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## Candidiasis: Introduction

The genus *Candida* encompasses more than 150 species, only a few of which cause disease in humans. With rare exceptions, the human pathogens are *C. albicans*, *C. guilliermondii*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *C. kefyr*, *C. lusitaniae*, *C. dubliniensis*, and *C. glabrata*. Ubiquitous in nature, these organisms are found on inanimate objects, in foods, and on animals and are normal commensals of humans. They inhabit the gastrointestinal tract (including the mouth and oropharynx), the female genital tract, and the skin. Although cases of candidiasis have been described since antiquity in debilitated patients, the advent of *Candida* species as common human pathogens dates to the introduction of modern therapeutic approaches that suppress normal host defense mechanisms. Of these relatively recent advances, the most important is the use of antibacterial agents that alter the normal human microbial flora and allow nonbacterial species to become more prevalent in the commensal flora. With the introduction of antifungal agents, the causes of *Candida* infections shifted from an almost complete dominance of *C. albicans* to the common involvement of *C. glabrata* and the other species listed above. The non-*albicans* species now account for approximately half of all cases of candidemia and hematogenously disseminated candidiasis. Recognition of this change is clinically important, since the various species differ in susceptibility to the newer antifungal agents. In developed countries, where medical therapeutics are commonly used, *Candida* species are now among the most common nosocomial pathogens. In the United States, these species are the fourth most common isolates from the blood of hospitalized patients.

*Candida* is a small, thin-walled, ovoid yeast that measures 4–6  $\mu\text{m}$  in diameter and reproduces by budding. Organisms of this genus occur in three forms in tissue: blastospores, pseudohyphae, and hyphae. *Candida* grows readily on simple medium; lysis centrifugation enhances its recovery from blood. Species are identified by biochemical testing (currently with automated devices) or on special agar.

## Etiologic Manifestations

### MUCOCUTANEOUS CANDIDIASIS

The organisms disseminate hematogenously and form microabscesses and small macroabscesses in major organs. Although the exact mechanism is not known, *thrush* is characterized by white, adherent, painless, discrete or confluent patches in the mouth, tongue, or esophagus, occasionally with fissuring at the corners of the mouth. This form of *Candida* disease may also occur as a consequence of bacterial suppression by antibacterial drugs; alternatively, in some instances, the organism may enter from the skin. A change from the blastospore stage to the pseudohyphal and hyphal stages is generally considered integral to the organism's penetration into tissue. However, *C. glabrata* can cause extensive infection even though it does not transform into pseudohyphae or hyphae. Numerous reviews of cases of hematogenously disseminated candidiasis have identified the following predisposing factors or conditions: antibacterial agents, indwelling intravascular catheters, hyperalimentation fluids, indwelling urinary catheters, parenteral glucocorticoids, respirators, neutropenia, abdominal and thoracic surgery, cytotoxic chemotherapy, and fungal nail infection rarely caused by this genus. Infants, an erythematous irritation with redness and pustules in the skin folds; balanitis, an erythematous-pustular infection of the glans penis; erosio interdigitalis peritonitis; an infection between the digits of the hands or toes; folliculitis with pustules developing most frequently in the area of the beard; perianal candidiasis, a pruritic, erythematous-pustular infection surrounding the anus; and diaper rash, a common erythematous-pustular perineal infection in infants. Generalized disseminated cutaneous candidiasis, another form of infection that occurs primarily in infants, is characterized by widespread eruptions over the trunk, thorax, and extremities. The diagnostic macronodular lesions of *and the neutrophil is the most important component of this defense. Although many immunocompetent individuals have antibodies to *Candida*, the role of these antibodies in defense against the organism is not clear.*

organs as well as the skin. While the lesions are seen predominantly in immunocompromised patients treated with cytotoxic drugs, they may also develop in patients without neutropenia.

### Figure 196-1



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: <http://www.accessmedicine.com>  
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**Macronodular skin lesions associated with hematogenously disseminated candidiasis.** *Candida* organisms are usually but not always visible on histopathologic examination. The fungi grow when a portion of the biopsied specimen is cultured. Therefore, for optimal identification, both histopathology and culture should be performed. (Image courtesy of Dr. Noah Craft and the Victor Newcomer collection at UCLA, archived by Logical Images, Inc., with permission.)

