidiasis*

— Oropharyngeal candidiasis

- The patient has a history of HIV infection, denture wear, diabetes mellitus, or frequent use of broad-spectrum antibiotics or inhaled steroids. Patients may be asymptomatic, but variable 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 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 also 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.
  - 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, or the presence of HIV infection or hematologic or solid organ malignancy. Patients may be asymptomatic, but variable symptoms may include the following:
    - No oral disease (> 50% of patients)
    - Dysphagia
    - Odynophagia
    - Retrosternal pain
    - Epigastric pain
    - Nausea and vomiting
  - Upon physical examination, oral candidiasis is nearly always present.
- Nonesophageal GI candidiasis
  - Most commonly, the patient's history includes an association with neoplastic disease of the GI tract. The stomach is found to be the second most commonly infected site after the esophagus. With less frequency, patients may have chronic gastric ulcerations, gastric perforations, or malignant gastric ulcers with concomitant candidal infection. The third most common site of infection (20%) is the small bowel. 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 are variable and depend 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
  - Occasionally, abdominal mass

### *Respiratory tract candidiasis*

The respiratory tract is frequently colonized with *Candida* species, especially in hospitalized patients. In ambulatory patients, 20—25% of the population is colonized by *Candida* species.

— Laryngeal candidiasis: This is very unusual but may be a source for disseminated candidiasis. Laryngeal candidiasis is primarily observed in patients with hematologic malignancies. The patient may have a sore throat and hoarseness. Physical examination findings are generally unremarkable, and the diagnosis is made by direct or indirect laryngoscopy.

— *Candida* tracheobronchitis: This is a rare form of candidiasis. Most patients with *Candida* tracheobronchitis are seropositive for HIV, or are severely immunocompromised, reporting fever, productive cough, and shortness of breath. Physical examination reveals dyspnea and scattered rhonchi. The diagnosis is generally made after bronchoscopy.

— *Candida* pneumonia: It does not exist alone and occurs only rarely as a part of disseminated candidiasis. The most common form is multiple abscesses due to hematogenous dissemination of *Candida* species. The high degree of colonization and isolation of *Candida* species from the respiratory tract makes diagnosing this entity difficult. The patient's history reveals similar risk factors for disseminated candidiasis, and patients report shortness of breath, cough, and respiratory distress. Physical examination reveals fever, dyspnea, and variable breath sounds, from clear, rhonchi to scattered rales.

### *Genitourinary tract candidiasis*

— Vulvovaginal candidiasis: 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 are usually erythematous, a thick curdlike discharge, and a normal cervix upon speculum examination.

— *Candida* balanitis: Patients report itchiness of the penis. Lesions and whitish patches are present. *Candida* balanitis is acquired through sexual intercourse with a partner who has VVC. Physical examination reveals vesicles on



the penis that develop later into patches resembling thrush. The rash may spread to the thighs, gluteal folds, buttocks, and scrotum.

— *Candida* cystitis: Many patients frequently 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; otherwise, examination 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, the distinction between invasive disease and colonization cannot be made solely on culture results because approximately 5–10% of all urine cultures are positive for *Candida*.

— Ascending pyelonephritis: The use of stents and indwelling devices, along with the presence of diabetes, is the major risk factor predisposing patients to ascending infection. The patient frequently has a history of 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 (12, 13).

#### — Candidemia

- *Candida* species currently are the fourth most commonly isolated organism in blood cultures, and *Candida* infection generally is considered a nosocomially acquired infection. The patient's history commonly reveals the following:
  - Several days of fever that is unresponsive to broad-spectrum antimicrobials; often the only marker of infection
  - Prolonged intravenous catheterization
  - A history of several key risk factors (see <http://www.emedicine.com/med/topic264.htm> Pathophysiology)
  - Possibly associated with multiorgan infection.
- Physical examination is remarkable for the following:
  - Fever
  - Macronodular skin lesions (approximately 10%)
  - Candidal endophthalmitis (approximately 10–28%)
  - 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: For the most part, this is observed secondary to prolonged central venous catheterization. Suppura-

tive thrombophlebitis manifests as fever and candidemia, which persist despite antifungal therapy and catheter removal. Sepsis also may be present.

