polysaccharide, a CSF or serum cryptococcal antigen level of ≥1:32, and concomitant glucocorticoid therapy or hematologic malignancy. A response to treatment does not guarantee cure since relapse of cryptococcosis is common even among patients with relatively intact immune systems. Complications of CNS cryptococcosis include cranial nerve deficits, vision loss, and cognitive impairment.

PREVENTION

No vaccine is available for cryptococcosis. In patients at high risk (e.g., those with advanced HIV infection and CD4+ T lymphocyte counts of <200/μL), primary prophylaxis with fluconazole (200 mg/d) is effective in reducing the prevalence of disease. Since antiretroviral therapy raises the CD4+ T lymphocyte count, it constitutes an immunologic form of prophylaxis. However, cryptococcosis in the setting of immune reconstitution has been reported in patients with HIV infection and in recipients of solid organ transplants.

240 Candidiasis

John E. Edwards, Jr.

The genus *Candida* encompasses more than 150 species, only a few of which cause disease in humans. With rare exceptions (although the exceptions are increasing in number), 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, 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 microbiota 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.

Candida is a small, thin-walled, ovoid yeast that measures 4–6 μm 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 (e.g., CHROMagar).

EPIDEMIOLOGY

Candida organisms are ubiquitous in nature; worldwide, these fungi are present in humans as commensals, in animals, in foods, and on inanimate objects. In developed countries, where advanced medical therapeutics are commonly used (see "Treatment," below), *Candida* species are now among the most common health care–associated pathogens. In the United States, these species are the fourth most common isolates from the blood of hospitalized patients. In countries where advanced medical care is rarely available, mucocutaneous *Candida* infections, such as thrush, are more common than deep organ infections, which rarely occur; however, the incidence of deep organ candidiasis increases steadily as advances in health care—such as therapy with broad-spectrum antibiotics, more aggressive treatment of cancer, and the use of immunosuppression for sustaining organ transplants—are introduced and implemented. In recent decades, as a result of the HIV epidemic, the incidence of thrush and *Candida* esophagitis has increased substantially. In aggregate, the global incidence of infections due to *Candida* species has risen steadily over the past few decades.

PATHOGENESIS

In the most serious form of *Candida* infection, the organisms disseminate hematogenously and form microabscesses and small macroabscesses in major organs. Although the exact mechanism is not known, *Candida* probably enters the bloodstream from mucosal surfaces after growing to large numbers 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. Adherence to both epithelial and endothelial cells, thought to be the first step in invasion and infection, has been studied extensively, and several adhesins have been identified. Biofilm formation also is considered important in pathogenesis. Numerous reviews of cases of hematogenously disseminated candidiasis have identified the predisposing factors or conditions associated with disseminated disease (Table 240-1). Women who receive antibacterial agents may develop vaginal candidiasis.

Innate immunity is the most important defense mechanism against hematogenously disseminated candidiasis, and the neutrophil is the most important component of this defense. Macrophages also play an important defensive role. STAT1, Dectin-1, CARD9, and T_H1 and T_H17 lymphocytes contribute significantly to innate defense (see "Clinical Manifestations," below). Although many immunocompetent individuals have antibodies to *Candida*, the role of these antibodies in defense against the organism is not clear. Multiple genetic polymorphisms that predispose to disseminated candidiasis will most likely be identified in future studies.

CLINICAL MANIFESTATIONS

Mucocutaneous Candidiasis *Thrush* is characterized by white, adherent, painless, discrete or confluent patches in the mouth, on the tongue, or in the esophagus, occasionally with fissuring at the corners of the mouth. This form of disease caused by *Candida* can also occur at points of contact with dentures. Organisms are identifiable in gram-stained scrapings from lesions. The occurrence of thrush in a young, otherwise healthy-appearing person should prompt an investigation for underlying HIV infection. More commonly, thrush is seen as a nonspecific manifestation of severe debilitating illness. Vulvovaginal candidiasis is accompanied by pruritus, pain, and vaginal discharge which is usually thin but may contain whitish "curds" in severe cases. A subset of patients with recurrent vulvovaginitis have a deficiency in the surface expression of Dectin-1, a major recognition factor for β-glucan on *Candida*. This deficiency leads to suboptimal functioning of the CARD9 pathway, which ultimately increases the propensity for recurrent vaginal infections.

TABLE 240-1 WELL-RECOGNIZED FACTORS AND CONDITIONS PREDISPOSING TO HEMATOGENOUSLY DISSEMINATED CANDIDIASIS

Antibacterial agents	Abdominal and thoracic surgery
Indwelling intravenous catheters	Cytotoxic chemotherapy
Hyperalimentation fluids	Immunosuppressive agents for organ transplantation
Indwelling urinary catheters	Respirators
Parenteral glucocorticoids	Neutropenia
Severe burns	Low birth weight (neonates)
HIV-associated low CD4+ T cell counts	Diabetes