*Chronic mucocutaneous candidiasis* is a heterogeneous infection of the hair, nails, skin, and mucous membranes that persists despite intermittent therapy. The onset of disease usually comes in infancy or within the first two decades of life but in rare cases can come in later life. The condition may be mild and limited to a specific area of the skin or nails, or it may take a severely disfiguring form (*Candida* granuloma) characterized by exophytic outgrowths on the skin. The condition is usually associated with specific immunologic dysfunction; most frequently reported is a failure of T lymphocytes to proliferate or to stimulate cytokines in response to stimulation by *Candida* antigens in vitro. Approximately half of patients have associated endocrine abnormalities that together are designated the autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome. This syndrome is due to mutations in the autoimmune regulator (*AIRE*) gene and is most prevalent among Finns, Iranian Jews, Sardinians, northern Italians, and Swedes. Conditions that usually follow the onset of the disease include hypoparathyroidism, adrenal insufficiency, autoimmune thyroiditis, Graves' disease, chronic active hepatitis, alopecia, juvenile-onset pernicious anemia, malabsorption, and primary hypogonadism. In addition, dental enamel dysplasia, vitiligo, pitted nail dystrophy, and calcification of the tympanic membranes may occur. Patients with chronic mucocutaneous candidiasis rarely develop hematogenously disseminated candidiasis, probably because their neutrophil function remains intact.

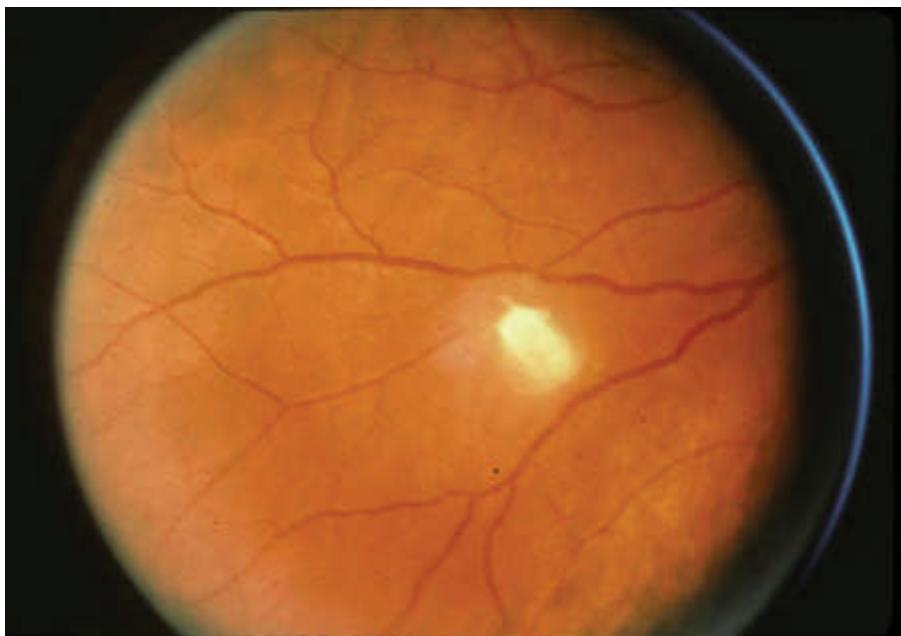
### DEEPLY INVASIVE CANDIDIASIS

Deeply invasive *Candida* infections may or may not be due to hematogenous seeding. Deep esophageal infection

may result from penetration by organisms from superficial esophageal erosions; joint or deep wound infection from contiguous spread of organisms from the skin; kidney infection from catheter-initiated spread of organisms through the urinary tract; infection of intraabdominal organs and the peritoneum from perforation of the gastrointestinal tract; and gallbladder infection from retrograde migration of organisms from the gastrointestinal tract into the biliary drainage system.

However, far more commonly, deeply invasive candidiasis is a result of hematogenous seeding of various organs as a complication of candidemia. Once the organism gains access to the intravascular compartment (either from the gastrointestinal tract or, less often, from the skin through the site of an indwelling intravascular catheter), it may spread hematogenously to a variety of deep organs. The brain, chorioretina (Fig. 196-2), heart, and kidneys are most commonly infected and the liver and spleen less commonly so (most often in neutropenic patients). In fact, nearly any organ can become involved, including the endocrine glands, pancreas, heart valves (native or prosthetic), skeletal muscle, joints (native or prosthetic), bone, and meninges. *Candida* organisms may also spread hematogenously to the skin and cause classic macronodular lesions (Fig. 196-1). Frequently, painful muscular involvement is also evident beneath the area of affected skin. Chorioretinal involvement and skin involvement are highly significant, since both findings are associated with a very high probability of abscess formation in multiple deep organs as a result of generalized hematogenous seeding. Ocular involvement (Fig. 196-2) may require specific treatment, such as partial vitrectomy to prevent permanent blindness. An ocular examination is indicated for all patients with candidemia, whether or not they have ocular manifestations.