- Endocarditis: The frequency of endocarditis has increased in the past few years. Endocarditis is the most common cause of fungal endocarditis and is primarily due to *Candida albicans* (> 60% of cases). The most common valves involved are the aortic and mitral. The 2 different forms of endocarditis are exogenous, which is secondary to direct infection during surgery, and endogenous, which is due to secondary spread during candidemia and disseminated candidiasis. Endocarditis is frequently associated with 4 main risk factors. These are (1) intravenous heroin use, which is frequently associated with infection due to *Candida parapsilosis*; (2) chemotherapy; (3) prosthetic valves (approximately 50%); and (4) prolonged use of central venous catheters.

— Disseminated candidiasis: This is frequently associated with multiple deep organ infections or may involve single organ infection. Unfortunately, patients with disseminated candidiasis, as many as 40–60% of them, may have blood culture results negative for *Candida* species. 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 (which may be the only symptom) with an unknown source and sepsis and septic shock.

— *Candida* endophthalmitis: The 2 forms of *Candida* endophthalmitis are the exogenous 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 is found in 10–28% of the patients with candidemia. The use of hematogenous candidal endophthalmitis as a marker of widespread disseminated candidiasis is important.

- The patient's history reveals a broad range of manifestations.
  - Eye injury
  - Ophthalmic surgery
  - Underlying risk factors for candidemia
  - Asymptomatic and detected upon physical examination
  - Ocular pain
  - Photophobia
  - Scotomas
  - Floaters
- Physical examination reveals fever.
- Upon fundoscopic examination, early lesions are the size of a pinhead, are off-white in color, and are found 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 ext-

end into the vitreous off the chorioretinal surface. They may be single or multiple.

— Renal candidiasis

- This is most frequently a consequence of candidemia and disseminated candidiasis. 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 is generally unremarkable, and renal candidiasis is diagnosed after urinalysis and renal biopsy. Otherwise, this condition is commonly diagnosed at autopsy.
- Physical examination reveals the following:
  - Fever
  - Nuchal rigidity
  - Confusion
  - Coma

— *Candida* arthritis, osteomyelitis, costochondritis, and myositis

- In the past, musculoskeletal infections were rare; currently, they are more common, due to the increased frequency of candidemia and disseminated candidiasis. The most common sites of involvement are the knee and vertebral column. The pattern of involvement is similar to the pattern observed in bacterial infections. The infection may be exogenous or endogenous. The exogenous infection is frequently due to direct inoculation of the organisms, such as postoperative infection or trauma. Affected sites include the following:
  - Ribs and leg bones (< 20 years)
  - 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 patient's history reveals underlying risk factors of disseminated candidiasis and localized pain over the affected site. The physical examination is frequently unremarkable; otherwise, it may reveal tenderness over the involved area, erythema, and bone deformity, occasionally with a draining sinus.
  - Arthritis: Generally, arthritis is a complication of disseminated candidiasis, but it 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, developing *Candida* arthritis after joint replacement is not uncommon.
  - Osteomyelitis: The 2 forms of osteomyelitis are exogenous infection and endogenous infection. The exogenous infection is frequently due to either direct inoculation of the organisms, such as

through postoperative infection, trauma, or steroid injections. The endogenous form of osteomyelitis is generally a complication of disseminated candidiasis. Most cases, due to hematogenous seeding, infect the vertebral disks and progress to diskitis with extension into the vertebrae from contiguous spread. Other bones affected include the wrist, femur, scapula, and proximal humerus.

- Costochondritis: This is rare and usually has 2 forms. Costochondritis usually results from either hematogenous spread or direct inoculation during surgery (median sternotomy). Frequently, costochondritis is associated with localized pain over the involved area.
- Myositis: This occurs infrequently, and an association with disseminated candidiasis is common. Most patients are neutropenic. People with myositis have a history of muscular pain.

— Myocarditis-pericarditis: This is due to hematogenous spread in association with disseminated disease and is rarely due to direct extension from the sternum or esophagus. Myocarditis-pericarditis occurs as diffuse abscesses scattered throughout the myocardium with normal cardiac tissue. In persons with disseminated candidiasis, the rate has been documented to be as high as 50%. The patient's history reveals serious complications in 10–20% of the cases without valve disease, fever and chills. Physical examination reveals fever, hypotension, shock, tachycardia, and new murmurs or rubs (changes in previously detected murmurs).

