ELSEVIER

Archives of Medical Research 36 (2005) 660–671

Archives of Medical Research

REVIEW ARTICLE

# Invasive Candidiasis in Immunocompromised Hospitalized Patients

Charles R. Sims,[a] Luis Ostrosky-Zeichner,[a] and John H. Rex[a,b]

[a]*Laboratory of Mycology Research, Division of Infectious Diseases, The University of Texas Health Science Center at Houston, Houston, Texas*
[b]*AstraZeneca Pharmaceuticals, Alderley House, Alderley Park, Macclesfield, United Kingdom*

Received for publication March 31, 2005; accepted May 24, 2005 (ARCMED-D-05-00121).

The frequency of infections by *Candida* species is increasing worldwide, with candidemia representing the fourth most common bloodstream infection in the U.S. The risk of infection is especially high in the immunocompromised, hospitalized patient. The treatment of and prophylaxis for *Candida* infection have led to the emergence of resistant species and the acquisition of resistance in previously susceptible species. Current therapeutic options include amphotericin B and its lipid compounds, fluconazole, itraconazole, voriconazole, and caspofungin. Research is focusing on better diagnostics and the evaluation of strategies such as prophylaxis in high-risk hosts and pre-emptive therapy. © 2005 IMSS. Published by Elsevier Inc.

*Key Words:* Invasive candidiasis, Clinical manifestations, Epidemiology, Treatment, Prophylaxis, Diagnostics.

## Introduction

*Candida* spp. cause a variety of clinical syndromes ranging from relatively trivial mucocutaneous infection to life-threatening candidemia and deeply invasive candidiasis. The reported frequency of *Candida* infections has increased, with candidemia now representing the fourth most common cause of nosocomial bloodstream infection in the U.S. (1). The infection rate has increased 219–487% between 1980 and 1989 (2,3). This trend has continued into the last decade (1) and has been reported internationally with studies from Europe (4), Canada (5), and Taiwan (6) where candidemia was the most common nosocomial bloodstream infection detected.

The cost of candidemia is enormous in terms of loss of life and monetary effect. Gross mortality is high with estimates between 20 and 60% and attributable mortality ranging from 15 to 49% (7–9). The estimated costs in the U.S. of treating a single episode of nosocomial candidemia are $34,123 per Medicare patient and $44,536 per private insurance patient (10). Other authors have noted that these numbers were calculated just after the introduction of fluconazole, prior to the widespread use of lipid preparations of amphotericin and prior to new, higher estimates of the incidence of candidemia (8/100,000 population). Using these data, the current annual monetary cost of candidemia in the U.S. may be approaching $1 billion (11).

## Epidemiology

Of the greater than 100 species of *Candida*, seven are well-known pathogens in humans, and many other species are described infrequently in epidemiological surveys, case reports, or short case series. The pathologic species are found as ubiquitous colonizers of humans, residing in the gastrointestinal tract, respiratory tract, vagina, urethra, on the skin, and under the fingernails. Many studies of *Candida* carriage estimate 25–50% oral colonization in healthy subjects (12). Higher rates are noted in HIV-infected patients (13), diabetics (especially type 1) (14), persons wearing dentures (15), patients with advanced cancer (16), and patients receiving chemotherapy for malignancy (17,18). *Candida* species are also found in the hospital environment in the air, on food, floors and other surfaces and objects, and on the hands of hospital personnel. Nosocomial spread among patients has been traced to hand carriage (19).

Multiple hospital studies have demonstrated the changing epidemiology of *Candida* infection over the last two decades. The incidence of candidemia has become more

Address reprint requests to: Charles R. Sims, Laboratory of Mycology Research, Division of Infectious Diseases, The University of Texas Health Science Center at Houston, 6431 Fannin Street, MSB 2.112, Houston, TX 77030; E-mail: Charles.R.Sims@uth.tmc.edu

0188-4409/05 $–see front matter. 
doi: 10.1016/j.arcmed.2005.05.015

**Table 1.** Risk factors and conditions associated with invasive candidiasis

| Primary risk factors | Associated conditions |
|---|---|
| Prolonged antibiotic use | Solid organ transplant |
| Central venous catheter | Bone marrow transplant |
| Prolonged length of stay in an ICU | Hematologic malignancy |
| Abdominal surgery | Very low birth weight neonate |
| Heavy colonization | Acid-suppressing medications |
| Hyperalimentation | Nasogastric tubes |
| Immunosuppression | Extensive burns |
| | Malnutrition |
| | Severe pancreatitis |
| | Acute renal failure |
| | Hemodialysis |

Data from References 7, 24, 37, 144, and 145.

frequent, with some investigators reporting 20-fold increases over the decades of the 1980s and 1990s (20,21). More than 50% of cases of candidemia occur in the medical and surgical intensive care units, which corresponds to a 10-fold increased risk when compared to the general wards (22,23).