**Figure 196-2**



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: <http://www.accessmedicine.com>  
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**Hematogenous *Candida* endophthalmitis.** A classic off-white lesion projecting from the chorioretina into the vitreous causes the surrounding haze. The lesion is composed primarily of inflammatory cells rather than organisms. Lesions of this type may progress to cause extensive vitreal inflammation and eventual loss of the eye. Partial vitrectomy, combined with IV and possibly intravitreal antifungal therapy, may be helpful in controlling the lesions. (Image courtesy of Dr. Gary Holland; with permission.)

## Diagnosis

The diagnosis of *Candida* infection is established by visualization of pseudohyphae or hyphae on wet mount

(saline and 10% KOH), tissue Gram's stain, periodic acid-Schiff stain, or methenamine silver stain in the presence of inflammation. Absence of organisms on hematoxylin-eosin staining does not reliably exclude *Candida* infection. The most challenging aspect of diagnosis is determining which patients with *Candida* isolates have hematogenously disseminated candidiasis. For instance, recovery of *Candida* from sputum, urine, or peritoneal catheters may indicate mere colonization rather than deep-seated infection, and *Candida* isolation from the blood of patients with indwelling intravascular catheters may reflect inconsequential seeding of the blood from or growth of the organisms on the catheter. Despite extensive research into both antigen and antibody detection systems, there is currently no widely available and validated diagnostic test to distinguish patients with inconsequential seeding of the blood from those whose positive blood cultures represent hematogenous dissemination to multiple organs. Many studies are under way to establish the utility of the  $\beta$ -glucan test. Meanwhile, the presence of ocular or macronodular skin lesions is highly suggestive of widespread infection of multiple deep organs.

## ***Candida* Infections: Treatment**

### **MUCOCUTANEOUS CANDIDA INFECTION**

The treatment of mucocutaneous candidiasis is summarized in Table 196-1.

**Table 196-1 Treatment of Mucocutaneous Candidal Infections**

Disease	Preferred Treatment	Alternatives
Cutaneous	Topical azole	Topical nystatin
Vulvovaginal	Oral fluconazole (150 mg) or azole cream or suppository	Nystatin suppository
Thrush	Clotrimazole troches	Nystatin
Esophageal	Fluconazole tablets (100–200 mg/d) or itraconazole solution (200 mg/d)	Caspofungin, micafungin, or amphotericin B

## **CANDIDEMIA AND SUSPECTED HEMATOGENOUSLY DISSEMINATED CANDIDIASIS**

All patients with candidemia are now treated with a systemic antifungal agent. A certain percentage of patients, including many of those who have candidemia associated with an indwelling intravascular catheter, probably have "benign" candidemia rather than deep-organ seeding. However, because there is no reliable way to distinguish benign candidemia from deep-organ infection, and because antifungal drugs less toxic than amphotericin B are available, it has become the standard of practice to treat all patients with candidemia, whether or not there is clinical evidence of deep-organ involvement. In addition, if an indwelling intravascular catheter may be involved, it is best to remove or replace the device whenever possible.

The drugs used for the treatment of candidemia and suspected disseminated candidiasis are listed in Table 196-2. Various lipid formulations of amphotericin B, three echinocandins, and the azoles fluconazole and voriconazole are used; no agent within a given class has been clearly identified as superior to the others. Most institutions choose an agent from each class on the basis of their own specific microbial epidemiology, strategies to minimize toxicities, and cost considerations. Unless azole resistance is considered likely, fluconazole is the agent of choice for the treatment of candidemia and suspected disseminated candidiasis in nonneutropenic, hemodynamically stable patients. Initial treatment in the context of likely azole resistance depends, as mentioned above, on the epidemiology of the individual hospital. For example, certain hospitals have a high rate of recovery of *C. glabrata*, while others do not. For hemodynamically unstable or neutropenic patients, initial treatment with broader-spectrum agents is desirable; these drugs include polyenes, echinocandins, or later-generation azoles such as voriconazole. Once the clinical response has been assessed and the pathogen specifically identified, the regimen can be altered accordingly. At present, the vast majority of *C. albicans* isolates are sensitive to fluconazole. Isolates of *C. glabrata* and *C. krusei* are less sensitive to fluconazole and

more sensitive to polyenes and echinocandins. *C. parapsilosis* is less sensitive to echinocandins in vitro, although the clinical significance of this finding is not known.