— *Candida* peritonitis

- The patient's history frequently reveals an association with GI tract surgery, viscous perforation, or peritoneal dialysis. *Candida* peritonitis tends to remain localized, and only in 15% of the cases does the infection disseminate into the blood stream. The range of manifestations is broad and includes fever and chills, abdominal pain and cramping, nausea and vomiting, and constipation.
- Physical examination is significant for 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 <http://www.emedicine.com/med/topic264.htm> Hepatosplenic candidiasis).

— *Candida* cholecystitis: This is rare and generally associated with bacterial cholangitis and ascending cholangitis. Most commonly, *Candida* cholecystitis is diagnosed at the time of surgery when a culture is obtained.

- The medically significant *Candida* species include the following:
  - *C. albicans*, the most common species identified (50—60%)
  - *C. glabrata* (15—20%)
  - *C. parapsilosis* (10—20%)
  - *C. tropicalis* (6—12%)
  - *C. krusei* (1—3%)
  - *C. kefyr* (< 5%)
  - *C. guilliermondi* (< 5%)
  - *C. lusitaniae* (< 5%)
  - *C. dubliniensis*, primarily recovered from patients who are positive for HIV.

— *C. glabrata* and *C. albicans* account for approximately 70—80% of yeast isolated from patients with invasive candidiasis. *C. glabrata* has recently become important because of its increasing incidence worldwide, and it is intrinsically less susceptible to azoles and amphotericin B.

— *C. krusei* is important because of its intrinsic resistance to ketoconazole and fluconazole (Diflucan). Additionally, 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 some *Candida* species, it is of clinical significance because it is frequently resistant to amphotericin B, although it remains susceptible to azoles and echinocandins.

— *C. parapsilosis* is an important species to consider in hospitalized patients with vascular catheters.

— *C. tropicalis* has been considered an important cause of candidemia in patients with cancer (leukemia), and in those who have undergone bone marrow transplantation.

### *Lab Studies*

— Unfortunately, findings from the laboratory studies are often nonspecific. 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. Patients who remain febrile despite broad-spectrum antibiotic therapy, with either persistent neutropenia or other risk factors and persistent leukocytosis, should be suspected of having systemic candidiasis. To be effective, therapy should be provided early and empirically in such patients.

— Cultures of nonsterile sites, although not useful for establishing a diagnosis, may demonstrate high degrees of candidal colonization. Positive culture results from sterile sites should be considered significant and as an evidence of infection.

- Mucocutaneous candidiasis

- Wet mount, scrapings or smears obtained from skin, nails, oral mucosa, or vaginal mucosa are examined under the microscope for hyphae, pseudohyphae, or budding yeast cells.
  - With a potassium hydroxide smear, the Gram stain methylene blue is useful to demonstrate fungal cells, directly.
  - Cultures of affected nails are helpful to diagnose onychomycosis versus noninfectious causes.
- Candidemia and disseminated candidiasis
- Blood cultures are helpful but are positive in only 50—60% of the cases of disseminated disease.
  - Urinalysis may be helpful, and results may be indicative of either colonization or renal candidiasis.
  - The serum 1—3 D-glucan detection assay (GlucateLL, FungiteLL) is a nonculture test, which was approved for use in the United States in May 2004. This assay measures the level of beta-glucan (a fungal cell wall component). In a large multicenter study, the assay had a high specificity and positive predictive value with highly reproducible results.
  - 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 imply the presence of invasive disease. Always consider positive results from these sites to be significant and to be an evidence of infection.
  - GI, respiratory, and urinary tract culture results positive for *Candida* may not represent invasive disease. However, consider the GI, respiratory, and urinary tract sites of colonization.
- Cutaneous candidiasis: Use a wet mount. Scrapings or smears obtained from skin or nails are examined under the microscope for hyphae, pseudohyphae, or budding yeast cells. Potassium hydroxide smears are also useful.
- Genitourinary candidiasis: Perform a urinalysis. Evidence of WBCs, RBCs, protein, and yeast cells can be found. Additionally, urine fungal cultures are useful.
- Respiratory tract candidiasis
- Sputum Gram stain demonstrates WBCs and yeast cells.
  - Sputum culture demonstrates *Candida* species.
  - Lung biopsy is mandatory to establish definitively the diagnosis of respiratory tract candidiasis, because the respiratory tract is frequently colonized with yeast.
- GI candidiasis: Endoscopy, with or without biopsy is necessary to establish the diagnosis.
- Focal hepatosplenic candidiasis: Elevation of the serum alkaline phosphatase level is common.

