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Current Epidemiology of *Candida* Infection

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Abstract

Candidemia and candidiasis are among the most frequent healthcare care-associated infections and lead to significant morbidity and mortality. The predominant species causing candidemia remains *Candida albicans*, but it has declined from the majority species to causing less than 50% of U.S. cases. Increasing proportions of infections are being caused by *C. glabrata*, which now causes almost 30% of U.S. cases, as well as *C. parapsilosis* and other non-*C. albicans* species. Outside the United States, the predominant species is dependent upon the region. Pediatric candidemia rates are declining in the U.S., but the cause of this decline has not been fully elucidated. While overall resistance to antifungal agents has remained low among *Candida* species, there is some concern for echinocandin resistance, as well as multidrug resistance, in *C. glabrata*. Although some aspects of candidemia and candidiasis have remained constant, rates, species, and susceptibility are in a constant state of flux.

Introduction

Invasive candidiasis (IC) is a devastating disease associated with high morbidity and mortality (1,2) occurring in both the young and the old and found throughout the world (3,4). In the U.S., *Candida* is the fourth leading cause of hospital-acquired (HA) bloodstream infections and the number three cause of bloodstream infections in the intensive care unit (ICU) (5,6). *Candida* is the third leading cause of central-line-associated bloodstream infections (CLABSIs) and the second leading cause of catheter-associated urinary tract infections in the U.S. (6). Although IC is not as prevalent as staphylococcal infections, some of the factors that distinguish *Candida* infections from bacterial infections are the increased mortality of IC, the higher associated costs, and the increased patient length of stay. For example, Morgan and colleagues determined that the cost associated with treating candidemia increased the total cost of hospitalization by \$19,000, with an additional 10-day length of stay (2). Zaoutis and colleagues used a national inpatient sample database to compare patients with and without a diagnosis of candidemia (7). Candidemia was associated with increased mortality, an additional 10-day length of stay, and a \$39,000 increase in

hospital charges in adult patients. For pediatric patients, candidemia equated to increased mortality, 21 additional days of hospitalization, and an increased hospital cost of \$92,000.

The epidemiology of *Candida* infections is not constant. Incidence rates, species distribution, and even antifungal susceptibility seem to be changing. In this review, the candidemia and IC burdens in adult and pediatric populations, *Candida* species distribution, and antifungal susceptibility are discussed.

Candidemia Burden in the Adult Population

Several studies have used different methodologies to show that the rate of candidemia has increased over the last decade. Cleveland and colleagues used population-based surveillance studies in Baltimore and Atlanta to directly calculate the rates of candidemia within those two cities (8). The population-based incidence rate of candidemia increased in Atlanta between 1992 and 2011 from 9.1 to 13.3 cases per 100,000 person years, an increase of 46%. The population-based rate also rose in Baltimore between 2000 and 2011 from 24.2 to 26.2 cases per 100,000 person years, a modest increase of only 8%. The median age of patients was 58 in both locations, the inci-

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dence rate was higher in black patients than in white patients, and the highest rates were in the oldest population, persons aged ≥ 65 years. The majority of patients had hospital onset candidemia (72%), followed by health care-associated community onset (primarily persons associated with long-term care facilities or who had recently been hospitalized; 25%) and community onset (3%). Using nationwide ICD-9 reporting codes and census population data, Zilberberg and colleagues examined U.S. candidemia rates between 2000 and 2005 (9). They noted a 52% increase in the population-adjusted candidemia rate during this period, from 3.7 cases per 100,000 persons in 2000 to 5.6 cases per 100,000 persons in 2005. A similar 49% increase was calculated when the data were examined as the number of candidemia-related hospitalizations. During the same period, the percentage of candidemia diagnoses remained steady at 14%, so this was not a reflection of increased recognition. Similar to the conclusions from population-based surveillance, the highest burden was in the oldest population (9).

The proportion of CLABSIs is decreasing. A recent report from the CDC comparing National Nosocomial Infections Surveillance data (1990 to 2004) to National Healthcare Safety Network (NHSN) data (2006 to 2010) shows that CLABSIs are decreasing in U.S. ICUs (10). This includes *Candida* CLABSIs, which modestly decreased by 13.5% between 2006 and 2010. This recent decrease contrasts with the period between 1990 and 2004, when the rates remained relatively constant. The recent decrease in central-line-associated candidemia may reflect a new trend that could affect overall candidemia rates. Further collection of data to monitor this trend is essential.