**Table 196-2 Available Agents for the Treatment of Disseminated Candidiasis**

Agent	Route of Administration	Comment
Amphotericin B deoxycholate	IV only	Being replaced by lipid formulations
Amphotericin B lipid formulations		Not FDA approved as primary therapy, but used commonly because less toxic than amphotericin B deoxycholate; ABCD associated with frequent infusion reactions
Liposomal (AmBisome, Abelcet)	IV only	
Lipid complex (ABLC)	IV only	
Colloidal dispersion (ABCD)	IV only	
Azoles		
Fluconazole	IV and oral	Most commonly used
Voriconazole	IV and oral	Multiple drug interactions
Echinocandins		Broad spectrum against <i>Candida</i> species
Caspofungin	IV only	Approved for disseminated candidiasis
Anidulafungin	IV only	Approved for disseminated candidiasis
Micafungin	IV only	Under evaluation for disseminated candidiasis

**Note:** Although ketoconazole is approved for the treatment of disseminated candidiasis, it has been replaced by the newer agents listed in this table.

**Abbreviation:** FDA, U.S. Food and Drug Administration.

Some generalizations about the management of specific *Candida* infections are possible. Recovery of *Candida* from sputum is almost never indicative of underlying pulmonary candidiasis and does not by itself warrant antifungal treatment. Similarly, *Candida* in the urine of a patient with an indwelling bladder catheter may represent colonization only rather than bladder or kidney infection; however, the threshold for systemic treatment is lower in severely ill patients in this category since it is not possible to distinguish colonization from lower or upper urinary tract infection. If the isolate is *C. albicans*, most clinicians use oral fluconazole rather than a bladder washout with amphotericin, which was more commonly used in the past. The significance of the recovery of *Candida* from abdominal drains in postoperative patients is also unclear, but again, the threshold for treatment is generally low because most of the affected patients have been subjected to factors predisposing to disseminated candidiasis.

Removal of the infected valve and long-term antifungal therapy constitute appropriate treatment for *Candida* endocarditis. Although definitive studies are not available, patients usually are treated for weeks with a systemic antifungal agent and then given chronic suppressive therapy for months or years (and sometimes indefinitely) with an oral azole.

Hematogenous *Candida* endophthalmitis is a special problem requiring ophthalmologic consultation. In lesions that are expanding or that threaten the macula, an IV polyene combined with flucytosine has been the regimen of choice. However, as more data on the azoles and echinocandins become available, new strategies may

evolve. Of paramount importance is the decision to perform a partial vitrectomy. This procedure debulks the infection and can preserve sight, which may otherwise be lost as a result of vitreal scarring. All patients with candidemia should undergo ophthalmologic examination because of the relatively high frequency of this ocular complication. Not only can this examination detect a developing eye lesion early in its course; in addition, identification of a lesion signifies a probability of ~90% of deep-organ abscesses and may prompt prolongation of therapy for candidemia beyond the recommended 2 weeks after the last positive blood culture.

Although the basis for the consensus is a very small data set, the recommended treatment for *Candida* meningitis is a polyene plus flucytosine. Successful treatment of *Candida*-infected prosthetic material (e.g., an artificial joint) nearly always requires removal of the infected material followed by long-term administration of an antifungal agent selected on the basis of the isolate's sensitivity and the logistics of administration.

## Prophylaxis

The use of antifungal agents to prevent *Candida* infections has been controversial, but some general principles have emerged. Most centers administer prophylactic fluconazole (400 mg/d) to recipients of allogeneic stem cell transplants. High-risk liver transplant recipients are also given fluconazole prophylaxis in most centers. The use of prophylaxis for neutropenic patients has varied considerably from center to center; most centers that elect to give prophylaxis to this population use either fluconazole or a comparatively low dose of an IV polyene—either amphotericin B deoxycholate or a lipid formulation of this agent. Some centers have used itraconazole suspension.

Prophylaxis is sometimes given to surgical patients at very high risk. The widespread use of prophylaxis in general surgical or medical intensive care units is not—and should not be—a common practice for three reasons: (1) the incidence of disseminated candidiasis is relatively low, (2) the cost-benefit ratio is suboptimal, and (3) increased resistance with widespread prophylaxis is a valid concern.

Prophylaxis for oropharyngeal or esophageal candidiasis in HIV-infected patients is not recommended unless there are frequent recurrences.

## Further Readings

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