— Species identification

- *C. albicans*, *C. dubliniensis*, and *C. stellatoidea* can be identified morphologically by germ-tube formation (hyphae are produced from yeast cells after 2–3 h of incubation) or biochemical assays.
- CHROMagar *Candida* allows presumptive identification of several *Candida* species by using color reactions in specialized media that demonstrate different colony colors, depending on the species of *Candida*.
- API 20C and API 32C are biochemical assays that allow the identification of different *Candida* species with more precision. These assays evaluate the assimilation of a number of carbon substrates and generate profiles used in the identification of different fungal species.

— Antifungal susceptibility testing

- *In vitro* susceptibility testing for *Candida* species is now standardized, using the National Committee for Clinical Laboratory Standards (NCCLS) microbroth dilution methodology (NCCLS M27-A2).
- Although not used as a standard of care, this method may be helpful in guiding difficult therapeutic decisions. Most of the difficult decisions are observed in antifungal, refractory, oral, or esophageal candidiasis in patients with advanced HIV disease.

— Nonculture *Candida* detection assays

- The *Candida* mannan assay has a sensitivity of 31–90% (less for non-*albicans* *Candida* species).
- The *Candida* heat labile antigen assay has a sensitivity of 10–71%.
- The D-arabinitol assay has a sensitivity of 50% but is not useful for infection with *C. krusei* or *C. glabrata*.
- The enolase assay has a sensitivity of 55–75%, which improves with serial testing.
- The 1–3 beta-D-glucan assay is an amebocyte lysis assay with a sensitivity of 75–100% and a specificity of 88–100% (broad-spectrum assay that detects *Aspergillus*, *Candida*, *Fusarium*, *Acremonium*, and *Saccharomyces* species). Beta-D-glucan is a component of the cell wall of a wide variety of fungi and can be detected by its ability to activate factor G of the horseshoe crab coagulation cascade. The Fungitell assay is used in the evaluation of invasive fungal infections caused by the species mentioned above to guide diagnosis. It does not detect infections caused by *Cryptococcus neoformans* and Zygomycetes.

— Molecular assays such as polymerase chain reaction tests and DNA probes are still under development and in the early reserach stage.

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## ЗНАЧАЈ РОДА *CANDIDA* ЗА ЉУДСКЕ УЗОРКЕ

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### Резиме

Микробиологија представља науку која се развија прогресивно. Најновија истраживања показују посебне измене на пољу дијагнозе и одговарајуће терапије. Током последње две декаде, кандида специјес добиле су на значају као узрочници морбидитета и морталитета код хоспитализованих пацијената. Изолација кандидида из крви или других стерилних подручја искључујући уринарни тракт, потврђује инвазивност кандидида. Кандида врсте налазе се на четвртом месту најчешћих узрочника који изазивају инфекције преко крви (кандидемија) у САД, а нарочито на одељењима интензивне неге где се код 1% пацијената ради о дубоким инфекцијама узрокованим кандидида врстама. Упркос увођењу новијих антикандида агенаса, инвазивна кандидијаза остаје и даље изазов за клиничаре и микробиологе. Разлози за пропусте у дијагностици укључују неспецифичне факторе ризика и клиничке манифестације, слабу осетљивост техника култивације кандидида и примену инвазивних метода за узорковање болесничког материјала у случају дубоке кандидијазе. Чак и када се инвазивна кандидијаза дијагностикује, култивација кандидида траје 2–3 дана, што доприноси порасту морталитета. Превентивно давање (емпиријска терапија) антикандида агенаса може побољшати преживљавање пацијената. Селективно и неселективно давање антикандида агенаса у виду профилаксе примењује се на неким одељењима интензивне неге. Остаје контроверзна улога антикандида профилаксе код таквих пацијената, с обзиром на њихов одговор на антимицробну терапију. Водич за актуелни третман кандидијазе Удружења за инфективне болести САД (ИДСА) није посебно дефинисао да ли емпиријска антикандида терапија треба да се примени код имунокомпетентних пацијента. Посебно је тешко применити оптималну антикандида стратегију код хоспитализованих пацијената на одељењима интензивне неге.