Candidemia and IC Burdens in the Pediatric Population The rate of candidemia in the pediatric population in the U.S. trends somewhat differently from the adult population. Multiple methodologies in multiple studies have documented decreasing rates of candidemia and IC in the pediatric population. In neonatal intensive care units (NICUs), the decrease in candidemia associated with CLABSIs as reflected in the NHSN database was dramatic (11). *Candida* CLABSIs decreased 75% in U.S. NICUs between 1999 and 2009. While there was no decrease in central-line use, several other factors may have contributed to this decline. Many hospitals implemented new central-line insertion and maintenance protocols that were targeted at lowering CLABSI rates. Increased use of prophylactic fluconazole in neonates may also have helped to lower the rate of infection (11). Among pediatric patients at a single U.S. pediatric hospital, investigators also noted a marked decrease in incidence of candidemia between 2004 and 2011. At the same time in this hospital, all CLABSIs decreased, and this decrease was attributed in part to new catheter “bundling” strategies that had been implemented (12). In recent population-based surveillance, candidemia rates in both the neonatal and pediatric populations showed significant drops in both Atlanta (1992 to 2011) and Baltimore (2000 to 2011). There was also an ongoing decline in the incidence of candidemia in infants <1 year old at both sites across the 3 years of surveillance (8). In a retrospective cross-sectional analysis of IC using ICD-9 codes in 43 U.S. pediatric hospitals conducted between 2003 and 2011, the authors noted

a 72% decrease in IC in the general pediatric population and a 91% decrease among neonates specifically (13). Taken together, these reports show a clear decline in the incidence of pediatric candidemia and IC.

Species Distribution in U.S. Adults

In the U.S., 92 to 95% of cases of IC are caused by the five most prevalent species, *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*, and this has remained constant over the last few decades (4,14-17). The proportion of infections caused by each of the five species has changed. In the 1980s *C. albicans* was isolated in the majority of cases, causing up to 76% of all *Candida* infections (18). The distribution of species started changing in the 1990s, with *C. albicans* becoming less predominant and other *Candida* species, including *C. glabrata*, proportionally increasing (19). The initial rise of *C. glabrata* may be under-appreciated, as prior to the 1990s, it was commonly known as *Torulopsis glabrata* and was not always considered among *Candida* species during surveillance. While *C. albicans* is still the *Candida* species most often isolated, it no longer causes the majority of IC; non-*C. albicans Candida* species now make up the majority of IC isolates in many hospitals in the U.S. Recent population-based candidemia surveillance in the U.S. cities of Atlanta and Baltimore illustrates this change (8,17). Longitudinal comparison of surveillance in Atlanta showed that the proportion of *C. albicans* candidemia infections dropped from 52% in 1992 to 41% in 2011. During the same time period, the proportion of *C. glabrata* candidemia infections rose from 12% to 27%. A similar trend was seen in Baltimore between 2000 and 2011, where the proportion of *C. albicans* candidemia infections dropped from 43% in 2000 to 34% in 2010. During the same period, the proportion of *C. parapsilosis* candidemia infections rose from 11% to 16%. The proportion of *C. glabrata* candidemia infections was already elevated in Baltimore in 2000 at 28%, but the proportion did rise to 31% by 2011.

A similar trend in species distribution was seen using both sentinel surveillance and a surveillance registry. Lyon and coworkers monitored 41 U.S. hospitals between 2004 and 2007 and collected 5,900 isolates causing IC. They reported that 44% of the isolates were *C. albicans*, 25% were *C. glabrata*, 18% were *C. parapsilosis*, and 9% were *C. tropicalis* (14). Remarkably similar distribution numbers were noted by the PATH Alliance registry of 3,648 patients with candidemia (16). In this 2004 to 2008 registry of candidemia from 23 U.S. and 2 Canadian medical centers, *C. albicans* was again the most prevalent species (42%), followed by *C. glabrata* (27%), *C. parapsilosis* (16%), and *C. tropicalis* (9%). The interpretation from all three of these studies is that, regardless of the data collection method, *C. albicans* is still the most common species causing IC in the U.S., but as a group, non-*albicans Candida* species surpass *C. albicans* in prevalence. The underlying questions that still remain to be answered are why this shift is taking place and where it will stop.

A very troubling finding is the number of cases of candidiasis that are caused by multiple concurrent species. The proportion of infections caused by multiple species has been reported to range as high as 3.6 to 5.7%, but more cases may be undiagnosed due to

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