General risk factors for candidiasis are related to the specific site of infection and to the disease process. The risks of invasive candidiasis have been extensively described and are summarized in Table 1 with the most important being antibiotic administration, central venous catheters, abdominal surgery, heavy colonization, prolonged stay in an ICU, and total parenteral nutrition (24,25). Other important, site-specific risks will be discussed with the individual disease process.

Table 2 summarizes the overall frequency distribution of *Candida* species causing disease in humans. Although *Candida albicans* remains the most common isolate, non-*albicans Candida* have greatly increased in frequency as the cause of invasive disease (7,26,27). In the 20 years prior to 1990, non-*albicans* species accounted for 10–40% of bloodstream infections in contrast to 35–65% of candidemia since that time. Patients with cancer bear the major burden of these infections with 40–70% of candidemia being due to non-*albicans* species in this population (7). In the U.S., there is significant regional variation in the rate of non-*albicans* bloodstream infection (28), and *C. glabrata* has become the most frequent non-*albicans* bloodstream isolate since 1995 (29). Although a few studies show increased minimum inhibitory concentrations (MICs) to antifungal drugs after chronic use (30), most studies show no change or only minimal change in the MIC of fluconazole and itraconazole to *C. albicans* (29). The use of these drugs has, however, resulted in a ''shift'' and the emergence of resistant non-*albicans* species with an overall increased level of fluconazole resistance for candidemic patients (26). In one study of the pre- and post-fluconazole effect, the incidence of *C. albicans* has decreased by 50% with a corresponding increase of *C. glabrata* infection by 100% (31). The non-*albicans Candida* species have several species-specific disease associations and risk factors that are summarized in Table 3.

## Sources of Candidemia: The Gut, the Skin, the Line or All of the Above?

The routes of invasion of *Candida* are given endogenous or exogenous. The endogenous route is the most important, as *Candida* infections originate predominantly from the patient's own colonizing organisms from the gastrointestinal tract and skin (27,32). Infection, however, requires some defect in the normal host immunity. Breakdowns in mucosal barriers related to surgery, chemotherapy-related mucositis, gastrointestinal malignancy, total parenteral nutrition (33), or head and neck radiation therapy are examples. Cutaneous barriers are disrupted by central venous catheters, burns, surgical wounds, and trauma. Cell-mediated immunity is impaired by immunosuppressant medications after transplantation, hyperglycemia, and corticosteroids. Overgrowth of *Candida* in the gastrointestinal and genitourinary tracts occurs with antibiotic use, pregnancy, and urinary catheterization. Neutropenia caused by chemotherapy decreases the body's ability to prevent colonizing organisms from becoming invasive. Critically ill

**Table 2.** Commonly reported species distribution (%) of *Candida* bloodstream isolates and general susceptibility of *Candida* species to antifungal agents

| Species | Frequency | Fluc | Itra | Vori | 5FC | Ampho | Caspo |
|---|---|---|---|---|---|---|---|
| *C. albicans* | 48.0–59.0 | S | S | S | S | S | S |
| *C. glabrata* | 12.0–24.0 | S-DD to R | S-DD to R | S to S-DD | S | S to I | S |
| *C. parapsilosis* | 7.0–11.0 | S | S | S | S | S | S (to I?) |
| *C. tropicalis* | 5.8–19.0 | S | S | S | S | S | S |
| *C. krusei* | 1.0–5.0 | R | S-DD to R | S to S-DD | I to R | S to I | S |
| *C. lusitaniae* | <1% | S | S | S | S | S to R | S |
| Other *Candida* spp. | 2.0–6.9 | V | V | V | V | V | V |

Data from Reference 95. Frequency data from the EIEIO (146), NEMIS (147), NNIS (148), SENTRY (149), and SCOPE (28) surveillance studies.
Abbreviations: Fluc, fluconazole; Itra, itraconazole; Vori, voriconazole; 5FC, flucytosine; Ampho, amophotericin-B; Caspo, caspofungin; S, susceptible; S-DD, susceptible dose dependent; I, intermediate; R, resistant; V, variable.